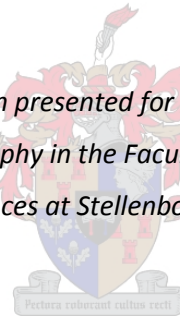


Congenital and genetic disruptions of human ocular motility and alignment – phenotypic / genotypic bi-directional algorithm

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*Dissertation presented for the degree of
Doctor of Philosophy in the Faculty of Medicine and
Health Sciences at Stellenbosch University*



Supervisor: Professor David Meyer

April 2019

DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes 8 first author and 38 co-authored original papers in peer reviewed journals or books. It also includes two publications in which I was a member of a research consortium that was involved in patient examination. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and for each of the cases where this is not the case a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

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Date: April 2019

Declaration by the candidate, Darren T. Oystreck:

In each publication where I am an author my primary role was generating and interpreting orthoptic information on subjects with the emphasis to detect and quantify anomalies of ocular alignment and motility. Secondary roles included creating and maintaining databases for our teams' on-going research projects; and creation of manuscript publications that met each journal's requirement for author's contribution. With regards to Chapters 2 to 10, the nature and scope of my contribution were as follows:

Chapter	Nature of contribution	Extent of contribution
2	Chapter creation: <ul style="list-style-type: none"> • Candidate responsible for entire chapter. 	100%
	Publications used in chapter: <ul style="list-style-type: none"> • Candidate performed examination on all but 4 subjects. • Responsible for orthoptic data in all examined subjects. This includes acquisition, analysis and interpretation. 	90%
	Contributed to the writing and editing of publications.	5-60%
3	Chapter creation:	100%

	<ul style="list-style-type: none"> • Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> • All subjects examined by candidate. • Acquisition, analysis and interpretation of orthoptic data. <p>Contributed to the writing and editing of publications.</p>	<p>100%</p> <p>60%</p> <p>40%</p>
4	<p>Chapter creation:</p> <ul style="list-style-type: none"> • Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> • All subjects examined by candidate. • Acquisition, analysis and interpretation of orthoptic data. <p>Contributed to the writing and editing of publications.</p>	<p>100%</p> <p>50%</p> <p>10-40%</p> <p>5-50%</p>
5	<p>Chapter creation:</p> <ul style="list-style-type: none"> • Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> • Charts reviewed for all subjects in Chaudhry 2012. • All subjects examined by candidate. • Acquisition, analysis and interpretation of orthoptic data. <p>Contributed to the writing and editing of publications.</p>	<p>100%</p> <p>100%</p> <p>100%</p> <p>90%</p> <p>15-75%</p>
6	<p>Chapter creation:</p> <ul style="list-style-type: none"> • Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> • All subjects examined by candidate. • Acquisition, analysis and interpretation of orthoptic data. <p>Contributed to the writing and editing of publications.</p>	<p>100%</p> <p>100%</p> <p>100%</p> <p>30%</p>
7	<p>Chapter creation:</p> <ul style="list-style-type: none"> • Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> • All subjects examined by candidate. • Acquisition, analysis and interpretation of orthoptic data. 	<p>100%</p> <p>95%</p> <p>90%</p>

	<p>Contributed to the writing and editing of publications.</p> <ul style="list-style-type: none"> Exception is Amouri 2009. Not involved in writing of manuscript. 	50%
8	<p>Chapter creation:</p> <ul style="list-style-type: none"> Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> All subjects examined by candidate. Acquisition, analysis and interpretation of orthoptic data. <p>Contributed to the writing and editing of publications. Exception is Gioia 2017 and Shaaban 2018. I was not involved in writing of manuscript (a member of Research consortium).</p>	<p>100%</p> <p>100%</p> <p>100%</p> <p>20-50%</p>
9	<p>Chapter creation:</p> <ul style="list-style-type: none"> Candidate responsible for entire chapter. <p>Publications used in chapter:</p> <ul style="list-style-type: none"> Acquisition, analysis and interpretation of orthoptic data. <p>Contributed to the writing and editing of publications.</p>	<p>100%</p> <p>100%</p> <p>50-90%</p>
10	<p>Chapter creation:</p> <ul style="list-style-type: none"> Candidate responsible for entire chapter. 	100%

Nature of contribution Extent of contribution

The publications included in this dissertation involved numerous investigators in many different specialties. The following individual is considered my main collaborator who can attest to my stated contributions.

Name	e-mail address	Nature of contribution
Dr. Thomas Bosley	tmbosley@gmail.com	Principal investigator in Saudi Arabia and Primary physician responsible for my work.

Declaration by co-author:

The undersigned hereby confirms that:

1. The declaration above accurately reflects the nature and extent of the contributions of the candidate for chapters 2-10,
2. Potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in chapters 2-10 of this dissertation.

Signature	Past institutional affiliations relevant to dissertation	Current institutional affiliation	Date
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Quote

An interesting story, an amazing adventure. It started with a single patient that expanded to involve numerous countries and even another planet. Who would have thought? It was “Magic”!

Dedication

I dedicate this dissertation to my numerous colleagues who taught me so much about the joys of science as well as life. My sincere gratitude to my supervisor, Professor David Meyer for his on-going support and motivation. Dr. Thomas (Mac) Bosley who has been the best mentor anyone could ever have. Finally, my deepest appreciation to my family – Leah, Sam, Amani, and Ilya. Your patience and sacrifice have meant so much. I look forward to beginning new chapters in new stories with you.

Summary

Our understanding of congenital and genetic disruption to human ocular motility and alignment has expanded significantly over the past 15 years due in large part to advances in genetics. This has permitted identification of many underlying genetic causes in several conditions and provided new insight into the development and function of the oculomotor system. However, this information has also disturbed current classification systems based almost exclusively on ocular motility characteristics resulting in a knowledge gap between clinicians and researchers.

As part of a team of researchers from several institutions a series of studies were conducted to better elucidate the clinical and genetic features in a large heterogeneous group of subjects with known or suspected congenital or genetic disorders affecting ocular motility and alignment.

This dissertation is the outcome of this work. It also provided an opportunity to assess the value of the orthoptic evaluation by critically evaluating ocular motility and alignment patterns in this population. The main objective was to identify key patterns that can be used to predict underlying genotypes. This could provide a more rapid, cost effective approach to these disorders and better define the role for the general ophthalmologist in the investigation.

This work spans over a decade and resulted in 47 publications that provide key pieces to the expanding body of knowledge in this field. Several publications served as reviews for knowledge translation for the ophthalmologist and one focuses on summarizing the orthoptic evaluation.

In total 845 enrolled subjects received orthoptic evaluations. This included 40 different diagnoses and 25 different genes with mutations identified. The orthoptic information in these subjects formulated part of all research team publications. Despite only scratching the surface

of the entire domain of genetic ocular motility and alignment disorders, this is likely is the largest and broadest collection of diagnoses in one report.

A new classification scheme is proposed, one that is based on the underlying pathomechanisms accounting for disruption to ocular motility and alignment. A simplified clinical approach has been developed for the general ophthalmologist to utilize key orthoptic assessments as aids in appropriately classifying encountered subjects. This is important as each diagnostic category of conditions generally requires different investigations and management.

This research also identified significant phenotypic overlap in genetically distinct disorders and phenotypic variability in the same genetic disorder. Therefore it is concluded that orthoptic features in isolation cannot be used to reliability predict the underlying genotype. The addition of information from other medical specialties improves this prediction. However, due to the currently small number of genotyped individuals in many of these rare disorders, more research is required before definitive genotype-phenotype spectrums can be identified. It is also emphasizes the need for standardization of the orthoptic assessment and reporting of the findings to ensure that similarities and differences be identified accurately.

Opsomming (Summary in Afrikaans)

Vordering met die kennis van genetika het ons instaat gestel om oor die afgelope 15 jaar beter insig te verkry in kongenitale en genetiese defekte in menslike okulêre motiliteit en belyning. Ons is in staat gestel om onderliggende genetiese oorsake in verskeie toestande te identifiseer sowel as om nuwe insigte te verskaf in die ontwikkeling en funksie van die okulomotoriese sisteem. Aangesien huidige klassifikasiesisteme byna uitsluitlik baseer is op oog motiliteitseienskappe, het hierdie nuwe kennis 'n gaping gelaat tussen klinici en navorsers.

As deel van 'n span navorsers vanuit verskeie inrigtings is 'n reeks studies gedoen om die kliniese en genetiese eienskappe van 'n groot heterogene groep persone met bekende, of vermoede genetiese toestande van die oogmotiliteits en belyningsstelsel beter te verklaar.

Hierdie proefskrif is die uitkoms van daardie werk. Dié navorsing het ook die geleentheid geskep om krities die waarde van ortoptiese evaluasies te ondersoek deur okulêre motiliteit en belyningspatrone in hierdie populasie te beskryf. Die hoofdoel was om sleutelpatrone te identifiseer wat gebruik kan word om onderliggende genotipes te voorspel. Hierdie bevindinge kan 'n vinnige en koste effektiewe benadering tot hierdie toestande wees en kan ook die rol van die algemene oftalmoloog in hierdie toetse vergemaklik.

Hierdie proefskrif dek meer as 'n dekade se werk en het 47 publikasies tot gevolg gehad wat almal stukkie in die legkaart van kennis in die veld verteenwoordig. Verskeie publikasies dien as oorsigsartikels om die bestaande kennis aan te bied aan oftalmoloë en een fokus op die ortoptiese ondersoek metodiek.

Vir dié studie is 845 pasiënte ortopties ondersoek. Die groep sluit 40 verskillende toestande en 25 verskillende geïdentifiseerde genes met hulle mutasies in. Die ortoptiese inligting van al die pasiënte was deel van die navorsingsgroep se publikasies. Hoewel daar duidelik net op die oppervlakte van die omvang van die genetiese oogmotiliteits en belynings toestande gekrap is, is hierdie waarskynlik die grootste en wydste versameling van diagnoses in een verslag.

'n Nuwe klassifikasie sisteem word voorgestel. Dis gebaseer op onderliggende patologiese meganismes wat verantwoordelik is vir defektiewe ooglobelyning en motiliteit. 'n Vereenvoudigde kliniese ondersoeksisteem is ontwikkel vir die algemene oftalmoloog waar sleutelpunt ortoptiese ondersoeke help om die korrekte klassifisering van pasiënte te bevestig. Hierdie sisteem is belangrik, want elke kategorie van toestande vereis verskillende ondersoeke en hanteringsstrategieë.

Hierdie navorsing het ook betekenisvolle oorsleuening identifiseer in toestande wat geneties ooreenstem. Ortoptiese bevindinge kan dus nie met absolute betroubaarheid gebruik word om onderliggende genotipes te identifiseer nie. Addisionele inligting van ander mediese spesialiteite verbeter egter die voorspelbaarheid. Omdat daar in vele gevalle van hierdie baie raar toestande nog te min genotiperingsgedoen is, is daar addisionele navorsing nodig voordat onbetwisbare genotipe-fenotipe korrelasies gedoen kan word. Die belang van standardisering van die ortoptiese assessering en rapportering van bevindinge word beklemtoon ten einde te verseker dat verskillende akkuraat identifiseer kan word.

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Chapter 1: Introduction

The field of genetics continues to expand with an ever increasing importance to medicine. The field of Ophthalmology has already incorporated genetic advances into clinical practice. Two such examples are Retinoblastoma and von Hippel-Lindau disease for which genetic testing is now recommended in patients, and frequently in other family members, whenever these conditions are suspected.^{1, 2}

Ocular misalignment between the visual axes of the two eyes (strabismus) is another ophthalmological disorder that occurs in 2-4% of the general population.³ Comitant forms are those in which the degree of ocular misalignment is the same in all directions of gaze, while incomitant or complex variants have changes in different gaze positions and are frequently associated with limitation of ocular movement in one or both eyes. Congenital forms are present at birth or recognized by 6 months of age. Until recently, distinctions between congenital or suspected familial/genetic forms of strabismus were based primarily on clinical and, in some cases by neuro-radiological features.⁴ However, genetic advances have permitted identification of several genes involved in a variety of components of the oculomotor system. A genetic distinction is extremely valuable because many of these disorders can have substantial clinical overlap despite differences in their underlying mechanisms. Additionally, some will have associated non-ophthalmologic features that may not always be obvious during a routine eye exam and require investigation by other medical specialities (e.g., deafness, autism, cerebral vascular anomalies, scoliosis, respiratory problems, and limb weakness).⁵⁻⁸

We are presently in an era where genes and genotype-phenotype correlations are being identified. Despite significant advances in investigational techniques, dissemination of this information has lagged. Several factors may account for this. First, the topic of ocular motility dysfunction and strabismus is vast, and no one area of ophthalmology is solely dedicated just to this field. Second, ocular motility dysfunction and ocular misalignment arising from congenital and/ or genetic problems are rare when compared to acquired causes. Typical ophthalmological practice patterns with homogenous regional patient populations infrequently permit even the most experienced ophthalmologist the opportunity to see many of these

syndromes. Finally, many of these conditions have clinical similarities. Therefore, difficulties in clinical distinction often prevent conducting a cost effective genetic analysis in situations where a genetic diagnosis may be needed.

Problem statement

The field of congenital and genetic disorders of human ocular motility and alignment has increased dramatically over the past decade and will continue to expand. Gaps have developed in classification systems and in the link between clinicians and researchers. Designing solutions to this issue requires a comprehensive review of the field with the goal of designing a better, more efficient diagnostic approach utilizing published cases, clinical experiences and prospectively collected data including ophthalmologic, neurologic, radiologic and genetic information.

Aim:

To design a comprehensive bi-directional diagnostic approach for the investigation of disruptions to human ocular motility and alignment arising from congenital and/or genetically defined causes.

Central research question: Can the orthoptic evaluation be an effective tool in the elucidation and distinction of different congenital and/or genetic disorders resulting in disturbance of ocular alignment and motility?

This will be feasible if the orthoptic evaluation can demonstrate:

There is phenotypic difference between genetically distinct conditions – **Hypothesis 1.**

There is phenotypic consistency between genetically identical conditions – **Hypothesis 2.**

Evidence used to address the central research question will arise from achieving each of the following research objectives.

Research objectives:

1. To design a clinical assessment protocol to assess disruptions of ocular motility and alignment.
2. To identify and characterize (congenital and/or genetic) disorders affecting ocular motility and alignment.
3. To consolidate the identified main phenotypes with confirmed genotypes.
4. Provide new insight into mechanisms affecting normal development and function of the oculomotor system.
5. Design a classification scheme based on mechanism accounting for disruption of ocular motility/alignment.
6. Create a simplified clinical approach for the general ophthalmologist.

Table 1.1 consolidates the above research statements.

Methods and Ethical requirements of the research

We conducted Institutional Review Board and Human Ethics committee approved projects at several institutions (**Table 1.2**) aimed at defining phenotypic and genetic characteristics in patients with suspected efferent system dysfunction. The retrospective component involves work done from January 2003 to August 2011. Prospective work began following ethics approval from Stellenbosch University August 5, 2011 (Ref no. N11/07/222).

This dissertation is a compilation of work done at 11 sites in 5 countries (Canada (1), United States (5), Saudi Arabia (2), England (1), Northern Ireland (1), Tunisia (1) and includes 47 publications. It involved the examination of 845 patients. The outcome of this has been summarized in the following chapters. Chapters 3-7 involve specific clinical diagnoses. Chapter 8 includes a group of heterogeneous disorders. Each chapter centers around publications identifying phenotype/genotype characteristics. Chapter 9 is a discussion of the central research question and incorporates information from the previous chapters. Chapter 10 are conclusions.

Tables

Table 1.1 Overview of research statements

Central research question: To determine if the orthoptic evaluation is an effective tool in the elucidation and distinction of congenital and/or genetic disturbances in ocular alignment and motility.	
Research aim: To design a bi-directional diagnostic approach to the investigation of disruptions to human ocular motility and alignment arising from congenital and/or genetically defined causes.	
Hypothesis 1	There is phenotypic difference between genetically distinct conditions? (Algorithm direction 1 – Phenotype predicts Genotype)
Hypothesis 2	There is phenotypic consistency between genetically identical conditions? (Algorithm direction 2 – Genotype predicts Phenotype)
Objectives	
Obj. 1	Design a clinical assessment protocol to assess disruptions of ocular motility and alignment.
Obj. 2	Identify and characterize (congenital and/or genetic) disorders affecting ocular motility and/or alignment.
Obj. 3	Consolidate the identified phenotypes with confirmed genotypes.
Obj. 4	Provide new insight into mechanisms affecting normal development and function of the oculomotor system.
Obj. 5	Design a classification scheme based on mechanism accounting for disruption of ocular motility/alignment
Obj. 6	Create a simplified clinical approach for the general ophthalmologist

Table 1.2 Approved research projects for enrollment of subjects

Project	Institution
project ID 542-7 - Hereditary ocular motility disorders	King Saud University, Riyadh, Saudi Arabia (KSU)
project ID 0424 - Genetic evaluation of congenital eyelid and/or motility abnormalities	King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia (KKESH)
project ID 05-03-036R - Genetic studies of strabismus, congenital cranial dysinnervation disorders (CCDD's) and their associated anomalies	Boston Children's Hospital, Boston, USA (BCH)

Chapter 2: Duane Retraction Syndrome (DRS)

Duane retraction syndrome (DRS) is a form of congenital complex strabismus. Despite its rarity in the general population it is considered the commonest form of complex strabismus presenting to the pediatric ophthalmology service. It is one of the first specialized forms of strabismus taught to ophthalmology resident and orthoptic students. It is considered to have consistent clinical ocular features and is generally considered a benign entity.

This chapter summarizes publications involving clinical characterization of DRS and identification of phenotype-genotype correlations.

This chapter has 3 main sections.

Section 1 outlines the publications defining the orthoptic features in patients with DRS. Section 2 involves subjects who already had an identified genetic mutation. The focus of these reports were to provide a comprehensive clinical description. Section 3 were prospective publications focused on genetic evaluation of subjects with DRS frequently associated with medical and developmental problems. We refer to these forms as syndromic DRS.

Section 1 - Defining DRS phenotypes

[Khan, A. O., & Oystreck, D. \(2006\). Clinical characteristics of bilateral Duane syndrome. J AAPOS, 10\(3\), 198-201.⁹](#)

[doi:10.1016/j.jaapos.2006.02.001](https://doi.org/10.1016/j.jaapos.2006.02.001)

- Click reference above to see full PDF article

We reported the clinical characteristics of individuals with non-operated bilateral DRS from one tertiary care facility in the Middle East (King Khaled Eye Specialist Hospital - KKESH). Two hundred and seventy charts of patients with DRS were retrospectively reviewed. Thirty seven patients were identified as having bilateral Duane syndrome (14%).

Significance of this paper was that it identified phenotypic differences between bilateral and unilateral cases. We observed a 59% male prevalence that was contrary to the 60% female prevalence reported in unilateral DRS. Bilateral cases were more likely to have primary position strabismus (78%) than unilateral cases (62%).

Findings from this regional population supported other bilateral DRS reports in the literature. An associated congenital ocular and non-ocular abnormalities was present in 24% of cases. This was consistent with reported prevalence of 8-57%. The breakdown was as follows: Associated ocular abnormality - 14%, non-ocular abnormality - 8%, both - 3%. Other similarities to the literature was the presence of the same DRS type in each eye (95%), presence of positive family history of strabismus (22%) and presence of amblyopia (16%).

Other key features included frequent utilization of an abnormal head posture (21/37- 59%). In all cases it was to permit monocular fixation and never for binocularity. No one in this series had a multisystem syndrome such as Okhiro syndrome, Wildervanck syndrome, or Holt-Oram syndrome. This was felt to be due to the referral pattern of the facility in which this study was undertaken. Patients referred to this eye hospital cannot have any serious medical issues. Those individuals are instead referred to the local University hospital (King Saud University). Key elements from this study were that it provided a comparison of DRS phenotype in an Arab population to other literature involving bilateral cases. It also highlighted some contrasts to unilateral cases (gender and strabismus patterns). Our study had a surprising low report of positive family history of strabismus and a low association of other congenital ocular and non-ocular anomalies.

[Khan, A. O., & Oystreck, D. T. \(2006\). Fixation preference for the affected eye in patients with unilateral Duane syndrome. J AAPOS, 10\(3\), 275-276.](#)¹⁰

doi:10.1016/j.jaapos.2006.01.009

- Click reference above to see full PDF article

Here we reported a small series of patients with unilateral DRS that preferred fixation with the involved eye. In 7/8 cases the reason was due to decreased vision in the non-DRS eye. In each case there was either uncorrected anisometropia and/or amblyopia. A literature review revealed there had only been 3 previously reported cases but no details were provided as to the reason. Another unique feature was that 2 patients had superimposed intermittent exotropia. In both cases the deviation decompensated into exotropia resulting in the patient adopting a small face turn towards the DRS eye to maintain fixation with the eye held in adduction (unable to abduct) while the contralateral non-DRS eye deviated out due to the exotropia tendency and full ocular motility. The other case with intermittent exotropia also had uncorrected anisometropia. The fixation preference could again be explained by better visual acuity in the DRS eye.

The significance of this paper brought attention to a rare feature of preferring fixation with the affected eye in the setting of a monocular motility deficit when binocular single vision cannot be achieved. It emphasizes the importance of a careful evaluation of the sensory and vision features on patients with strabismus. This will later be used as the frame work in a future publication that standardizes the orthoptic evaluation.¹¹

[Khan, A. O., Oystreck, D. T., Wilken, K., & Akbar, F. \(2007\). Duane retraction syndrome on the Arabian Peninsula. *Strabismus*, 15\(4\), 205-208.](#)¹²

doi:10.1080/09273970701632023

- Click reference above to see full PDF article

This publication was the largest series of DRS reported to date and the first large series from the Middle East. It summarized the clinical findings in 404 DRS patients from the Arabian Peninsula and provided a comparison to other large studies.

Main findings:

- Gender: Females 55%; Males 45%
- Laterality: unilateral 86%; bilateral 14%
- Affected eye: Left 79%; Right 35% (included bilateral cases)
- Types: I 78%; II 19%; III 19%
- A further breakdown of findings in unilateral and bilateral were also given

The significance of this paper was that it confirmed the clinical features of an almost exclusively non-syndromic DRS Arab population. It also determined that the high number of patients from consanguineous marriage in this region did not affect the clinical presentation. Clinical features were comparable to those of other large series from other parts of the world. **Table 2.1** shows clinical similarities between 196 patients identified globally through the Orbit international E-consultation program and our retrospective cohort of 404 patients. In both series left eye involvement, affecting females, and limitation of abduction (Type 1) were the commonest presentations.

This publication also increased the number of reported bilateral cases in 2005⁹ from 37 to 57 with findings still supporting a preponderance for male involvement (56% vs 44% M-F). We also encouraged other authors to carefully report clinical characteristics of bilateral cases and to use clearly-defined diagnostic criteria to do so.

Outstanding issues related to this paper was that the population was likely skewed to sporadic non-syndromic forms of DRS. Therefore a complete picture of DRS was not possible given the referral pattern to the institution where the study was conducted (KKESH). Strabismic patients with associated medical or neurologic disease are referred to the local University hospital (King Saud University). Despite consistency of the ocular features to other studies, it highlights how reported variation in prevalence of associated anomalies can arise from how intensely patients are investigated and the referral base from which these patients come. Despite this limitation the ocular features provided the context for later publications that specifically involved syndromic and genetic forms.

During work on our retrospective papers it became evident we would need to work collaboratively with other researchers and institutions to adequately define the full phenotypic spectrum of subjects with DRS that would include medical and eventual genetic investigations.

Section 2 – Reporting Genotype – Phenotype correlation.

In 2002, just prior to our publications in section 1, a new classification system emerged for certain forms of congenital ocular motility disorders. DRS was one of several forms included. These disorders were termed the Congenital Cranial Dysinnervation Disorders (CCDDs).¹³ This inception paper marked the cusp of the genetic era in the field of congenital ocular motility disorders. Advances in genetic technology were starting to seed the expansion of our understanding of many of these disorders, including DRS. The timing of this was ideal for our Middle East team as we just began a collaboration with the Engle lab in Boston, USA. This group was able to conduct genetic evaluations in patients we identified from our previous work. My role in this collaboration was to create a standardized clinical approach to confirm the ocular diagnosis and identify fields in which similar subjects and their families would be categorized as we moved forward with additional medical and genetic investigations. This effort led to three publications between 2005 and 2008 defining a new monogenic CCDD with DRS as a main feature.^{5, 14, 15} This was my first opportunity to define orthoptic features,

and our research team's first opportunity to define the clinical spectrum of a genetically defined population of subjects with DRS. These publications contributed to increasing our understanding of underlying the pathophysiology of cranial nerve and human development.

These publications are summarized here:

[Tischfield, M. A., Bosley, T. M., Salih, M. A., Alorainy, I. A., Sener, E. C., Nester, M. J., Oystreck, D.T., . . . Engle, E. C. \(2005\). Homozygous HOXA1 mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. Nat Genet, 37\(10\), 1035-1037.](#)¹⁴

[doi:10.1038/ng1636](https://doi.org/10.1038/ng1636)

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At this time it was reported that most forms of DRS are sporadic, with 5-10% being inherited in an autosomal dominant fashion with previous reports of families with bilateral horizontal gaze anomalies.¹⁶ Mutations in one gene (*SALL4*) was already known to result in autosomal dominant DRS.¹⁷ A locus for bilateral DRS was known and referred to as DURS2.¹⁸ The phenotype would be expanded to include other ocular associations^{19, 20} and the gene would later be identified as *CHN1*.²¹

Here we reported 9 individuals with syndromic bilateral DRS from 5 families in whom were found to have homozygous mutations in the *HOXA1* gene. It demonstrated the absence of cranial nerve six bilaterally in the one appropriately imaged subject with thin sliced MRI. It also included the genetic analysis of another geographically distinct population with a similar reported phenotype. The clinical features of these Native American subjects had previously been described and referred to as the Athabascan Brainstem Dysgenesis Syndrome (ABDS).¹⁶ Our genetic elucidation paper was the first report of a human homozygous HOX gene mutation, the first report of a new gene causing syndromic DRS, and the first autosomal recessive form of DRS. This report identified another monogenic CCDD and provided further evidence that CCDDs are due to primary cranial nerve maldevelopment.

The paper provided a brief overview of the phenotype. Main clinical features included bilateral DRS (9/9) associated with profound sensorineural deafness (8/9) with external ear defects (3/9). Delayed motor milestones (7/9) and Autism spectrum disorder (2/3). This syndrome also included significant neuro-imaging features. Imaging was obtained in 8 individuals and demonstrated the cerebrum, cerebellum and brainstem were normal. In the one patient that was appropriately studied Cranial nerve 6 was absent. In 7 individuals with deafness all had inner ear abnormalities that included common cavity deformity (5/7) or cochlea aplasia (2/7). The one patient with normal hearing had normal inner ear anatomy. Skull base imaging with computed tomography was obtained in 3 individuals. One had bilateral absence of the carotid canal and two had unilateral absence of the carotid canal. Magnetic resonance angiography (MRA) of the head and neck was obtained in 4/8 and head only in 3/8. All were found to have an internal carotid artery (ICA) malformation that ranged from unilateral hypoplasia to bilateral agenesis.

This article also provided the opportunity to directly compare two geographical distinct subject with the same genetic mutation. A notable observation was that the ABDS patients had central hypoventilation syndrome, mental retardation, some had with facial weakness, vocal cord paralysis and contruncal heart defects (e.g. Tetralogy of Fallot and double aortic arch) that were not present in the BSAS subjects. Confirmation of *HOXA1* mutations in two similar but at times phenotypically distinct conditions resulted in the coining of a new condition now referred to as *HOXA1*-related syndromes.

Arising from this publication was the identification of consistent features of *HOXA1* syndrome namely horizontal gaze restriction, although reported as bilateral DRS in BSAS and horizontal gaze palsy-like in ABDS, and sensorineural hearing loss in almost all patients. However, marked phenotypic variability could also be present. Further evaluation of more genotyped individuals needed to better define the phenotypic spectrum. This paper also identified previously unknown developmental function of *HOXA1*. More investigation would be needed to determine its role in vasculo or angiogenesis, inner ear development, and cognitive and behavioral impairment that included autism (BSAS) and mental retardation (ABDS). The gene was thought

to only be expressed in developing hindbrain. These anomalies suggest role in forebrain and cerebellar development.

The final point is that the reporting of horizontal gaze restriction needs to be standardized as the mechanism underlying DRS and true horizontal gaze palsy were very different. The absence of Cranial nerve 6 in the one BSAS patient suggests DRS rather than horizontal gaze palsy.

[Bosley, T. M., Salih, M. A., Alorainy, I. A., Oystreck, D. T., Nester, M., Abu-Amero, K. K., Tischfield, M.A., Engle, E. C. \(2007\). Clinical characterization of the HOXA1 syndrome BSAS variant. *Neurology*, 69\(12\), 1245-1253.](#)⁵

[doi:10.1212/01.wnl.0000276947.59704.cf](https://doi.org/10.1212/01.wnl.0000276947.59704.cf)

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Here we reported a more detailed clinical description of the 8 individuals from the 2005 paper and 1 new patient. In this report there was an emphasis to more clearly define the ocular phenotype by including an in depth description of the motor, sensory and visual aspects of the orthoptic evaluation.¹¹

This was important for several reasons. There were several poor clinical descriptions in genetic reports of subjects with presumed DRS. A recent report had just come out describing novel neuro-imaging findings in DRS subjects (DURS2 phenotype) identifying wide spread orbital dysinnervation where 7/8 affected individuals had bilateral DRS in addition to other orbital involvement.²² We also knew homozygous mutations in HOXA1 can result in two phenotypes – BSAS and ABDS, each involving a geographically distinct population, with ABDS individuals appearing to have more severe medical phenotypes. We also previously highlighted the discrepancy in ocular motility description of subjects with ABDS for versus BSAS.

This 2007 publication reported the BSAS variant found in Saudi Arabian and Turkish populations can be summarized as having Bilateral DRS Type 3, deafness and inner ear malformations, cerebrovascular anomalies, and cognitive dysfunction. The ABDS variant found in Native

American population are reported as having horizontal gaze restriction, deafness, internal carotid artery abnormalities with extra features that include Central hypoventilation, facial and bulbar weakness, conotruncal heart defects, and mental retardation.

Significance of this paper:

This comprehensive phenotypic report of a genetically defined syndromic Duane condition (synDRS) provided distinctions between other genetic forms of DRS and other overlapping congenital eye movement disorders within the CCDD domain. Provided is a Table emphasizing genetic, clinical, and neuro-imaging features important to distinguish between three overlapping conditions - BSAS, ABDS, and HGPPS (described in Chapter 8). It also confirmed lack of other orbital dysinnervation reported in DURS2.

This paper also extended the BSAS phenotype and highlighted several non-ophthalmic associations requiring medical investigation. This includes evaluation for deafness, delayed motor milestones, behavioral abnormalities, and cerebrovascular and cardiac anomalies. It also documented the clinical variability that can occur in identical HOXA1 mutations within an isolated ethnic population. This could specifically involve ocular motility. Despite all individuals meeting the criteria for bilateral DRS the extent of horizontal eye movements could vary between individuals and between eyes.

This variability was also shown to extend beyond ocular motility. For example, subject 8 had a mild phenotype with bilateral DRS with modest adduction, normal hearing, only left ICA hypoplasia, and normal cognition. Subject 5 had a severe phenotype with no observed horizontal eye movements, deafness, common cavity deformity bilaterally, absent ICA bilaterally, and autism.

Several significant orthoptic features were identified. We confirmed ocular motility deficit is always bilateral and limited to horizontal movements. All strabismus patterns can be classified as bilateral DRS Type 3. Ocular alignment includes orthotropic and esotropic eye positions. Subjects have normal afferent visual functioning with 3 patients demonstrating Fusion. Some nuances to the cardinal features of DRS were also identified. Six subjects had obvious bilateral globe retraction on attempted adduction. However, 1 had unilateral globe retraction

despite having bilateral motility deficit and an older sister with unequivocal globe retraction bilaterally, and two patients did not have observed globe retraction. Both of these individuals had severe autism that may have interfered with ability to cooperate. Globe retraction with convergence was observed in 3 subjects.

One patient had an element of accommodative esotropia superimposed on DRS. At the time of publication this may have been the first report of the coexistence of these two strabismic conditions. The only report that could be found in the literature came in 2014.²³

Significant Neuro-imaging (CT, MRI, MRA) features included normal appearing orbits and extra-ocular muscles (eoms). The latter suggests the lateral rectus muscle is receiving sufficient innervation for myofiber survival.

Clinical, radiological, and mouse model studies suggest partial or complete absence of the abducens nucleus and nerve bilaterally. Differences in residual adduction and presence of mild abduction in two patients may imply variable depletion of abducens motoneurons and interneurons in addition to degree of anomalous innervation from CN3 to the lateral rectus.

Vascular defects in BSAS appeared to be clinically silent but probably put patients at increased risk of cerebrovascular compromise. Delayed motor development may be explained by lack of vestibular system. Presence of autism or autistic features implies this disorder extends beyond the brainstem.

Similarities with thalidomide embryopathy suggest that the teratogenic effects of early thalidomide exposure may be due to interactions with the HOX cascade.

Outstanding issues:

Identification of 1 patient with normal hearing and normal inner ear anatomy highlights the need for full investigations of all genotyped individuals. This comes back to the issue of requiring a genetic diagnosis and served as a main reason to establish a formal ophthalmic genetics program at King Saud University where the majority of work on the dissertation was completed.

The absence of globe retraction raised an interesting issue. Does the absence of globe retraction in the setting of significant horizontal gaze limitation suggest another etiological

mechanism may be responsible? This was addressed in another publication in which I examined 25/40 subjects included but was not involved in the writing of the manuscript.²⁴ (See appendix chapter 2 for full article)

All patients we identified to date came through our neuro-ophthalmology clinic as a result of their ocular motility disturbance. At this time the prevalence of *HOXA1* mutations in a deafness clinic was unknown. This was later addressed in another publication.²⁵ (See appendix chapter 2 for full article)

[Bosley, T. M., Alorainy, I. A., Salih, M. A., Aldhalaan, H. M., Abu-Amero, K. K., Oystreck, D. T., Tischfield, M.A., Engle, E.C., Erickson, R. P. \(2008\). The clinical spectrum of homozygous *HOXA1* mutations. *Am J Med Genet A*, 146A\(10\), 1235-1240.](#)¹⁵

[doi:10.1002/ajmg.a.32262](https://doi.org/10.1002/ajmg.a.32262)

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This article further increased our understanding of the phenotypic presentation. It confirmed certain features were consistently present such as abnormal horizontal ocular motility and deafness. However the ocular motility phenotype was expanded by identifying two patients with full horizontal ocular motility, one of whom had mild unilateral ptosis and limitation of elevation. All ABDS patients were reported as having bilateral horizontal gaze palsy. It should be noted I did not examine the ABDS individuals.

Publication summary and significant findings:

This article further increased our understanding of the phenotypic presentation in genetically confirmed cases of *HOXA1*. Here we report the clinical findings in 9 new individuals (6 families) with *HOXA1* mutations having BSAS or ABDS. This included 6 individuals from 3 Saudi families and 3 individuals from 3 Native American families. Noteworthy documentation included a Table outlining the *HOXA1* mutations, cardiac defects, cognitive problems, and medical features for this syndrome, the frequency of clinical characteristics, and an illustration of the spectrum of horizontal gaze deficits.

Additional features were identified in the BSAS population. This included identification of cardiac defects, facial twitching and grimacing (but not facial weakness), another 3 individuals with absent horizontal gaze without observed globe retraction, two individuals with full horizontal gaze and normal hearing of which one was also the only patient to demonstrate a unilateral elevation deficit with ipsilateral ptosis. Prior to this 1 subject had been found to have normal hearing but did have bilateral DRS. Given these findings it was felt abnormal ocular motility and deafness were considered absolute and essential for this diagnosis. This report also confirmed the absence of cranial nerve 6 bilaterally in another BSAS patient.

Inclusion of these 9 new individuals blurred the distinction between homozygous *HOXA1* BSAS and ABDS variants. Identification of more individuals with absent horizontal gaze and absence of globe retraction suggests that the same genetic mutation can result in an ocular motility phenotype of either horizontal gaze palsy or DRS. In both cases cranial nerve 6 is absent but with variable dysinnervation of the lateral rectus.

This report also expanded the severity gradient. ABDS seems to represent the severe end of *HOXA1* clinical spectrum while the other end has milder versions of BSAS including isolated bilateral DRS^{5,14} and isolated mild congenital hearing loss (see subject C4). It also highlighted features that are more consistent with a particular variant. Facial and bulbar weakness and symptomatic central hypoventilation still only present among ABDS population, while autism and somatic abnormalities are only observed in BSAS.

The major clinical features may arise when the gene fails to be expressed correctly in the hindbrain neuroectoderm and notochord early in gestation. This results, at least at times, in the loss of rhombomere 5 (and the abducens nuclei, leading to aberrant innervation of the lateral rectus muscles and bilateral DRS), abnormal vasculogenesis (and congenital cerebrovascular and cardiovascular anomalies), and possibly disturbed development of serotonergic neurons in the brainstem (resulting in autistic behavior). It may also lead to defective induction of otic vesicle development and abnormal or absent development of the inner ear.

The *HOXA1* spectrum was further summarized into the context of other CCDDs in a 2011 review article²⁶ with an update in 2013.²⁷ PDFs of these publications are included in the appendix for Chapter 9.

Summary of the HOXA1-related syndromes

Homozygous HOXA1 mutations were first detected in our Saudi Arabian subjects with bilateral DRS, bilateral deafness, and cerebrovascular and/or cardiovascular congenital anomalies.

Subsequent evaluation of additional subjects determined that homozygous *HOXA1* mutations may occur without deafness and DRS. Other features are also variable, including the degree of DRS (type 1 versus type 3), the presence of dysmorphism, or autism.

Two follow up publications were done investigating the role of *HOXA1* in individuals with Moebius syndrome²⁴ (Chapter 4) and with non-syndromic isolated deafness.²⁵ Full articles available in appendix chapter 2.

[Rankin, J. K., Andrews, C., Chan, W. M., & Engle, E. C. \(2010\). HOXA1 mutations are not a common cause of Mobius syndrome. J AAPOS, 14\(1\), 78-80.24.](#)²⁴

[doi:10.1016/j.jaapos.2009.11.007](https://doi.org/10.1016/j.jaapos.2009.11.007)

- Candidate was not involved in the writing of this manuscript, however I did examine all individuals to confirm ocular motility phenotype.
- Click reference above to see full PDF article

The HOXA1-related syndromes result from autosomal-recessive truncating mutations in the homeobox transcription factor, *HOXA1*. Limited horizontal gaze and sensorineural deafness are the most common features; affected individuals can also have facial weakness, mental retardation, autism, motor disabilities, central hypoventilation, carotid artery, and/or conotruncal heart defects. Moebius syndrome is also phenotypically heterogeneous, with minimal diagnostic criteria of nonprogressive facial weakness and impaired ocular abduction; mental retardation, autism, motor disabilities, additional eye movements restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities also occur. We asked, given the phenotypic overlap between these syndromes and the variable expressivity of both disorders, whether individuals with Moebius syndrome might harbor mutations in *HOXA1*. Our results suggest that *HOXA1* mutations are not a common cause of sporadic Moebius syndrome in the general population.

[Abu-Amero, K. K., Hagr, A. A., Almomani, M. O., Azad, T. A., Alorainy, I. A., Oystreck, D. T., & Bosley, T. M. \(2014\). HOXA1 Mutations are Not Commonly Associated with Non-Syndromic Deafness. *Can J Neurol Sci*, 41\(4\), 448-451.25.](#)²⁵

PMID: 24878468

OBJECTIVE: Homozygous homeobox A1 (HOXA1) mutations cause a spectrum of abnormalities in humans including bilateral profound deafness. This study evaluates the possible role of HOXA1 mutations in familial, non-syndromic sensorineural deafness. **METHODS:** Forty-eight unrelated Middle Eastern families with either consanguinity or familial deafness were identified in a large deafness clinic, and the proband from each family was evaluated by chart review, audiogram, neuroimaging, and HOXA1 sequencing. **RESULTS:** All 48 probands had normal neuro-ophthalmologic and general medical examinations except for refractive errors. All had congenital non-syndromic sensorineural hearing loss that was symmetric bilaterally and profound (>90 dBHL) in 33 individuals and varied from 40 to 90 dBHL in the remainder. Thirty-nine of these individuals had neuroimaging studies, all documenting normal internal carotid arteries and normal 6th, 7th, and 8th cranial nerves bilaterally. Of these, 27 had normal internal ear structures with the remaining 12 having mild to modest developmental abnormalities of the cochlea, semicircular canals, and/or vestibular aqueduct. No patient had homozygous HOXA1 mutations. **CONCLUSIONS:** None of these patients with non-syndromic deafness had HOXA1 mutations. None had major inner ear anomalies, obvious cerebrovascular defects, or recognized congenital heart disease. HOXA1 is likely not a common cause of non-syndromic deafness in this Middle Eastern population.

Section 3 – Genetic investigation of DRS

Following the publications in Section 2 we focused on further investigating the genetics of DRS. This section is an overview of our results.

From January 2011 - July 2013 a total of 111 subjects met the clinical characteristics for DRS. All subjects were enrolled either at KSU or KKESH. **Table 2.2** is an overview of this population. Subjects were divided into three groups. Group 1 are those with DRS as an isolated finding, referred to as non-syndromic DRS (nsDRS). Group 2 are subjects in which DRS is not an isolated finding. Here DRS is found in association with at least one other non-ocular motility anomaly. This could include a medical diagnosis, e.g. Duchene muscular dystrophy, deafness, or an associated developmental anomaly such as clinodactyly, club foot etc. This group is referred to as syndromic DRS (synDRS). Group 3 had nsDRS associated with another congenital cranial dysinnervation disorder (CCDD) phenotype. This group is referred to as DRS plus.

Table 2.2 provides a summary of the genetic analysis for all DRS groups. DNA samples were obtained in 58% (64/111) of subjects. Confirmation of a suspected mutation or discovery of a novel genetic mutation occurred in 55% of these (35/64). Twenty-five percent (16/64) were negative for mutations for known CCDD genes at that time, or following chromosomal analysis with array CGH technology. Results of genetic analysis are still pending in the remaining 25% (16/64).

Subjects were identified at the time of their initial visit to either the pediatric ophthalmology or neuro-ophthalmology service. Subjects were then enrolled into an IRB approved research study at the appropriate institution. This occurred at the initial visit or during a subsequent evaluation. After enrollment and informed consent, subjects underwent a full orthoptic evaluation. As part of our clinical protocol subjects also underwent a pediatric ophthalmology or neuro-ophthalmology assessment or both. Some subjects also had neuro-imaging and additional medical investigations.

In total 33 subjects with genetic results were reported in 12 publications.^{5, 14, 15, 28-37} Ten were reported prior to initiation of the dissertation.^{5, 14, 15, 37} These publications are shown in **Table 2.3**. Abstracts of the prospective publications for 21 subjects are provided here.

[Abu-Amero, K. K., Kondkar, A. A., Salih, M. A., Alorainy, I. A., Khan, A. O., Oystreck, D.T., & Bosley, T. M. \(2013\). Partial chromosome 7 duplication with a phenotype mimicking the HOXA1 spectrum disorder. *Ophthalmic Genet*, 34\(1-2\), 90-96.28.](#)²⁸

doi:10.3109/13816810.2012.718850

- Click reference above to see full PDF article

Purpose: To evaluate possible monogenic and chromosomal anomalies in a subject with bilateral Duane retraction syndrome and hearing impairment resulting in a phenotype resembling the HOXA1 spectrum disorder.

Methods: Sequencing HOXA1 and performing high resolution array comparative genomic hybridization (array CGH).

Results: The proband had bilateral Duane retraction syndrome (DRS) with severe hearing loss bilaterally and an absent right vertebral artery, mimicking the major features of the Bosley-Salih-Alorainy variant of the HOXA1 spectrum. However, he also had developmental delay, mild mental retardation, and seizures. His parents were not related, but his father had milder sensorineural hearing loss bilaterally, and two paternal uncles and a paternal cousin had seizures. Neuroimaging revealed moderate maldevelopment of inner ear bony anatomy bilaterally. HOXA1 sequencing was normal, but array CGH revealed a small partial duplication of chromosome 7 encompassing only the PTPRN2 gene (protein tyrosine phosphatase, receptor type, N polypeptide 2) that was not present in his parents, an unaffected brother, or 53 normal ethnically-matched individuals.

Conclusions: PTPRN2 is not yet linked to a genetic syndrome, although its expression has been identified in the adult human brain, in certain tumors, and in association with type 1 diabetes mellitus. The phenotype of this patient is strikingly similar to, but not identical to, that of the HOXA1 spectrum disorder. The findings in this patient raise the possibility that PTPRN2 may be active during early development of the human brainstem and that its overexpression may cause bilateral DRS with hearing loss as occurs in patients with homozygous HOXA1 mutations.

[Abu-Amero, K. K., Kondkar, A. A., Alorainy, I. A., Khan, A. O., Al-Enazy, L. A., Oystreck, D. T., & Bosley, T. M. \(2014\). Xq26.3 microdeletion in a male with Wildervanck Syndrome. *Ophthalmic Genet*, 35\(1\), 18-24.29.](#)²⁹

[doi:10.3109/13816810.2013.766218](https://doi.org/10.3109/13816810.2013.766218)

- Click reference above to see full PDF article

Background: Wildervanck Syndrome (WS; cervico-oculo-acoustic syndrome) consists of Duane retraction syndrome (DRS), the Klippel-Feil anomaly, and congenital deafness. It is much more common in females than males and could be due to an X-linked mutation that is lethal to hemizygous males. We present the genetic evaluation of a male with WS and his family.

Materials and Methods: Clinical evaluation and neuroimaging, sequencing of candidate genes, and array comparative genomic hybridization.

Results: The patient had bilateral type 1 DRS, fusion of almost the entire cervical spine, and bilateral severe sensorineural hearing loss due to bilateral cochlear dysplasia; he also had congenital heart disease requiring surgery. His parents were unrelated, and he had eight unaffected siblings. The patient had no mutation found by Sanger sequencing of HOXA1, KIF21A, SALL4, and CHN1. He had a 3kB deletion in the X-chromosome at Xq26.3 that was not found in his mother, one unaffected sibling, or 56 healthy controls of matching ethnicity.

This deletion encompassed only one gene, Fibroblast Growth Factor Homologous Factor 13 (FGF13), which encodes a 216-amino acid protein that acts intracellularly in neurons throughout brain development.

Conclusions: Analysis of this patient's phenotype and genotype open the possibility that X-chromosome deletions may be a cause of WS with larger deletions being lethal to males and that FGF13 mutations may be a cause of WS.

[Abu-Amero, K. K., Kondkar, A. A., Al Otaibi, A., Alorainy, I. A., Khan, A. O., Hellani, A. M., Oystreck, D.T., and Bosley, T. M. \(2015\). Partial duplication of chromosome 19 associated with syndromic duane retraction syndrome. *Ophthalmic Genet*, 36\(1\), 14-20.30.](#)

[doi:10.3109/13816810.2013.827218](https://doi.org/10.3109/13816810.2013.827218)

- Click reference above to see full PDF article

Background: To evaluate possible monogenic and chromosomal anomalies in a patient with unilateral Duane retraction syndrome, modest dysmorphism, cerebral white matter abnormalities, and normal cognitive function.

Materials and Methods: Performing high-resolution array comparative genomic hybridization (array CGH) and sequencing of HOXA1, KIF21A, SALL4, and CHN1 genes.

Results: The proband had unilateral Duane retraction syndrome (DRS) type III on the right with low-set ears, prominent forehead, clinodactyly, and a history of frequent infections during early childhood. Motor development and cognitive function were normal. Parents were not related, and no other family member was similarly affected. MRI revealed multiple small areas of high signal on T2 weighted images in cerebral white matter oriented along white matter tracts. Sequencing of HOXA1, KIF21A, SALL4, and CHN1 did not reveal any mutation(s). Array CGH

showed a 95Kb de novo duplication on chromosome 19q13.4 encompassing four killer cell immunoglobulin-like receptor (KIR) genes.

Conclusions: KIR genes have not previously been linked to a developmental syndrome, although they are known to be expressed in the human brain and brainstem and to be associated with certain infections and autoimmune diseases, including some affecting the nervous system. DRS and brain neuroimaging abnormalities may imply a central and peripheral oligodendrocyte abnormality related in some fashion to an immunomodulatory disturbance.

[Abu-Amero, K. K., Kondkar, A., Hellani, A. M., Oystreck, D. T., Khan, A. O., & Bosley, T. M. \(2015\). Nicotinic Receptor Mutation in a Mildly Dysmorphic Girl with Duane Retraction Syndrome. *Ophthalmic Genet*, 36\(2\), 99-104.31.](#)³¹

[doi:10.3109/13816810.2013.835431](https://doi.org/10.3109/13816810.2013.835431)

- Click reference above to see full PDF article

Background: To evaluate possible monogenic and chromosomal anomalies in a patient with unilateral Duane retraction syndrome and modest dysmorphism.

Materials and Methods: Clinical evaluation, sequencing of candidate genes, and array comparative genomic hybridization (array CGH).

Results: The proband had unilateral Duane retraction syndrome (DRS) with low-set ears bilaterally, a high arched palate, and clinodactyly. Motor development and cognitive function were normal. Parents were first cousins, but no other family member was similarly affected. No mutations were detected in the HOXA1, KIF21A, SALL4, TUBB3, and CHN1 genes. Array CGH revealed a 16Kb de novo deletion at chromosome 8p11.2 that encompassed a portion of only one gene, the Cholinergic Receptor, Nicotinic, Beta-3 (CHRN3, Neuronal). This gene encodes a protein that is involved in the nicotinic acetylcholine receptor on neurons. It interacts functionally with other genes that code components of the acetylcholine receptor.

Conclusions: This patient's chromosomal abnormality affected only one gene that is highly expressed in the brainstem and brain, involved in neurotransmission, and could be related to her Duane retraction syndrome.

[Abu-Amero, K. K., Bosley, T. M., Kondkar, A. A., Oystreck, D. T., & Khan, A. O. \(2015\). CCDD Phenotype Associated with a Small Chromosome 2 Deletion. *Semin Ophthalmol*, 30\(5-6\), 435-442.32.](#)³²

[doi:10.3109/08820538.2013.874474](https://doi.org/10.3109/08820538.2013.874474)

- Click reference above to see full PDF article

Purpose: Some individuals are born with congenital limitation of ocular motility, often associated with ptosis and retraction of the globe. Many of these disorders are now known as the congenital cranial dysinnervation disorders (CCDDs). While several genes have been associated with CCDD phenotypes, there are still patients for whom the genetic basis has not been identified.

Methods: Clinical evaluation and neuroimaging, sequencing of candidate genes, and array comparative genomic hybridization (array CGH).

Results: The patient was a four year- old girl with mild dysmorphism; bilateral mild ptosis; substantial limitation of abduction OS with milder limitations of abduction OD, adduction OS, and vertical gaze OS; and retraction OS>OD on attempted adduction. No mutations were detected in the HOXA1, KIF21A, SALL4, TUBB3, and CHN1 genes. Array CGH revealed a 8 Kb de novo deletion on chromosome 2 (2q24.3) that encompassed a portion of only one gene, the Xin Actin-binding Repeat containing 2 (Gene Symbol XIRP2; NM_001079810). This gene encodes a protein that is involved in muscle development and protecting actin filaments from depolymerization. It interacts functionally with 10 other proteins playing a similar role in muscle development.

Conclusions: This patient's chromosomal abnormality affected only one gene that currently seems involved only in muscle development. All other genes currently associated with the CCDDs affect neurologic development. Genetic information from this patient implies that genes involved in development and maintenance of extraocular muscles can cause congenital ocular motility disorders as well.

[Abu-Amero, K. K., Kondkar, A. A., Oystreck, D. T., Khan, A. O., & Bosley, T. M. \(2014\). Microdeletions involving chromosomes 12 and 22 associated with syndromic Duane retraction syndrome. *Ophthalmic Genet*, 35\(3\), 162-169.33.](#)³³

[doi:10.3109/13816810.2014.921317](https://doi.org/10.3109/13816810.2014.921317)

- Click reference above to see full PDF article

Background: Duane retraction syndrome (DRS) is the most common of the congenital cranial Dysinnervation disorders (CCDDs). CCDDs can be monogenic or chromosomal in origin. Identification of the genetic cause(s) in patients and families with DRS facilitates definitive diagnosis and provides insights into these developmental errors.

Materials and Methods: This study described a young girl with DRS on the left and several additional developmental abnormalities. Clinical examination including neuroimaging, sequencing of candidate genes associated with DRS, and array comparative genomic hybridization (array CGH) were performed.

Results: The proband had unilateral DRS type 3 on the left with somewhat low-set ears, mild motor delay with normal intelligence, and an asymmetric neck without a palpable right sternocleidomastoid muscle. Spine X-rays revealed a Klippel-Feil syndrome (KFS) and an MRI showed a webbed neck. She also had spina bifida at C8-T1 and a submucosal cleft palate. The

parents of the proband were related with no other family member affected similarly. Sequencing of SALL4, CHN1, HOXA1, and TUBB3 did not show any mutation. Array CGH revealed de novo deletions of 21 Kb on chromosome 12q24.31 and 11 Kb on chromosome 22q13.31, each encompassing only one gene, ring finger protein 34, E3 ubiquitin protein ligase (RNF34) and peroxisome proliferator-activated receptor alpha (PPARA) respectively.

Conclusions: This patient presents an unusual phenotype associated with a unique combination of two chromosomal microdeletions.

[Bosley, T. M., Salih, M. A., Alkhalidi, H., Oystreck, D. T., El Khashab, H. Y., Kondkar, A. A., & Abu-Amero, K. K. \(2016\). Duane retraction syndrome in a patient with Duchenne muscular dystrophy. *Ophthalmic Genet*, 37\(3\), 276-280.34.](#)³⁴

[doi:10.3109/13816810.2015.1039139](https://doi.org/10.3109/13816810.2015.1039139)

- Click reference above to see full PDF article

PURPOSE: We describe the clinical features of a boy with bilateral Duane retraction syndrome (DRS), Duchenne muscular dystrophy (DMD), and other medical problems.

METHODS: The child was followed-up for five years; his chart was reviewed, including the results of a muscle biopsy and genetic testing. Multiplex ligation-dependent probe amplification (MLPA) was used to interrogate deletions/duplications in the dystrophin gene.

RESULTS: The proband had bilateral DRS with otherwise normal ocular motility; he also had developmental delay, mild mental retardation, and seizures. Clinical diagnosis of DMD included progressive proximal weakness, highly elevated creatine kinase levels, and a muscle biopsy showing significant dystrophic changes including contracted, degenerative, and regenerative fibers, and negative dystrophin immunostaining. MLPA documented duplication of exons 3 and 4 of the dystrophin gene.

CONCLUSIONS: This boy is the third patient to be reported with DRS and DMD, the second with bilateral DRS and the only one with other neurologic features. Mutated dystrophin is present in extraocular muscles and in the central nervous system (CNS) in DMD, leaving open the question of whether this co-occurrence is the result of the genetic muscle abnormality, CNS effects caused by dystrophin mutations, or chance.

[Abu-Amero, K. K., Kondkar, A. A., Odan, H. A., Khan, A. O., Oystreck, D. T., & Bosley, T. M. \(2016\). Duane Retraction Syndrome Associated with a Small X Chromosome Deletion. *Can J Neurol Sci*, 43\(3\), 445-447.](#)³⁵
doi:10.1017/cjn.2015.358

- Click reference above to see full PDF article

Overview:

This was a single case of 16 year old female with syndromic bilateral DRS type 3. Her main features in addition to the DRS were cleft palate and mildly reduced hearing. All CCDD appropriate genes were screened and found to be negative. As a result this patient underwent high-resolution array-comparative genomic hybridization (array CGH) analysis and found to have a 12-kb deletion in chromosome X encompassing part of only the *dystrophin gene (DMD)*.

This is another report in which a chromosomal anomaly involving a single gene was isolated in an individual with congenital complex strabismus. However complex congenital strabismus was not isolated in this family. Two other members were examined and confirmed to have disturbance of ocular alignment and motility. The proband's mother had a history of previous strabismus surgery. Her right eye had a marked abduction deficit with globe retraction on adduction. Her left eye had a substantial adduction deficit with a mild abduction deficit and globe retraction on attempted adduction. The proband's younger brother had clinical features most consistent with a congenital left superior oblique palsy.

Significance of this paper:

- This is another report where a mutation in a gene linked to myopathic processes is present. We previously reported another case of congenital eye movement disorder associated with the gene XIRP2³² that is involved predominantly in muscle development, implying that the primary genetic abnormality in some subjects with congenital ocular motility abnormalities may be related to muscle development.
- This is the first report describing mutation in dystrophin gene in a female with DRS. Three previous reports were males. Of interest subject had a cleft palate as mutations in dystrophin gene have been associated with oral clefts.
- This report suggests further evaluation on a larger group of subjects with syndromic or non-syndromic DRS may be required to determine changes in the dystrophin gene.
- Argument given for dystrophin to play a potential role in DRS is as follows:
 - In DMD functional dystrophin is missing in postsynaptic regions of cerebellum and cerebral cortex.
 - CNS involvement is confirmed by presence of cognitive deficits and increased cortical excitability
 - Presence of dystrophin mutations in either neurologic or ocular muscle tissue (or both) might play a role in this subject.
 - In particular, dystrophin in the embryonic lateral rectus muscle could be a factor at times in the process of establishing normal development of eom function and innervation, and dystrophin mutations at times may disturb that process.
- Re-introduces the possibility that at times, some CCDD phenotypes may be related to both myopathic and neurogenic factors.

[Abu-Amero, K. K., Khan, A. O., Oystreck, D. T., Kondkar, A. A., & Bosley, T. M. \(2016\). The genetics of nonsyndromic bilateral Duane retraction syndrome. J AAPPoS, 20\(5\), 396-400 e392.](#)³⁶

[doi:10.1016/j.jaapos.2016.06.008](https://doi.org/10.1016/j.jaapos.2016.06.008)

- Click reference above to see full PDF article

Purpose: To assess the importance of monogenic mutations and chromosomal copy number variants (CNVs) in the occurrence of nonsyndromic bilateral Duane retraction syndrome (bilateral nsDRS).

Methods: The medical records of 12 patients with bilateral nsDRS were reviewed. Genes associated with DRS and associated congenital cranial dysinnervation disorders (SALL4, CHN1, HOXA1, TUBB3, and KIF21A) were sequenced in the standard fashion in each patient. Array comparative genomic hybridization (array CGH) was performed using Affymetrix Cytogenetics Whole-Genome 2.7M array, and the results were analyzed using Affymetrix Chromosome Analysis Suite v1.2. CNVs were assessed as unlikely to be pathologic if they were also present in the Database of Genomic Variants (DGV) or our local database of array CGH results in 150 normal individuals of Middle Eastern ethnicity.

Results: No patient had a sequence mutation in SALL4, CHN1, HOXA1, TUBB3, or KIF21A. These 12 patients each had 36-42 chromosomal deletions and/or duplications (mean with standard deviation, 26.25 +/- 6.77), but all of these CNVs were present either in the DGV or in our local database of normal individuals of similar ethnicity and, therefore, are considered nonpathogenic.

Conclusions: The results reported here suggest that bilateral nsDRS is not usually associated with mutations in these genes or with chromosomal CNVs. Current evidence suggests other factors such as epigenetic and/or teratogenic abnormalities may be a potential cause of bilateral nsDRS.

Tables

Table 2.1. Geographical consistency in DRS

Site	Orbis international E-consultation program	King Khaled Eye Specialist Hospital
Number	196	404
Laterality	Unilateral = 90% <ul style="list-style-type: none"> • 34% RE • 66% LE Bilateral = 10%	Unilateral = 86% <ul style="list-style-type: none"> • 24% RE • 76% LE Bilateral = 14%
Gender	Male = 34% Female = 66%	Male = 45% Female = 55%
Type	I > III > II	I (78%) > III (19%) > II (4%)

Table 2.2 Genetic results of subjects with DRS

Group	Dx.	No.	Sample obtained	Genetic results		
				Known	Screen negative	Pending
1	nsDRS	57	19	0	12	7
2	synDRS	53	44	35*	3	10
3	DRS plus	1	1		1	
Total		111	64	35	16	16

Dx = Clinical category; No. = number of subjects; nsDRS = non-syndromic Duane retraction syndrome; synDRS = syndromic Duane retraction syndrome; DRS plus = nsDRS with other ocular dysmotility phenotype. *Genetics confirmed in a similarly affected family member.

Table 2.3 Published DRS subjects

No.	Notes	Ref
8/9	Genetic mutation confirmed subjects 1 subject not phenotyped by DTO.	14
9/9	Genetic mutation confirmed in subjects Contains 8 subjects reported in 2005 Tischfield and 1 new subject	5
4/9	Genetic mutation confirmed in subjects. Only 4 subjects determined to have DRS. Of the remaining 5, 2 had full ocular movements and 3 were reported as having horizontal gaze palsy but were not phenotyped by DTO	15
1/3	1 subject with bilateral DRS and synergistic divergence was mutation negative when screened for known CCDD genes. (See chapter 8.2.1)	37
1/1	Genetic mutation confirmed in subject	28
1/1	Genetic mutation confirmed in subject	29
1/1	Genetic mutation confirmed in subject	30
1/1	Genetic mutation confirmed in subject	31
1/1	Genetic mutation confirmed in subject	33
1/1	Genetic mutation confirmed in subject	32
1/1	Genetic mutation confirmed in subject	34
1/1	Genetic mutation confirmed in subject	35
12/12	All subjects with bilateral nsDRS were negative for genetic mutation	36
33pts		

No. = number of subjects with DRS; Ref = Reference number

Chapter 3: Moebius syndrome (MBS)

Moebius syndrome is a complex developmental disorder of the hindbrain with a broad phenotype often overlapping with other syndromes. It is felt to have multiple etiological mechanisms with a yet unknown genetic component.

The major impact of our work has been to improve the clinical diagnostic criteria for this condition permitting better distinction of subjects with MBS from those having similar but etiologically distinct conditions.

As of 2016, a total of 123 subjects have been examined with a presumed diagnosis of MBS. An additional 45 subjects have since been examined but are not included in this dissertation. The investigations of these 123 subjects has resulted in 5 publications to date. **Table 3.1** summarizes these reports.

Important findings were that it is not uncommon for patients presenting with a diagnosis of with MBS to actually not have the condition. The genetic basis of MBS remains unknown however the phenotypic and genetic distinction of MBS from other overlapping disorders is now better elucidated as illustrated in the PDF article included this chapter.

Tables

Table 3.1. Publications arising from the assessment of MBS subjects.

Publication	Significant findings	Chapter discussed
Rankin 2010 ²⁴	Reports 25 subjects that would later be included in MacKinnon 2014. Due to phenotypic overlap with HOXA1 spectrum, these subjects were analyzed for mutations in HOXA1 gene. All were mutation negative for HOXA1 mutations.	Chapter 2
Webb 2012 ³⁸	Reported 2 siblings that would be later included in MacKinnon 2014. Both were found to have mutations in <i>HOXB1</i> gene and did not meet minimum diagnostic criteria for MBS.	Chapter 8
Chew 2013 ³⁹	Report includes 2 subjects that would later be included in MacKinnon 2014. Both were found to have <i>TUBB3 – E410K</i> mutations and did not meet minimum diagnostic criteria for MBS.	Chapter 4
MacKinnon 2014 ⁴⁰	See full article below. Summary of non-MBS subjects identified: 2 patients – mother and son with autosomal dominant congenital facial palsy (HCFP) 2 siblings with comitant strabismus, facial palsy and sensorineural hearing loss who were positive for mutation in <i>HOXB1</i> (see Webb 2012) 4 unrelated subjects found to have mutations in <i>TUBB3</i> . <ul style="list-style-type: none"> • 2 subjects with <i>TUBB3-E410K</i> mutations (see Chew 2013) • 1 subject with <i>TUBB3-262H</i> mutation • 1 subject with <i>TUBB3-E410V</i> mutation 	Chapter 3
2017 Di Gioia ⁴¹	Identifies Carey-Fineman-Ziter syndrome (CFZS), a congenital myopathy, as another explanation for an atypical MBS phenotype.	Chapter 8

MacKinnon, S., **Oystreck, D. T.**, Andrews, C., Chan, W. M., Hunter, D. G., & Engle, E. C. (2014). Diagnostic distinctions and genetic analysis of patients diagnosed with moebius syndrome. *Ophthalmology*, 121(7), 1461-1468.⁴⁰
[doi:10.1016/j.ophtha.2014.01.006](https://doi.org/10.1016/j.ophtha.2014.01.006)

OBJECTIVE: To improve diagnostic assessment in Moebius syndrome by (1) creating more selective diagnostic subgroups and (2) conducting genetic evaluation in a large patient cohort.

DESIGN: Prospective, observational study.

PARTICIPANTS: Attendees of 3 consecutive Moebius syndrome conferences held in the United States, with a prior diagnosis of Moebius syndrome, were invited to participate.

METHODS: Participants underwent standardized ophthalmologic examination for Moebius syndrome minimum diagnostic criteria (MDC) (congenital, nonprogressive facial palsy, and abduction deficit) and genetic testing for HOXA1, HOXB1, and TUBB3 mutations.

MAIN OUTCOME MEASURES: The number of patients meeting MDC and the number of patients with confirmed genetic mutation.

RESULTS: A total of 112 participants from 107 families enrolled. Nineteen percent of participants (21/112) did not meet accepted MDC for Moebius syndrome because they had abduction deficits without facial palsy or facial palsy with full ocular motility. All 5 families with 2 affected individuals had at least 1 family member in this category, including 2 siblings with comitant strabismus who harbored a HOXB1 mutation. Four unrelated participants, also not meeting MDC, had large-angle exotropia, vertical gaze deficiency, and ptosis consistent with congenital fibrosis of the extraocular muscles type 3 (CFEOM3); 1 patient harbored a novel TUBB3 mutation, and 3 patients harbored previously reported de novo TUBB3 mutations. Three percent of participants (3/112) met MDC but also had restricted vertical gaze. The remaining 88

participants (79%) met MDC and had full vertical gaze. This group had relatively homogeneous findings, and none had a family history of Moebius syndrome. Two previously undescribed phenomena were observed in this category: (1) volitional Bell's phenomenon and (2) intorsion with fixation.

CONCLUSIONS: Although the genetic contributors to classic Moebius syndrome remain elusive, accuracy in clinical evaluation will properly subdivide patients to facilitate genetic testing as new candidate genes are identified. Failure to test ocular motility may lead to misdiagnosis of Moebius syndrome, especially in patients who have facial palsy with full ductions. Patients with exotropia, vertical gaze limitation, and ptosis do not have classic Moebius syndrome and may have TUBB3 mutations associated with CFEOM3. To optimize genetic analysis, we propose adding "full vertical motility" to the MDC for Moebius syndrome.

Diagnostic Distinctions and Genetic Analysis of Patients Diagnosed with Moebius Syndrome

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Objective: To improve diagnostic assessment in Moebius syndrome by (1) creating more selective diagnostic subgroups and (2) conducting genetic evaluation in a large patient cohort.

Design: Prospective, observational study.

Participants: Attendees of 3 consecutive Moebius syndrome conferences held in the United States, with a prior diagnosis of Moebius syndrome, were invited to participate.

Methods: Participants underwent standardized ophthalmologic examination for Moebius syndrome minimum diagnostic criteria (MDC) (congenital, nonprogressive facial palsy, and abduction deficit) and genetic testing for *HOXA1*, *HOXB1*, and *TUBB3* mutations.

Main Outcome Measures: The number of patients meeting MDC and the number of patients with confirmed genetic mutation.

Results: A total of 112 participants from 107 families enrolled. Nineteen percent of participants (21/112) did not meet accepted MDC for Moebius syndrome because they had abduction deficits without facial palsy or facial palsy with full ocular motility. All 5 families with 2 affected individuals had at least 1 family member in this category, including 2 siblings with comitant strabismus who harbored a *HOXB1* mutation. Four unrelated participants, also not meeting MDC, had large-angle exotropia, vertical gaze deficiency, and ptosis consistent with congenital fibrosis of the extraocular muscles type 3 (CFEOM3); 1 patient harbored a novel *TUBB3* mutation, and 3 patients harbored previously reported de novo *TUBB3* mutations. Three percent of participants (3/112) met MDC but also had restricted vertical gaze. The remaining 88 participants (79%) met MDC and had full vertical gaze. This group had relatively homogeneous findings, and none had a family history of Moebius syndrome. Two previously undescribed phenomena were observed in this category: (1) volitional Bell's phenomenon and (2) intorsion with fixation.

Conclusions: Although the genetic contributors to classic Moebius syndrome remain elusive, accuracy in clinical evaluation will properly subdivide patients to facilitate genetic testing as new candidate genes are identified. Failure to test ocular motility may lead to misdiagnosis of Moebius syndrome, especially in patients who have facial palsy with full ductions. Patients with exotropia, vertical gaze limitation, and ptosis do not have classic Moebius syndrome and may have *TUBB3* mutations associated with CFEOM3. To optimize genetic analysis, we propose adding "full vertical motility" to the MDC for Moebius syndrome. *Ophthalmology* 2014;121:1461-1468 © 2014 by the American Academy of Ophthalmology.



Supplemental material is available at www.aaojournal.org.

Moebius syndrome is a complex, rare developmental anomaly of the hindbrain that has been described historically as the combination of congenital palsies of the abducens and facial nerves,¹ frequently with additional features, including orofacial malformations, limb defects, and musculoskeletal, behavioral, and cognitive abnormalities.²⁻⁷ Although a compilation of clinical,⁸⁻¹² neuropathologic,¹³⁻¹⁸ and radiologic¹⁹⁻²¹ reports suggest that Moebius syndrome is not a single disease entity,²² these and many other studies of the condition are confounded by variable diagnostic criteria.^{22,23} This lack of standardized diagnostic criteria complicates the clinical assessment, determination of prognosis, and genetic analysis of patients with Moebius syndrome. To address this concern, a group of clinicians and researchers met in 2007 at the biannual Moebius Syndrome Foundation research meeting and defined the minimum diagnostic criteria (MDC) for classic Moebius syndrome

as "congenital, uni- or bilateral, nonprogressive facial weakness and limited abduction of the eye(s)."¹¹

The purpose of this report is to characterize the ocular and facial phenotypes of a large number of individuals diagnosed with Moebius syndrome to determine whether they meet MDC. We also screened participants' DNA for mutations in the *HOXA1*, *HOXB1*, and *TUBB3* genes (reported to cause atypical forms of Moebius syndrome)²⁴⁻²⁷ in an attempt to identify genetic causes underlying the disorder.

Methods

Research participants with a prior diagnosis of Moebius syndrome and their family members were recruited from 3 consecutive international Moebius Syndrome Conferences organized by the Moebius Syndrome Foundation (8th, 9th, and 10th conferences

Chapter 4: Congenital Fibrosis of the Extraocular muscles (CFEOM)

This chapter involves a heterogeneous group of disorders defined by having congenital non-progressive ocular motility deficits associated with ptosis. These are referred to as congenital fibrosis of the extraocular muscles (CFEOM).

The work presented here summarizes the enrolled subject population. It includes publications that enhance clinical descriptions in genetically confirmed variants as well as report new genetic syndromes that include CFEOM. At initiation of the dissertation three main phenotypes were reported, each already having an identified monogenic cause. CFEOM1 was an autosomal dominant form arising from mutations in *KIF21A*, CFEOM2 was autosomal recessive arising from mutations in *PHOX2A*, while CFEOM3 was autosomal dominant but had a greater phenotypic spectrum. Mutations in two different genes could lead to a CFEOM3 phenotype. First was *KIF21A*, but found to rarely be the cause of CFEOM1. The second gene was *TUBB3* and could result in isolated CFEOM or CFEOM associated with neurologic, cognitive, or medical problems. As a result there was a need to expand the classification of CFEOM3 to include CFEOM3A and CFEOM3A plus when due to mutations in *TUBB3*, and CFEOM3B in the setting of *KIF21A* mutations. This expansion started the unravelling of a classification system, which up to that point, had good phenotype-genotype correlations. This became more evident as additional individuals were genotyped. An overview of the status of CFEOM at this time was reported as part of a textbook chapter in 2010⁴² ([link to full PDF](#)) and in 2011 as part of a review article²⁶ ([link to full PDF](#)). These in part led to the development of the KSU ophthalmic genetics program as it was clear more phenotypes and genotypes were yet to be identified.

Summary of CFEOM research

A total of 105 subjects (13% total population) met criteria for CFEOM. A genetic diagnosis was confirmed in 47/105 subjects (45%). Results are still pending 28/105 (27%). Three individuals given a diagnosis of CFEOM were negative for a mutation in the known CFEOM genes and the currently known CCDD genes. This suggests most CFEOM phenotypes arise from mutations in previously identified genes, highlighting the importance of a careful clinical evaluation. It also indicates additional genotypes still need to be identified. **Table 4.1** provides a breakdown of the CFEOM type and the results of the genetic analysis. Given that two genes accounted for 98% of all CFEOM this should be ideal for genotype-phenotype correlations. However, this would not be the case.

Thirty-five subjects were reported in 8 publications of which the candidate was an author in 7 (**Table 4.2**).^{26, 39, 40, 42-46} The 28 subjects reported prior to initiation of the dissertation were instrumental in identifying orthoptic features to better distinguish CFEOM variants from other congenital eye movement disorders, as well as the CFEOM subtypes from each other. These are summarized below and organized by clinical diagnosis and any accompanying publication.

CFEOM1

A total of 20 subjects were given a CFEOM1 phenotype. Four members from 1 family were found to have mutation in *KIF21A*. Features of this family were included in review articles outlining phenotypic distinctions from other CFEOM variants.^{26, 42, 45} Full articles are included in appendix section for chapter 4⁴² and in chapter 9.^{26, 45} Genetic results are pending in the majority of these individuals (14/20).

CFEOM2

Twenty-eight subjects were found to have a CFEOM2 phenotype of which 22 undergoing genetic analysis were confirmed to have mutations in the same gene (*PHOX2A*). A cohort of this group was extensively studied and reported in the following two publications.

[Bosley, T. M., Oystreck, D. T., Robertson, R. L., al Awad, A., Abu-Amero, K., & Engle, E. C. \(2006\). Neurological features of congenital fibrosis of the extraocular muscles type 2 with mutations in PHOX2A. *Brain*, 129\(Pt 9\), 2363-2374.⁴⁴ doi:10.1093/brain/awl161](#)

- Click reference above to see full PDF article

Congenital fibrosis of the extraocular muscles type 2 (CFEOM2) is a complex strabismus syndrome that results from mutations in the homeodomain transcription factor *PHOX2A*. To define the clinical and neuroimaging features of patients with this autosomal recessive syndrome, we studied 15 patients with genetically defined CFEOM2. All patients underwent full neurological, neuro-ophthalmological and orthoptic assessments. Twelve patients had pupillary pharmacological testing and nine had 3.0 tesla MRI of the brain, brainstem and orbits. Patients were born with severe bilateral ptosis and exotropia with almost complete bilateral absence of adduction, elevation, depression and intorsion. Variable abduction was present prior to strabismus surgery in 14 patients, and central ocular motility reflexes (smooth pursuit, saccades, vestibulo-ocular reflex and optokinetic reflex) were intact except for convergence. Pupillary light and near reflexes were not present, but irises were anatomically normal and responded to pupillary pharmacology. Neuroimaging of brain and brainstem was remarkable for the anatomical absence of cranial nerve (CN) 3 and probably CN 4 bilaterally. Therefore, the CFEOM2 phenotype and neuroimaging are both consistent with the congenital absence of CNs 3 and 4. Additional features included presence of most central ocular motility reflexes, a central lack of pupillary responsiveness of uncertain etiology and modest phenotypic variability that does not correlate with specific *PHOX2A* mutations. Clinical presentation, neuroimaging and *Phox2a*^{-/-} animal models all support the concept that CFEOM2 is a primary neurogenic abnormality with secondary myopathic changes.

Significance of publication:

This was the first formal phenotypic description of individuals with *PHOX2A* mutations.

Characterization of orthoptic features and neuro-imaging findings confirmed CFEOM2 due to

PHOX2A mutations fall within in the category of CCDD and that *PHOX2A* does not affect supranuclear or central horizontal gaze mechanisms. It also confirmed a lack of mutation-phenotype correlations and verified that mutations to date result in complete loss of function. It also determined these individuals do not have major somatic anomalies or other autonomic, cognitive or focal neurological abnormalities.

The complex strabismus patterns in these individuals led to further refinement of an ocular alignment and motility scoring template that would be applied to all future subjects. This included modification of traditional scoring method to include deficits greater than -4 and the need to document 'resting' globe positions. This was also the first CCDD confirmed to have pupil involvement and led to the development of a pupil testing protocol when evaluating other CCDDs.

[Khan, A. O., Almutlaq, M., Oystreck, D. T., Engle, E. C., Abu-Amero, K., & Bosley, T. \(2016\). Retinal Dysfunction in Patients with Congenital Fibrosis of the Extraocular Muscles Type 2. *Ophthalmic Genet*, 37\(2\), 130-136.](#)⁴⁶

[doi:10.3109/13816810.2014.926942](https://doi.org/10.3109/13816810.2014.926942)

- Click reference above to see full PDF article

INTRODUCTION: Congenital fibrosis of the extraocular muscles type 2 (CFEOM2) is a distinct non-syndromic form of congenital incomitant strabismus secondary to orbital dysinnervation from recessive mutations in the gene *PHOX2A*. The phenotype includes bilateral ptosis, very large angle exotropia, ophthalmoplegia, and poorly-reactive pupils. Other than amblyopia, afferent visual dysfunction has not been considered part of CFEOM2; however, we have repeatedly observed non-amblyopic subnormal vision in affected patients. The purpose of this study was to document this recurrent feature of the phenotype.

METHODS: A retrospective case series (2002-2012).

RESULTS: Eighteen patients (four families) were identified; all affected individuals had confirmed homozygous recessive *PHOX2A* mutations except one individual for whom genetic testing was not done because of multiple genetically confirmed family members. Age at assessment ranged from 5-62 years old (median 10 years old). All patients had decreased best-corrected visual acuity not completely explainable by amblyopia in both the preferred and non-preferred eye. In those patients who had further ancillary testing, visual fields (five patients) and electroretinography (10 patients) confirmed abnormalities not ascribable to amblyopia.

CONCLUSIONS: In addition to a distinct form of congenital incomitant strabismus, the phenotype of CFEOM2 includes subnormal vision consistent with retinal dysfunction. This could be the direct result of *PHOX2A* mutations or a secondary effect of orbital dysinnervation.

Significance of publication:

This study demonstrated this CFEOM subtype may have afferent system defect in conjunction with significant efferent system dysfunction. Therefore individuals with suspected or confirmed CCDDs should have a complete ophthalmological evaluation.

CFEOM3

Fifty-seven subjects had a phenotype consistent with CFEOM3. Eighteen subjects were confirmed to have a mutation in one of two genes, *TUBB3* (n=10) or *KIF21A* (n=8) while 3 individuals were mutation negative for all known CCDD genes. Twelve patients were reported in 6 publications.^{26, 39, 40, 42, 43, 45} Three of these publications are outlined below, another 3 are discussed later in Chapter 8.

Yamada, K., Chan, W. M., Andrews, C., Bosley, T. M., Sener, E. C., Zwaan, J. T., et al (2004). Identification of KIF21A mutations as a rare cause of congenital fibrosis of the extraocular muscles type 3 (CFEOM3). *Invest Ophthalmol Vis Sci*, 45(7), 2218-2223.⁴³

PMID: [15223798](https://pubmed.ncbi.nlm.nih.gov/15223798/)

- No PDF provided

PURPOSE: Three congenital fibrosis of the extraocular muscles phenotypes (CFEOM1-3) have been identified. Each represents a specific form of paralytic strabismus characterized by congenital restrictive ophthalmoplegia, often with accompanying ptosis. It has been demonstrated that CFEOM1 results from mutations in KIF21A and CFEOM2 from mutations in PHOX2A. This study was conducted to determine the incidence of KIF21A and PHOX2A mutations among individuals with the third CFEOM phenotype, CFEOM3.

METHODS: All pedigrees and sporadic individuals with CFEOM3 in the authors' database were identified, whether the pedigrees were linked or consistent with linkage to the FEOM1, FEOM2, and/or FEOM3 loci was determined, and the appropriate pedigrees and the sporadic individuals were screened for mutations in KIF21A and PHOX2A.

RESULTS: Twelve CFEOM3 pedigrees and 10 CFEOM3 sporadic individuals were identified in the database. The structures of eight of the pedigrees permitted the generation of meaningful linkage data. KIF21A was screened in 17 probands, and mutations were identified in two CFEOM3 pedigrees. One pedigree harbored a novel mutation (2841G-->A, M947I) and one harbored the most common and recurrent of the CFEOM1 mutations identified previously (2860C-->T, R954W). None of CFEOM3 pedigrees or sporadic individuals harbored mutations in PHOX2A.

CONCLUSIONS: The results demonstrate that KIF21A mutations are a rare cause of CFEOM3 and that KIF21A mutations can be nonpenetrant. Although KIF21A is the first gene to be associated

with CFEOM3, the results imply that mutations in the unidentified FEOM3 gene are the more common cause of this phenotype.

Significance of publication:

The candidate was not part of this publication. However affected individuals from the Saudi family were later examined by myself and confirmed to have a CFEOM3 phenotype.

Two of five affected members from a second Saudi family (not published - ID 322987-7, 322969-6) were also found to have CFEOM3 phenotypes further weakening the once definitive CFEOM1-*KIF21A* phenotype-genotype correlation.

Oystreck 2011²⁶ p70-71 provides a full description of one member from each CFEOM-*KIF21A* family. Full article is provided in chapter 9. [\(link to full PDF\)](#)

[Chew, S., Balasubramanian, R., Chan, W. M., Kang, P. B., Andrews, C., Webb, B. D., MacKinnon, S.E., Oystreck, D.T., Rankin, J, Crawford, T.O., Geraghty, M., Pomeroy, S.L., Crowley Jr, W.F., Jabs, E.W., Hunter, D.G., Grant, P, Engle, E.C. \(2013\). A novel syndrome caused by the E410K amino acid substitution in the neuronal beta-tubulin isotype 3. *Brain*, 136\(Pt 2\), 522-535.³⁹
doi:10.1093/brain/aws345](#)

- Click reference above to see full PDF article
- Briefly discussed in chapter 3

Missense mutations in TUBB3, the gene that encodes the neuronal-specific protein beta-tubulin isotype 3, can cause isolated or syndromic congenital fibrosis of the extraocular muscles, a form of complex congenital strabismus characterized by cranial nerve misguidance. One of the eight TUBB3 mutations reported to cause congenital fibrosis of the extraocular muscles, c.1228G>A results in a TUBB3 E410K amino acid substitution that directly alters a kinesin motor protein binding site. We report the detailed phenotypes of eight unrelated individuals who harbour this de novo mutation, and thus define the 'TUBB3 E410K syndrome'. Individuals harbouring this mutation were previously reported to have congenital fibrosis of the extraocular muscles, facial weakness, developmental delay and possible peripheral neuropathy. We now confirm by electrophysiology that a progressive sensorimotor polyneuropathy does indeed segregate with the mutation, and expand the TUBB3 E410K phenotype to include Kallmann syndrome (hypogonadotropic hypogonadism and anosmia), stereotyped midface hypoplasia, intellectual disabilities and, in some cases, vocal cord paralysis, tracheomalacia and cyclic vomiting. Neuroimaging reveals a thin corpus callosum and anterior commissure, and hypoplastic to absent olfactory sulci, olfactory bulbs and oculomotor and facial nerves, which support underlying abnormalities in axon guidance and maintenance. Thus, the E410K substitution defines a new genetic aetiology for Moebius syndrome, Kallmann syndrome and cyclic vomiting. Moreover, the c.1228G>A mutation was absent in DNA from approximately 600 individuals who had either Kallmann syndrome or isolated or syndromic ocular and/or facial dysmotility disorders, but who did not have the combined features of the TUBB3 E410K syndrome, highlighting the specificity of this phenotype-genotype correlation. The definition of

the *TUBB3* E410K syndrome will allow clinicians to identify affected individuals and predict the mutation based on clinical features alone.

Significance of publication:

Further confirmation CFEOM arises from mutation in *TUBB3*. Also confirms another syndromic CFEOM3 phenotype and supports the increasing information that there are mutation-specific *TUBB3* phenotypes.

Mackinnon, S., **Oystreck, D. T.**, Andrews, C., Chan, W. M., Hunter, D. G., & Engle, E. C. (2014). Diagnostic distinctions and genetic analysis of patients diagnosed with moebius syndrome. *Ophthalmology*, 121(7), 1461-1468.⁴⁰

[doi:10.1016/j.ophtha.2014.01.006](https://doi.org/10.1016/j.ophtha.2014.01.006)

- See chapter 3 for full article

OBJECTIVE: To improve diagnostic assessment in Moebius syndrome by (1) creating more selective diagnostic subgroups and (2) conducting genetic evaluation in a large patient cohort.

DESIGN: Prospective, observational study.

PARTICIPANTS: Attendees of 3 consecutive Moebius syndrome conferences held in the United States, with a prior diagnosis of Moebius syndrome, were invited to participate. **METHODS:** Participants underwent standardized ophthalmologic examination for Moebius syndrome minimum diagnostic criteria (MDC) (congenital, nonprogressive facial palsy, and abduction deficit) and genetic testing for HOXA1, HOXB1, and TUBB3 mutations.

MAIN OUTCOME MEASURES: The number of patients meeting MDC and the number of patients with confirmed genetic mutation.

RESULTS: A total of 112 participants from 107 families enrolled. Nineteen percent of participants (21/112) did not meet accepted MDC for Moebius syndrome because they had abduction deficits without facial palsy or facial palsy with full ocular motility. All 5 families with 2 affected individuals had at least 1 family member in this category, including 2 siblings with comitant strabismus who harbored a HOXB1 mutation. Four unrelated participants, also not meeting MDC, had large-angle exotropia, vertical gaze deficiency, and ptosis consistent with congenital fibrosis of the extraocular muscles type 3 (CFEOM3); 1 patient harbored a novel TUBB3 mutation, and 3 patients harbored previously reported de novo TUBB3 mutations. Three percent of participants (3/112) met MDC but also had restricted vertical gaze. The remaining 88 participants (79%) met MDC and had full vertical gaze. This group had relatively homogeneous

findings, and none had a family history of Moebius syndrome. Two previously undescribed phenomena were observed in this category: (1) volitional Bell's phenomenon and (2) intorsion with fixation.

CONCLUSIONS: Although the genetic contributors to classic Moebius syndrome remain elusive, accuracy in clinical evaluation will properly subdivide patients to facilitate genetic testing as new candidate genes are identified. Failure to test ocular motility may lead to misdiagnosis of Moebius syndrome, especially in patients who have facial palsy with full ductions. Patients with exotropia, vertical gaze limitation, and ptosis do not have classic Moebius syndrome and may have *TUBB3* mutations associated with CFEOM3. To optimize genetic analysis, we propose adding "full vertical motility" to the MDC for Moebius syndrome.

Significance of publication:

Careful orthoptic evaluations identified CFEOM3 phenotypes in a large population of individuals with presumed MBS (see Chapter 3). In all four cases a mutation in *TUBB3* was found showing evidence that the term MBS-like used in previous reports are likely patients with CFEOM due to *TUBB3* mutations.

Tables

Table 4.1 Genetic results of subjects with CFEOM

Dx	No.	Sample obtained	Genetic results		
			Known	Screen negative	Pending
CFEOM1	20	16	4	0	12
CFEOM2	28	23	22*	0	3
CFEOM3	57	35	18*	3	13
Total	105	74	47	0	28

Dx = Clinical diagnosis; No. = number of subjects; CFEOM1, 2, or 3 = congenital fibrosis of the extraocular muscles type 1, 2, or 3.

*Genetic mutations were presumed in 1 patient with CFEOM2 and 6 patients with CFEOM3 due to having a similarly affected sibling with confirmed mutation in the gene.

Table 4.2 Published CFEOM subjects

No.	Significant findings	Ref	Chapter discussed
6/63	Subjects reported as part of large multisite study investigating <i>KIF21A</i> as the cause of CFEOM3. 1 st paper to report <i>KIF21A</i> mutations can result in CFEOM3 phenotype. Candidate not an author but would later phenotype all 6 of these individuals (family 1) and report two members in future publications focusing on phenotype-genotype correlations. ^{26, 45}	43	Chapter 4
15/15	Detailed neurologic and orthoptic reports on subjects with mutations in <i>PHOX2A</i> .	44	Chapter 4
5/12	Report of CFEOM1,2, and 3 phenotypes as part of textbook chapter.	42	Chapter 4
6/9	Report of CFEOM1,2, and 3 phenotypes as part of a Review article.	26	Chapter 9
1/5	Describes subject with CFEOM3 due to mutation in <i>KIF21A</i> .	45	Chapter 9
2/8	Reports new syndrome arising from novel de novo mutation in <i>TUBB3</i> .	39	Chapter 4
4/112	Reports subjects with atypical MBS phenotype have CFEOM due to specific <i>TUBB3</i> mutations.	40	Chapter 3
14/18	Investigation of afferent visual functioning in genetically confirmed subjects with CFEOM2	46	Chapter 4
35pts†			

No. = number of patients with CFEOM examined by candidate/total number of subjects in publication;
Ref = Reference; † = Subjects counted only once. Several have been reported in more than 1 publication.

Chapter 5: Orbitofacial neurofibromatosis type 1 (OFNF)

Neurofibromatosis is an autosomal dominant, neurocutaneous disorder. We examined 96 subjects with NF1 and noticed some individuals had a more severe phenotype consisting of neurofibromas involving the lid, brow, face, and orbit. We referred to this group as orbitofacial neurofibromatosis type 1 (OFNF). The original intent of our research was to perform expression studies in families with multiple affected members with OFNF and/or NF1. All individuals enrolled into this study were screened for neurofibromas and received an orthoptic examination to determine their binocular vision status.

The following publications arose from the assessment of 62 individuals with OFNF. Reported here were the clinical features and treatment outcomes,⁴⁷ afferent system disorders,⁴⁸ and disruptions to ocular motility and alignment⁴⁹ in this unique population.

[Chaudhry, I. A., Morales, J., Shamsi, F. A., Al-Rashed, W., Elzaridi, E., Arat, Y. O., Jacquemin, C., Oystreck, D.T., Bosley, T. M. \(2012\). Orbitofacial neurofibromatosis: clinical characteristics and treatment outcome. *Eye \(Lond\)*, 26\(4\), 583-592.⁴⁷](#)

[doi:10.1038/eye.2011.336](https://doi.org/10.1038/eye.2011.336)

- Click reference above to see full PDF article

PURPOSE: To report clinical observations and surgical management in a large series of patients with orbitofacial neurofibromatosis type 1 (OFNF).

PATIENTS AND METHODS: Patients were identified and medical records reviewed for demographic data, ophthalmologic examinations, surgical interventions, and procedure outcome to create a retrospective, non-comparative case series of patients with OFNF seen at one medical centre over a 23-year period.

RESULTS: Sixty patients with OFNF (31 females and 29 males; mean age, 14 years) were followed for an average of 5.7 years. Presenting signs and symptoms included eyelid swelling in all patients, ptosis in 56 (93.3%), proptosis in 34 (56.6%), dystopia or strabismus in 30 (50%),

and decreased visual acuity in 50 (83.3%). Surgical intervention included ptosis repair in 54 (90%; mean 1.6 surgical procedures), facial and orbital tumour debulking in 54 (90%; mean 2.3 surgeries), and canthoplasty in 28 (46.6%) patients. Eleven patients required enucleation or exenteration of a blind eye.

CONCLUSION: Patients with OFNF often require multiple procedures to preserve vision, prevent additional disfigurement, and achieve cosmetic rehabilitation. Patients need regular ophthalmological monitoring given the potential for progressive visual and cosmetic consequences.

Significance of publication:

This retrospective study led to formal prospective research projects that would eventually include multiple institutions and several sub-specialties within ophthalmology as well as radiology, and genetics.

Oystreck, D. T., Morales, J., Chaudhry, I., Alorainy, I. A., Elkhamary, S. M., Pasha, T. M., & Bosley, T. M. (2012). Visual loss in orbitofacial neurofibromatosis type 1. *Ophthalmology*, *119*(10), 2168-2173.

[doi:10.1016/j.ophtha.2012.04.032](https://doi.org/10.1016/j.ophtha.2012.04.032)

- Full article provided below

PURPOSE: On occasion, neurofibromas in neurofibromatosis type 1 may be present on the lid, brow, or face of an infant or child, a circumstance commonly referred to as "orbitofacial neurofibromatosis" (OFNF). The present study evaluates the causes and extent of visual loss in a group of patients with OFNF.

DESIGN: Case series. **PARTICIPANTS:** Fifty-five patients with OFNF. **METHODS:** Retrospective medical record review and reexamination of selected patients from one institution. **MAIN**

OUTCOME MEASURES: Visual acuity and identification of underlying cause of reduced vision.

RESULTS: Fifty patients with unilateral OFNF (23 male, 27 female, aged 4-48 years at last visit) and 5 patients with bilateral OFNF (2 male, 3 female, aged 15-43 years) had adequate information available to assess afferent visual functioning. Nine patients (4 male, 5 female, aged 4-28 years) had optic pathway glioma (OPG) in addition to OFNF. Patients were followed as long as 27 years (mean 8.4 years). Thirty-nine patients (71% of total) had visual acuity of $\leq 20/60$ on the side of OFNF involvement (or the side of worse OFNF involvement in patients with bilateral disease). One or more causes of amblyopia were present in 29 of these patients, 19 patients had organic disease of the eye (e.g., glaucoma or retinal detachment) or the afferent system (e.g., OPG), and 12 patients had correctable refractive errors.

CONCLUSIONS: Visual loss in this OFNF cohort was common, typically profound, and usually multifactorial. Some causes of visual loss (including congenital glaucoma with buphthalmos and retinal detachment, disconjugate gaze due in part to distorted skull development causing strabismic amblyopia, and OPG) were difficult to treat adequately and tended to cause progressive, profound visual loss. Therefore, careful observation should be made during the period of visual immaturity for possible causes of amblyopia that might be treatable, such as refractive changes, occlusion of the visual axis, or congenital glaucoma. As affected individuals get older, physicians must be vigilant for the progression of optic nerve disease due to glaucoma or OPG and to the possibility that vision might be improved by refraction.

Visual Loss in Orbitofacial Neurofibromatosis Type 1

Darren T. Oystreck, MMedSci, OC(C),^{1,4} Jose Morales, MD,² Imtiaz Chaudhry, MD, PhD,² Ibrahim A. Alorainy, MD,³ Sahar M. Elkhamary, MD,² Taha M. U. Pasha, MBBS,¹ Thomas M. Bosley, MD¹

Purpose: On occasion, neurofibromas in neurofibromatosis type 1 may be present on the lid, brow, or face of an infant or child, a circumstance commonly referred to as "orbitofacial neurofibromatosis" (OFNF). The present study evaluates the causes and extent of visual loss in a group of patients with OFNF.

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Methods: Retrospective medical record review and reexamination of selected patients from one institution.

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Conclusions: Visual loss in this OFNF cohort was common, typically profound, and usually multifactorial. Some causes of visual loss (including congenital glaucoma with buphthalmos and retinal detachment, disconjugate gaze due in part to distorted skull development causing strabismic amblyopia, and OPG) were difficult to treat adequately and tended to cause progressive, profound visual loss. Therefore, careful observation should be made during the period of visual immaturity for possible causes of amblyopia that might be treatable, such as refractive changes, occlusion of the visual axis, or congenital glaucoma. As affected individuals get older, physicians must be vigilant for the progression of optic nerve disease due to glaucoma or OPG and to the possibility that vision might be improved by refraction.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology* 2012;119:2168–2173 © 2012 by the American Academy of Ophthalmology.

Neurofibromatosis type 1 (NF1; von Recklinghausen disease; Online Mendelian Inheritance in Man 162200) is a fairly frequent (1 in 3000 live births) autosomal dominant, neurocutaneous disorder that has considerable clinical variability, the potential for multisystem involvement,¹ and the possibility of malignant transformation.² Neurofibromas can also cause devastating functional and cosmetic effects. In orbitofacial neurofibromatosis (OFNF) type 1, which occurs in 1% to 22% of patients with NF1, neurofibromas may result in progressive, disfiguring tumors of the orbit and face.^{3,4}

Orbitofacial neurofibromatosis has been recognized as a unique variant of NF1 for many years.^{5–7} From earliest reports, neurofibromas involving the face in infancy and early childhood have been recognized as virtually a separate syndrome because of the aggressiveness of these infiltrating tumors.⁸ For reasons not currently understood, these tumors almost always occur over only 1 side of the face, typically favoring the upper eyelid, brow, and temporal region, although bilateral OFNF has been reported.^{9–11} Tumors in the

orbitofacial region generally have a higher growth rate than neurofibromas elsewhere in the body; aggressiveness is most striking in early childhood and tends to improve somewhat as the individual ages.^{8,10,12}

Substantial attention has been given to the natural history and treatment of optic pathway gliomas (OPGs),^{13–16} but the visual consequences of OFNF have not received as much attention. Globe enlargement affecting refraction occurs frequently on the affected side of patients with OFNF;¹⁷ some of these patients develop glaucoma, but others do not.^{9,11} Both neuroimaging^{9,18,19} and clinical reports²⁰ have documented that neurofibromas are commonly present in the orbit and cavernous sinus and are frequently contiguous to globes that are abnormally large and to bony changes in the skull and orbit.²¹ This suggests the possibility of optic nerve compression by neurofibroma or dysplastic bone within the orbital structure, but the visual implications of these observations have not been carefully evaluated. This study evaluates the frequency, severity, and cause of visual loss in a large group of patients with OFNF.

Oystreck, D. T., Alorainy, I. A., Morales, J., Chaudhry, I. A., Elkhamary, S. M., & Bosley, T. M. (2014). Ocular motility abnormalities in orbitofacial neurofibromatosis type 1. *J AAPOS*, *18*(4), 338-343.

[doi:10.1016/j.jaapos.2014.02.018](https://doi.org/10.1016/j.jaapos.2014.02.018)

- Full article provided below

PURPOSE: To evaluate the causes of ocular motility disturbances in a group of patients with orbitofacial neurofibromatosis (OFNF) with neurofibromas on the lid, brow, face, or in the orbit from infancy or early childhood.

METHODS: The medical records of patients with OFNF from one institution were retrospectively reviewed; selected patients were reexamined.

RESULTS: A total of 45 patients with unilateral OFNF and 4 with bilateral OFNF were included. Of these, 14 had no strabismus and relatively good vision, with no ductional abnormalities on either side despite large globes, sphenoid dysplasia, and neurofibromas in the orbit and/or cavernous sinus in many. The 8 patients with comitant strabismus also had no ductional abnormalities with a similar constellation of anatomic abnormalities, but these patients all had poor vision in at least one eye. The 27 patients with incomitant strabismus all had downward displacement of the globe and limited ductions.

CONCLUSIONS: The pathologic anatomic changes associated with OFNF do not always cause ocular motility abnormalities: strabismus generally was not present when ocular motility was full and visual acuity was good. Comitant strabismus occurred in the setting of full ocular motility with reduced vision in at least one eye. Incomitant strabismus was always accompanied by reduced vision and a ductional abnormality in one or both eyes due to anatomic abnormalities of the orbit and skull.

Ocular motility abnormalities in orbitofacial neurofibromatosis type 1

Darren T. Oystreck, MMedSci,^{a,d} Ibrahim A. Alorainy, MD,^b Jose Morales, MD,^c
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PURPOSE	To evaluate the causes of ocular motility disturbances in a group of patients with orbitofacial neurofibromatosis (OFNF) with neurofibromas on the lid, brow, face, or in the orbit from infancy or early childhood.
METHODS	The medical records of patients with OFNF from one institution were retrospectively reviewed; selected patients were reexamined.
RESULTS	A total of 45 patients with unilateral OFNF and 4 with bilateral OFNF were included. Of these, 14 had no strabismus and relatively good vision, with no ductional abnormalities on either side despite large globes, sphenoid dysplasia, and neurofibromas in the orbit and/or cavernous sinus in many. The 8 patients with comitant strabismus also had no ductional abnormalities with a similar constellation of anatomic abnormalities, but these patients all had poor vision in at least one eye. The 27 patients with incomitant strabismus all had downward displacement of the globe and limited ductions.
CONCLUSIONS	The pathologic anatomic changes associated with OFNF do not always cause ocular motility abnormalities: strabismus generally was not present when ocular motility was full and visual acuity was good. Comitant strabismus occurred in the setting of full ocular motility with reduced vision in at least one eye. Incomitant strabismus was always accompanied by reduced vision and a ductional abnormality in one or both eyes due to anatomic abnormalities of the orbit and skull. (J AAPOS 2014;18:338-343)

Neurofibromatosis type 1 (NF1; von Recklinghausen disease; OMIM 162200) is a fairly frequent (1 in 3000 live births), autosomal dominant, neurocutaneous disorder with considerable clinical variability.¹ In orbitofacial NF1 (OFNF), neurofibromas (NFs) cause progressive, often disfiguring tumors of the lid, brow, temple, face, and orbit.^{2,3} Orbitofacial neurofibromatosis has long been recognized as a unique variant of NF1.⁴⁻⁷ The earliest reports recognized neurofibromas involving the face or orbit during infancy and early childhood as virtually a separate syndrome because of the aggressiveness of these infiltrating tumors.^{2,8} Tumors in the orbitofacial region generally have a much higher growth rate than neurofibromas elsewhere in the body and often result in recurrence that requires debulking surgery for cosmetic and functional

reasons.⁹ Tumor growth rate tends to improve somewhat as the individual ages^{8,10,11}; however, processes affecting afferent¹² and efferent visual functioning are set in motion during the visually immature period of childhood.

Apart from the disfiguring characteristics of tumors of OFNF, certain pathological processes related to the disease may be important factors contributing to ocular motility abnormalities. Facial NFs occurring early in life are commonly associated with sphenoid dysplasia, a prominent skull feature with radiologic characteristics that include defects in the greater sphenoid wing and enlargement of the middle cranial fossa.^{13,14} The orbit is often affected by these changes, with bone erosion associated with contiguous tumor and decalcification and distortion of the orbital walls.¹⁵ The globe may be enlarged in NF1, sometimes due to congenital glaucoma but often even in the absence of glaucoma,¹⁶ resulting in refractive changes. Current neuroimaging has dramatically improved the ability to resolve subtle soft-tissue and bone changes due to NF infiltration of orbital nerves, sclera, choroid, extraocular muscles, optic nerve sheath, and cavernous sinus.¹⁷ Both neuroimaging^{15,18} and clinical reports^{19,20} have now shown that NFs are frequently present near orbital and skull changes,²¹ implying that many of these developmental abnormalities are caused indirectly by contiguous tumor.

Decreased visual acuity,¹² a large and displaced globe, skull and orbital deformity, and tumor within the orbit and cavernous sinus are potential causes of

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Chapter 6: Congenital Myasthenic Syndrome (CMS)

In some circumstances ocular motility can be disturbed by dysfunction at the neuromuscular junction (NMJ). The commonest reason is acquired autoimmune myasthenia gravis and Lambert-Eaton syndromes.

However, there are genetic variants referred to as Congenital Myasthenic Syndromes (CMS).

CMS is a heterogeneous group of inherited disorders in which there is impairment of neuromuscular transmission due to dysfunction of the structure or functionality of the neuromuscular synapse. Several responsible mechanisms have been identified; however, in all cases appropriate achievement of muscle depolarization is compromised.

Identification of specific clinical clues are used to help suggest a diagnosis of CMS. A diagnosis of CMS should be considered in infants with feeding difficulties that include poor suck and swallow, respiratory failure that may include apneic crisis, and hypotonia⁸ all of which may be variable.⁵⁰ Age at onset is typically in the neonatal period but it can be late childhood or beyond depending on the variant. Description of ocular motility features are limited in the literature, and when given subjects are generally described as having variable ptosis and ophthalmoparesis.

At present, determining the underlying mechanism has not been reliable, although accuracy can be improved with the addition of morphologic examination of the NMJ and with neurophysiological studies. However, these are time consuming, prone to artifact and not feasible in neonates that are generally unwell.⁸

The advent of new genetic tools has permitted a classification of CMS based on molecular details. This affords the opportunity to answer several important questions:

- Elucidating phenotypic characteristics for each genetically distinct variant.
- To investigate unique features to a specific gene mutation or the presence of a mutation specific phenotypes, both of which could be used to make a clinical diagnosis which in turn may predict the molecular diagnosis in other subjects.

CMS research overview:

With these questions in mind our team set out to identify and investigate subjects with CMS.

This chapter includes 3 publications involving 4 subjects.

[Salih, M. A., Oystreck, D. T., Al-Faky, Y. H., Kabiraj, M., Omer, M. I., Subahi, E. M., Beeson, D., Abu-Amero, K.K., Bosley, T. M. \(2011\). Congenital myasthenic syndrome due to homozygous CHRNE mutations: report of patients in Arabia. J Neuroophthalmol, 31\(1\), 42-47.⁵¹](#)

[doi:10.1097/WNO.0b013e3181f50bea](https://doi.org/10.1097/WNO.0b013e3181f50bea)

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We describe the clinical characteristics of 3 siblings from 1 family with congenital myasthenic syndrome due to homozygous mutations of the gene coding for the epsilon subunit of the acetylcholine receptor (CHRNE). Onset of symptoms occurred in the first few months of life with ptosis, restricted ocular motility, mild proximal weakness, and difficulty swallowing. Multiple hospital admissions were required due to recurrent pulmonary infections. There was no decremental conduction on repetitive nerve stimulation, but jitter was increased on single fiber electromyography. Since early childhood, our patients have done well without pulmonary or bulbar symptoms and with partial improvement on pyridostigmine therapy. Response of ptosis to diagnostic ice pack test was striking. Although these siblings have a clinical history and examination findings typical of homozygous CHRNE mutations, the clinical presentation of congenital myasthenia subtypes is variable, and accurate genotyping is essential in choosing the appropriate treatment.

Significance of Publication:

This paper reported the clinical features in the first family from the Arabian Peninsula confirmed to have autosomal recessive mutations in *CHRNE*. This afforded the opportunity to assess orthoptic features in a group of patients in which a molecular diagnosis was already known. This study was instrumental in shaping the concept of using an orthoptic evaluation to identify conditions with differing pathomechanisms affecting ocular alignment and motility.

The homozygous mutations in *CHNRE* reported in this paper are responsible for coding the epsilon subunit of the receptor and result in deficient postsynaptic AChR (MIM 608931). However different mutations in the same gene can result in a fast channel syndrome (abnormally brief channel opening; MIM 616324) that can have autosomal recessive or dominant inheritance. Other mutations can result in autosomal recessive slow channel syndrome (prolonged synaptic current; MIM 605809) leading to depolarization block. Therefore the CMS-*CHRNE* variant in this paper highlighted the importance of needing to identify the specific mutation. This information is crucial to administering appropriate medical therapy. Mutations leading to AChR deficiency and fast channel syndrome respond to anticholinesterase therapy while this must be avoided in the slow channel syndrome variant.

This paper also provided information about key clinical features.

- A positive response to the ice pack test can be present in at least CMS due to *CHNRE* mutation.
- Demonstrated history and clinical features were not diagnostic for CMS arising from *CHRNE* mutations as many of these features also overlap with other CMS subtypes.
- Presence of normal pupillary response to light helps distinguish this variant from CMS due to *COLQ* mutation.

Following this publication, the candidate as part of the research team, set out to systematically conduct orthoptic evaluations in future patients diagnosed with CMS. Over the next 3 years another 7 subjects would be enrolled for genetic analysis. **Table 6.1** outlines the total population of CMS subjects.

[Salih, M. A., Salih, M. A., Mustafa, A. A., Oystreck, D. T., Attia, K. M., El-Sadig, S. M., Hamed, A.A., Hajjar, W.M., Bosley, T. M. \(2013\). Ocular Neostigmine Drops for Diagnosing Myasthenia Gravis. J Neurol Neurophysiol \(S11:004\).⁵¹](#)

[doi:10.4172/2155-9562.S11-004](https://doi.org/10.4172/2155-9562.S11-004)

- Click reference above to see full PDF article

Introduction: A variety of tests have been devised for the diagnosis of myasthenia gravis (MG). The best known of these (Tensilon test, using intravenous edrophonium chloride) may cause serious complications (bradycardia and syncope) dictating cardiac monitoring during the procedure. Ocular neostigmine drops, a simple procedure, may significantly reduce the risk of diagnostic testing for possible MG.

Method: To investigate its efficacy, the miotic effect of neostigmine was explored using 30 rabbits. One drop of sterile neostigmine solution (2.5 mg/ml) was instilled into the right eye (RE) of each rabbit using the left eye (LE), which received sterile normal saline, as control. Serial assessments of pupillary size were done. One drop of neostigmine was instilled daily for 7 days to investigate its safety. Six patients (aged 4.5–55y, median=42y, mean=36.4y) with MG had the same test and were observed for increase of the palpebral fissure height (documented by photography).

Results: At baseline there was no significant difference in the mean [SD] pupillary size of the rabbits between the RE (7 mm [1.07]) and LE (7 mm [1.07]), $p=0.63$). Significant miotic effect was observed in the RE compared to the LE at 30, 60 and 90 minutes (respectively, 4.8 mm [1.86] vs 7.0 mm [1.09], $p=0.0001$; 4.8 mm [1.86] vs 7.0 mm [1.09], $p=0.0001$; and 3.2 [0.76] vs 7.0 [0.0], $p=0.013$). Administration of one drop of neostigmine daily for 7 days caused no ocular inflammation. All six patients with MG had an observable increase of the palpebral fissure height (documented by photography) of at least 2 mm, 30 minutes after neostigmine instillation. The response was dramatic in the three patients with no prior treatment for MG.

Conclusion: Ocular neostigmine drops is a safe, simple and efficient diagnostic test for MG.

Overview of the publication:

This paper investigated the safety and efficacy of using a novel topical agent (IV neostigmine solution) to aid in the clinical diagnosis of autoimmune MG. The first part of the study involved 30 New Zealand white rabbits to determine effectiveness of the drop. This was confirmed by documenting the miotic effect on the pupil and duration of action. The rabbits were also monitored for any adverse effects such as ocular irritation or obvious systemic effects. The second part of the study included 6 patients with symptomatic autoimmune MG. One drop of IV neostigmine solution (2.5 mg/ml) was applied to each eye with appropriate manual punctal occlusion. Effect was determined as a change in ptosis 15 minutes after application. Subjects were also monitored for cholinergic systemic or ocular irritation.

Significance of the publication:

Reduction of ptosis in subjects with autoimmune MG following single drop topical instillation of IV neostigmine solution to the eyes confirmed this method could be added to other clinical methods already employed such as IV edrophonium and ice pack test. All 6 subjects in this study had a minimum 2 mm reduction of ptosis after 30 minutes. None had ocular or systemic side effects. Patients receiving no prior pharmacological treatment are expected to have a greater response. IV edrophonium has been abandoned by many ophthalmological clinics due to potential serious cholinergic effects, the need to have staff trained in cardiac resuscitation and availability of atropine, and lack of availability in hospitals within developing countries. Additionally, certain CMS variants can have a significant deterioration with the use of acetylcholinesterase and therefore this method should be avoided if CMS is suspected. The ice pack test required lid cooling for 2-5 minutes is not generally tolerated by children. Ocular neostigmine drops could provide a safe, simple and efficient alternative diagnostic method for MG. This method still requires careful investigation in CMS variants in which systemic anticholinesterase agents are contraindicated such as mutations in *COLQ*, *MUSK*, *DOK7*, and those resulting in slow channel syndromes.^{52, 53}

[Alaraj, A. M., Oystreck, D. T., & Bosley, T. M. \(2013\). Variable ptosis after botulinum toxin type a injection with positive ice test mimicking ocular myasthenia gravis. J Neuroophthalmol, 33\(2\), 169-171.⁷⁷](#)

[doi:10.1097/WNO.0b013e31828bb19b](https://doi.org/10.1097/WNO.0b013e31828bb19b)

- Click reference above to see full PDF article

We describe a patient who received cosmetic botulinum toxin type A injections to the brow and subsequently developed unilateral ptosis that was variable during examination and was transiently improved after the ice pack test. Ptosis gradually resolved spontaneously over approximately 3 months. This is the third patient to have variable ptosis documented after botulinum toxin type A injection to the brow and the second to have a positive ice test. The ice test is not completely specific for myasthenia gravis but may, at times, improve ptosis resulting from other defects at the neuromuscular junction. Wound botulism now is much more common because of illicit drug use, and the ice test also might be positive in this setting.

Overview of the publication:

This report included a single subject with variable unilateral ptosis that included Cogan lid twitch and worsening with sustained up gaze due to recent botulinum toxin type A injection to the ipsilateral forehead.

Significance of publication:

- Botulism is a differential diagnosis for infants with presumed abnormal neuromuscular transmission not due to CMS.
- We previously reported a positive response to the ice pack test in at least CMS due to autosomal recessive CHRNE variant. A positive response in this subject with botulinum paralysis reduces the specificity of the ice pack test which needs to be kept in mind.

Discussion

Despite the limited number of enrolled patients with a diagnosis of CMS, the resulting publications identified features to help the clinician distinguish this rare group of disorders from other categories of congenital and/or genetic eye movement disorders. It also provides a detailed description about orthoptic features specific to *CHRNE* mutations. This has not been reported before. However, it does not permit a definitive statement about motility features that may be used to distinguish between various CMS subtypes. Affected family members reported in Salih et al. 2010⁵¹ had consistent ocular features, however additional affected individuals from other families would be need to be examined to determine the full spectrum of involvement.

Appendix Table 6.3 highlights ophthalmological features in various CMS sub-types. Most descriptions are vague with suggestion that pupils may play a small role.

Engel 2015 outlined a set of clinical features to guide clinicians to assist predicating the molecular diagnosis (see **Appendix Table 6.3**).⁵⁴ The inclusion of ocular phenotypes by these authors was only mentioned in *COLQ* mutations and *Laminin* β 2 highlighting a need for more investigations to determine the benefit of assessing ocular features to aid in distinguishing between CMS subtypes. Differences, if found, may be related to a structural difference and gene expression within the extraocular muscle endplates.⁵⁵

A final note is that additional material has been included in the appendix section for this chapter. It contains a summary of a literature review done by the candidate in preparation for proposed prospective research projects in this topic. This information has been included only for interest.

Tables

Table 6.1 Genetic results of subjects with CMS

Genetic results*	No.
<i>CHRNE</i>	3 (3 sibs)
<i>COLQ</i>	1
<i>MUSK</i>	2
Unknown	4

*confirmed mutation in the gene listed.

No. = number of enrolled subjects

Chapter 7: Horizontal Gaze Palsy and Progressive Scoliosis (HGPPS)

HGPPS is a unique autosomal recessive disorder defined by congenital horizontal gaze palsy associated with scoliosis. However it is generally described in the context of an ocular myopathy, namely progressive external ophthalmoplegia.⁵⁶

Identification of the loci confirmed the association of congenital horizontal gaze palsy and early onset progressive scoliosis.⁵⁷ The mutated gene was identified (*ROBO3*) and the phenotype expanded to include evidence of uncrossed corticospinal and dorsal column-medial lemniscus pathways.⁵⁸

Summary of HGPPS research:

At the start of my research HGPPS was already known as a monogenic ocular motility disorder with profound anatomic maldevelopment of brainstem, including failure of at least two long neuronal tracts to decussate.

The candidate examined a total of 33 subjects with a diagnosis of HGPPS. Of these, 24 had genetic confirmation of the diagnosis and 21 were included in 3 publications focused on elucidating the phenotype. This was important as it was one of the first conditions in which our team could study genotype-phenotype correlations.

[Bosley, T. M., Salih, M. A., Jen, J. C., Lin, D. D., Oystreck, D., Abu-Amero, K. K., MacDonald, M.D., al Zayed, Z., al Dhalaan, H., Kansue, T., Stigsby, B., Baloh, R. W. \(2005\). Neurologic features of horizontal gaze palsy and progressive scoliosis with mutations in ROBO3. *Neurology*, 64\(7\), 1196-1203.](#)⁶

[doi:10.1212/01.WNL.0000156349.01765.2B](https://doi.org/10.1212/01.WNL.0000156349.01765.2B)

- Click reference above to see full PDF article

OBJECTIVE: To review the neurologic, neuroradiologic, and electrophysiologic features of autosomal recessive horizontal gaze palsy and progressive scoliosis (HGPPS), a syndrome caused by mutation of the ROBO3 gene on chromosome 11 and associated with defective decussation of certain brainstem neuronal systems.

METHODS: The authors examined 11 individuals with HGPPS from five genotyped families with HGPPS. Eight individuals had brain MRI, and six had electrophysiologic studies.

RESULTS: Horizontal gaze palsy was fully penetrant, present at birth, and total or almost total in all affected individuals. Convergence, ocular alignment, congenital nystagmus, and vertical smooth pursuit defects were variable between individuals. All patients developed progressive scoliosis during early childhood. All appropriately studied patients had hypoplasia of the pons and cerebellar peduncles with both anterior and posterior midline clefts of the pons and medulla and electrophysiologic evidence of ipsilateral corticospinal and dorsal column-medial lemniscus tract innervation. Heterozygotes were unaffected.

CONCLUSIONS: The major clinical characteristics of horizontal gaze palsy and progressive scoliosis were congenital horizontal gaze palsy and progressive scoliosis with some variability in both ocular motility and degree of scoliosis. The syndrome also includes a distinctive brainstem malformation and defective crossing of some brainstem neuronal pathways.

Significance of the publication:

This paper was the first major clinical description of genetically defined individuals with HGPPS. Prior to this the best clinical description was from 1975 involving a single family with multiple affected individuals with presumably the same congenital disorder.⁵⁹

This is also the largest series of genetically defined individuals to date and the first cohort having detailed orthoptic evaluations. This paper expanded the phenotype. It was first description of the binocular vision status; first report of intermittent vertical strabismus, that when present dampened the nystagmus; and reported absence of facial weakness that had been reported in previous series.⁶⁰

This report set the template for future ocular motility descriptions of this disorder.

It also further confirmed known genetic, clinical and neuroanatomical features specific to HGPPS. This includes mutations in both copies of ROBO3; congenital complete or almost complete absence of conjugate horizontal gaze; followed by progressive scoliosis during childhood; and a developmental malformation of the brainstem that consists at least in part of uncrossed corticospinal and dorsal column pathways.

The report also suggested this is a central ocular motility defect arising from hypoplasia of the pons. Lower efferent system is intact as noted by the presence of cranial nerve 3 and 6 and normal extraocular muscle anatomy on neuro-imaging. We were also able to confirm the congenital onset of the ocular motility deficit by parental history and examination of two infants less than 1 year of age; normal afferent and overall normal ophthalmological exam; normal forced ductions; and that scoliosis remains the most important reason for making an early diagnosis.

[Khan, A. O., Oystreck, D. T., Al-Tassan, N., Al-Sharif, L., & Bosley, T. M. \(2008\). Bilateral synergistic convergence associated with homozygous ROB03 mutation \(p.Pro771Leu\). *Ophthalmology*, 115\(12\), 2262-2265.⁶¹
doi:10.1016/j.ophtha.2008.08.010](#)

- Click reference above to see full PDF article

OBJECTIVE: To document the phenotype and determine the genotype of a child with synergistic convergence. **DESIGN:** Interventional case report.

PARTICIPANTS: Patient and nuclear family (7 members total).

METHODS: Ophthalmologic, neurologic, and radiologic examination of the proband; venous blood sampling for candidate gene testing of the proband; venous blood sampling for confirmatory testing in other family members.

MAIN OUTCOME MEASURES: Clinical and radiologic observations in proband and candidate gene results. **RESULTS:** The proband, a 9-year-old girl, substituted convergence for horizontal gaze (synergistic convergence) since birth. She also had conjugate pendular nystagmus, asynchronous blinking, and high myopia. No family member had ophthalmologic or medical symptoms. Neuroradiologic imaging revealed hindbrain dysplasia and modest scoliosis.

Sequencing of ROB03, the gene associated with horizontal gaze palsy and progressive scoliosis, revealed a novel missense mutation (p.Pro771Leu) that altered an evolutionarily conserved amino acid. Screening the family for this mutation confirmed that both parents were carriers and identified 2 sisters as carriers and 2 brothers as noncarriers.

CONCLUSIONS: This is the second reported patient with synergistic convergence and the first associated with a documented pathologic genotype. Unlike the previously reported case (which occurred in the setting of the cranial dysinnervation disorder congenital fibrosis of the extraocular muscles), our patient presumably has a supranuclear cause.

Significance of the publication:

First report of a central etiology for synergistic convergence in a genetically confirmed subject with HGPPS.

[Amouri, R., Nehdi, H., Bouhlal, Y., Kefi, M., Larnaout, A., & Hentati, F. \(2009\). Allelic ROBO3 heterogeneity in Tunisian patients with horizontal gaze palsy with progressive scoliosis. *J Mol Neurosci*, 39\(3\), 337-341.⁶²
doi:10.1007/s12031-009-9217-4](#)

- Click reference above to see full PDF article

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder characterized by the congenital absence of horizontal gaze, progressive scoliosis, and failure of the corticospinal and somatosensory axon tracts to decussate in the medulla. HGPPS is caused by mutations of the ROBO3 gene, which encodes a protein that shares homology with the roundabout family of transmembrane receptors that are important in axon guidance and neuronal migration. To date, over 15 mutations have been found in consanguineous families of Greek, Italian, Turkish, Pakistani, Saudi Arabian, and Indian descent. To detail clinical, cerebral magnetic resonance imaging (MRI) and genetic findings of ten HGPPS patients from four unrelated Tunisian families. Four unrelated consanguineous Tunisian families with a total of ten patients suffering from horizontal gaze palsy with progressive scoliosis. Genetic linkage analysis and direct sequencing of the ROBO3 gene. All patients shared similar clinical gaze movement abnormalities and variable degrees of scoliosis. Four distinct homozygous mutations were identified. This study extends the molecular spectrum of the ROBO3 gene and the geographic origin of patients with ROBO3 gene mutations, and underlines the homogeneity of the motor ocular syndrome whatever type of mutation is encountered.

Comment about Amouri 2009.

The candidate performed all orthoptic evaluations on these individuals during an invited research trip to Tunisia. The objective was to help the local research team evaluate individuals and confirm the clinical diagnosis prior to conducting expensive genetic evaluations. These evaluations were later used in this publication. This work was only acknowledged in the publication by thanking our research lead Dr. Thomas Bosley. The publication has been

included in the Appendix as it represents the first group of individuals with genetically confirmed HGPPS not having severe scoliosis. Our figures were not published.

Chapter 8: Other disorders disrupting ocular motility and alignment

Each of the previous chapters addressed a single clinical diagnosis that was often the focus of specific research project. This chapter encompasses several additional diagnoses encountered. These have been categorized into groups with similar mechanisms accounting for ocular motility and/or alignment dysfunction.

8.1 Myopathic disorders

A total of 12 subjects fall into this category. Six were published in 3 articles.

An additional 3 subjects with synDRS, published as cases studies (see chapter 2), have been included here as well (section 8.1.1) as genetic analysis revealed mutations in genes associated with muscle function and development.

8.1.1 CCDD phenotype

Three subjects with synDRS had mutations in genes associated with muscle development. Each subject was reported in a different publication.^{32, 34, 35} These reports were presented in chapter 2.

[Abu-Amero, K. K., Bosley, T. M., Kondkar, A. A., Oystreck, D. T., & Khan, A. O. \(2015\). CCDD Phenotype Associated with a Small Chromosome 2 Deletion. Semin Ophthalmol, 30\(5-6\), 435-442.](#)³²

[doi:10.3109/08820538.2013.874474](https://doi.org/10.3109/08820538.2013.874474)

- Click reference above to see full PDF article

[Bosley, T. M., Salih, M. A., Alkhalidi, H., Oystreck, D. T., El Khashab, H. Y., Kondkar, A. A., & Abu-Amero, K. K. \(2016\). Duane retraction syndrome in a patient with Duchenne muscular dystrophy. *Ophthalmic Genet*, 37\(3\), 276-280.](#)³⁴

[doi:10.3109/13816810.2015.1039139](https://doi.org/10.3109/13816810.2015.1039139)

- Click reference above to see full PDF article

[Abu-Amero, K. K., Kondkar, A. A., Odan, H. A., Khan, A. O., Oystreck, D. T., & Bosley, T. M. \(2016\). Duane Retraction Syndrome Associated with a Small X Chromosome Deletion. *Can J Neurol Sci*, 43\(3\), 445-447.](#)³⁵

[doi:10.1017/cjn.2015.358](https://doi.org/10.1017/cjn.2015.358)

- Click reference above to see full PDF article

These papers suggest some forms of DRS may arise from mutations in genes related to muscle development, or a developmental insult affecting multiple systems. One should also consider these may represent unrelated co-existing cases of DRS. However the associated syndromic features warrants suspicion for a unifying mechanism.

8.1.2 Carey-Fineman-Ziter syndrome (CFZS)

[Di Gioia, S. A., Connors, S., Matsunami, N., Cannavino, J., Rose, M. F., Gillette, N. M., et al. \(2017\). A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome. Nat Commun, 8, 16077.](#)⁴¹

[doi:10.1038/ncomms16077](https://doi.org/10.1038/ncomms16077)

- Click reference above to see full PDF article
- Discussed briefly in chapter 3

Multinucleate cellular syncytial formation is a hallmark of skeletal muscle differentiation. Myomaker, encoded by *Mymk* (*Tmem8c*), is a well-conserved plasma membrane protein required for myoblast fusion to form multinucleated myotubes in mouse, chick, and zebrafish. Here, we report that autosomal recessive mutations in *MYMK* (OMIM 615345) cause Carey-Fineman-Ziter syndrome in humans (CFZS; OMIM 254940) by reducing but not eliminating *MYMK* function. We characterize *MYMK*-CFZS as a congenital myopathy with marked facial weakness and additional clinical and pathologic features that distinguish it from other congenital neuromuscular syndromes. We show that a heterologous cell fusion assay in vitro and allelic complementation experiments in *mymk* knockdown and *mymkinsT/insT* zebrafish in vivo can differentiate between *MYMK* wild type, hypomorphic and null alleles. Collectively, these data establish that *MYMK* activity is necessary for normal muscle development and maintenance in humans, and expand the spectrum of congenital myopathies to include cell-cell fusion deficits.

Significance of the publication:

This represents one of the identified phenotypes that overlapped with MBS, i.e. Atypical MBS, MBS-like disorder. The genetic and phenotypic elucidation of this disorder arose from the identification of a subject that did not meet our designated criteria for MBS.

8.1.3 Oculopharyngeal muscular dystrophy (OPMD)

Oystreck, D. T., Salih, M. A., & Bosley, T. M. (2011). When straight eyes won't move: phenotypic overlap of genetically distinct ocular motility disturbances. *Can J Ophthalmol*, 46(6), 477-480.⁴⁵

[doi:10.1016/j.jcjo.2011.09.009](https://doi.org/10.1016/j.jcjo.2011.09.009)

- Click link to see full PDF [Straight eyes 2011](#)

OBJECTIVE: To describe the phenotypic similarity in a series of patients with genetically distinct ocular motility disturbances involving straight eyes and different ocular motor pathology.

DESIGN: Retrospective case series.

PARTICIPANTS: Clinical and genetic evaluation of 5 patients with straight eyes in the primary position and abnormalities of ocular motility. **RESULTS:** Patients with oculopharyngeal muscular dystrophy, congenital myasthenic syndrome, congenital fibrosis of the extraocular muscles type 3, Bosley-Salih-Alorainy syndrome, and horizontal gaze palsy and progressive scoliosis all had straight eyes in primary position and restricted ocular motility. History, ocular motility patterns, systemic features of individual syndromes, and genetic screening were important diagnostically.

CONCLUSIONS: A number of congenital and genetic ocular motility syndromes may result in substantial phenotypic overlap, particularly when eyes are straight in primary position and nonophthalmologic features are not apparent or not observed. The range of disorders that may fall into this category is discussed.

Significance of the publication:

This was patient 1 from the above publication. It highlighted specific phenotypic overlap (i.e. straight eyes) in genetically distinct conditions.

8.1.4 Kearns-Sayre Syndrome

[Kozak, I., Oystreck, D. T., Abu-Amero, K. K., ..., Bosley, T. M. \(2016\). New Observations Regarding the Retinopathy of Genetically Confirmed Kearns-Sayre Syndrome. Retin Cases Brief Rep.](#)⁷⁹

[doi:10.1097/ICB.0000000000000503](https://doi.org/10.1097/ICB.0000000000000503)

- Click reference above to see full PDF article

PURPOSE: To report novel retinal findings in Kearns-Sayre syndrome and correlate degree of retinopathy with other clinical findings.

METHODS: Observational case series of patients from Saudi Arabia with retinal and neuroophthalmologic examinations, medical chart review, and mitochondrial genetic evaluation.

RESULTS: The three unrelated patients had progressive external ophthalmoplegia and pigmentary retinopathy bilaterally. Muscle biopsy in two of the cases revealed mitochondrial myopathy. All three had abnormal findings on neuroimaging and modestly reduced visual acuity in both eyes with a variable pigmentary retinopathy. One of the patients had bilateral subretinal fibrosis with a full-thickness macular hole in the right eye. All three patients had single, large-scale mitochondrial DNA (mtDNA) deletions (5.0-7.6 kb in size) with blood mtDNA heteroplasmy levels ranging from below 20% to 57%. Severity of pigmentary retinopathy did not correlate with severity of progressive external ophthalmoplegia, but did correspond grossly with electroretinographic abnormalities, just as the degree of ocular motility restriction and ptosis in each patient correlated with the size of their extraocular muscles on neuroimaging. In addition, the size of the single, large-scale mtDNA deletion and level of mtDNA heteroplasmy corresponded with degree of ocular motility restriction but not with severity of retinopathy.

CONCLUSION: Subretinal fibrosis and macular hole are novel retinal observations which expand clinical profile in Kearns-Sayre syndrome. Genetic testing for mtDNA deletions and

heteroplasmy in blood, muscle biopsy, careful ocular and retinal examination including electroretinography, and imaging are indispensable tests for this condition.

Significance of the publication:

Attempted to construct phenotype-genotype correlation. Numbers of subjects were too small.

Disorder represents a progressive and severe form of external ophthalmoplegia. Muscle weakness is not restricted to eyes. It is one of the few conditions included that also has afferent system dysfunction. Genetics involve mutations in the mitochondrial DNA.

8.2 Maldevelopment of cranial nerve development

This section includes subjects with confirmed congenital maldevelopment of extraocular innervation that does not fit in with any of the previous diagnosis discussed, e.g., DRS, CFEOM, MBS, or HGPPS. This includes 7 subjects reported in 5 publications. Two of these publications are presented here.

8.2.1 Synergistic Divergence

[Oystreck, D. T., Khan, A. O., Vila-Coro, A. A., Oworu, O., Al-Tassan, N., Chan, W. M., Engle, E.C., Bosley, T. M. \(2009\). Synergistic divergence: a distinct ocular motility dysinnervation pattern. Invest Ophthalmol Vis Sci, 50\(11\), 5213-5216.](#)³⁷

[doi:10.1167/iovs.08-2928](https://doi.org/10.1167/iovs.08-2928)

- Click reference above to see full PDF article

PURPOSE: To summarize the clinical, neuroradiologic, and genetic observations in a group of patients with unilateral synergistic divergence (SD).

METHODS: Five unrelated patients with unilateral SD underwent ophthalmic and orthoptic examinations; three of them also had magnetic resonance imaging of the brain and orbits. Three patients underwent genetic evaluation of genes known to affect ocular motility: *KIF21A*, *PHOX2A*, *HOXA1*, and *ROBO3*.

RESULTS: The patients did not meet the clinical criteria for CFEOM types 1, 2, or 3. Each patient had severe adduction weakness on the affected side and large-angle exotropia in primary gaze that increased on attempted contralateral gaze because of anomalous abduction. Magnetic resonance imaging revealed a much smaller medial rectus muscle in the involved SD orbit. Oculomotor cranial nerves were present in the one patient imaged appropriately. Genetic sequencing in three patients revealed no mutations in *KIF21A*, *PHOX2A*, *HOXA1*, or *ROBO3*.

CONCLUSIONS: SD should be classified as a distinct congenital ocular motility pattern within congenital cranial dysinnervation disorders. It may be caused by denervation of the medial rectus with dysinnervation of the ipsilateral lateral rectus by the oculomotor nerve precipitated by genetic abnormalities (some currently identified) or by local environmental, teratogenic, or epigenetic disturbances.

Significance of the publication:

Highlighted the importance of careful phenotyping similarly affected individuals. It also represented the limitation of genetic elucidation of disorders and importance of waiting.

Patient 2 was later described in two additional publications. One that confirmed an autosomal recessive mutation in *COL25A1*, a gene involved in axonal guidance and cytoskeletal microtubule function.⁶³ The second describe the phenotype in more detail reporting that when this gene is mutated it can lead to abnormal ocular motor neuron development resulting in a variable combination of phenotypes including, synergistic divergence, congenital ptosis and/or DRS.⁶⁴

8.2.2 Hereditary Congenital Facial Paresis-3 (HCFP3-*HOXB1*)

[Webb, B. D., Shaaban, S., Gaspar, H., Cunha, L. F., Schubert, C. R., Hao, K., Robson, C.D., Chan, W., Andrews, C., MacKinnon, S., **Oystreck, D.T.**, Hunter, D.G., Iacovelli, A.J., Ye X., Camminady, A., Engle, E.C., Jabs, E. W. \(2012\). *HOXB1* founder mutation in humans recapitulates the phenotype of *Hoxb1*^{-/-} mice. *Am J Hum Genet*, 91\(1\), 171-179.](#)³⁸

[doi:10.1016/j.ajhg.2012.05.018](https://doi.org/10.1016/j.ajhg.2012.05.018)

- Click reference above to see full PDF article
- Discussed briefly in chapter 3

Members of the highly conserved homeobox (HOX) gene family encode transcription factors that confer cellular and tissue identities along the antero-posterior axis of mice and humans. We have identified a founder homozygous missense mutation in *HOXB1* in two families from a conservative German American population. The resulting phenotype includes bilateral facial palsy, hearing loss, and strabismus and correlates extensively with the previously reported *Hoxb1*^(-/-) mouse phenotype. The missense variant is predicted to result in the substitution of a cysteine for an arginine at amino acid residue 207 (Arg207Cys), which corresponds to the highly conserved Arg5 of the homeodomain. Arg5 interacts with thymine in the minor groove of DNA through hydrogen bonding and electrostatic attraction. Molecular modeling and an in vitro DNA-protein binding assay predict that the mutation would disrupt these interactions, destabilize the *HOXB1*:*PBX1*:DNA complex, and alter *HOXB1* transcriptional activity.

Significance of the publication:

Represents another phenotype originally mistaken as MBS. Two siblings in this report were identified during our examination of subjects at the International Moebius conference as not having minimum diagnostic criteria.⁴⁰ This paper reports the identified mutation as being pathogenic. This identifies the third HCFP3 phenotype (OMIM 614744).

8.3. Neurologic/CNS related disorders predominantly affecting ocular motility

The candidate had the opportunity to conduct orthoptic evaluations patients with various neurological disorders. In total this included 5 disorders involving 30 subjects. This resulted in two publications addressing the effect of cerebellar dysfunction on the ocular motility phenotype.

8.3.1 Ataxia Telangiectasia-like disorder

[Khan, A. O., Oystreck, D. T., Koenig, M., & Salih, M. A. \(2008\). Ophthalmic features of ataxia telangiectasia-like disorder. *J AAPOS*, 12\(2\), 186-189.](#)⁶⁵

[doi:10.1016/j.jaapos.2007.09.016](https://doi.org/10.1016/j.jaapos.2007.09.016)

- Click reference above to see full PDF article

INTRODUCTION: Ataxia telangiectasia (AT) is a recessive neurodegenerative disease due to a faulty repair mechanism for breaks in double-stranded DNA (ATM mutation). Ophthalmic features of AT include conjunctival telangiectasia, strabismus, saccadic dysfunction with head thrusts, and convergence insufficiency. Ataxia telangiectasia-like syndrome (ATLD) is a more recently recognized condition due to homozygous mutation in MRE11, a gene also involved in the cellular repair response to double-stranded DNA breaks; ophthalmic features of ATLD are not well described. The purpose of this article is to describe the ophthalmic features of ATLD.

METHODS: Full ophthalmologic and orthoptic evaluations were obtained in 13 individuals: 10 previously reported ATLD patients, an additional related ATLD patient, and 3 nonaffected relatives. All individuals were from three unrelated consanguineous Saudi Arabian families harboring an MRE11 mutation (W210C). Age range was from 2 to 40 years of age.

RESULTS: No affected patient had structural ocular abnormality (eg, conjunctival telangiectasia), manifest strabismus at distance, or duction limitation. All but one (the youngest) had saccadic dysfunction (without head thrusts). Most patients had abnormal convergence. Older patients had nystagmus with abnormalities in smooth pursuit and vestibular ocular reflex. All patients had cerebellar atrophy by neuroimaging and slowly progressive ataxia. The unaffected heterozygous relatives had unremarkable ophthalmic and neurologic examinations.

CONCLUSIONS: Saccadic dysfunction without head thrusts and convergence abnormality are common in ATLD secondary to homozygous W210C MRE11 mutation. Older patients have nystagmus with abnormalities in smooth pursuit and vestibular ocular reflex. Eye movement control systems apparently deteriorate with time in this rare neurological disease. Ophthalmic features of AT that were not observed in any of our ATLD patients include conjunctival telangiectasia, head thrusting, and manifest strabismus at distance.

8.3.2 Joubert syndrome

[Khan, A. O., Oystreck, D. T., Seidahmed, M. Z., Aldrees, A., Elmalik, S. A., Alorainy, I. A., & Salih, M. A. \(2008\). Ophthalmic features of Joubert syndrome. *Ophthalmology*, 115\(12\), 2286-2289.⁶⁶ doi:10.1016/j.opthta.2008.08.005](#)

- Click reference above to see full PDF article

PURPOSE: Joubert syndrome (Online Mendelian Inheritance in Man 213300) is a rare autosomal recessive congenital malformation of the brainstem and cerebellar vermis. Diagnosis is based on characteristic clinical features (e.g., hypotonia, episodic hyperpnea, developmental delay, progressive ataxia) and is confirmed by distinctive neuroradiologic findings (e.g., the "molar tooth" sign). Variable ophthalmic features have been mentioned in prior reports; however, most do not detail eye findings and the few that do were before the publication of suggested diagnostic criteria. The objective of the current study is to describe the ophthalmic phenotype

in a cohort of patients with Joubert syndrome for whom the diagnosis was made using current diagnostic criteria.

DESIGN: Prospective case series.

PARTICIPANTS: Eight children diagnosed clinically with radiologic confirmation.

METHODS: Ophthalmic examination and visual electrophysiology.

MAIN OUTCOME MEASURES: Ocular and oculomotor examination (as allowed by patient cooperation), electroretinography, flash visual-evoked potential (fVEP).

RESULTS: Patients' ages ranged from 7 months to 10 years. Saccadic dysfunction was observed in all cooperative patients (6/6); compensatory head thrusts or turns were present in all except the youngest patient (7 months of age). Most patients (5/8) had primary-position nystagmus (see-saw in 3/5). Abnormal pursuit (3/7) and a dystrophic retinal appearance (3/8) were also seen. One patient had bilateral asymmetric ptosis with unilateral lid elevation during ipsilateral abduction. Electroretinography findings were normal for all 8 patients. Seven patients underwent fVEP; 6 were abnormal (asymmetric) and one was not interpretable because of study artifact.

CONCLUSIONS: Ophthalmologists should be aware that saccadic dysfunction (typically with head thrusts) and primary position nystagmus (typically see-saw) in a developmentally delayed child suggest the diagnosis of Joubert syndrome, especially if a dystrophic retinal appearance is also present. Our findings of asymmetric fVEPs and see-saw nystagmus suggest an abnormality in optic nerve decussation, consistent with the concept that impaired axonal guidance occurs in patients with Joubert syndrome.

Discussion:

Subjects with either Ataxia-Oculomotor Apraxia 2 (AOA2), Ataxia Teleganectasia (AT), or Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) were also examined, demonstrating a similar effect on the ocular motor system due to cerebellar dysfunction. These disorders suggests the need for a specific category in which to group such conditions.

8.4 Neurologic disorders predominantly affecting ocular alignment (Strabismus)

This section represents subjects with neurological abnormalities involving abnormal ocular alignment but with intact ocular motility.

This group involves 46 subjects with 7 different neurological disorders. A total of 41 subjects were published in 5 papers that included mutations in 4 different genes and 1 chromosomal anomaly. It is felt the genetic mutation was not directly responsible for the strabismus. However it highlights secondary effects that may occur in genetic disorders affecting the brain. The vast majority of subjects had full ocular excursions, however the associated comitant strabismus present in most subjects was proposed to be secondary to sensory strabismus from organic anterior visual pathway defects, or from abnormal posterior visual pathway deficits inhibiting normal binocular function. One group included here did have normal ocular alignment and motility but were included to illustrate the need for careful orthoptic testing.

8.4.1 Lipoid Proteinosis

[Salih, M. A., Abu-Amero, K. K., Alrasheed, S., Alorainy, I. A., Liu, L., McGrath, J. A., Van Maldergem, L., Al-Faley, Y.H., AlSuhaybani, A.H., Oystreck, D.T., Bosley, T. M. \(2011\). Molecular and neurological characterizations of three Saudi families with lipoid proteinosis. BMC Med Genet, 12, 31.](#)⁶⁷

[doi:10.1186/1471-2350-12-31](https://doi.org/10.1186/1471-2350-12-31)

- Click reference above to see full PDF article

BACKGROUND: Lipoid proteinosis is a rare autosomal recessive disease characterized by cutaneous and mucosal lesions and hoarseness appearing in early childhood. It is caused by homozygous or compound heterozygous mutations in the ECM1 gene. The disease is largely uncharacterized in Arab population and the mutation(s) spectrum in the Arab population is largely unknown. We report the neurologic and neuroradiologic characteristics and ECM1 gene mutations of seven individuals with lipoid proteinosis (LP) from three unrelated consanguineous families.

METHODS: Clinical, neurologic, and neuro-ophthalmologic examinations; skin histopathology; brain CT and MRI; and sequencing of the full ECM1 gene.

RESULTS: All seven affected individuals had skin scarring and hoarseness from early childhood. The two children in Family 1 had worse skin involvement and worse hoarseness than affected children of Families 2 and 3. Both children in Family 1 were modestly mentally retarded, and one had typical calcifications of the amygdalae on CT scan. Affected individuals in Families 2 and 3 had no gross neurologic, neurodevelopmental, or neuroimaging abnormalities. Skin histopathology was compatible with LP in all three families. Sequencing the full coding region of ECM1 gene revealed two novel mutations in Family 1 (c.1300-1301delAA) and Family 2 (p.Cys269Tyr) and in Family 3 a previously described 1163 bp deletion starting 34 bp into intron 8.

CONCLUSIONS: These individuals illustrate the neurologic spectrum of LP, including variable mental retardation, personality changes, and mesial temporal calcification and imply that significant neurologic involvement may be somewhat less common than previously thought. The cause of neurologic abnormalities was not clear from either neuroimaging or from what is known about ECM1 function. The severity of dermatologic abnormalities and hoarseness generally correlated with neurologic abnormalities, with Family 1 being somewhat more affected in all spheres than the other two families. Nevertheless, phenotype-genotype correlation was not obvious, possibly because of difficulty quantifying the neurologic phenotype and because of genetic complexity.

Significance of the publication:

All subjects were referred to our neuro-ophthalmology service because of strabismus. Careful orthoptic investigation revealed all genotyped individuals had normal ocular alignment and motility. This publication has been included to illustrate the importance of including the orthoptic evaluation. These individuals may have inappropriately been reported as having strabismus by investigators who were not able to appropriately assess the ocular alignment. It also represents a gene we determined is not pathogenic for strabismus.

8.4.2 Carbonic anhydrase type II deficiency syndrome

[Bosley, T. M., Salih, M. A., Alorainy, I. A., Islam, M. Z., Oystreck, D. T., Suliman, O. S., al Malki, S., Suhaibani, A.H., Khiari, H., Beckers, S., van Wesenbeeck, L., Perdu, B., AlDrees, A., Elmalik, S.S., Van Hul, W., Abu-Amero, K. K. \(2011\). The neurology of carbonic anhydrase type II deficiency syndrome. *Brain*, 134\(Pt 12\), 3499-3512.](#)⁶⁸

[doi:10.1093/brain/awr302](https://doi.org/10.1093/brain/awr302)

- Click reference above to see full PDF article

Carbonic anhydrase type II deficiency syndrome is an uncommon autosomal recessive disease with cardinal features including osteopetrosis, renal tubular acidosis and brain calcifications. We describe the neurological, neuro-ophthalmological and neuroradiological features of 23 individuals (10 males, 13 females; ages at final examination 2-29 years) from 10 unrelated consanguineous families with carbonic anhydrase type II deficiency syndrome due to homozygous intron 2 splice site mutation (the 'Arabic mutation'). All patients had osteopetrosis, renal tubular acidosis, developmental delay, short stature and craniofacial disproportion with large cranial vault and broad forehead. Mental retardation was present in approximately two-thirds and varied from mild to severe. General neurological examinations were unremarkable except for one patient with brisk deep tendon reflexes and two with severe mental retardation and spastic quadriparesis. Globes and retinae were normal, but optic nerve involvement was present in 23/46 eyes and was variable in severity, random in occurrence and statistically correlated with degree of optic canal narrowing. Ocular motility was full except for partial ductional limitations in two individuals. Saccadic abnormalities were present in two, while half of these patients had sensory or accommodative strabismus, and seven had congenital nystagmus. These abnormalities were most commonly associated with afferent disturbances, but a minor brainstem component to this disorder remains possible. All internal auditory canals were normal in size, and no patient had clinically significant hearing loss. Neuroimaging was performed in 18 patients and repeated over as long as 10 years. Brain calcification was generally progressive and followed a distinct distribution, involving predominantly basal ganglia and thalami and grey-white matter junction in frontal regions

more than posterior regions. At least one child had no brain calcification at age 9 years, indicating that brain calcification may not always be present in carbonic anhydrase type II deficiency syndrome during childhood. Variability of brain calcification, cognitive disturbance and optic nerve involvement may imply additional genetic or epigenetic influences affecting the course of the disease. However, the overall phenotype of the disorder in this group of patients was somewhat less severe than reported previously, raising the possibility that early treatment of systemic acidosis with bicarbonate may be crucial in the outcome of this uncommon autosomal recessive problem.

8.4.3 Autosomal Recessive C12orf57

[Salih, M. A., Tzschach, A., Oystreck, D. T., ..., Bosley, T. M. \(2013\). A newly recognized autosomal recessive syndrome affecting neurologic function and vision. Am J Med Genet A, 161A\(6\), 1207-1213.](#)⁶⁹

[doi:10.1002/ajmg.a.35850](https://doi.org/10.1002/ajmg.a.35850)

- Click reference above to see full PDF article

Genetic factors represent an important etiologic group in the causation of intellectual disability. We describe a Saudi Arabian family with closely related parents in which four of six children were affected by a congenital cognitive disturbance. The four individuals (aged 18, 16, 13, and 2 years when last examined) had motor and cognitive delay with seizures in early childhood, and three of the four (sparing only the youngest child) had progressive, severe cognitive decline with spasticity. Two affected children had ocular malformations, and the three older children had progressive visual loss. The youngest had normal globes with good functional vision when last examined but exhibited the oculodigital sign, which may signify a subclinical visual deficit. A potentially deleterious nucleotide change (c.1A>G; p.Met1Val) in the C12orf57 gene was homozygous in all affected individuals, heterozygous in the parents, and absent in an unaffected sibling and >350 normal individuals. This gene has no known function. This family manifests an autosomal recessive syndrome with some phenotypic variability that includes

abnormal development of brain and eyes, delayed cognitive and motor milestones, seizures, and a severe cognitive and visual decline that is associated with a homozygous variant in a newly identified gene.

8.4.4 Partial mosaic trisomy 8

[Abu-Amero, K. K., Kondkar, A. A., Salih, M. A., Al-Husain, M., Al Shammari, M., Zeidan, G., Oystreck, D.T., Hellani, A.M., Kentab, A.Y., Bosley, T. M. \(2013\). Ophthalmologic observations in a patient with partial mosaic trisomy 8. *Ophthalmic Genet*, 34\(4\), 249-253.](#)⁷⁰

[doi:10.3109/13816810.2012.762933](https://doi.org/10.3109/13816810.2012.762933)

- Click reference above to see full PDF article

BACKGROUND: To carefully assess the phenotype and genotype of a patient with partial mosaic trisomy 8 with particular attention to ophthalmologic features.

METHODS: Ophthalmologic and neuro-ophthalmologic examination; neuroimaging; conventional karyotyping; and array comparative genomic hybridization (CGH).

RESULTS: The proband was the only affected child of a non-consanguineous family. At birth she was noted to have facial dysmorphism including telecanthus, low set ears, prominent nares, and an everted lower lip. She had an accommodative esotropia with otherwise normal globes, optic nerves, retinae, and orbits. She also had delayed motor milestones and mild mental retardation associated with agenesis of the corpus callosum. Both karyotyping and array CGH documented mosaic partial trisomy of chromosome 8 that included all of the "q" arm and part of the proximal "p" arm.

CONCLUSIONS: This girl had a number of the classic features of mosaic trisomy 8, including an accommodative esotropia with none of the other ocular and orbital anomalies described in patients with mosaic trisomy 8. This report constitutes an initial effort to create a virtual

database of patients with mosaic chromosome 8 in which careful phenotype-genotype correlation employing high resolution array CGH may help identify clues regarding the genetic etiology of ophthalmologic features of this syndrome.

8.4.5 Isolated sulfite oxidase deficiency

[Bosley, T. M., Alorainy, I. A., Oystreck, D. T., Hellani, A. M., Seidahmed, M. Z., Osman Mel, F., Sabry, M.A., Rashed, M.S., Al-Yamani, E.A., Abu-Amero, K.K., Salih, M. A. \(2014\). Neurologic injury in isolated sulfite oxidase deficiency. *Can J Neurol Sci*, 41\(1\), 42-48.](#)⁷¹

PMID: 24384336

- Click reference above to see full PDF article

Background: We review clinical, neuroimaging, and genetic information on six individuals with isolated sulfite oxidase deficiency (ISOD).

Methods: All patients were examined, and clinical records, biochemistry, neuroimaging, and sulfite oxidase gene (SUOX) sequencing were reviewed.

Results: Data was available on six individuals from four nuclear families affected by ISOD. Each individual began to seize within the first week of life. neurologic development was arrested at brainstem reflexes, and severe microcephaly developed rapidly. neuroimaging within days of birth revealed hypoplasia of the cerebellum and corpus callosum and damage to the supratentorial brain looking like severe hypoxic-ischemic injury that evolved into cystic hemispheric white matter changes. Affected individuals all had elevated urinary S-sulfocysteine and normal urinary xanthine and hypoxanthine levels diagnostic of ISOD. Genetic studies confirmed SUOX mutations in four patients.

Conclusions: ISOD impairs systemic sulfite metabolism, and yet this genetic disease affects only the brain with damage that is commonly confused with the clinical and radiologic features of severe hypoxic-ischemic encephalopathy.

Notes:

Orthoptic assessment was conducted on 3 of the 6 individuals. Ocular motility was grossly full but alignment was variable with poor or no attention to visual targets. Biochemical diagnosis was confirmed in 6, genetic confirmation in 4.

Significance of this publication:

These individuals represented a group in which ocular alignment and excursion of ocular motility was variable due to profound brain dysfunction. Subjects did not have visually guided eye movements but rather roving movements. The publication highlights brain development conditions resulting in cortical blindness with subsequent effects on the oculomotor system, e.g. roving eye movements, variable strabismus, and sensory nystagmus.

8.5 Strabismus with full ocular motility in neurologically normal

This section represents a large group of subjects who were neurologically normal, full ocular motility, and comitant strabismus who also have at least two other similarly affected family members.

This comprises two populations of subjects and represents on-going work as a member of the international Strabismus Genetics Research Consortium.

One group was enrolled into the KSU project 542-7 where all examinations were done in Riyadh, Saudi Arabia. However genetic investigations were done with a collaborating research team at Boston Children's Hospital (Engle lab) who were also investigating the genetics of familial forms of simple strabismus. We enrolled a total of 204 subjects from 50 Arab families. DNA samples were obtained in 160 subjects. Two siblings were found to have a mutation in *HOXA1*, one of whom was published in a previous *HOXA1* publication⁵. Results are pending on the remaining samples.

A second group involves roughly 50 subjects I examined at Boston Children's Hospital who were enrollment into their Simple strabismus project.

One publication has recently been published.

8.5.1 Comitant esotropia

[Shaaban, S., MacKinnon, S., Andrews, C., Staffieri, S. E., Maconachie, G. D. E., Chan, W. M., et al. \(2018\). Genome-Wide Association Study Identifies a Susceptibility Locus for Comitant Esotropia and Suggests a Parent-of-Origin Effect. Invest Ophthalmol Vis Sci, 59\(10\), 4054-4064.⁷² doi:10.1167/iovs.18-24082 002](#)

- Click reference above to see full PDF article
- Candidate was not involved in the writing of this publication but was involved in the examination and classification of subjects enrolled in this project. This is discussed in more detail in chapter 9.
- An update to the genetic findings in this population has just been accepted as a poster at the 2019 AAPOS conference in San Diego, CA, USA.

Purpose: To identify genetic variants conferring susceptibility to esotropia. Esotropia is the most common form of comitant strabismus, has its highest incidence in European ancestry populations, and is believed to be inherited as a complex trait.

Methods: White European American discovery cohorts with nonaccommodative (826 cases and 2991 controls) or accommodative (224 cases and 749 controls) esotropia were investigated. White European Australian and United Kingdom cohorts with nonaccommodative (689 cases and 1448 controls) or accommodative (66 cases and 264 controls) esotropia were tested for replication. We performed a genome-wide case-control association study using a mixed linear additive model. Meta-analyses of discovery and replication cohorts were then conducted.

Results: A significant association with nonaccommodative esotropia was discovered (odds ratio [OR] = 1.41, $P = 2.84 \times 10^{-9}$) and replicated (OR = 1.23, $P = 0.01$) at rs2244352 [T] located within intron 1 of the WRB (tryptophan rich basic protein) gene on chromosome 21 (meta-analysis OR = 1.33, $P = 9.58 \times 10^{-11}$). This single nucleotide polymorphism (SNP) is differentially methylated, and there is a statistically significant skew toward paternal inheritance in the discovery cohort. Meta-analysis of the accommodative discovery and replication cohorts

identified an association with rs912759 [T] (OR = 0.59, P = 1.89×10^{-08}), an intergenic SNP on chromosome 1p31.1.

Conclusions: This is the first genome-wide association study (GWAS) to identify significant associations in esotropia and suggests a parent-of-origin effect. Additional cohorts will permit replication and extension of these findings. Future studies of rs2244352 and WRB should provide insight into pathophysiological mechanisms underlying comitant strabismus.

Chapter 9: Phenotypic-genotypic bi-directional algorithm overview & Summary

Project design

All subjects were enrolled into an REB approved institutional project. (see chapter 1 **Table 1.2**)

The research was conducted under several grants and different principal investigators. (**Table 9.0**) The central focus of these institutional research projects, and the resultant publications, varied. Main topics included genetic, radiologic, neurologic and medical domains.

The candidate was a member of these international research teams and was involved in the assessment of all subjects. My contribution was as a certified orthoptist having expertise in the evaluation of ocular motility disorders. This afforded a unique opportunity to study the orthoptic features in a large cohort of subjects with rare and heterogeneous conditions in which disturbance of ocular motility and alignment were common features.

The *central research question* was whether the orthoptic evaluation can be an effective tool in the elucidation and distinction of congenital and/or genetic disorders with disturbance of ocular alignment and motility. If true, this could lead to designing a bi-directional diagnostic algorithm in which orthoptic features serve as the starting point in the investigation of these subjects. Therefore all studies done by our research teams required conducting an orthoptic evaluation. In most cases this was administered in conjunction with additional assessments as part of a larger institutional study. These assessments most often included neuro-ophthalmology, pediatric ophthalmology and genetics; frequently included radiology, pediatric neurology; and as needed ENT, audiology, pediatrics, and psychology as per study protocols. The method of genetic investigations were determined by the research lab conducting the assessment and the study protocol in which the subject was enrolled. Molecular investigation techniques included sequencing of candidate genes, array comparative genomic hybridization (array CGH) and whole exome or genome screening.

Table 9.0. Research grants in which candidate work was performed

Agency	Grant ID	PI
KSU	Deanship scientific research RGP-VPP-301	Salih
KACST	AT-30-20 AT-29-31 07-581	Abu-Amero
NEI	R01 EY 15298	Engle

KSU = King Saud University; KACST = King Abdulaziz City for Science and Technology; NEI = National Eye Institute.

Addressing the main research question and proposed aim of the research

The **central research question**: Is the orthoptic evaluation an effective tool in the elucidation and distinction of congenital and/or genetic disturbances in ocular alignment and motility?

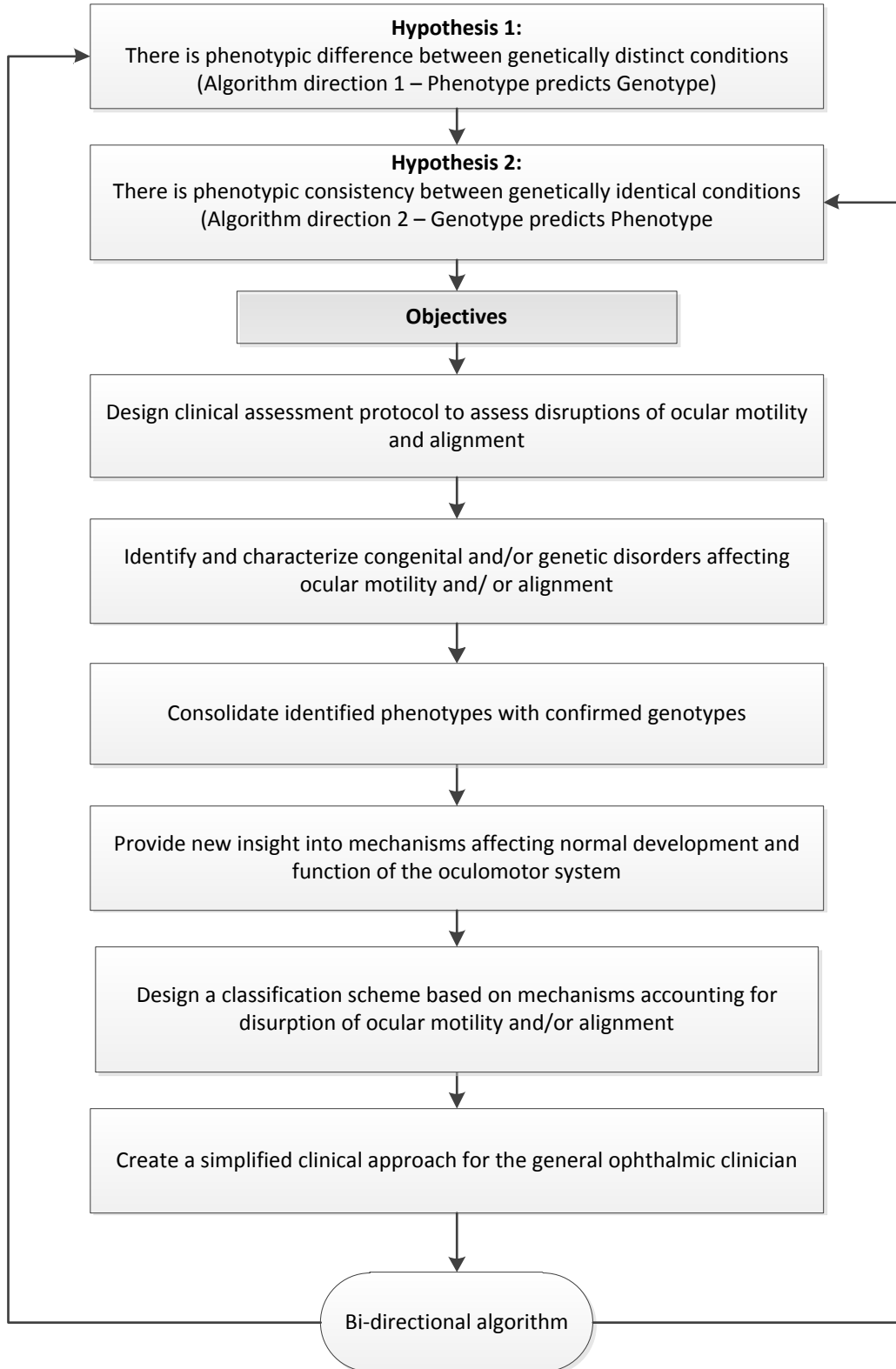
Research aim: To design a bi-directional diagnostic clinical algorithm in which identified phenotypes can accurately predict the genotype (direction 1 – phenotype predicts genotype), conversely to identify genotypes that will allow the clinician to accurately predict an expectant phenotype (direction 2 – genotype predicts phenotype).

The benefits of such an algorithm would improve accuracy of the diagnosis, permit earlier and more appropriate referrals to other medical specialists, ensure cost effective genetic investigations, and permit more targeted management strategies with clearer outcome goals.

The central research question and aim are explored through two hypothesis and developed through addressing 6 objectives. **(Fig 9.1)**

This chapter presents evidence for each objective.

Figure 9.1. Construction of a bi-directional algorithm



Objective 1: Design a clinical assessment protocol to assess disruptions of ocular alignment and motility.

Outcome: Met with regards to current knowledge and understanding of the conditions.

Evidence:

- RP 0424 datasheet [\(link to document\)](#)
- NANOS/CHB datasheet [\(link to document\)](#)
- Example of MBS datasheet [\(link to document\)](#)
- Textbook Chapter – The Orthoptic evaluation [\(link to PDF\)](#)

Discussion:

Chapter 2 includes early publications that led to my involvement in this topic. This was the start of a conscious effort by a team of clinicians to further pursue research in the field of congenital ocular motility disorders by elucidating the clinical spectrum of newly identified genetic syndromes. Early success with key publications led to the creation of a larger multidisciplinary team that included myself as the ocular motility expert. This in turn resulted in the eventual initiation of the ophthalmic genetics research program at King Saud University in Riyadh, Saudi Arabia that I would join in 2008.

My involvement within these research teams included standardizing the clinical approach to evaluating and documenting ocular involvement.

Outcome:

Candidate designed data collection forms; standardized the assessment, scoring and terminology used in the evaluation of subjects. This permitted consistent, detailed descriptions for disorders encountered, which proved useful to identify important similarities and distinctions within this population.

Identified limitations:

Despite great efforts, a single standard investigation on all subjects was not achieved. This was due in large part to the different requirements for each project and the different services and clinical specialists available at the various institutions. However, the basic orthoptic evaluation was consistent. Modification was required in situations of poor cognitive ability or bilateral visual deficits. An unabridged approach was published as a textbook chapter.¹¹ A PDF of the editor's final copy has been provided in appendix section for chapter 9.

No single data collection form or database could be utilized. Most projects required use of a specific form and data storage location. The candidate adapted to the needs and requests of different stakeholders. Examples are provided in appendix chapter 9.

Objective 2: Identification and characterization of congenital and/or genetic disorders affecting ocular motility and alignment

Outcome: Met

The total number of subjects examined and charts reviewed (retrospective reports) related to the dissertation is estimated at 1409.

Of these, 564 were excluded for the following reasons:

- 404 subjects reviewed as part of the DRS retrospective publications^{9, 12}
- 60 OFNF subject reported in the retrospective OFNF treatment publication.⁴⁷
- ~50 subjects examined as part of the Boston Children's Hospital Simple Strabismus study⁷²
- 50 subjects (15 families) with at least two family members having congenital motor nystagmus with apparent normal afferent visual functioning. It was decided to not include this group as full investigations were not complete at the time of this writing.

This left a total of 845 subjects enrolled with 40 different clinical diagnoses identified.

Objective 3: To consolidate the identified main phenotypes with confirmed genotypes

Outcome: Met

Evidence: Table 9.3.1, 9.3.2, 9.3.3

Phenotyping:

All subjects underwent substantial investigations that involved multiple specialties to provide as much phenotypic information as possible. My role was to perform an orthoptic evaluation to identify strabismus and/or ocular motility abnormalities. In most cases the orthoptic exam was done as part of a subject's regular ophthalmological visit to Pediatric ophthalmology or Neuro-ophthalmology. In other cases it was conducted as part of a research clinic.

Genotyping:

All institutional approved research projects that subjects were enrolled involved genetic investigations. DNA samples were obtained in 72% (609/845) of subjects. However a genetic diagnosis was confirmed in 33% (281/845) of all subjects, either by analysis of DNA or by confirmation in a similarly affected family member. **Table 9.3.1** lists the outcomes.

Consolidating confirmed genotypes to phenotypes:

A total of 25 genes were identified as having a mutation. Two show evidence for mutation-specific phenotypes (*TUBB3*, *CHRNE*), one had marked variable expression (*NF1*). One condition involved mitochondrial DNA deletions. Several subjects had a chromosomal anomalies, which in all but one case (partial chromosome 8 trisomy) involved a single gene. **Table 9.3.2** provides a full list of the genetic results linked to the pertinent diagnosis.

Characterization of disorders and genetics:

The candidate authored 43 peer reviewed articles, 1 textbook chapter, and participated in two publications as a consortium member that described the clinical, and when known, genetic details of 349 subjects. Included in this list are 5 invited publications.^{27, 42, 73-75} A textbook chapter defining the orthoptic evaluation also arose from work on defining the best approach to the assessment of binocular vision disorders.¹¹ **Tables 9.3.3** list the publications by date of acceptance.

Table 9.3.1 Genetic results in subject population n= 845

	n total population	% total population
Sample obtained	609	72%
Results pending*	378/609	
Initial results negative	21/609	
Results known[¥]	281/865	33%

*Awaiting DNA analysis; ¥ Genetics confirmed by DNA analysis or by genetic confirmation in similarly affected family member.

Table 9.3.2 Summary of genetic results in subject population

Chapter 2 - DRS						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
<i>HOXA1</i>	Homo sapiens homeobox A1	*142955	AR	7p15.2	28	synDRS BSAS ABDS HOXA1 syndrome
<i>PTPRN2</i>	protein tyrosine phosphatase, receptor type, N polypeptide 2	*601698	Chrm	7q36.3	1	synDRS
<i>FGF13</i>	Fibroblast growth factor homologous factor 13	*300070	Chrm	Xq26.3- q27.1	1	synDRS (WS)
<i>KIR</i>	killer cell immunoglobulin-like receptor		Chrm	19q13.4	1	synDRS
<i>CHRN3, Neuronal</i>	Cholinergic Receptor, Nictoinic, Beta-3	*118508	Chrm	8p11.2	1	synDRS
<i>XIRP2</i>	Xin Actin-binding Repeat containing 2	*609778	Chrm	2q24.3	1	synDRS
<i>RNF34</i>	ring finger protein 34, E3 ubiquitin protein ligase	*608299	Chrm	12q24.31	1	synDRS
<i>PPARA</i>	peroxisome proliferator-activated receptor alpha	+170998	Chrm	22q13.31		
<i>DMD</i>	dystrophin	*300377	Chrm	Xp21.2- p21.1	2	synDRS
<i>COL25A1</i>	collagen type XXV alpha 1	*610004	AR	4q25	2	nsDRS
<i>Non pathogenic CNV</i>						Bilateral nsDRS

Chapter 3 - MBS						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
----	-----				123	MBS
<i>TUBB3</i>	See chapter 4					
<i>HOXB1</i>	See chapter 8					

Chapter 4 - CFEOM						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
<i>KIF21A</i>	kinesin family member 21A	*608283	AD	12q12	12	CFEOM1 > CFEOM3
<i>PHOX2A</i>	Aristaless Homebox, Drosophila, Homolog of (ARIX)	*602753	AR	11q13.4	22	CFEOM2
<i>TUBB3</i>	Tubulin, Beta-3	*602661	De novo AD	16q24.3	10	CFEOM3 plus
	TUBB3 - E410K				2	
	TUBB3 – E417H				2	
	TUBB3 – R262H				1	
	TUBB3 – mutation not specified				5	

Chapter 5 - OFNF						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
<i>NF1</i>	Neurofibromin 1	*613113	AD	17q11.2	96*	NF1 OFNF

*includes all subjects having either NF1 or OFNF

Chapter 6 - CMS						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
<i>CHRNE</i>	Cholinergic Receptor, Nicotinic, Epsilon Polypeptide	* 100725	AR	17p13.2	3	CMS (3 MIM phenotypes)
<i>COLQ</i>	Collagenic Tail of Endplate Acetylcholinesterase	*603033	AR	3p25.1	1	CMS5 (pheno MIM 603034)
<i>MUSK</i>	Muscle, Skeletal, Receptor Tyrosine Kinase	*601296	AR	9q31.3	2	CMS9 (pheno MIM 616325)

Chapter 7 - HGPPS						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
<i>ROBO3</i>	Roundabout, Drosophila, Homolog of, 3	*608630	AR	11q24.2	25	HGPPS

Chapter 8 - Miscellaneous						
Gene/ Locus	Gene full name	Gene MIM	Inher	Cyto loc.	No. genotyped	Dx linked in dissertation
MtDNA	N/A (Mitochondrial DNA deletions)	----	Mito		3	KSS
<i>MRE11A</i>	Meiotic recombination 11, <i>S. Cerevisiae</i> , homolog of, A	*600814	AR	11q21	14	ATLD1
<i>C12orf57</i>	Chromosome 12 open reading frame 57	*615140	AR	12p13.31	4	Abn brain and eye (Temtys)
<i>Chrm 8</i>	Chromosome 8 Partial trisomy	---	de novo	8q & p	1	Accommodative ET
<i>SUOX</i>	Sulfite oxidase	*606887	AR	12q13.2	3	ISOD
<i>CA2</i>	Carbonic Anhydrase II	*611492	AR	8q21.2	23	CADS, Marble Brain, Osteopetrosis
<i>ECM1</i>	Extracellular matrix protein 1	*602201	AR	1q21.2	7	Lipoid Proteinosis
<i>PABPN1</i>	Polyadenylate-binding protein, nuclear, 1	*602279	AD	14q11.2	1	OPMD
<i>HOXB1</i>	Homo sapiens homeobox B1	*142968	AR	17q21.32	2	HCFP3

Full spelling of diagnoses are given in legend for **Table 9.6**.

Table 9.3.3 List of candidate's publications related to dissertation

Paper	Cty	Acpt for Pub	Reference title and journal	Thesis Ref #
1	2	2004 12	Neurologic features of horizontal gaze palsy and progressive scoliosis with mutations in ROBO3. Neurology. 2005;64(7):1196-203.	6
2	2	2005 10	Clinical characteristics of bilateral Duane syndrome. Journal of AAPOS. 2006;10(3):198-201	9
3	2	2005 10	Homozygous HOXA1 mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. Nature genetics. 2005;37(10):1035-7	14
4	2	2006 01	Fixation preference for the affected eye in patients with unilateral Duane syndrome. Journal of AAPOS. 2006;10(3):275-6.	10
5	2	2006 05	Neurological features of congenital fibrosis of the extraocular muscles type 2 with mutations in PHOX2A. Brain. 2006;129(Pt 9):2363-74	44
6	2	2007 06	Duane retraction syndrome on the Arabian Peninsula. Strabismus. 2007;15(4):205-8	12
7	2	2007 09	Clinical characterization of the HOXA1 syndrome BSAS variant. Neurology. 2007;69(12):1245-53	5
8	1	2007 09	Ophthalmic features of ataxia telangiectasia-like disorder. Journal of AAPOS. 2008;12(2):186-9	65
9	2	2008 01	The clinical spectrum of homozygous HOXA1 mutations. American journal of medical genetics Part A. 2008;146A(10):1235-40	15
10	1	2008 08	Ophthalmic features of Joubert syndrome. Ophthalmology. 2008;115(12):2286-9	66
11	2	2008 08	Bilateral synergistic convergence associated with homozygous ROBO3 mutation (p.Pro771Leu). Ophthalmology. 2008;115(12):2262-5	61
12	2	2009 08	Synergistic divergence: a distinct ocular motility dysinnervation pattern. Invest Ophthalmol Vis Sci. 2009;50(11):5213-6	37
13	2	2010	Congenital Cranial Dysinnervation Disorders. 2010. In: Encyclopedia of the Eye [Internet]. Elsevier; [346-55]	42
14	5	2010 01	Congenital myasthenic syndrome due to homozygous CHRNE mutations: report of patients in Arabia. Journal of neuro-ophthalmology. 2011;31(1):42-7	51
15	2	2011 01	Recent progress in understanding congenital cranial dysinnervation disorders. Journal of neuro-ophthalmology. 2011;31(1):69-77	26
16	1	2011 02	Molecular and neurological characterizations of three Saudi families with lipid proteinosis. BMC medical genetics. 2011;12:31	67
17	1,2,4	2011 07	When straight eyes won't move: phenotypic overlap of genetically distinct ocular motility disturbances. Can J Ophthalmol. 2011;46(6):477-80	45
18	1	2011 09	The neurology of carbonic anhydrase type II deficiency syndrome. Brain.2011;134(Pt 12):3499-512	68
19	3	2011 10	Orbitofacial neurofibromatosis: clinical characteristics and treatment outcome. Eye (Lond). 2012;26(4):583-92	47

Paper	Cty	Accpt for Pub	Reference title and journal	Thesis Ref #
20	3	2012 04	Visual loss in orbitofacial neurofibromatosis type 1. Ophthalmology. 2012;119(10):2168-73	48
21	2,6	2012 05	HOXB1 founder mutation in humans recapitulates the phenotype of Hoxb1^{-/-} mice. American journal of human genetics	38
22	6	2012 05	Comitant strabismus: Perspectives, present and future. Saudi journal of ophthalmology. 2012;26(3):265-70	73
23	2	2012 07	Partial chromosome 7 duplication with a phenotype mimicking the HOXA1 spectrum disorder. Ophthalmic genetics. 2013;34(1-2):90-6.	28
24	2	2012 11	A novel syndrome caused by the E410K amino acid substitution in the neuronal beta-tubulin isotype 3. Brain. 2013;136(Pt 2):522-35	39
25	1	2012 12	A newly recognized autosomal recessive syndrome affecting neurologic function and vision. American journal of medical genetics Part A. 2013;161A(6):1207-13	69
26	6	2012 12	Ophthalmologic observations in a patient with partial mosaic trisomy 8. Ophthalmic genetics. 2013;34(4):249-53	70
27	2	2013 01	Xq26.3 microdeletion in a male with Wildervanck Syndrome. Ophthalmic genetics. 2014;35(1):18-24	29
28	3	2013 03	Ocular Neostigmine Drops for Diagnosing Myasthenia Gravis. J Neurol Neurophysiol. 2013(S11:004)	76
29	3	2013 05	Variable ptosis after botulinum toxin type a injection with positive ice test mimicking ocular myasthenia gravis. Journal of neuro-ophthalmology. 2013;33(2):169-71	77
30	2	2013 07	Partial duplication of chromosome 19 associated with syndromic duane retraction syndrome. Ophthalmic genetics. 2015;36(1):14-20	30
31	1	2013 07	Neurologic injury in isolated sulfite oxidase deficiency. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2014;41(1):42-8	71
32	2	2013 08	Nicotinic Receptor Mutation in a Mildly Dysmorphic Girl with Duane Retraction Syndrome. Ophthalmic genetics. 2015;36(2):99-104.	31
33	2	2013 09	Congenital cranial dysinnervation disorders: a concept in evolution. Current opinion in ophthalmology. 2013;24(5):398-406	27
34	2	2013 12	CCDD Phenotype Associated with a Small Chromosome 2 Deletion. Seminars in ophthalmology. 2015;30(5-6):435-42.	32
35	2	2014 01	HOXA1 Mutations are Not Commonly Associated with Non-Syndromic Deafness. Can J Neurol Sci. 2014;41(4):448-51	78
36	2,3,6	2014 01	Diagnostic distinctions and genetic analysis of patients diagnosed with moebius syndrome. Ophthalmology. 2014;121(7):1461-8	40
37	2	2014 03	Microdeletions involving chromosomes 12 and 22 associated with syndromic Duane retraction syndrome. Ophthalmic genetics. 2014;35(3):162-9	33
38	2	2014 05	Retinal Dysfunction in Patients with Congenital Fibrosis of the Extraocular Muscles Type 2. Ophthalmic genetics. 2016;37(2):130-6	46

Paper	Cty	Accpt for Pub	Reference title and journal	Thesis Ref #
39	2	2015 01	Congenital and Genetic Ocular Motility Disorders: Update and Considerations. Am Orthopt J. 2015;65:58-66	74
40	2,4	2015 04	Duane retraction syndrome in a patient with Duchenne muscular dystrophy. Ophthalmic genetics. 2016:1-5	34
41	2,4	2015 12	Duane Retraction Syndrome Associated with a Small X Chromosome Deletion. Can J Neurol Sci 2016;43(3):445-7	35
42	2	2016 06	The genetics of nonsyndromic bilateral Duane retraction syndrome. Journal of AAPOS. 2016;20(5):396-400 e2.	36
43	4	2016 12	New Observations Regarding the Retinopathy of Genetically Confirmed Kearns-Sayre Syndrome. Retin Cases Brief Rep 2018; 12(4):349-358	79
44		2017	The orthoptic evaluation – chapter 75. In Taylor & Hoyt's pediatric ophthalmology and strabismus, 5 th edition, Eds. Lambert SR, Lyons CJ.2017	11
45	2	2018 01	Ophthalmoplegia and Congenital Cranial Dysinnervation Disorders. J Binocul Vis Ocul Motil 2018;1:31-33	75
Publications as a consortium member – not involved in writing manuscript				
46	4	2017 07	A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome (Moebius Syndrome Research Consortium)	41
47	6	2018 08	Genome-Wide Association Study Identifies a Susceptibility Locus for Comitant Esotropia and Suggests a Parent-of-Origin Effect. Invest Ophthalmol Vis Sci 2018; 59:4054-4064 (Strabismus Genetics Research, Consortium)	72

Cyt = Classification category (see category distinctions below); Accpt for Pub = date accepted for publication (YYYY/MM)

Category distinctions:

- 1 = Neurological or Central Nervous System Disorders
- 2 = Disorders of Cranial Nerve development (CCDDs)
- 3 = Disorders of Orbital development
- 4 = Myopathic disorders
- 5 = Disorders of Neuromuscular junction
- 6 = Disorders of Simple strabismus

Objective 4: Provide new insight into mechanisms affecting normal development and function of the oculomotor system

Outcome: Met

Evidence: Table 9.4.1

An anticipated outcome of studying a large cohort of subjects with rare disorders was to gain insight into mechanisms affecting the normal development and function of the oculomotor system. By integrating the results of the genetic evaluation with detailed clinical evaluations including the orthoptic evaluation, neuro-radiology, and findings from other medical specialties, new and existing mechanisms were identified.

A list of the involved gene, chromosome, mitochondrial DNA are provided in **Table 9.4.1** with a reference to the relevant candidate publication discussing the impact on the oculomotor system and proposed mechanism. The Table has been sorted into groups based on known or presumed impact to the function of the oculomotor system.

Group 1: Genes with direct impact

- Involved in cranial nerve development, maintenance and axonal guidance
- Involved in neuromuscular junction function
- Involved in cerebellum function

Group 2: Genes with an indirect impact

- Defective gene function leading to abnormal orbital anatomy with a secondary effect on binocular vision, globe position, and/or motility
- Defective gene function leading to structural anomaly or a functional anomaly of the visual pathway resulting in defective visual processing or a sensory strabismus

Group 3: Genes with an unknown role

- Identification of a genetic mutation that could not reliably be attributed to the observed oculomotor dysfunction. In many cases in this group the publication was the first report, or most detailed description, of a detected ocular motor anomaly when one was present.

Table 9.4.1 Grouping of genes based on known or presumed role in the development and function of the oculomotor system.

Group 1	Ref	Group 2	Ref	Group 3	Ref
<i>HOXA1*</i>	14	<i>NF1</i>	47	<i>PTPRN2</i>	28
<i>COL25A1</i>	37, 63	<i>C12orf57</i>	69	<i>FGF13</i>	29
<i>KIF21A</i>	26	<i>SUOX</i>	71	<i>KIR</i>	30
<i>PHOX2A</i>	26, 44			<i>CHRNA3, Neuronal</i>	31
<i>TUBB3*</i>	39, 40, 74			<i>XIRP2</i>	32
<i>CHRNE</i>	51			<i>RNF34</i>	33
<i>COLQ</i>	exam			<i>PPARA</i>	33
<i>MUSK</i>	exam			<i>DMD</i>	34, 35
<i>ROBO3</i>	6			<i>CA2</i>	68
<i>MtDNA del</i>	79			<i>ECM1*</i>	67
<i>MRE11A</i>	65			<i>HOXB1*</i>	38
<i>PABPN1</i>	45				

Ref = relevant candidate publication; exam = as determined by candidate examination and literature

Group 1 = genes when mutated having a direct impact on function of the oculomotor system

Group 2 = genes when mutated having an indirect (secondary) impact on function of the oculomotor system

Group 3 = genes when mutated having no known impact on function of the oculomotor system.

*reported cases of full eye movements

Objective 5: Design a classification scheme based on mechanism accounting for disruption of ocular motility and/or alignment

Outcome: Met

Evidence: Objectives 1-4

Addressing objective 5 is possible by meeting criteria for objectives 1-4.

Objective 1 provided the bases in which ocular motility and alignment data could be standardized to ensure accurate and consistent data was collected in a population with complex ocular motility disorders.

Objective 2 confirmed diagnoses in which identified phenotypes could be applied and studied.

Objective 3 consolidated these phenotypes with identified genotypes.

Objective 4 provided evidence about underlying mechanisms accounting for a disturbance in the oculomotor system in genetically confirmed diagnoses. This established which genetic disorders were likely pathogenic.

Objective 5 incorporates the information from the preceding objectives to propose a classification system that encompass the relevant encountered disorders.

Creating a classification system:

A review of the literature and observations of our clinical findings suggests a classification scheme based exclusively on clinical phenotype is not be reliable.

Examples include unraveling of the original CFEOM classification based on ocular motility patterns as more genetic information was elucidated, and an overestimation of the value of confirming DRS to predict genotype as was determined in many of our publications.

As a result it became apparent a scheme based on pathomechanisms would be more ideal. However, it requires investigations that go beyond orthoptic features. This approach is presented in the following paragraphs. Note however, objective 6 returns to the notion of beginning with the orthoptic phenotype as the initial approach.

Based on known/proposed gene functions and documented phenotypes the following classification scheme is proposed.

Category 1: Neurological or Central Nervous system related disorders

Involves ocular motility and alignment disorders arising from a disturbance to normal neurologic or central nervous system function. Innervational connections and structure of the extraocular muscles are normal. The commonest issues in our population involved abnormal function of the central eye movement systems due to supranuclear disturbances involving cerebellar, thalamic, and cortical white matter neuronal functioning. This predominantly affected ocular motility rather than inducing strabismus. Another mechanism arose from abnormal cortical functioning in which normal visual processing and/or binocularity may not be possible resulting in sensory strabismus or roving eye movements.

Observed oculomotor anomalies usually occurred after birth and tended to be progressive.

Key candidate publications pertaining to this category are listed in **Table 9.3.3**

Category 2: Congenital Cranial Dysinnervation disorders

This involves a heterogeneous group of neurogenic syndromes that arise from brainstem and cranial nerve maldevelopment. Most result in absent or misinnervation of extraocular muscles, lids, and/or facial muscles. However these can arise from congenital brainstem malformation involving cranial nerve nuclei or gaze centres (e.g. MBS, HGPPS); or congenitally aplastic or hypoplastic cranial nerves (*KIF21A*, *TUBB3*). This is the only category involving dysinnervation of the extraocular muscles.

This category comprised the diagnoses discussed in chapters 2-4 and chapter 8 (section 8.2.1 and 8.2.2). Key candidate publications pertaining to this category are listed in **Table 9.3.3**

[Bosley, T. M., Abu-Amero, K. K., & Oystreck, D. T. \(2013\). Congenital cranial dysinnervation disorders: a concept in evolution. *Curr Opin Ophthalmol*, 24\(5\), 398-406.²⁷](#)

[doi:10.1097/ICU.0b013e3283645ad6](https://doi.org/10.1097/ICU.0b013e3283645ad6)

- The article provides the largest overview on this category.
- Click reference above to see full PDF article

Category 3: Disruption to orbital anatomy

This involves conditions that predominantly affect the orbital development or disrupt the integrity of the orbital anatomy resulting in dysfunction to ocular motility or more commonly alignment. This category does not involve pathology affecting extraocular muscle development or innervation.

This category comprised the diagnosis in chapter 5.

Key candidate publications pertaining to this category are listed in **Table 9.3.3**

Category 4: Myopathic disorders

This category involves disorders affecting extraocular muscle physiology or structure without innervational disturbances.

This category comprised diagnoses in chapter 8 sections 8.1.2, 8.1.3, and 8.1.4

Key candidate publications pertaining to this category are listed in **Table 9.3.3**

Category 5: Disorders of the neuromuscular junction

Defects of the neuromuscular junction comprises a heterogeneous group of disorders caused by mutations in different genes that affect neuromuscular transmission. Mutations in several genes will inhibit neuromuscular transmission by affecting structure or function of the neuromuscular synapse. Several disorders within this group disrupt eye movements, however ocular alignment is generally not disturbed.

This category comprised the diagnosis in chapter 6.

Key candidate publications pertaining to this category are listed in **Table 9.3.3**

Category 6: Simple strabismus

This category involves subjects with manifest strabismus that is either congenital or familial (at least 2 other affected family members). This group has normal extraocular muscle function, innervation and structure. Subjects are considered neurologically normal.

This category was discussed briefly in chapter 8 (section 8.5)

Key candidate publications pertaining to this category are listed in **Table 9.3.3**

Category 7 (additional): Multiple mechanisms

This category was added to accommodate the 8 subjects that had features consistent with more than one of the above categories. These individuals are extremely interesting and likely hold the key to additional information related to oculomotor system development.

Not categorized, but also worth mentioning were two other populations of subjects. The first group comprised 31 subjects in which a definitive clinical diagnosis could not be made. These subjects were found within categories 1-4. The second group consisted of 5 subjects that had multiple diagnoses from within the same category. Both groups also represent interesting populations worth further investigations.

Table 9.5.1 groups all enrolled subjects by category. It includes the clinical diagnoses and genes for each category as well as the number of subjects genotyped and the outcome. This Table is considered a major outcome of this research.

Summary:

Objective 5 represents what could be considered a penultimate classification for congenital and/or genetic disorders of ocular motility and alignment. This is a scheme that incorporates clinical, radiological, and molecular information to elucidate the underlying pathomechanism, which is then used as a category. This classification is now possible due to recent advances in genetics and radiology. Incorporation of investigations by multiple specialties is required for this classification. However, this should now be considered the gold standard approach within a research environment. We demonstrated this approach by the large number of authors and medical specialties included in many of our publications. It is anticipated as more information is generated through careful clinical assessments and collaborative work between multi-disciplines this classification system will become more informative and useful to the general ophthalmologist.

Table 9.5.1 Subject classification based on underlying pathomechanism

Category 1: Neuro / CNS

Diagnosis	No.	Genetics known		Genetics unknown	No.
Unable to specify	7	molecular diagnosis	48	results pending	14
JBS	11	affected family member	13	screen negative	0
AT	2		61	no sample	4
ATLD	14				18
AOA2	2				
ISOD	3	Gene		Pts Published	No.
ARSACS	4	MRE11A	14	Yes	57
Cockayne	1	C12orf57	4		
CADS	23	SUOX	3		
TEMTYS	4	CA2	23		
LP*	7	ECM1	7		
Mul pheno same cat	1	chromosomal (no gene)	0		
Total	79	Total	51		

Category 2: CCDD

Diagnosis	No.	Genetics known		Genetics unknown	No.
Unable to specify	17	molecular diagnosis	96	results pending	207
CFEOM	105	affected family member	10	screen negative	21
CFEOM1 (20)			106	no sample	84
CFEOM2 (28)					312
CFEOM3 (57)					
DRS	108	Gene		Pts Published	No.
nsDRS (56)		ROBO3	24	Yes	197
synDRS (52)		PHOX2A	22		
MBS	123	KIF21A	12		
HGPPS	33	HOXA1	25		
MGJW	3	PTPRN2	1		
Isolated SD	2	RNF34	1		
Isolated Ptosis*	4	PPARA	1		
Isolated FP*	17	DMD	2		
CN4 palsy	1	TUBB3	10		
DEP	1	KIR	1		
Mul pheno same cat	4	CHRN3	1		
Total	418	XIRP2	1		
		FGF13	1		
		COL25A1	2		
		Chromosomal (no gene)	2		

			106		
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Category 3: Orbit

Diagnosis	No.	Genetics known		Genetics unknown	No.
Unable to specify	2	molecular diagnosis	32	results pending	5
NF1	34	affected family member	64	screen negative	0
OFNF	62		96	no sample	5
Plagio	3				10
BS	5				
Mul pheno same cat	0	Gene		Pts Published	No.
Total	106	NF1	96	Yes	79

Category 4: Myopathy

Diagnosis	No.	Genetics known		Genetics unknown	No.
Unable to specify	5	molecular diagnosis	6	results pending	2
CPEO	2	affected family member	0	screen negative	0
OMPD	1		6	no sample	5
KSS	4				7
CFZS	1				
Total	12				
		Gene		Pts Published	No.
		PABPN1	1	Yes	6
		mtDNA del	4		
		MYMK	1		

Category 5: Neuromuscular junction

Diagnosis	No.	Genetics known		Genetics unknown	No.
MG	8	molecular diagnosis	6	results pending	3
CMS	10	affected family member	0	screen negative	0
Total	18		6	no sample	9
					12
		Gene		Pts Published	No.
		COLQ	1	Yes	4
		CHRNE	3		
		MUSK	2		
			6		

Category 6: Simple strabismus

Diagnosis	No.	Genetics known		Genetics unknown	No.
Eso	52	molecular diagnosis	2	results pending	160
Inf ET	9		2	screen negative	0
AET	94			no sample	42
EXO	36				202
Strab assc	12	Gene			
HT	1	HOXA1	2	Pts Published	No.
Total	204	Total	2	Yes	2

Category 7: Multiple mechanisms

Diagnosis	No.	Genetics known		Genetics unknown	No.
Multiple	8	molecular diagnosis	4	results pending	4
Total	8		4	screen negative	0
					4
		Gene		Pts Published	No.
		HOXA1	2	Yes	7
		HOXB1	2		
			4		

*Disorders not affecting ocular motility or alignment. These have been included in the table for completeness to illustrate total diagnoses encountered in this category.

Legend for diagnoses/phenotypes in Table 9.5.1

Abbrev	Pheno OMIM	Diagnosis
AET		Accommodative Esotropia
AOA2	#606002	Ataxia-Oculomotor Apraxia 2
ARSACS	#270550	Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay
AT	#208900	Ataxia Teleganectasia
ATLD	#604391	Ataxia Teleganectasia-like disorder 1
BS	%616407	Brown syndrome
CADS	#259730	Carbonic anhydrase type II deficiency syndrome
CFEOM1	#135700	Congenital Fibrosis of the Extraocular Muscles Type 1
CFEOM2	#602078	Congenital Fibrosis of the Extraocular Muscles Type 2
CFEOM3	#600638	Congenital Fibrosis of the Extraocular Muscles Type 3

CMS		congenital myasthenic syndrome; CMS9 MIM 616325 (CHRNE); CMS5 MIM 603034 (COLQ); CMS9 (MUSK)
CN4 palsy	136480	isolated congenital fourth nerve palsy
Cockayne	#216400	Cockayne syndrome
CPEO		Chronic progressive external ophthalmoplegia
DEP		monocular elevation deficiency (Double elevator palsy)
DRS	126800%	Duane Retraction Syndrome (unspecified)
ESO		Esotropia, intermittent esotropia, non accommodative esotropia with full ocular movements
EXO		Exotropia, Intermittent exotropia with full ocular movements
FP		isolated Facial palsy; HCFP1 (#601471); HCFP2 (#604185); HCFP3 (#614744) due to HOXB1;
HGPPS	#607313	Horizontal Gaze Palsy and Progressive Scoliosis
HT		vertical strabismus with full ocular movements
Inf ET		Infantile Esotropia
ISOD	#272300	Isolated Sulfite Oxidase Deficiency
JBS	#614464	Joubert syndrome (several genotypes)
KSS	#530000	Kearns-Sayre Syndrome
LP	#247100	Lipoid Proteinosis of Urbach and Wiethe
MBS	157900%	Moebius syndrome
MG	254200	autoimmune Myasthenia Gravis
MGJW		isolated Marcus Gunn Jaw Winking
Multiple phenotypes		Features consistent with diagnoses in more than 1 category
NF1	#162200	Neurofibromatosis, Type 1; von Recklinghausen disease
nsDRS		Duane Retraction Syndrome (nonsyndromic); may include BSAS
NT SPD		diagnosis not specified
OFNF	#162200	Orbitofacial Neurofibromatosis
OPMD	#164300	Oculopharyngeal muscular dystrophy
Plagio		Plagiocephaly (Craniosynostosis)
Ptosis	300245%	isolated ptosis
SC		isolated Synergistic Convergence
SD		Isolated Synergistic Divergence
Strb Assc		Strabismus associated condition
synDRS		Duane Retraction Syndrome (syndromic); includes BSAS (#601536) ; Wildervanck (%314600); Chr7 dup
TEMTYS	#218340	Temtamy syndrome

Objective 6: Designing a simplified clinical approach to these conditions

Outcome: Met.

Objective 5 determined a definitive diagnosis for ocular motility disorders often requires in depth investigations from multiple specialties with an increasing importance on genetics. However, in most cases a proband presents first to the general ophthalmologist who is then tasked with beginning the investigation process. The following is a simplified approach recommended for the general clinician who may find him/herself in this situation. It arises from our experiences examining a large number of individuals with complex strabismus. The foundation is utilization of the orthoptic evaluation.

Presented are two algorithms. Algorithm 1 is meant to assign a subject into the appropriate category (see chapter 9 – objective 5). Algorithm 2 is meant to help narrow down the diagnosis within a particular category and to help focus subsequent investigations, e.g. radiology protocols, genetic technique.

Algorithm 1 can be easily utilized by the general ophthalmologist. Algorithm 2 requires a more in depth assessment of the oculomotor system and quantification of confirmed anomalies. Therefore it may not always be feasible for the general clinician.

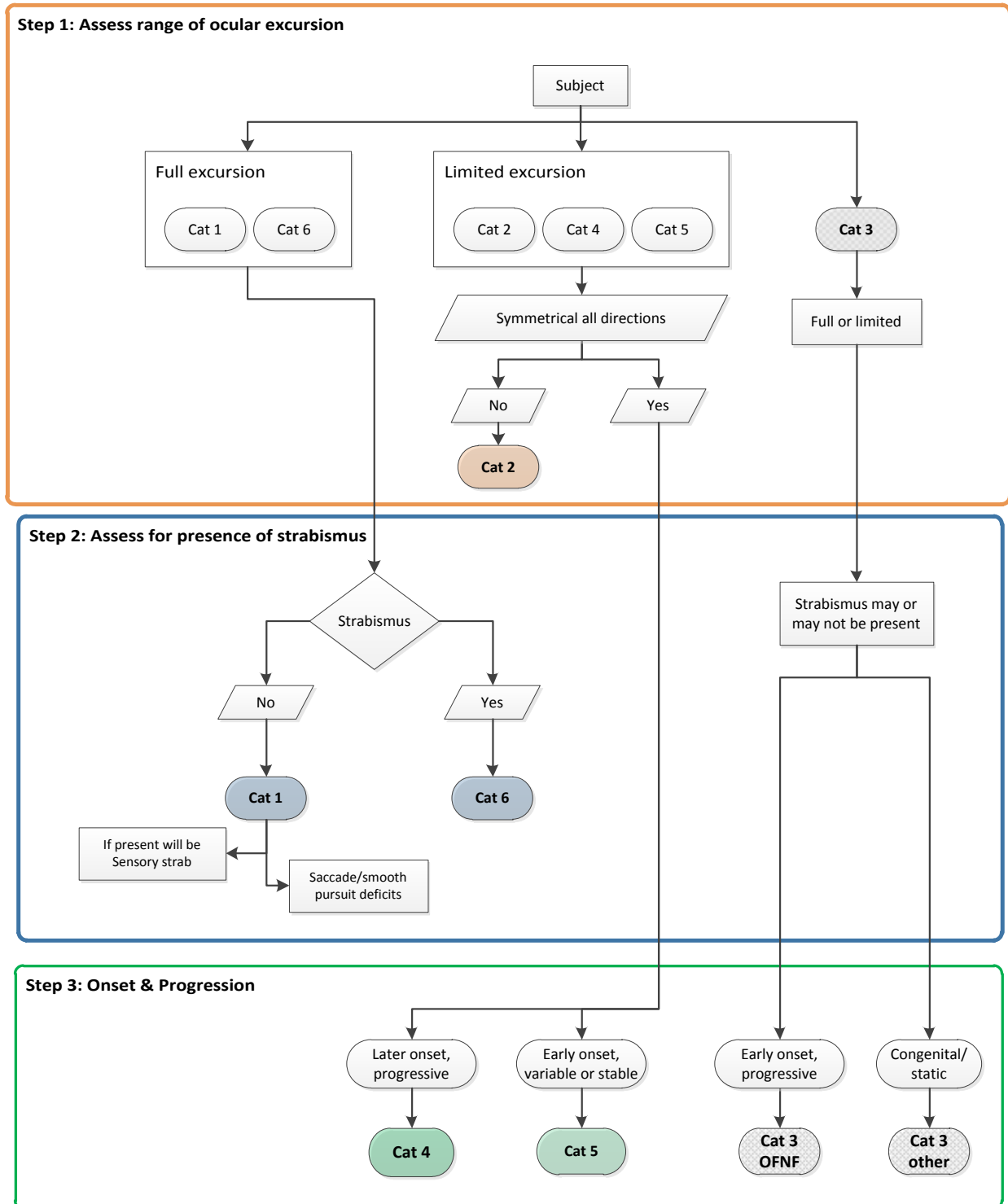
The following sections have been discussed in part within our publications. However, the concepts are amalgamated here for clarity.

Algorithm 1: Getting into the right category – Clinician’s role

The primary objective is for the clinician to assign a ‘new patient’ into the appropriate category. This is possible because most categories (based on pathomechanisms) demonstrate enough phenotypic distinctions (hypothesis 1 can be assumed to be at least partially correct) that assessment of a few key features can be utilized effectively.

Understanding that a complete orthoptic evaluation is not always feasible, presented here is an abbreviated orthoptic evaluation that focuses on two components. These are considered simple and reliable. **Figure 9.6.1** outlines this as a 3 step process. This algorithm can identify a category 2 condition in one step and category 1, 6, 4, and 5 in two steps. However, it is not adequate for category 3 diagnoses because of marked variability.

Figure 9.6.1 Step 1 – Key features to identify category



Cat 1 = Neuro/CNS; Cat 2 = CCDD; Cat 3 = Orbit; Cat 4 = Myopathy; Cat 5 = NMJ; Cat 6 = Simple strab

Step 1 – Assess degree of ocular excursions

Ocular excursions refer to the degree of ocular movement elicited with a duction. This does not assess the quality of movement, but only whether the eye can achieve full movement into all directions. An inability to achieve a full range of movement, regardless of direction or amount, separates categories 1 and 6 from 2,4,5. Further distinction is made by judging symmetry of the limited movements. Asymmetrical limitations are those in which limitation only occurs in specific directions or are of significantly different amounts. This is characteristic of category 2 disorders (CCDDs). Symmetrical limitations are approximately the same amount in both eyes and in all positions. Category 4 and 5 generally have symmetrical limitations. These can then be distinguished from each other by proceeding directly to Step 3.

Outcome: Confirms Category 2
Advance to Step 2 to confirm if Category 1 or 6 diagnosis
Advance to Step 3 to confirm if Category 4 or 5 diagnosis

Step 2 – Assess for strabismus

This distinguishes category 1 from 6. Assessment of ocular alignment is only required in primary position where the goal is to detect a manifest strabismus. Direction and size are not required at this time. Category 1 conditions tend to maintain good eye alignment while category 6 must have the presence of a manifest deviation in association with full ocular excursion. Exceptions can occur in category 1 as some patients will have variable strabismus secondary to profound bilateral visual loss.

Outcome: Distinguishes between Category 1 and 6

Step 3 – Onset and progression

Although useful for all categories, determination of age at onset and history of progression of ocular dysmotility can distinguish between category 4 and 5. Both tend to have symmetrical limitations of eye movement however age at onset tends to be later in category 4 with a greater preponderance of increasing severity with advancing age.

Outcome: Distinguishes between Category 4 and 5.

Algorithm 2: Narrowing down the correct diagnosis

After a patient has been categorized the next step is to attempt to narrow down a specific diagnosis. The orthoptic evaluation can again be valuable starting point. However, this time a more in depth assessment of ocular movements, strabismus patterns, and assessment of other associated ocular features is required. These are described below and were part of all subject evaluations in our studies. A more in depth description of the evaluation is provided in ‘The Orthoptic Evaluation’ chapter.¹¹

Detailed assessment of ocular movements:

This has 3 main components, each with several sub-components. **Table 9.6.1** describes the significance of each to the appropriate category.

1) Identification and quantification of ductional deficits

- Unilateral / bilateral
- Horizontal, vertical, combination
- Small, moderate, marked

2) Evaluation of eye movement subsystems

- Smooth pursuit
- Saccades
- Vergence
- Vestibular ocular reflex
- Bell’s phenomenon
- Fixation stability

3) Determination of dyskinetic eye movements suggestive of dysinnervation:

These are unintended globe and/or lid movement activated by anomalous innervation to the muscles.

- globe contraction during attempted adduction
- simultaneous divergence during attempted horizontal gaze – synergistic divergence

- simultaneous convergence during attempted horizontal gaze or attempted up gaze – synergistic convergence
- vertical movement of an eye during attempted horizontal gaze
- anomalous lid movement during eye or jaw movement

Table 9.6.1. Assessment of ocular movements

Ocular movement	Remarks
Normal	Category 6 – exclusive Overlap with some diagnoses in Category 1, 3, 4 (early age).
Ductional deficit	Category 2 - mandatory feature <ul style="list-style-type: none"> • Can be associated with globe(s) fixed in position away from primary position due to tight or atrophic eoms. <p>Category 3 (OFNF) may involve ductional deficit; globe may be positioned away from primary due to orbital bone anomalies resulting in hypoglobus</p> <p>Category 4 & 5 have symmetrical deficits.</p> <ul style="list-style-type: none"> • Category 4 tends to have later onset and progressive. • Category 5 can be variable but overall stable in degree of maximum limitations. <p>Overlap with diagnoses in Category 2, 3, 4 (untreated), 5 (late stage)</p>
Abnormal ocular motility subsystems	Category 1 – hallmark finding is full ocular excursions but with poor quality eye movements as a result of defective smooth pursuit and/or saccades. <p>Category 2,4, and 5 may have perceived deficits of vergence however these are not due to primary deficit of the vergence system.</p> <p>Overlap with Category 4 and 5 but abnormality due to different pathomechanisms</p>
Dysinnervation	Category - exclusive to this group <ul style="list-style-type: none"> • May have multiple dysinnervation patterns in same patient • May have similar dysinnervation patterns between different CCDDs

Detailed assessment of strabismus patterns:

Table 9.6.2 describes strabismus patterns significant to each category.

- 1) Direction: Eso, Exo, Hyper, Hypo, Torsional or combination
- 2) Size: Tiny to large angle deviations
- 3) Comitancy: Comitant vs incomitant
- 4) Control: Latent, manifest, intermittent
- 5) Globe position: Some categories have diagnoses in which one or both globes are in a fixed position. Movement is limited from that position

Table 9.6.2 Assessment of strabismus patterns

Strabismus	Remarks
Incomitant strabismus	Category 2 - Pathognomonic Category 3 – frequent feature Overlap patterns between Category 2 and 3
Comitant strabismus	Category 1 – may occur as sensory strabismus Category 3 – may occur as sensory strabismus Category 6 - Pathognomonic <ul style="list-style-type: none"> • A and V pattern and distance near disparity included in the setting of absent ductional deficits. Overlap in direction and size between Category 1, 3 and 6
No manifest deviation	Category 1 – common in setting of good vision in either eye Category 3 – not uncommon in setting of good vision in either eye Category 4 and 5 – common feature. Achievable as the associated limitation of ocular movements are symmetrical <ul style="list-style-type: none"> • Generally have associated near Exodeviations due to limited convergence ability.
Globe position	Category 2 <ul style="list-style-type: none"> • Fixed positions may include Adduction, Abduction, Infraduction and Supraduction (rare). • Arises from tightness of a hypoplastic fibrotic extraocular muscle, or from secondary contracture of a normal ipsilateral antagonist muscle. Category 3 <ul style="list-style-type: none"> • Down ward displaced globe position (hypoglobus). • Occurs in setting of orbital bony dysplasia.

Assessment of other ocular features:

Additional features include lid function and position, pupil function and appearance, presence of nystagmus or intrusion to fixation, anomalous head postures, age at onset, and progression.

Table 9.6.3 outlines these features and their significance to each category.

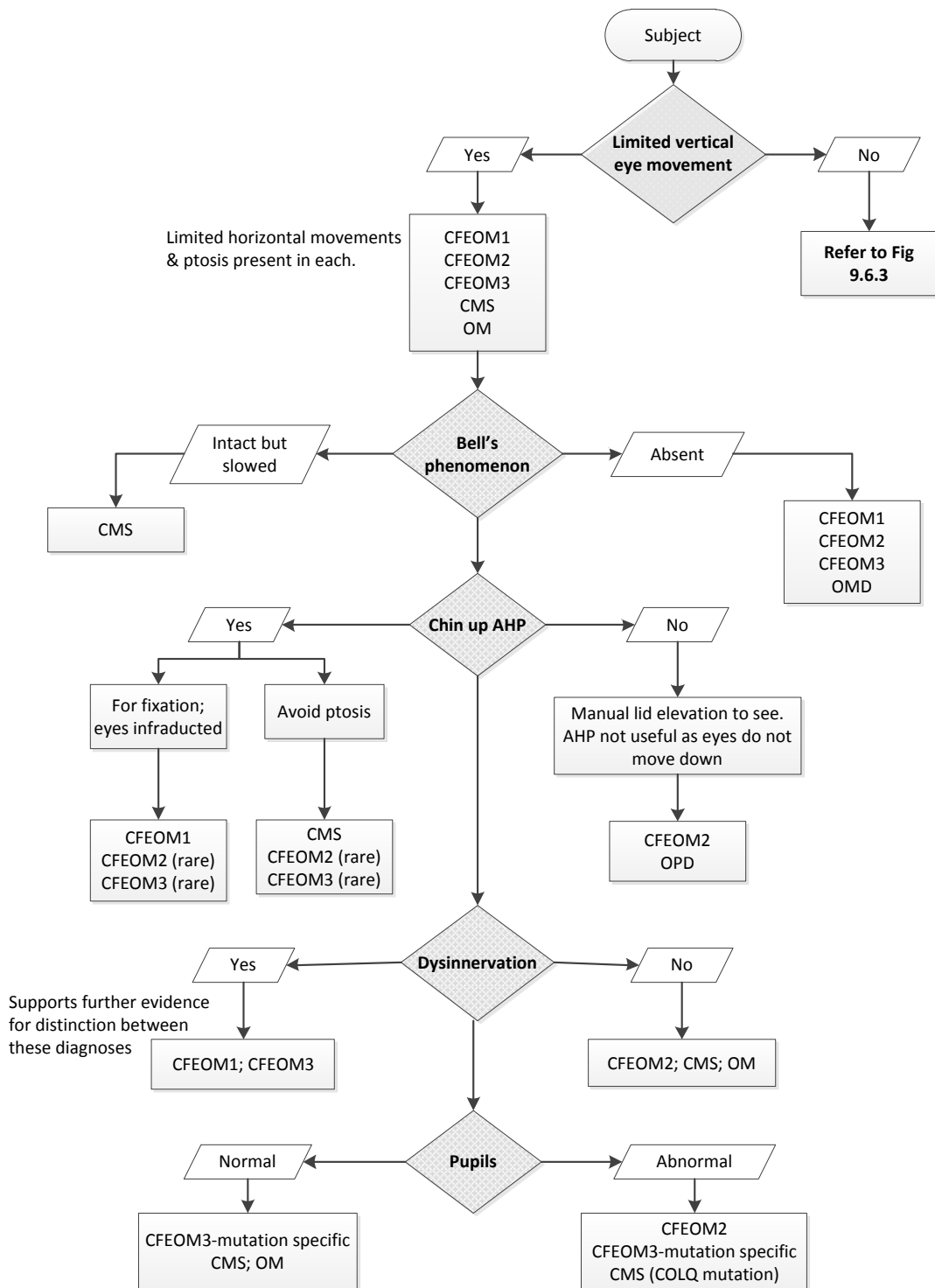
Utilization of different orthoptic features can be used to create a multitude of diagnostic algorithms. Provided here is one example that has proved effective. This algorithm that starts with vertical gaze. **Figure 9.6.2** illustrates the flow pathway for a subject with limited vertical eye movement. **Figure 9.6.3** is the flow pathway for a subject with full vertical eye movement. **Table 9.6.4** is another example. This one assesses degree of ocular motility in subjects with no manifest deviation in primary position. What should be apparent in these examples is that no one pathway consistently leads to a single diagnosis. A similar algorithm in subjects with these characteristics was described in our 'straight eyes' publication.⁴⁵ The article proposed 3 key steps to distinguish the overlapping phenotype of having straight eyes in primary position. Step 1 started with a detailed history focusing on age at onset of symptoms and signs. Step 2 involved a careful assessment of ocular motility that also included looking for evidence of dysinnervation. Step 3 requires looking for additional non-ophthalmological features. In each case, the subject had a different diagnosis arising from a different gene mutation. This is significant as it highlights the limitations of relying on diagnostic criteria arising solely from the orthoptic evaluation and the need to incorporate additional investigations.

This then opens up discussions related to the central research question and confirming the hypotheses. These is addressed in the following section - 9.7

Table 9.6.3 Additional ocular features

Feature	Remarks															
Lid position	Ptosis is a feature common to most categories but with differing mechanisms accounting for it.															
	<table border="1"> <thead> <tr> <th>Category</th> <th>Mechanism</th> <th>Feature</th> </tr> </thead> <tbody> <tr> <td>2</td> <td>Neurogenic</td> <td>Congenital/static</td> </tr> <tr> <td>3</td> <td>Pseudo when due to hypotropia or hypoglobus. True ptosis may occur secondary to mass effect (Neurofibroma)</td> <td>Acquired Progressive</td> </tr> <tr> <td>4</td> <td>Myopathic process</td> <td>Acquired, progressive</td> </tr> <tr> <td>5</td> <td>Defect of neuromuscular transmission</td> <td>Congenital/acquired; variable</td> </tr> </tbody> </table>	Category	Mechanism	Feature	2	Neurogenic	Congenital/static	3	Pseudo when due to hypotropia or hypoglobus. True ptosis may occur secondary to mass effect (Neurofibroma)	Acquired Progressive	4	Myopathic process	Acquired, progressive	5	Defect of neuromuscular transmission	Congenital/acquired; variable
	Category	Mechanism	Feature													
	2	Neurogenic	Congenital/static													
	3	Pseudo when due to hypotropia or hypoglobus. True ptosis may occur secondary to mass effect (Neurofibroma)	Acquired Progressive													
	4	Myopathic process	Acquired, progressive													
5	Defect of neuromuscular transmission	Congenital/acquired; variable														
Category 1 and 6 - True ptosis not expected																
Lids – blinking	Category 2 <ul style="list-style-type: none"> • blink asymmetry evident in HGPPS • slowed lid closure on side of cranial nerve 7 weakness (MBS, HCFP-<i>HOXB1</i>) 															
Pupils	Category 2: Abnormal reactivity and shape in some forms in Category 2 <ul style="list-style-type: none"> • CFEOM2 due to mutation in <i>PHOX2A</i> • CFEOM3 due to specific mutations in <i>TUBB3</i> Category 5 – slowed pupillary responses in variants due to end-plate AChE deficiency (mutation in <i>COLQ</i>)															
Nystagmus	Category 1 – common, may include ocular intrusions Category 2 – specific to HGPPS Category 3 – pulsatile exophthalmos – not true nystagmus; rare feature															
Anomalous head postures	Category 1 – evident as head thrusting to compensate for defective eye movements Category 2 – Common. Serves several purposes which all may be present in the same subject. <ul style="list-style-type: none"> • To achieve ocular alignment permitting fusion • To achieve monocular fixation in an eye with severely restricted movement • To clear visual axis to avoid ptosis Category 3 – Common in setting of ptosis due to lid mass. Adopted initially to avoid ptosis to permit bifoveal fixation. Tends to be abandoned in time due to progressive lid tumor size completely covering the eye. Category 4 and 5 – common <ul style="list-style-type: none"> • Head movement to compensate for defective eye movements • To clear visual axes in setting of bilateral ptosis 															

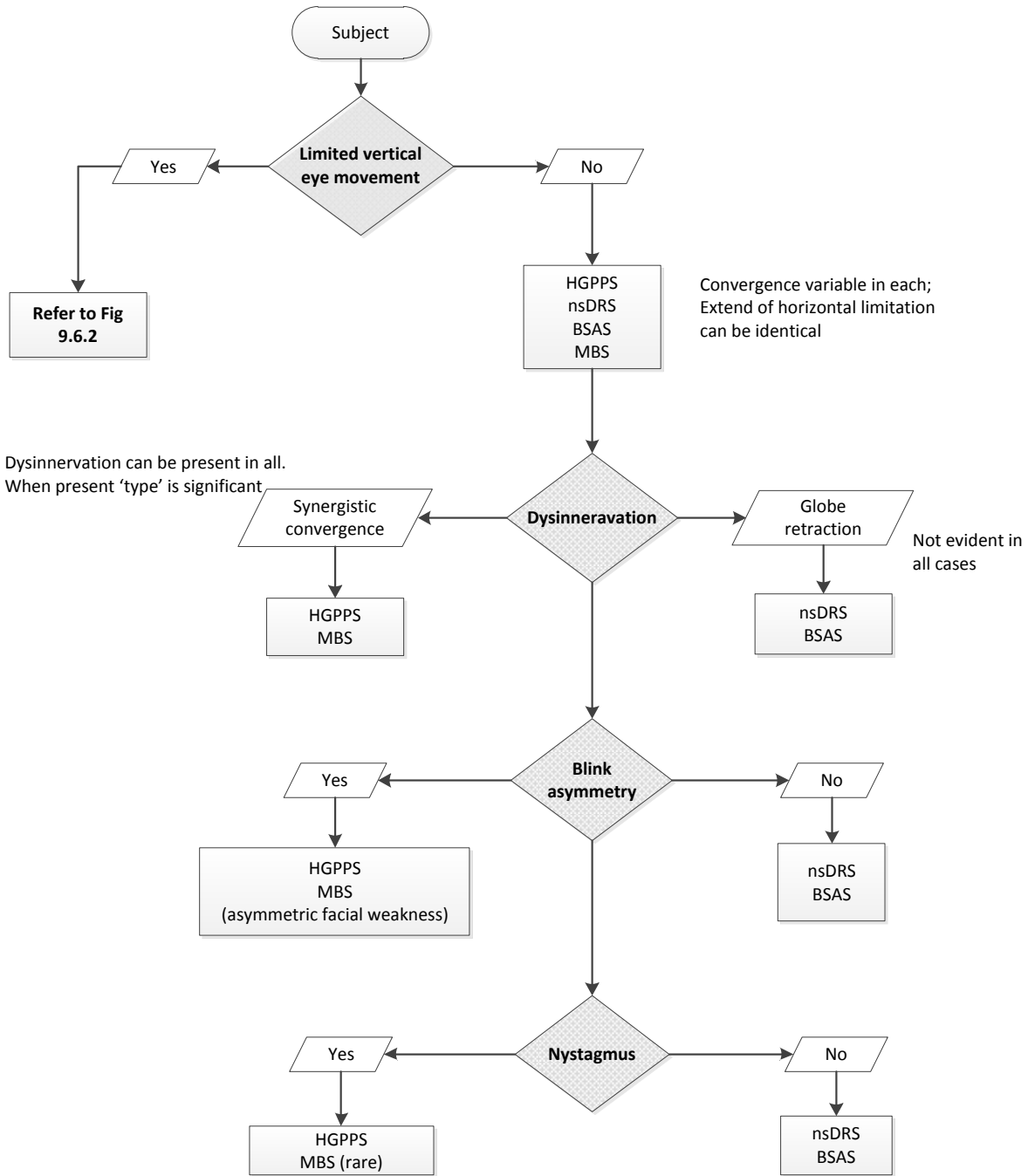
Figure 9.6.2 Flow chart for select diagnoses in category 2,4, & 5. Part A – limited vertical eye movement



Flowchart based on predominantly of ocular motility features

CFEOM = congenital fibrosis of the extraocular muscles; CMS = congenital myasthenic syndrome; OM = ocular myopathy; AHP = anomalous head posture

Figure 9.6.3 Flow chart for select diagnoses in category 2,4, & 5. Part B - full vertical eye movement



HGPPS = Horizontal gaze palsy with progressive scoliosis; nsDRS = non-syndromic Duane retraction syndrome; BSAS = Bosley-Salih-Alorainy syndrome; MBS = Moebius syndrome

Table. 9.6.4 Evaluation of Ductions in patients with 'straight eyes'

I. Bilateral Horizontal limitation		
Complete <ul style="list-style-type: none"> ● HGPPS ● BSAS ● MBS ● OPMD (late) ● CPEO (late) 	Partial <ul style="list-style-type: none"> ● HGPPS ● BSAS ● MBS ● CFEOM3 ● OPMD (early) ● CPEO (early) ● CMS 	Associated dysinnervation patterns <ul style="list-style-type: none"> ● HGPPS – SC ● BSAS – SC, GR ● MBS – SC ● CFEOM3 – SC, GR (rare)
II. Isolated Vertical limitation		
<ul style="list-style-type: none"> ● None 		
III. Vertical and Horizontal limitation		
<ul style="list-style-type: none"> ● CFEOM3 (rare) ● CMS ● OPMD 		
IV. Full excursion (H&V) – abnormal eye movement sub-systems		
<ul style="list-style-type: none"> ● AT ● ATLD ● JBS 		

HGPPS = Horizontal Gaze Palsy with Progressive Scoliosis; BSAS = Bosley-Salih-Alorainy Syndrome; MBS = Moebius syndrome; OPMD = Oculopharyngeal Muscular Dystrophy; CPEO = Chronic Progressive External Ophthalmoplegia; CMS = Congenital Myasthenic Syndrome; SC = synergistic convergence; GR = globe retraction on attempted adduction; CFEOM2 = Congenital Fibrosis of the Extraocular Muscles Type 2; AT = Ataxia Telangiectasia; ATLD = Ataxia Telangiectasia-Like Disorder; JBS = Joubert syndrome

Section 9.7 – Addressing research question and bi-directional algorithm

Outcome: Partially met, due to the complexity of the cases and constantly evolving knowledge.

The design and testing of a bi-directional algorithm was central to this dissertation. It was to be based on orthoptic features that could identify phenotypes that would effectively predict genotypes, and conversely when a genotype was known, predict the expectant phenotype.

Our approach was as follows:

Step 1: Define ocular motility phenotypes

Step 2: Link to an already recognized diagnosis

Step 3: Enhance accuracy of diagnosis with careful observation of other associated features

Step 4: Obtain a genetic confirmation in as many cases as possible

After examining 845 subjects with 40 identified diagnoses (several subjects without a definitive diagnosis) and 25 different genes, the following conclusions have been made:

Regarding Hypothesis 1: There is phenotypic difference between genetically distinct conditions (Algorithm direction 1 – Phenotype predicts Genotype)

Although our reports have identified many differences between genetically distinct conditions, there is too much overlap both in the orthoptic features as well as the overall phenotype to reliability and consistently confirm a genotype.

Regarding Hypothesis 2: There is phenotypic consistency between genetically identical conditions (Algorithm direction 2 – Genotype predicts Phenotype)

This was initially promising. However most diagnoses did not have enough subjects genotyped. Of the 609 subjects with a DNA sample obtained, the genetic analysis is still pending in 62% (378/609). These results would likely add valuable information to this issue.

This warrants some discussion involving the category with the largest number of subjects – category 2 CCDDs. We felt this group had the greatest chance of establishing a feasible bi-directional algorithm. However, the following reasons are presented as to why this did not come to fruition.

A new field – limited data:

The majority of our publications described novel findings in newly elucidated genetic conditions or provided the first phenotypic report of previously genetically defined subjects. This meant very few of our publications were actually able to add to a pool of previously reported cases. It suggests there is still not enough information available in which to base a reliable algorithm. At present new conditions are still arising that may further hinder this effort and the literature is still lacking an adequate number of detailed phenotypic descriptions in genotype subjects.

Phenotypic overlap between distinct disorders:

Table 9.7.1 provides a few examples of the overlap we identified between different CCDDs. The appropriate candidate publication is given that describes this in more detail.

Table 9.7.1 Examples of phenotypic overlap between distinct CCDDs.

CCDD	Comments	Ref
Bilateral horizontal gaze dysfunction	HOXA1 syndrome; HGPPS- <i>ROBO3</i> ; MBS	
Abnormal convergence	nsDRS – uni or bilateral; synDRS; MBS Note: convergence may also be normal in each	
Synergistic divergence	Isolated SD; DRS- <i>COL25A1</i>	37, 63
Synergistic convergence	HGPPS- <i>ROBO3</i> ; MBS	6, 40, 61
Nystagmus	HGPPS- <i>ROBO3</i> ; MBS	6, 40
Globe retraction on attempted adduction	nsDRS; synDRS Note: absence in setting of a marked ipsilateral abduction deficit does not rule out anomalous innervation between horizontal recti HGPPS- <i>ROBO3</i> – 1 case (not reported)	5, 15
Autism	BSAS- <i>HOXA1</i> , synDRS- <i>PTPRN2</i> ; MBS	14, 28, 40
Neck/Spine anomaly	HGPPS, synDRS- <i>FGF13</i> (Wildervanck), synDRS- <i>RNF35/PPARA</i>	6, 29, 33
Hearing deficit/Deafness	BSAS- <i>HOXA1</i> , synDRS- <i>PTPRN2</i> , synDRS- <i>FGF13</i> , synDRS- <i>DMD</i> , DRS+SD (pt#2), MBS, HCFP3- <i>HOXB1</i>	14, 28, 29, 35, 37, 38, 40
Ptosis	CFEOM, BSAS- <i>HOXA1</i> (1pt), synDRS- <i>XIRP2</i>	15, 32
Facial palsy	HCFP- <i>HOXB1</i> , CFEOM- <i>TUBB3</i> , CFEOM – mutation negative for known CCDD genes (not reported)	38, 39

Ref = candidate reference; ns = non-syndromic; syn = syndromic

Phenotypic variability between patients with the same genetic disorder:

A key learning point was the discovery that phenotypic differences can exist within the same genetic disorder and even within the same family of affected family members.

Some noteworthy examples include:

HGPPS-*ROBO3*

- Scoliosis in subjects were generally severe⁶ however mild forms were confirmed well.^{61, 62}
- Degree of horizontal gaze limitation was not always complete and could be asymmetrical.^{6, 61}

- Presence and size of primary position strabismus could vary even between affected siblings.⁶

HOXA1 spectrum

- More severe phenotype in ABDS¹⁵
- Reported case with full eye movements⁵
- Reported case of normal hearing^{5, 15}
- Several individuals examined (not reported) had other co-existing genetic disorders – Retinitis pigmentosa or albinism, thus further blurring the borders of the HOXA1 spectrum.

CFEOM2-PHOX2A

- Difference in resting globe position⁴⁴

CFEOM3-KIF21A family

- Five family members with CFEOM due to mutation in *KIF21A*. Not all individuals met criteria for CFEOM1, therefore the entire family is labelled as CFEOM3

Despite rejecting the hypotheses and falling short of constructing a bi-directional algorithm I feel the work in this dissertation has significantly moved this concept forward by populating the literature with detailed descriptions of orthoptic features for numerous conditions. The resultant publications are also felt to have significantly impacted the field of congenital and/or genetic disorders of ocular motility and strabismus through adequately addressing all intended objectives.

Published evidence has minimized the gap between clinician (general and expert) and researcher. Within our research teams there is now a greater understanding and appreciation for the need to work more collaboratively to ensure investigations are appropriate, efficient and results are additive to completing the picture of any individual.

Summary of candidate first author publications for this section:

The following publications provide evidence for the statements in the previous section. These publications generally discuss the significance of certain orthoptic features in making a specific diagnosis both positively as well as highlighting the limitations. They also highlight the role of the orthoptic evaluation within a larger investigational paradigm that is required for these complex disorders. Areas frequently included involve neuro-ophthalmology, pediatric ophthalmology, radiology and genetics. The take away point here is that there is no clear advantage of beginning with one investigational starting point over another – only that making a definitive diagnosis, or recognizing a novel condition (or novel phenotype in a previously known condition) requires input from a combination of investigators. However, the candidate believes there is sufficient evidence to suggest starting with orthoptics moves the team forward significantly.

Oystreck, D. T., Engle, E. C., & Bosley, T. M. (2011). Recent progress in understanding congenital cranial dysinnervation disorders. *J Neuroophthalmol*, 31(1), 69-77.²⁶

[doi:10.1097/WNO.0b013e31820d0756](https://doi.org/10.1097/WNO.0b013e31820d0756)

BACKGROUND: In 2002, the new term congenital cranial dysinnervation disorder (CCDD) was proposed as a substitute for the traditional concept of congenital fibrosis of the extraocular muscles (CFEOM) based on mounting genetic, neuropathologic, and imaging evidence, suggesting that many, if not all, of these disorders result from a primary neurologic maldevelopment rather than from a muscle abnormality. This report provides an update 8 years after that original report.

EVIDENCE ACQUISITION: Review of pertinent articles published from January 2003 until June 2010 describing CCDD variants identified under PubMed MeSH terms congenital fibrosis of the extraocular muscles, congenital cranial dysinnervation disorders, individual phenotypes included under the term CCDD, and congenital ocular motility disorders.

RESULTS: At present, a total of 7 disease genes and 10 phenotypes fall under the CCDD umbrella. A number of additional loci and phenotypes still await gene elucidation, with the anticipation that more syndromes and genes will be identified in the future. Identification of genes and their function, along with advances in neuroimaging, have expanded our understanding of the mechanisms underlying several anomalous eye movement patterns.

CONCLUSIONS: Current evidence still supports the concept that the CCDDs are primarily due to neurogenic disturbances of brainstem or cranial nerve development. Several CCDDs are now known to have nonophthalmologic associations involving neurologic, neuroanatomic, cerebrovascular, cardiovascular, and skeletal abnormalities.

State-of-the-Art Review

Section Editors: Grant T. Liu, MD
Randy H. Kardon, MD, PhD**Recent Progress in Understanding Congenital Cranial Dysinnervation Disorders**

Darren T. Oystreck, OC(C) MMedSci, Elizabeth C. Engle, MD, Thomas M. Bosley, MD

Background: In 2002, the new term congenital cranial dysinnervation disorder (CCDD) was proposed as a substitute for the traditional concept of congenital fibrosis of the extraocular muscles (CFEOM) based on mounting genetic, neuropathologic, and imaging evidence, suggesting that many, if not all, of these disorders result from a primary neurologic maldevelopment rather than from a muscle abnormality. This report provides an update 8 years after that original report.

Evidence Acquisition: Review of pertinent articles published from January 2003 until June 2010 describing CCDD variants identified under PubMed MeSH terms congenital fibrosis of the extraocular muscles, congenital cranial dysinnervation disorders, individual phenotypes included under the term CCDD, and congenital ocular motility disorders.

Results: At present, a total of 7 disease genes and 10 phenotypes fall under the CCDD umbrella. A number of additional loci and phenotypes still await gene elucidation, with the anticipation that more syndromes and genes will be identified in the future. Identification of genes and their function, along with advances in neuroimaging, have expanded our understanding of the mechanisms underlying several anomalous eye movement patterns.

Conclusions: Current evidence still supports the concept that the CCDDs are primarily due to neurogenic disturbances of brainstem or cranial nerve development. Several CCDDs are now known to have nonophthalmologic associations involving neurologic, neuroanatomic, cerebrovascular, cardiovascular, and skeletal abnormalities.

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CONGENITAL FIBROSIS OF THE EXTRAOCULAR MUSCLES TO CONGENITAL CRANIAL DYSINNERVATION DISORDERS

During the last half of the 20th century, pediatric ophthalmologists recognized that certain children were born with congenital ocular motility abnormalities associated with fibrotic extraocular muscles. This observation led to the concept of "congenital fibrosis of the extraocular muscles" (CFEOM) because of the assumption that the primary problem was a congenital abnormality of muscle development (1,2). The most common of these disorders is Duane retraction syndrome (DRS), although a number of other sporadic and familial congenital ocular motility syndromes were also recognized.

As time passed, evidence accumulated that a number of these syndromes had a neurogenic etiology. Therefore, in 2002, an alternative concept of "congenital cranial dysinnervation disorders" (CCDDs) was proposed (3), shifting the focus away from muscle development and toward a likely neurogenic etiology of congenital abnormalities of ocular muscle and facial innervation. Developments in the past 8 years have supported this concept, since all identified genes responsible for CCDDs affect brainstem and/or cranial nerve development. The purpose of this review is to update the original report proposing the CCDD concept (3) because much has happened over the past 8 years. Many of the syndromes described here are uncommon, and a number have autosomal recessive etiologies that make their occurrence more frequent in specific areas of the world. Yet with increased international travel, a patient with any one of these disorders might walk into the office of an ophthalmologist or neurologist anywhere in the world. Therefore, clinicians should be familiar with this heterogeneous group of syndromes. Not included here (or within

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Oystreck, D. T., Salih, M. A., & Bosley, T. M. (2011). When straight eyes won't move: phenotypic overlap of genetically distinct ocular motility disturbances. *Can J Ophthalmol*, 46(6), 477-480.⁴⁵
[doi:10.1016/j.jcjo.2011.09.009](https://doi.org/10.1016/j.jcjo.2011.09.009)

OBJECTIVE: To describe the phenotypic similarity in a series of patients with genetically distinct ocular motility disturbances involving straight eyes and different ocular motor pathology.

DESIGN: Retrospective case series. **PARTICIPANTS:** Clinical and genetic evaluation of 5 patients with straight eyes in the primary position and abnormalities of ocular motility.

RESULTS: Patients with oculopharyngeal muscular dystrophy, congenital myasthenic syndrome, congenital fibrosis of the extraocular muscles type 3, Bosley-Salih-Alorainy syndrome, and horizontal gaze palsy and progressive scoliosis all had straight eyes in primary position and restricted ocular motility. History, ocular motility patterns, systemic features of individual syndromes, and genetic screening were important diagnostically.

CONCLUSIONS: A number of congenital and genetic ocular motility syndromes may result in substantial phenotypic overlap, particularly when eyes are straight in primary position and nonophthalmologic features are not apparent or not observed. The range of disorders that may fall into this category is discussed.

When straight eyes won't move: phenotypic overlap of genetically distinct ocular motility disturbances

Darren T. Oystreck, MMedSci, OC(C)*[‡], Mustafa A. Salih, MD, DrMedSci[‡],
Thomas M. Bosley, MD*

ABSTRACT • RÉSUMÉ

Objective: To describe the phenotypic similarity in a series of patients with genetically distinct ocular motility disturbances involving straight eyes and different ocular motor pathology.

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Conclusions: A number of congenital and genetic ocular motility syndromes may result in substantial phenotypic overlap, particularly when eyes are straight in primary position and nonophthalmologic features are not apparent or not observed. The range of disorders that may fall into this category is discussed.

Objet : Description de la similarité phénotypique chez une série de patients ayant des troubles génétiques distincts de motilité oculaire impliquant les yeux en ligne droite et diverses pathologies motrices oculaires.

Nature : Rétrospective d'une série de cas.

Participants : Évaluation clinique et génétique de cinq patients avec les yeux droits en position primaire et des anomalies de motilité oculaire.

Résultats : Les patients ayant une dystrophie musculaire oculopharyngée, un syndrome myasthénique congénital, une fibrose congénitale des muscles extraoculaires type 3, le syndrome Bosley-Salih-Alorainy et une paralysie du regard horizontal avec scoliose évolutive avaient tous les yeux droits en position primaire et une motilité oculaire restreinte. L'historique, les types de motilité oculaire, les caractéristiques systémiques des syndromes individuels et le dépistage génétique sont importants pour le diagnostic.

Conclusions : Un certain nombre de syndromes congénitaux et génétiques de motilité oculaire peuvent résulter d'un chevauchement phénotypique substantiel, notamment quand les yeux sont droits en position primaire et que les caractéristiques non ophtalmologiques ne sont pas apparentes ou pas observées. La gamme des désordres qui peuvent tomber dans cette catégorie fait l'objet de discussions.

At times, patients may have straight eyes in primary gaze despite the presence of marked restriction of ocular motility. Perhaps the most common of these situations is Duane retraction syndrome, in which eyes are commonly straight but abduction and/or adduction is limited. However, there are other, more unusual, congenital and genetic disorders that may present as straight eyes that do not move normally, putting the physician on less familiar ground. Diagnostic groups within this category include myopathies affecting ocular motility,¹ congenital defects in the neuromuscular junction,² and congenital cranial dysinnervation disorders.^{3,4} We present 5 patients illustrating the potential phenotypic overlap in these categories because some familiarity with these diagnoses is helpful in sorting through the diagnostic possibilities.

Case reports

Five patients presented to the hospitals of King Saud University in Riyadh, Saudi Arabia, with the complaint of ptosis or restricted ocular motility. All had comprehensive

clinical, neuro-ophthalmologic, and ophthalmologic examinations, and genetic evaluation identified the mutated gene in 4. These patients signed informed consent for genetic evaluation under a project approved by the institutional review board.

Patient 1. A 47-year-old male presented with progressive ptosis and gradual restriction of ocular movements over many years. His major complaints were the need to hold a lid up to see while driving and intermittent difficulties with swallowing liquids. Ocular motility examination revealed almost complete bilateral ophthalmoparesis and ptosis covering the pupillary axis OU (Fig. 1, A1–A5). He had frontal balding, substantial weakness and wasting of facial muscles, moderate proximal > distal muscle weakness, and nasal speech. His 30-year-old son complained of some decreased muscle strength recently, and his exam revealed full eye movements, no ptosis, and modest weakness of the

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Oystreck, D. T., & Lyons, C. J. (2012). Comitant strabismus: Perspectives, present and future. *Saudi J Ophthalmol*, 26(3), 265-270.⁷³
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Comitant strabismus is a common condition affecting infants, children and adults. Its impact on the affected patient may be severe resulting in visual loss, lack of binocularity, diplopia, social stigma and multiple corrective surgeries within the affected individual's lifespan. It is therefore important that this prevalent disorder should be better understood. We review the current understanding of the demographics and what is known of the etiology, risk factors and genetics of strabismus. We stress the importance of careful clinical assessment in classifying strabismus, and the common pitfalls in the measurement and pre-operative sensory work-up of the strabismic patient. The fact strabismus is comitant does not indicate it is benign: acute onset of comitant esotropia may be a presenting sign of pontine or cerebellar tumor. Lastly, we review the impact of genetics on our understanding of strabismus. While the causes of many types of congenital incomitant strabismus have been elucidated through careful observation and genetic screening, the genetics of comitant strabismus are more complex and multifactorial. Only through careful study and recruitment of large groups of affected individuals and families can we start to answer the question: why is this group of patients pre-disposed to develop strabismus. Doing so will help identify patients at risk, to spare them from the significant morbidity associated with this common disorder.

Comitant strabismus: Perspectives, present and future

Darren T. Oystreck, MMedSci, OC(C)^{a,b,*}; Christopher J. Lyons, MB, FRCS, FRCSC^c

Abstract

Comitant strabismus is a common condition affecting infants, children and adults. Its impact on the affected patient may be severe resulting in visual loss, lack of binocularity, diplopia, social stigma and multiple corrective surgeries within the affected individual's lifespan. It is therefore important that this prevalent disorder should be better understood.

We review the current understanding of the demographics and what is known of the etiology, risk factors and genetics of strabismus. We stress the importance of careful clinical assessment in classifying strabismus, and the common pitfalls in the measurement and pre-operative sensory work-up of the strabismic patient. The fact strabismus is comitant does not indicate it is benign: acute onset of comitant esotropia may be a presenting sign of pontine or cerebellar tumor.

Lastly, we review the impact of genetics on our understanding of strabismus. While the causes of many types of congenital incomitant strabismus have been elucidated through careful observation and genetic screening, the genetics of comitant strabismus are more complex and multifactorial. Only through careful study and recruitment of large groups of affected individuals and families can we start to answer the question: why is this group of patients pre-disposed to develop strabismus. Doing so will help identify patients at risk, to spare them from the significant morbidity associated with this common disorder.

Keywords: Strabismus, Comitant strabismus, Genetics, Management, Demographics

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Defining comitant strabismus

Strabismus is best defined as a condition in which only one of the 2 eyes is directed at the object of interest. If the angle of ocular misalignment is equal in all fields of gaze, remains the same regardless of which eye is used for fixation, and if the eye movements are all full, the strabismus is described as comitant.¹ Conversely, incomitant strabismus generally results from limitation of eye movement associated with paralytic or mechanical etiologies. Comitant strabismus develops most commonly in early childhood but can do so at any age particularly in the presence of monocular visual loss.

Demographics and prevalence

Population studies, mostly from Western European and North American populations suggest the mean prevalence of strabismus is between 2% and 5% with esodeviations outnumbering exodeviations in these populations.² However, data from some Asian studies report slightly lower prevalence^{3–5} and exodeviations being more common than esodeviations.^{6,7}

Recently some interesting trends have come to light regarding the number of new cases presenting for management as well as their diagnosis. Several studies from different countries have reported a decrease in the number of new

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Concepts regarding certain forms of congenital eye movement disorders have recently changed, due in large part to new genetic evidence identifying causative genes and their role in the development of extraocular muscle innervation. This group is now referred to as the Congenital Cranial Dysinnervation Disorders (CCDDs). Careful assessment of phenotypic features that include both ophthalmological and non-ophthalmological features in genetically defined individuals has led to the development of a more robust classification system. Correlating phenotypes with new genetically defined syndromes has improved the ability of the clinician/researcher to better determine a definitive diagnosis in patients with complex ocular motility disorders. Nevertheless, more work is still required.

The John Pratt-Johnson Annual Lecture

Congenital and Genetic Ocular Motility Disorders: Update and Considerations

Darren Oystreck, M.Med.Sci., O.C.(C.), C.O.M.T.^{1,3}

ABSTRACT

Concepts regarding certain forms of congenital eye movement disorders have recently changed, due in large part to new genetic evidence identifying causative genes and their role in the development of extracellular muscle innervation. This group is now referred to as the Congenital Cranial Dysinnervation Disorders (CCDDs). Careful assessment of phenotypic features that include both ophthalmological and non-ophthalmological features in genetically defined individuals has led to the development of a more robust classification system. Correlating phenotypes with new genetically defined syndromes has improved the ability of the clinician/researcher to better determine a definitive diagnosis in patients with complex ocular motility disorders. Nevertheless, more work is still required.

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INTRODUCTION

I am honored to be given the opportunity to present this year's Pratt-Johnson Lecture. I first met Dr. Pratt-Johnson when I was an ophthalmic student in the newly re-opened Vancouver Ophthalmic Training program under Geraldine Tillson. Geraldine, of course, was the other member of a dynamic duo that demonstrated the ideal symbiotic relationship

Oystreck, D. T. (2018). Ophthalmoplegia and Congenital Cranial Dysinnervation Disorders. *Journal of Binocular Vision and Ocular Motility*, 68(1), 31-33.⁷⁵
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Some forms of ophthalmoplegia are congenital and fall into the category of Congenital Cranial Dysinnervation Disorders (CCDDs). These disorders arise from a primary defect of cranial nucleus/nerve development or guidance. Many have substantial limitations of ocular motility with or without other associated features. The type and degree of ophthalmoplegia can be similar between CCDD subtypes as well as with non-congenital forms of ophthalmoplegia. Therefore diagnostic confirmation often requires neuro-imaging and/or genetic investigations. The clinician should consider this category in cases of ophthalmoplegia that are congenital and nonprogressive in nature.

Ophthalmoplegia and Congenital Cranial Dysinnervation Disorders

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ABSTRACT

Some forms of ophthalmoplegia are congenital and fall into the category of Congenital Cranial Dysinnervation Disorders (CCDDs). These disorders arise from a primary defect of cranial nucleus/nerve development or guidance. Many have substantial limitations of ocular motility with or without other associated features. The type and degree of ophthalmoplegia can be similar between CCDD subtypes as well as with non-congenital forms of ophthalmoplegia. Therefore diagnostic confirmation often requires neuro-imaging and/or genetic investigations. The clinician should consider this category in cases of ophthalmoplegia that are congenital and nonprogressive in nature.

KEYWORDS

Congenital cranial dysinnervation disorders; HOXA1 syndrome; Moebius syndrome; congenital fibrosis of the extraocular muscles; horizontal gaze palsy and progressive scoliosis; congenital ophthalmoplegia

Introduction

The congenital cranial dysinnervation disorders (CCDDs) represent a group of developmental disorders that commonly involve disturbances to ocular motility. Most cases are bilateral and severe enough to be considered ophthalmoplegia. To put this group into perspective it is said strabismus affects 4% of the general population. Congenitally incomitant forms account for roughly 5% of this group and includes those falling into the CCDD category.¹ So the number of individuals with this diagnosis is small but not trivial.

Many of the conditions encompassed within the CCDDs are not new; what is new is how we define them. Prior to 2003 many of these disorders were described as restrictive ophthalmoplegia that is both congenital and non-progressive in nature. Most were referred to as the Congenital Fibrosis syndromes which was a term used because of the appearance of fibrotic muscles noted at the time of strabismus surgery.^{2,3} However in 2003 following advances in genetics and neuro-imaging this entity was renamed the CCDDs,⁴ a term that better reflects that these disorders result from developmental errors in innervation of the lids, extraocular muscles, and/or facial muscles. The fibrotic muscles noted are now considered a secondary effect from a primary disturbance of innervation.

Table 1 illustrates the current CCDDs involving restricted ocular motility. The original term congenital fibrosis has been modified into congenital fibrosis of

the extraocular muscles (CFEOM) and is now considered a CCDD sub-group. CFEOM types predominantly affect vertical eye movements and arise from maldevelopment of cranial nerve III but may also involve other cranial nerves.⁵⁻⁷ The bold text in the table represents those CCDDs predominantly or exclusively affecting horizontal gaze and arise from maldevelopment or dis-connectivity of cranial nerve/nucleus VI. A sub-group (Moebius syndrome) also has concurrent involvement of cranial nerve VII. Many CCDDs now have a molecular diagnosis.⁸

Select examples of CCDD (ophthalmoplegia) phenotypes

Patients with a diagnosis of congenital fibrosis of the extraocular muscles (CFEOM) are most likely to present with congenital forms of ophthalmoplegia. What is interesting (and unfortunate) is that this group can have many clinical presentations. The following illustrates only four such examples seen by our strabismus team in the Department of Ophthalmology at King Saud University in Riyadh, Saudi Arabia.

Subject A was a 10 year old boy with a marked chin-up head posture. Both eyes could achieve elevation to midline but not above. Further attempts to elevate his eyes resulted in simultaneous convergence referred to as synergistic convergence and represents congenital misinnervation. He also had marked asymmetric ptosis with



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Table 9.7.2 provides additional evidence supporting this section. It includes a list of oral and poster presentations given on this topic.

Table 9.7.2. Candidate oral and poster presentations relevant to dissertation.

DARREN THOMAS OYSTRECK

PRESENTATIONS – National & International

2018 Jun	World Ophthalmology Congress, Barcelona, Spain <ul style="list-style-type: none"> • Invited symposium presenter - CCDDs • Congenital Fibrosis of the Extraocular Muscles
2017 Nov	American Academy of Ophthalmology meeting, New Orleans, LA AAO/AOC/AACO annual symposium – Ophthalmoplegia: When the Eyes Don't Move. <ul style="list-style-type: none"> • Ophthalmoplegia and Congenital Cranial Dysinnervation Disorders <p>American Association of Certified Orthoptists – Workshop</p> <ul style="list-style-type: none"> • ABCs of the CCDDs (Congenital Cranial Dysinnervation Disorders)
2016 Jun	XIIIth International Orthoptic Congress, Rotterdam, The Netherlands <ul style="list-style-type: none"> • Phenotype modification after genetic analysis – another look at Moebius syndrome
2015 Aug	International Society for Genetic Eye Diseases & Retinoblastoma, Halifax, Canada <ul style="list-style-type: none"> • Presenter "Congenital eye movement disorders: Improving phenotypic descriptions after genetic analysis - another look at Moebius syndrome"
2014 Nov	International Ophthalmological Conference, Kuwait <ul style="list-style-type: none"> • Invited speaker • Concomitant strabismus – thoughts and approaches, past present and future
2014 Jun	Canadian Ophthalmological Society meeting, Halifax, Canada <ul style="list-style-type: none"> • The John Pratt-Johnson lecture: Congenital and genetic ocular motility disorders – concepts for the development of a clinical algorithm
2014 May	American Association of Certified Orthoptists Easter Regional Meeting, Boston, USA. <ul style="list-style-type: none"> • Invited speaker "Congenital Ocular Motility Disorders – An Introduction to the CCDDs" • Presenter - Complex Motility Workshop
2013 Mar	Combined meeting of the 30 th King Khaled Eye Specialist Hospital & the 25 th Scientific session of the Saudi Ophthalmological Society, Riyadh, Saudi Arabia <ul style="list-style-type: none"> • Presenter "Abnormal head postures"

Chapter 10: Conclusions

Synopsis:

There are many disorders involving dysfunction of ocular motility and alignment with most resulting in complex patterns of strabismus. Some of these are congenital and suspected of having underlying genetic causes. Recent advances in investigational techniques have provided more information about the underlying mechanisms accounting for these conditions. This has however resulted in an expanding knowledge gap for the front line clinician.

The candidate had the unique opportunity to study a large heterogeneous group of individuals with these disorders at a time when technology advances were just beginning (e.g. genetics and radiology) to conduct this work within environments affording significant resources to actively investigate and define complete clinical and genetic features of these conditions.

As a result the material contained in this dissertation could be considered one of the largest collection of subjects with congenital and genetic disorders of ocular motility and strabismus.

Through careful orthoptic assessments the clinical 'phenotype' pertaining to ocular movements and alignment was defined in 845 enrolled subjects with 40 different diagnoses. Genetic results would reveal these involved mutations in 25 different genes.

Attainment of this information was only possible through the candidate's involvement as a member of various research teams working within large institutional research projects. The magnitude of this project would have been substantially less if designed as a prospective assessment of patients in an orthoptic clinic. Subject population and access to resources would have been major limiting factors.

Additionally, integration into large research teams permitted the acquisition of resources to conduct detailed medical investigations by several specialties on a large population of these subjects.

My main role as a member of these teams serves as the basis of this dissertation. That is to evaluate the role of the orthoptic evaluation, and to determine if orthoptic features can be used to effectively predict the genotype in known genetic conditions or identify patterns suggestive of novel syndromes.

This was addressed through completing several research objectives. These are summarized as follows:

Objective 1 - Standardization of the orthoptic evaluation was achieved. Many of these disorders have complex motility patterns. At initiation of this work there was no standardized approach to the evaluation of subjects or to the consistency in the reporting of features in the literature.

Objective 2 - Identification and concise characterization of orthoptic features was completed in a large number of rare conditions. Again, this was possible because of the unique environment in the candidate worked. Duplication of a similar project would be extremely difficult, if not impossible, for most clinicians.

Objective 3 - Consolidation of the orthoptic features in a large number of genetically confirmed diagnoses was also achieved. Access to this number of genotyped subjects was a major accomplishment in the project. It was crucial when assessing genotype-phenotype correlations.

Objective 4 - Identification of new mechanisms or providing additional evidence of proposed mechanisms disrupting oculomotor function was achieved. This was done through combining results of molecular testing, with detailed orthoptic examinations and results of investigations

from other medical specialties. This 'perfect environment' permitted detailed descriptions for all encountered conditions, many of which were original descriptions. This also determined which gene mutations were pathogenic to the oculomotor system as not all were despite initial suspicions.

Objective 5 - Achievement of the preceding 4 objectives led to proposing a new classification scheme. Through this work it was demonstrated clinical features alone, and genetic results alone, are not beneficial to the clinician. Rather proposed is a scheme that combines a molecular diagnosis with documenting the effect on development and function of the oculomotor system. This permits conditions to be categorized based on the underlying pathomechanism. However, the initial categorization of subject begins with the identification of ocular motility patterns. The scheme outlined requires more development, however the 6 categories presented provide a reasonable meeting point between clinicians and researchers thus reducing the knowledge gap.

Objective 6 - During development of the classification scheme (objective 5) the candidate was able to provide a simplified clinical approach for the general ophthalmologist. This aids in classifying subject appropriately and again further reduces the knowledge gap.

Hypotheses:

Once objectives 1-6 were addressed the necessary information to accept or reject the hypothesis was available.

Hypothesis 1 states that there are phenotypic (orthoptic) differences between genetically distinct conditions.

Hypothesis 2 states that there will be phenotypic consistency between genetically identical conditions.

The analysis shows that Hypothesis 1 can be rejected. The orthoptic features in isolation can adequately categorize subjects (Classification scheme 1-6) however it cannot reliably predict the genotype. Prediction can be improved if additional medical information is added, e.g. radiology, neurology etc. However, more genotyped subjects are required to better define the most consistent features.

Hypothesis 2 must also be rejected. The reports contained within the dissertation suggest substantial variability between subjects, and even within family members with the same genetic diagnosis. This not only includes ocular motility disturbance but also for the associated conditions, e.g. deafness, spine/neck anomalies.

As a result a bi-directional algorithm is not feasible at this time.

Originality of research

The work within this dissertation can be considered original on many accounts.

First, performing orthoptic evaluations and reporting the outcomes on a large heterogeneous population of subjects with congenital and/or genetic disorder of motility and strabismus has never been done to this magnitude.

Second, integrating this information with results of other investigations resulted in numerous publications in high impact journals reporting novel genetic findings and new syndromes (HOXA1 syndrome, *TUBB3-E410K*, *HCFP-HOXB1*, synDRS variants), complete descriptions of rare disorders (*HGPPS-ROBO3*; *CFEOM-PHOX2A*; *OFNF*) or proposed new diagnostic criteria for complex developmental disorders (MBS). Noteworthy is the number of different journals in which the publications occurred. Inclusion of ocular motility features into this variety of domains is a testament to the novelty of these conditions and lack of reporting that currently exists in the literature.

Third, formally assessing the value of the orthoptic features in the elucidation of complex ocular motility disorders to this degree has not been done previously. Certainly not involving the number of conditions included here. This permitted the ability to construct a classification scheme based, in part, on ocular motility distinctions. It also creates the foundation on which to continue development a bi-directional algorithm where phenotype predicts genotype and genotype predicts genotype. This will require continued careful clinical observations and more genotyped individuals.

Contributions to existing knowledge

A total of 41% (349/845) of enrolled subjects were published in 47 different papers. Many were in high impact journals with a high number of citations. Several were within invited review articles. Further knowledge translation has occurred with pediatric ophthalmology and orthoptic colleagues through participation at national and international conferences via poster or oral presentations or within symposia. This has forged new collaborations and a network of clinicians in which these conditions are discussed. This work has also been acknowledged by invitations to write Review articles. All of this speaks to the uniqueness and importance of these findings in relationship to disruptions of development and function of the oculomotor system.

The publications provide the most detailed, and often an original description, for numerous complex disorders resulting in ocular dysmotility. Critical analysis of the orthoptic features was vital in defining differences and similarities between conditions. The publications also set a new bench mark for future publications to achieve when describing ocular motility features.

We demonstrated the importance of team approach to achieve high level research outcomes. This was represented by the large number of authors from multiple specialties that were included in publications elucidating an encountered condition.

Information arising from this work also been taken up by the public. It has been used by the HGPPS family support group that was initiated by the parents one of our Canadian subjects. The Moebius syndrome foundation (<https://moebiusyndrome.org>) has also used results from our MBS publication to inform the public about ocular involvement.

We have identified the need for medical investigation on some forms of CCDDs. These have been outlined in detail in the review articles.

Several novel observations were made. Examples include intorsion with fixation and volitional Bell's phenomenon in MBS; asymmetric blinking in HGPPS; manual lid elevation in CFEOM2; and identification of several compensatory mechanism utilized by subjects. Novel approaches to clinical testing were also developed. One example was modifying the cover test in subjects with significant restriction of motility to detect small manifest strabismus.

Knowledge gained by candidate

I started this work as a clinician. I ended as a clinician-scientist. I have acquired a deep understanding about the requirements for conducting high level research and the keys to successful completion of projects. Several examples are provided. One is that I have learned the importance of interprofessional collaboration. I have witnessed how a strong team can convert a good project into one that is world class. From this I have gained a greater appreciation of the information that can be provided by other medical specialties, which in turn has provided me with a greater understanding about the conditions we encountered that goes well beyond the 'eyes'. I am also adept at understanding communication dynamics with collaborators, co-authors, clinicians, geneticists, and even research assistants. This work has also changed my perspective in the clinic. I now consciously evaluate everything that I do as part of my evaluation to ensure the right information is being collected with on-going attention to features that are most characteristics to each diagnosis.

I have also developed skills related to generating publications. I have mastered literature reviews, learned how to write manuscripts, learned how to submit manuscripts, and how to handle Reviewer comments (that was a tough one). In almost all publications I was the one who took consent for clinical photographs, took the photograph, then photoshopped and edited for publication.

General statements

Motivation for pursuing a PhD.

I consider myself a clinician with an expertise in the evaluation of ocular motility, alignment and binocular vision. Within my career I have been fortunate to have worked with expert clinicians and researchers in several institutions, both within North America and abroad. This has provided me with a unique opportunity to engage in research projects spanning over a decade. The outcome of these efforts has led to new discoveries that has had a profound impact in my field. The attraction to pursue a PhD with the Department of Ophthalmology at Stellenbosch University arose from two main reasons. First, it provided an opportunity to work with talented supervisor who could provide expert guidance in the development and completion of work at this level. Second, formally pursuing a PhD and completing a dissertation would permit (and require) high level reflection of this vast wealth of knowledge that had accumulated and was anticipated to continue to expand over the subsequent years. This explains the inclusion of several publications preceding my enrollment in 2011. Each was a stepping stone for a later publication with all eventually leading the requirements for a PhD.

Hurdles and design approach:

For this project to be as successful as it was, an unconventional approach was required.

A big part of this project was assessing genotype-phenotype correlations. In an ideal study, subjects would be enrolled. Testing would be administered (e.g. phenotyping and genotyping). Results would then be analysis and comments made.

In reality this could not be controlled. At times subjects would present for an assessment who were already genotyped. Conversely, it was not uncommon for the genetic results to be completed several years after phenotyping. At other times complete phenotyping could also take several months due to the number of additional investigations that were required as part of the larger institutional research project the subject was enrolled under. Keeping track of what was completed, what was still outstanding, all within a constantly growing subject population usually fell to me. This was not a trivial task.

Additionally, it was not uncommon to have multiple active studies. Note the accepted publication dates for different papers involving different topics. This was both an advantage and disadvantage. The advantage was that this level of activity afforded the opportunity to exam large numbers of individuals with numerous (and extremely rare) disorders. However this 'shot gun' approach made it difficult to focus on a single topic at any one time. The candidate spent most of his time collecting data for several studies and then writing appropriate publications for the appropriate journal. This also led to the next issue – duration to complete dissertation.

Dissertation took maximum length.

The candidate formally left the ophthalmic genetic program at King Saud University in July 2013 to accept a new position at Dalhousie University in Canada. It was through this program that the majority of work was conducted. However, because of the large volume of data that was collected during this time, manuscripts were still being designed and written for publication well after my departure. Deferring completion of the dissertation therefore permitted several more important publications to be included. It also permitted more genetic results to become known. Patience in this regard has proven significant for some of our syndromic DRS subjects, atypical MBS subjects, and most recently simple strabismus subjects.

Breadth of topic.

In hind sight the scope of this dissertation may have been too ambitious. Integration of a large number of publications including a vast array of conditions limits the ability to take a deep dive into any one condition or concept. However, after consideration I felt this dissertation in its present state most accurately reflects my research experience in this field.

It should be pointed out that the decision to study a vast number of diagnoses was not an active decision on my part, but rather arose out of necessity. Again, my work was conducted under several institutional research projects. The approach taken by our research teams was to examine and document as many subjects as possible as there was no certainty what subject or condition would provide the next break through following genetic investigations. As a result, the dissertation includes virtually all conditions we encountered, all genes with mutations identified, and very likely every orthoptic phenotype that is humanly possible to observe. When I analyzed all of the data collected it comprises 159GB containing 22 977 files in 2990 folders. The candidate is unaware of a collection of information of this magnitude anywhere on this subject.

Therefore this dissertation throws a 'net' around the topic of congenital/genetic ocular motility and strabismus disorders by including a wide spectrum of reports. This may be viewed as a limitation. However, after consultation with colleagues it was felt that publications providing clear clinical descriptions for these extremely rare and complex disorders is helpful. However, the addition of proposing a broad classification scheme and providing a simple clinical approach to the patient suspect of having one of these disorders was extremely beneficial, as it provides the clinician a foundation from which to begin. This was identified as something missing in the literature and helps bridge the gap between the general clinician and the new concepts that now exist in this field.

Future directions

Specific:

- I will continue my on-going collaboration with the Strabismus Research consortium and the Moebius Syndrome Research Consortium.
- Work will continue to expand a CCDD clinic at my home institution. We are now receiving patient referrals from across Canada and have recently established a relationship with the Engle lab in Boston to conduct the genetic investigations.
- I plan to continue enhancing the classification scheme with any new subjects we report and from new reports arising in the literature. The goal is to still achieve a bi-directional algorithm.

Potential future publications:

- On-going work with the ophthalmic genetic program in Saudi Arabia is presently on hiatus. However there are still several outstanding subject populations that require attention. One group are additional cases of syndromic DRS who are still awaiting genetic analysis. Another group are subjects with CFEOM in whom an initial screen of the currently known CCDD genes was negative. Another significant population involve our 204 subjects in category 6 with simple strabismus having at least two other affected family members. Detailed orthoptic and pediatric ophthalmology features for this entire group is complete. Status of the genetic evaluation is pending.

Planned knowledge translation manuscripts:

- Two topics identified by my general ophthalmology and orthoptic colleagues include a review article discussing the dysinnervational patterns we encountered, the other is a review of the compensatory mechanisms adopted by our subjects. We feel this needs to be addressed by describing these in more detail and providing an explanation of the significance each feature has in the domain of complex strabismus.
- Another ambitious endeavor is to expand the description of the classification scheme (objective 6) and publish each as a separate review article or textbook chapter.

Global aspirations:

- Unification of research efforts in this field. Much of this work has been done in collaboration with the Engle lab at Boston Children's hospital. Our successes have proven that international collaboration works, and from a resource perspective is much more efficient. Designation of a single major genetic lab capable of collecting samples from around the world and pool rare cases together to conduct more powerful genetic investigations should be sought. This is occurring now to some degree. The candidate was involved in standardizing the incoming clinical information to the Engle lab which is expanding its role as an international collaboration site.
- Development of an ocular motility gene chip. A lot of effort went into analyzing phenotype-genotype correlations in order to try and accurately confirm a diagnosis. As more subjects are genotyped certain genes/gene mutations are now identifying as the main cause of certain disorders. Development of gene chip that can screen for mutations in the most popular genes may become the most cost effective first step in the approach to these subjects.

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Appendix

Appendix Table A – Abbreviation list.

Abbreviation	Term
ABDS	Athabaskan Brainstem Dysgenesis Syndrome
ACh	Acetylcholine
AChR	Acetylcholine receptor
AD	Autosomal dominant
AET	Accommodative esotropia
AHP	Anomalous head posture
AOA2	Ataxia-Oculomotor Apraxia 2
AR	Autosomal recessive
ARSACS	Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay
AT	Ataxia telangiectasia
ATLD	Ataxia telangiectasia-like syndrome
BS	Brown syndrome
BSAS	Bosley-Salih-Alorainy syndrome
CADS	Carbonic anhydrase type II deficiency syndrome
Cat	Category
CCDD	Congenital Cranial Dysinnervation Disorders
CFEOM	Congenital Fibrosis of the Extraocular Muscles
CFZS	Carey-Fineman-Ziter syndrome
CHB	Children's Hospital Boston
Chrm	Chromosome
CGH	Comparative genomic hybridization
CMS	Congenital myasthenic syndrome
CN	Cranial nerve
CNS	Central nervous system
CNV	Copy number variation
CPEO	Chronic progressive external ophthalmoplegia
CT	Computed tomography
DEP	Double elevator palsy
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
DRS	Duane Retraction Syndrome
DURS2	Locus for bilateral DRS
ENT	Ear nose and throat
eom	Extra-ocular muscle
ESO	Esotropia, intermittent esotropia, non accommodative esotropia with full ocular movements
EXO	Exotropia, intermittent exotropia, with full ocular movements
FP	Facial palsy
GR	Globe retraction
GWAS	Genome-wide association study
HCFP	Hereditary congenital facial paresis
HGPPS	Horizontal Gaze Palsy and Progressive Scoliosis

Hyper	Hypertropia
Hypo	Hypotropia
HT	vertical strabismus with full ocular movements
ICA	Internal carotid artery
Inf ET	Infantile Esotropia
ISOD	Isolated sulfite oxidase deficiency
JBS	Joubert syndrome
KACST	King Abdulaziz City for Science and Technology
KKESH	King Khaled Eye Specialist Hospital
KFS	Klippel-Feil syndrome
KSS	Kearns-Sayre Syndrome
KSU	King Saud University
LP	Lipoid proteinosis
MBS	Moebius syndrome
MDC	Minimum diagnostic criteria
MG	Myasthenia gravis
MGJW	Marcus Gunn Jaw Winking
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NANOS	North American Neuro-ophthalmological Society
NEI	National Eye Institute
nsDRS	Non-syndromic Duane Retraction syndrome
NT SPD	diagnosis not specified
Obj	objective
OD	Right eye
OFNF	Orbitofacial neurofibromatosis
OMIM	Online Mendelian Inheritance in Man
OMPD	Oculopharyngeal muscular dystrophy
OPG	Optic pathway glioma
OS	Left eye
Plagio	Plagiocephaly (Craniosynostosis)
SC	Synergistic convergence
SD	Synergistic divergence
Strab assc	Strabismus associated
synDRS	Syndromic Duane Retraction syndrome
TEMTYS	Temtamy syndrome

Gene and gene mutation abbreviations not included. These are provided in Tables within Chapter 9

Publication list for Chapter 2

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Khan, A. O., & Oystreck, D. (2006). Clinical characteristics of bilateral Duane syndrome. *J AAPOS*, 10(3), 198-201.

Clinical Characteristics of Bilateral Duane Syndrome

Arif O. Khan MD, and Darren Oystreck OC(C)

Purpose: To describe the clinical characteristics of bilateral Duane syndrome. **Methods:** Retrospective medical record review (1982 to 2003) for patients with a diagnosis of Duane syndrome (examined by a pediatric ophthalmologist) who were bilaterally affected and had no prior ocular surgery. Data collected included type of Duane syndrome, gender, family history for strabismus, abnormal head position, versions, strabismus measurements, associated ocular and/or nonocular abnormalities, and amblyopia status. **Results:** Of 270 patients with the diagnosis of Duane syndrome, 37 (14%) were bilaterally affected. None had ocular surgery prior to referral. Twenty-two (59%) were male, 35 (95%) had the same Duane syndrome type in both eyes, 29 (78%) had strabismus in primary position, 9 (24%) had ocular and nonocular congenital abnormalities, 6 (16%) had amblyopia, and 8 (22%) had a recorded strabismus family history. **Conclusions:** Unlike unilateral Duane syndrome, bilateral Duane syndrome may be more common in males and associated with a higher prevalence of strabismus in primary gaze position. The prevalences of amblyopia, positive strabismus family history, and associated congenital abnormalities in this series of bilateral cases is similar to the reported prevalence. (*J AAPOS* 2006;10:198-201)

Duane retraction syndrome (DRS) is a congenital cranial dysinnervation disorder¹ that is characterized by paradoxical lateral rectus muscle innervation of the affected eye by axons meant to innervate the ipsilateral medial rectus muscle (with resultant varying degrees of cocontraction).² Huber's classification system groups cases into Type I (limited abduction with normal to near normal adduction), Type II (limited adduction with normal to near normal abduction), and Type III (limited abduction and adduction).² Prior reviews of DRS, comprising mostly unilateral cases, report a 1 to 4% proportion of all strabismus cases, typically sporadic occurrence (with 5 to 10% autosomal-dominant inheritance), associated congenital abnormalities (15 to 50%), and a preponderance of the following: females (60%), left eyes (72%), and Type I (78%).³⁻¹⁵ Most prior reviews provide little information regarding the characteristics of bilateral cases (representing 15 to 20% of cases).³⁻¹⁵ Bilateral DRS is the subject of this clinical report.

METHODS

After Institutional Review Board and Human Ethics Committee approval were obtained from the King Khaled Eye

Specialist Hospital (Riyadh, Saudi Arabia), medical records coded with the diagnosis of DRS from 1982 to 2003 were reviewed for the following criteria: (1) diagnosis of DRS by a pediatric ophthalmologist; (2) both eyes affected; and (3) no prior ophthalmic surgery when first referred. Thirty-seven medical records that met the criteria were identified. All were referred because of abnormal eye movements and/or abnormal head posturing. Data collected included type of DRS, gender, family history of strabismus, abnormal head position, versions, strabismus measurements, associated ocular and nonocular abnormalities, and amblyopia status.

RESULTS

Two hundred seventy medical records were identified as definitive DRS, and 37 of these (14%) were bilateral cases (Table 1). All 37 had documented signs of cocontraction. There were 22 (59%) males and 15 (41%) females. If one assumes that 60% of all DRS patients are female as quoted in prior general reviews,³ the likelihood of 22 (or more) patients being male in this case series is only 0.013 (ie, it is very unlikely). This probability is calculated from the binomial probability distribution for two exclusive outcomes, $(N!/(R!(N-R)!))p^R(1-p)^{N-R}$, where N = the number of occurrences (37 subjects), R = the number of times a particular outcome is observed (22 males), and p = the probability for the particular outcome to be observed for any single occurrence (0.40 prevalence of males in prior DRS reviews).

Most eyes were Type I, and most patients had the same type in both eyes: 25 (68%) were bilateral Type I, 1 (3%) was bilateral Type II, and 9 (24%) were bilateral Type III. Mixed types were seen in two patients (5%): Type III OD

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Fixation Preference for the Affected Eye in Patients With Unilateral Duane Syndrome

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Duane retraction syndrome is a congenital incomitant strabismus caused by dysinnervation of the medial and lateral rectus muscles.¹ Patients with unilateral Duane syndrome (80-90% of cases)¹ who exhibit a fixation preference tend to prefer the unaffected eye.¹⁻⁷ We describe 8 patients with unilateral Duane syndrome who prefer the affected eye. The most frequent associated ophthalmic finding was decreased vision in the unaffected eye from anisometropia and/or amblyopia. An additional associated finding was decompensated intermittent exotropia in 2 patients.

CASE SERIES

Institutional Review Board and Human Ethics Committee approval were obtained for a retrospective review of Duane syndrome. Of 270 records coded with diagnosis of Duane syndrome from patients referred to the King Khaled Eye Specialist Hospital (Riyadh, Saudi Arabia) from 1982 to 2003, 8 were given a diagnosis of unilateral Duane syndrome with clear fixation preference for the affected eye. All 8 patients had a diagnosis of Type I Duane syndrome, and none had other significant congenital or medical problems. All were referred because of abnormal eye position and/or abnormal head posturing. Data collected included reason for referral, age, gender, abnormal head position, ocular motility, strabismic measurements, amblyopia status, and cycloplegic refraction. Patient characteristics are summarized in Table 1.

DISCUSSION

At least 3 cases of fixation preference for the affected eye with unilateral amblyopia affecting the unaffected eye have been mentioned in the literature, but no details were provided regarding these cases.^{2,3} Previous reviews do not address preference for the affected eye in unilateral Duane syndrome.¹⁻⁷ Intuitively, one would expect to find decreased vision in the unaffected eye from common phe-

nomena, such as uncorrected anisometropia and/or amblyopia in such patients.

In this report, uncorrected anisometropia and/or amblyopia in the unaffected eye was indeed the most frequent characteristic associated with fixation preference for the affected eye (seven out of eight patients). For the patients with uncorrected anisometropia without amblyopia (patients 2, 5, and 7), the minimal spherical difference observed was + 1.25 (patient 5, the preferred eye being + 0.25 whereas the contralateral eye was -1.00). Presumably uncorrected blur in the contralateral eye led patients to prefer fixation with the affected eye. These patients may have had a greater degree of uncorrected anisometropia in early childhood; the results of previous cycloplegic refractions are not available. Patient 6 had amblyopia in his contralateral eye for reasons that are not clear from the medical record. An initial favorable response to patching treatment was recorded; however, the visual acuity of his contralateral eye returned to its prepatching level after the patient became noncompliant with treatment.

An additional observed association was that of decompensated intermittent exotropia. Patient 3 had a previously documented intermittent exotropia that decompensated into a constant exotropia, as did patient 2 (who also had anisometropia). In these 2 patients with exotropia and Type I Duane syndrome, the abduction limitation of the affected eye could have forced the patient to switch fixation to the affected eye by preventing manifestation of exotropia in that eye whereas the unaffected eye underwent exotropic drift. Both of these patients preferred a face turn contralateral to the eye affected with Duane syndrome. Such a face turn caused relative inward deviation of the affected eye, presumably allowing it better alignment with the contralateral exotropic eye.

In conclusion, in this case series of unilateral Duane syndrome with fixation preference for the affected eye, as would be expected the most common associated ophthalmic finding was decreased vision from uncorrected anisometropia and/or amblyopia in the unaffected eye. An additional observed association was that of decompensated intermittent exotropia. In this situation, the abduction limitation of the affected eye likely allowed it a fixation advantage whereas the contralateral eye underwent exotropic drift.

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ORIGINAL PAPER

Duane Retraction Syndrome on the Arabian Peninsula

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ABSTRACT *Purpose* To describe the clinical features of patients from the Arabian Peninsula with Duane retraction syndrome (DRS). *Methods* Retrospective chart review of patients referred to the King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia from 1982 to 2003 with a diagnosis of DRS. Patients having had prior strabismus surgery were excluded. *Results* Of 404 DRS patients, 347 (86%) were unilateral, 57 (14%) were bilateral, and 111 (27%) had amblyopia. There were 221 (55%) females and 182 (45%) males. The Huber classification was as follows: 315 (78%) Type I, 16 (4%) Type II, and 77 (19%) Type III. Of the 57 bilateral cases, 25 (44%) were female and 32 (56%) were male. *Discussion* Overall, the clinical features of DRS patients referred to a Riyadh eye hospital are similar to those reported in series throughout the world. However, our referred bilateral DRS patients are more commonly male. The clinical features of bilateral DRS deserve further worldwide study.

KEYWORDS Duane retraction syndrome; clinical characteristics; Huber classification; Saudi Arabia

INTRODUCTION

Duane retraction syndrome (DRS) is a congenital incomitant strabismus characterized by varying degrees of medial rectus and lateral rectus co-contraction during attempted adduction (DeRespinis et al., 1993). It can be considered a congenital cranial innervation disorder due to paradoxical innervation of the lateral rectus muscle by axons intended for the ipsilateral medial rectus muscle (Gotowski et al., 2003). DRS is often subjectively described using Huber's classification system: Type I (limited abduction with normal to near normal abduction), Type II (limited adduction with normal to near normal abduction), and Type III (limited abduction and adduction) (Huber, 1974). The purpose of this report, the first large DRS clinical series from the Middle East, is to summarize the clinical findings in 404 DRS patients from the Arabian Peninsula in the context of other large studies (Isenberg & Urist, 1977; Kirkham, 1970; Marshman et al., 2000; Mauro et al., 1979; O'Malley et al., 1982; Park et al., 2005; Pfaffenbach et al., 1972; Raab, 1986; Ro et al., 1989; Shauly et al., 1993; Tredici & Von Noorden, 1985; Zhang, 1997).

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BRIEF COMMUNICATIONS

nature
genetics

Homozygous *HOXA1* mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development

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We identified homozygous truncating mutations in *HOXA1* in three genetically isolated human populations. The resulting phenotype includes horizontal gaze abnormalities, deafness, facial weakness, hypoventilation, vascular malformations of the internal carotid arteries and cardiac outflow tract, mental retardation and autism spectrum disorder. This is the first report to our knowledge of viable homozygous truncating mutations in any human *HOX* gene and of a mendelian disorder resulting from mutations in a human *HOX* gene critical for development of the central nervous system.

We observed an autosomal recessive syndrome in five consanguineous families, four Saudi Arabian and one Turkish (Supplementary Fig. 1 online), which we called Bosley-Salih-Alorainy syndrome (BSAS; Supplementary Table 1 online). All nine affected individuals had bilateral Duane syndrome, a congenital horizontal eye movement disorder (Fig. 1a). Eight affected individuals had profound sensorineural deafness, and three had external ear defects. Seven affected individuals had delayed motor milestones. Two individuals with BSAS from different Saudi Arabian families were cognitively and behaviorally impaired and met DSM-IV criteria for autism spectrum disorder. Their parents did not have features of BSAS.

Eight individuals with BSAS underwent brain magnetic resonance or computed tomography imaging (Supplementary Methods online). In thin magnetic resonance sections through the caudal pons from one affected individual, we could not identify exiting abducens cranial nerves, although we could identify them in control images. Otherwise, the cerebrum, cerebellum and brainstem appeared normal (Fig. 1b).

We imaged the inner ear in seven of eight individuals with deafness and found bilateral absence of the cochlea, semicircular canals and vestibule (common cavity deformity) in five of them (Fig. 1c,d) and

cochlea aplasia in two. The ninth individual had normal hearing and inner ear anatomy.

Three individuals with BSAS had computed tomography imaging of the skull base. One had bilateral absence and two had left-sided absence of the carotid canal (Fig. 1e), the foramen through which the internal carotid artery (ICA) normally enters the skull. Four individuals underwent magnetic resonance angiography (MRA) of both the head and neck, and three individuals underwent MRA of the head only. All had variable ICA malformations, ranging from unilateral hypoplasia to bilateral agenesis (Fig. 1f-h and Supplementary Table 1 online).

We carried out SNP-based linkage analysis of the largest family with BSAS (Supplementary Fig. 1 online) and identified a single, fully informative 8.5-Mb region flanked by rs763543 and rs177962 on chromosome 7p15.3-p14.3 in which only the affected children were homozygous. Further analysis with additional microsatellite markers (Supplementary Table 2 online) confirmed coinheritance of the haplotype with disease status in all five pedigrees with BSAS and also identified a homozygous ~300-kb subregion on 7p15.2 that was haploidentical in affected Saudi Arabian individuals, suggestive of a founder mutation in the Saudi Arabian population (Supplementary Fig. 1 online). The maximum combined two-point lod score was 7.7 (Supplementary Table 3 online).

The *HOXA* cluster falls in the haploidentical region, and we analyzed *HOXA1* for mutations because there are similarities between the BSAS phenotype and the pathology of the *Hoxa1*^{-/-} mouse¹⁻³. Sequence analysis showed that Saudi Arabian individuals with BSAS carried a homozygous guanine insertion, 175-176insG, putatively resulting in a reading frame shift and the introduction of a premature stop codon (Fig. 2a,b and Supplementary Fig. 1 online). The Turkish individual with BSAS had a homozygous 84C→G mutation, resulting in the substitution of a stop codon for a tyrosine residue (Y28X; Fig. 2c and Supplementary Fig. 1 online). Both mutations were heterozygous in parents of affected individuals, cosegregated appropriately in each family and were not present on 354 chromosomes of mixed ethnicity (including 128 Saudi Arabian and 26 Turkish). The mutations are predicted to affect the synthesis of all three human *HOXA1* transcripts⁴ (Fig. 2) and to result in loss of *HOXA1* function.

Heterozygous mutations have been documented in four human *HOX* genes⁵⁻⁷ located near the 5' ends of the A or D clusters. These mutations lead primarily to malformed distal extremities. Human mutations have not been described in 3' *HOX* genes essential for head and central nervous system patterning. *Hoxa1*, the most 3' gene in cluster A, is the first of the *Hox* genes expressed in mammals and is

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Clinical characterization of the HOXA1 syndrome BSAS variant

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ABSTRACT

Background: The Bosley-Salih-Alorainy syndrome (BSAS) variant of the congenital human *HOXA1* syndrome results from autosomal recessive truncating *HOXA1* mutations. We describe the currently recognized spectrum of ocular motility, inner ear malformations, cerebrovascular anomalies, and cognitive function.

Methods: We examined nine affected individuals from five consanguineous Saudi Arabian families, all of whom harbored the same 175-176insG homozygous mutation in the *HOXA1* gene. Patients underwent complete neurologic, neuro-ophthalmologic, orthoptic, and neuropsychological examinations. Six individuals had CT, and six had MRI of the head.

Results: All nine individuals had bilateral Duane retraction syndrome (DRS) type 3, but extent of abduction and adduction varied between eyes and individuals. Eight patients were deaf with the common cavity deformity of the inner ear, while one patient had normal hearing and skull base development. Six had delayed motor milestones, and two had cognitive and behavioral abnormalities meeting Diagnostic and Statistical Manual of Mental Disorders-IV criteria for autism spectrum disorder. MRI of the orbits, extraocular muscles, brainstem, and supratentorial brain appeared normal. All six appropriately studied patients had cerebrovascular malformations ranging from unilateral internal carotid artery hypoplasia to bilateral agenesis.

Conclusions: This report extends the Bosley-Salih-Alorainy syndrome phenotype and documents the clinical variability resulting from identical *HOXA1* mutations within an isolated ethnic population. Similarities between this syndrome and thalidomide embryopathy suggest that the teratogenic effects of early thalidomide exposure in humans may be due to interaction with the HOX cascade. *Neurology*® 2007;69:1245-1253

GLOSSARY

ABDS = Athabaskan brainstem dysgenesis syndrome; **BSAS** = Bosley-Salih-Alorainy syndrome; **CARS** = Childhood Autism Rating Scale; **CCA** = common carotid artery; **CCD** = common cavity deformity; **CN** = cranial nerve; **C-splna** = cervical spine; **DRS** = Duane retraction syndrome; **DSM-4** = Diagnostic and Statistical Manual of Mental Disorders; **ET** = esotropia; **IAC** = internal auditory canal; **ICA** = internal carotid artery; **MRA** = magnetic resonance angiography; **NA** = not available; **OD** = right eye; **ortho** = orthophoria; **OS** = left eye; **OU** = both eyes; **PCom** = posterior communicating artery; **TOF** = time-of-flight; **US** = ultrasound; **VAB** = Vineland Adaptive Behavior; **WNL** = within normal limits; **XT** = exotropia.

We recently reported a new Mendelian syndrome associated with truncating mutations in *HOXA1*,¹ a homeodomain transcription factor critical for the proper development of hindbrain rhombomeres in mice.^{2,3} Homozygous 175-176insG guanine base-pair insertions were found in several families from Saudi Arabia, while a homozygous 84C>G nonsense mutation resulted in the substitution of a stop codon for a tyrosine residue (Y28X) in a Turkish individual. These two mutations cause a phenotype, referred to as the Bosley-Salih-Alorainy syndrome (BSAS; OMIM #601536), characterized by bilateral

Supplemental data at www.neurology.org

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The Clinical Spectrum of Homozygous *HOXA1* Mutations

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We describe nine previously unreported individuals from six families who have homozygous mutations of *HOXA1* and either the Bosley–Salih–Alorainy syndrome (BSAS) or the Athabascan brainstem dysgenesis syndrome (ABDS). Congenital heart disease was present in four BSAS patients, two of whom had neither deafness nor horizontal gaze restriction, thus raising the possibility that cardiovascular malformations might be a clinically isolated, or relatively isolated, manifestation of homozygous *HOXA1* mutations. Two ABDS

probands had relatively mild mental retardation. These individuals blur the clinical distinctions between the BSAS and ABDS *HOXA1* variants and broaden the phenotype and genotype of the homozygous *HOXA1* mutation clinical spectrum. © 2008 Wiley-Liss, Inc.

Key words: *HOXA1*; Duane syndrome; deafness; cerebrovascular malformation; BSAS; ABDS

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INTRODUCTION

We recently reported a Mendelian syndrome associated with truncating mutations in *HOXA1* [Tischfield et al., 2005], a homeodomain transcription factor critical for the proper development of hind-brain rhombomeres [Lufkin et al., 1991; Chisaka et al., 1992]. Homozygous 175-176insG guanine base-pair insertions were found in several families from Saudi Arabia, while a homozygous 84C>G nonsense mutation resulted in substitution of a stop codon for a tyrosine residue in a Turkish individual. These two mutations cause a phenotype referred to as the Bosley–Salih–Alorainy syndrome (BSAS; OMIM #601536) characterized by bilateral Duane retraction syndrome (DRS) type 3, deafness, malformations of the cerebral vasculature, and autism in some patients [Tischfield et al., 2005; Bosley et al.,

2007]. This syndrome differed from another homozygous *HOXA1* variant, the Athabascan brainstem dysgenesis syndrome (ABDS) reported in native Americans, which is marked by horizontal gaze restriction, deafness, mental retardation, facial and

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Short Reports

HOXA1 mutations are not a common cause of Möbius syndrome

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The *HOXA1*-related syndromes result from autosomal-recessive truncating mutations in the homeobox transcription factor, *HOXA1*. Limited horizontal gaze and sensorineural deafness are the most common features; affected individuals can also have facial weakness, mental retardation, autism, motor disabilities, central hypoventilation, carotid artery, and/or conotruncal heart defects. Möbius syndrome is also phenotypically heterogeneous, with minimal diagnostic criteria of nonprogressive facial weakness and impaired ocular abduction; mental retardation, autism, motor disabilities, additional eye movements restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities also occur. We asked, given the phenotypic overlap between these syndromes and the variable expressivity of both disorders, whether individuals with Möbius syndrome might harbor mutations in *HOXA1*. Our results suggest that *HOXA1* mutations are not a common cause of sporadic Möbius syndrome in the general population.

HOXAI-related syndromes include the Bosley-Salih-Alorainy syndrome, identified in Saudi Arabian and Turkish families, and the Athabaskan brainstem dysgenesis syndrome, identified in Native American families.^{1,2} Both result from autosomal-recessive truncating mutations in the homeobox transcription factor, *HOXA1*. The *HOXA1*-related syndrome phenotype is variable. The most common features in affected individuals are limited horizontal gaze (diagnosed as Duane syndrome in Bosley-Salih-Alorainy syndrome patients and horizontal gaze palsy in Athabaskan brainstem dysgenesis syndrome patients) and sensorineural deafness; facial weakness,

mental retardation, autism, motor disabilities, central hypoventilation, carotid artery, and/or conotruncal heart defects also occur.^{1,2} The minimal diagnostic criteria for Möbius syndrome, which is also phenotypically heterogeneous, are nonprogressive facial weakness and impaired ocular abduction.^{3,4} Affected individuals can also have mental retardation, autism, motor disabilities, additional eye-movement restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities.³

Approximately 20% of reported individuals with the *HOXA1*-related syndromes have both facial weakness and horizontal gaze palsy and thus meet diagnostic criteria for Möbius syndrome. Among this subgroup to date, none has globe retraction, all have deafness and central hypoventilation, and half have conotruncal cardiac defects.^{1,2,5,6} We asked whether, given the phenotypic overlap between these syndromes and the variable expressivity of both disorders, individuals with Möbius syndrome might harbor mutations in *HOXA1*.

Methods

This study was approved by the local institutional review board and conducted in accordance with the Health Insurance Portability and Accountability Act, with written informed consent of the participants and/or their guardians. We identified 40 probands with Möbius syndrome from among the participants enrolled in our study of complex strabismus, 25 of whom were recruited from the 8th International Moebius Syndrome Conference in 2008. All probands met the minimal criteria of Möbius syndrome as defined by consensus statement of the Moebius Syndrome Foundation Research Conference in April 2007, namely, "congenital, uni- or bilateral non-progressive facial weakness and limited abduction of the eye(s)."⁴ Each participant underwent an orthoptic and targeted general examination, or records of these examinations were reviewed, and each submitted a blood or salivary sample for DNA extraction. Genomic DNA was extracted from participants' blood by the use of Qiagen GenTA Puregene DNA Isolation Kits (Valencia, CA) or saliva samples by the use of DNA Genotek Oragene saliva and saliva swab kits (Karata, Ontario, Canada). *HOXA1* exons and their flanking intronic sequences were amplified, sequenced, and analyzed as previously described.¹

Results

Probands included individuals of European and South, Central, and North American origin, including those of white, black, Hispanic, Native American, and Asian extraction.

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ORIGINAL ARTICLE

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HOXA1 Mutations are Not Commonly Associated with Non-Syndromic Deafness

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ABSTRACT: Objective: Homozygous homeobox A1 (*HOXA1*) mutations cause a spectrum of abnormalities in humans including bilateral profound deafness. This study evaluates the possible role of *HOXA1* mutations in familial, non-syndromic sensorineural deafness. **Methods:** Forty-eight unrelated Middle Eastern families with either consanguinity or familial deafness were identified in a large deafness clinic, and the proband from each family was evaluated by chart review, audiogram, neuroimaging, and *HOXA1* sequencing. **Results:** All 48 probands had normal neuro-ophthalmologic and general medical examinations except for refractive errors. All had congenital non-syndromic sensorineural hearing loss that was symmetric bilaterally and profound (>90 dBHL) in 33 individuals and varied from 40 to 90 dBHL in the remainder. Thirty-nine of these individuals had neuroimaging studies, all documenting normal internal carotid arteries and normal 6th, 7th, and 8th cranial nerves bilaterally. Of these, 27 had normal internal ear structures with the remaining 12 having mild to modest developmental abnormalities of the cochlea, semicircular canals, and/or vestibular aqueduct. No patient had homozygous *HOXA1* mutations. **Conclusion:** None of these patients with non-syndromic deafness had *HOXA1* mutations. None had major inner ear anomalies, obvious cerebrovascular defects, or recognized congenital heart disease. *HOXA1* is likely not a common cause of non-syndromic deafness in this Middle Eastern population.

RÉSUMÉ: Des mutations de *HOXA1* ne sont pas fréquemment associées à la surdité non syndromique. **Objectif:** Les mutations de la séquence homéotique A1 (*HOXA1*) à l'état homozygote causent un spectre d'anomalies chez les humains dont une surdité bilatérale profonde. Dans cette étude, nous avons évalué la possibilité que des mutations de *HOXA1* jouent un rôle dans la surdité de perception familiale non syndromique. **Méthode :** Quarante-huit familles non apparentées du Moyen Orient présentant de la consanguinité ou une surdité familiale ont été identifiées dans une clinique de surdité à haut volume de patients et le cas index de chaque famille a été étudié au moyen d'une revue du dossier, d'un audiogramme, de tests de neuroimagerie et par séquençage de *HOXA1*. **Résultats :** Chez les 48 cas index l'examen neuro-ophthalmologique et l'examen clinique général étaient normaux, sauf pour la présence d'anomalies de la réfraction. Tous présentaient une surdité de perception non syndromique, qui était bilatérale et symétrique, et qui était profonde (>90 dbhl) chez 33 patients et de 40 à 90 dbhl chez les autres. Les artères carotides internes bilatérales étaient normales ainsi que les 6e, 7e et 8e nerfs crâniens bilatéraux chez 39 de ces individus qui ont subi des examens de neuroimagerie. Parmi eux, la structure de l'oreille interne était normale chez 27 ; les 12 autres présentaient des anomalies de développement de légères à modérées de la cochlée, des canaux semi-circulaires et/ou de l'aqueduc de Sylvius. Aucun patient n'était porteur de mutations de *HOXA1* à l'état homozygote. **Conclusions :** Aucun de ces patients atteints de surdité non syndromique n'était porteur de mutations de *HOXA1*. Aucun d'eux n'était porteur d'anomalie importante de l'oreille interne, d'anomalie cérébrovasculaire évidente ou de maladie cardiaque congénitale reconnue. Il est probable que *HOXA1* ne soit pas une cause fréquente de surdité non syndromique dans cette population du Moyen Orient.

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Hearing loss is relatively common in humans. Around 3/1000 infants have some congenital hearing loss, with severe or profound congenital hearing loss (bad enough to preclude normal speech development) estimated to occur in about 1 in 1000 births. Approximately 50% of individuals with severe childhood deafness are thought to have genetic causes^{1,2}, of which nearly 70% worldwide are thought to be autosomal recessive³. Approximately 70% of congenital deafness associated with genetic factors are classified as non-syndromic, and more than 400 forms of syndromic deafness can be diagnosed in the remaining 30% because of associated clinical findings⁴.

In 2003, several consanguineous families in Saudi Arabia were found to have a previously unreported syndrome consisting

most notably of deafness, bilateral Duane retraction syndrome (DRS), and cerebrovascular and cardiovascular malformations^{5,6}. Genome-wide screen revealed homozygous mutations in the Homozygous homeobox A1 (*HOXA1*) gene that presumably

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CASE REPORT

Partial chromosome 7 duplication with a phenotype mimicking the HOXA1 spectrum disorder

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ABSTRACT

Purpose: To evaluate possible monogenic and chromosomal anomalies in a patient with bilateral Duane retraction syndrome and hearing impairment resulting in a phenotype resembling the HOXA1 spectrum disorder.

Methods: Sequencing HOXA1 and performing high resolution array comparative genomic hybridization (arrayCGH).

Results: The proband had bilateral Duane retraction syndrome (DRS) with severe hearing loss bilaterally and an absent right vertebral artery, mimicking the major features of the Bosley-Salih-Alorainy variant of the HOXA1 spectrum. However, he also had developmental delay, mild mental retardation, and seizures. His parents were not related, but his father had milder sensorineural hearing loss bilaterally, and two paternal uncles and a paternal cousin had seizures. Neuroimaging revealed moderate maldevelopment of inner ear bony anatomy bilaterally. HOXA1 sequencing was normal, but arrayCGH revealed a small partial duplication of chromosome 7 encompassing only the PTPRN2 gene (protein tyrosine phosphatase, receptor type, N polypeptide 2) that was not present in his parents, an unaffected brother, or 53 normal ethnically-matched individuals.

Conclusions: PTPRN2 is not yet linked to a genetic syndrome, although its expression has been identified in the adult human brain, in certain tumors, and in association with type 1 diabetes mellitus. The phenotype of this patient is strikingly similar to, but not identical to, that of the HOXA1 spectrum disorder. The findings in this patient raise the possibility that PTPRN2 may be active during early development of the human brainstem and that its overexpression may cause bilateral DRS with hearing loss as occurs in patients with homozygous HOXA1 mutations.

KEYWORDS: Duane retraction syndrome, Congenital hearing impairment, HOXA1 spectrum, Array comparative genomic hybridization, Mental retardation, Seizures

INTRODUCTION

Bilateral Duane retraction syndrome (DRS) occurs in association with bilateral hearing impairment in a number of congenital syndromes. These include at least: (1) the Bosley Salih Alorainy Syndrome (BSAS; OMIM 601536)¹ caused by autosomal recessive mutations in HOXA1 that result in bilateral DRS type 3, bilateral deafness associated commonly with severe inner ear maldevelopment, cerebrovascular anomalies, and occasionally autism,^{2,3} (2) Duane-radial ray syndrome (DRRS; OMIM 607323)⁴ caused

by autosomal dominant mutations in SALL4 resulting in unilateral or bilateral DRS, upper limb anomalies, and renal anomalies,^{3,4} (3) Duane retraction syndrome 2 (DRS2; OMIM 604356)⁷ caused by autosomal dominant mutations in CHN1 and resulting in unilateral or bilateral DRS, unilateral congenital ptosis, and unilateral deafness,⁸⁻¹⁰ (4) the Townes-Brocks syndrome (TBS; OMIM 107480)¹¹ caused by autosomal dominant mutations in SALL1 that result in anal anomalies, dysplastic ears, abnormal thumbs, conductive or sensorineural deafness, cardiac and renal anomalies, and rarely DRS,^{12,13} and (5)

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RESEARCH REPORT

Xq26.3 Microdeletion in a Male with Wildervanck Syndrome

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ABSTRACT

Background: Wildervanck Syndrome (WS; cervico-oculo-acoustic syndrome) consists of Duane retraction syndrome (DRS), the Klippel-Feil anomaly, and congenital deafness. It is much more common in females than males and could be due to an X-linked mutation that is lethal to hemizygous males. We present the genetic evaluation of a male with WS and his family.

Materials and Methods: Clinical evaluation and neuroimaging, sequencing of candidate genes, and array comparative genomic hybridization.

Results: The patient had bilateral type 1 DRS, fusion of almost the entire cervical spine, and bilateral severe sensorineural hearing loss due to bilateral cochlear dysplasia; he also had congenital heart disease requiring surgery. His parents were unrelated, and he had eight unaffected siblings. The patient had no mutation found by Sanger sequencing of *HOXA1*, *KIF21A*, *SALL4*, and *CHN1*. He had a 3kB deletion in the X-chromosome at Xq26.3 that was not found in his mother, one unaffected sibling, or 56 healthy controls of matching ethnicity. This deletion encompassed only one gene, Fibroblast Growth Factor Homologous Factor 13 (*FGF13*), which encodes a 216-amino acid protein that acts intracellularly in neurons throughout brain development.

Conclusions: Analysis of this patient's phenotype and genotype open the possibility that X-chromosome deletions may be a cause of WS with larger deletions being lethal to males and that *FGF13* mutations may be a cause of WS.

Keywords: Cervico-oculo-acoustic syndrome, chromosome deletion, congenital deafness, Duane retraction syndrome, Klippel-Feil anomaly, Wildervanck syndrome, x-linked

INTRODUCTION

Wildervanck syndrome (WS, OMIM 314600), or the cervico-oculo-acoustic syndrome,¹ is an uncommon^{1,2} congenital syndrome defined by the co-occurrence of the Klippel-Feil anomaly (congenital fusion of cervical vertebra; OMIM 118100), Duane retraction syndrome (DRS, OMIM 126800), and congenital deafness that may be sensorineural, conductive, or mixed.³ There have been reports of WS patients with additional

features such as cervical spinal cord developmental abnormalities,^{4,5} facial palsy,⁶ other neurologic developmental abnormalities,⁷ cardiac abnormalities,⁸ cleft palate,^{2,9} and ectopia lentis. The possible genetic etiology of the syndrome is not yet defined, but the fact that it occurs much more commonly in females¹ has led to the hypothesis that it is an X-linked disorder that is lethal to hemizygous males.¹⁰

We describe the phenotype of a male with sporadic WS, including congenital heart disease requiring

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RESEARCH REPORT

Partial Duplication of Chromosome 19 Associated with Syndromic Duane Retraction Syndrome

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ABSTRACT

Background: To evaluate possible monogenic and chromosomal anomalies in a patient with unilateral Duane retraction syndrome, modest dysmorphism, cerebral white matter abnormalities, and normal cognitive function.

Materials and Methods: Performing high-resolution array comparative genomic hybridization (array CGH) and sequencing of *HOXA1*, *KIF21A*, *SALL4*, and *CHN1* genes.

Results: The proband had unilateral Duane retraction syndrome (DRS) type III on the right with low-set ears, prominent forehead, clinodactyly, and a history of frequent infections during early childhood. Motor development and cognitive function were normal. Parents were not related, and no other family member was similarly affected. MRI revealed multiple small areas of high signal on T2 weighted images in cerebral white matter oriented along white matter tracts. Sequencing of *HOXA1*, *KIF21A*, *SALL4*, and *CHN1* did not reveal any mutation(s). Array CGH showed a 95 Kb *de novo* duplication on chromosome 19q13.4 encompassing four killer cell immunoglobulin-like receptor (*KIR*) genes.

Conclusions: *KIR* genes have not previously been linked to a developmental syndrome, although they are known to be expressed in the human brain and brainstem and to be associated with certain infections and autoimmune diseases, including some affecting the nervous system. DRS and brain neuroimaging abnormalities may imply a central and peripheral oligodendrocyte abnormality related in some fashion to an immunomodulatory disturbance.

Keywords: Clinodactyly, Duane retraction syndrome, killer cell immunoglobulin-like receptor, *KIR* gene, low-set ears, oligodendrocyte

INTRODUCTION

Duane retraction syndrome (DRS) is usually isolated and sporadic. However, three monogenic DRS syndromes have now been reported: Duane Radial Ray Syndrome (DRRS; OMIM 607323) due to autosomal dominant mutations in the sal-like 4 (*SALL4*) gene that cause unilateral or bilateral DRS associated with

radial dysplasia that may also be unilateral or bilateral, variable deafness, and sometimes other somatic malformations;^{1,2} Duane Retraction Syndrome 2 (DURS2; OMIM 604356) due to autosomal dominant mutations of *chimerin 1* (*CHN1*) that are most commonly associated with bilateral DRS with some vertical gaze abnormalities and rare somatic disturbances;^{3,4} and the Bosley-Salih-Alorainy syndrome

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RESEARCH REPORT

Nicotinic Receptor Mutation in a Mildly Dysmorphic Girl with Duane Retraction Syndrome

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ABSTRACT

Background: To evaluate possible monogenic and chromosomal anomalies in a patient with unilateral Duane retraction syndrome and modest dysmorphism.

Materials and Methods: Clinical evaluation, sequencing of candidate genes, and array comparative genomic hybridization (array CGH).

Results: The proband had unilateral Duane retraction syndrome (DRS) with low-set ears bilaterally, a high arched palate, and clinodactyly. Motor development and cognitive function were normal. Parents were first cousins, but no other family member was similarly affected. No mutations were detected in the *HOXA1*, *KIF21A*, *SALLA*, *TUBB3*, and *CHNI* genes. Array CGH revealed a 16 Kb *de novo* deletion at chromosome 8p11.2 that encompassed a portion of only one gene, the Cholinergic Receptor, Nicotinic, Beta-3 (*CHRN3*, Neuronal). This gene encodes a protein that is involved in the nicotinic acetylcholine receptor on neurons. It interacts functionally with other genes that code components of the acetylcholine receptor.

Conclusions: This patient's chromosomal abnormality affected only one gene that is highly expressed in the brainstem and brain, involved in neurotransmission, and could be related to her Duane retraction syndrome.

Keywords: Beta-3 (*CHRN3*, neuronal), cholinergic receptor nicotinic, clinodactyly, Duane retraction syndrome, low-set ears, syndromic Duane syndrome

INTRODUCTION

Duane retraction syndrome (DRS) is usually isolated and sporadic. However, three monogenic DRS syndromes have now been reported including Duane Radial Ray Syndrome (DRRS; OMIM 607323) due to autosomal dominant mutations in the *SALL4* gene,^{1,2} Duane Retraction Syndrome 2 (DURS2, OMIM 604356) due to autosomal dominant mutations of *CHNI*,^{3,4} and the Bosley-Salih-Alorainy syndrome (BSAS) in which autosomal recessive mutations of *HOXA1* occur.⁵⁻⁷ Genetic causes of syndromic DRS are not always associated with recognized monogenic

syndromes. A number of syndromic DRS patients have been reported in association with a variety of different chromosomal copy number variations (CNVs) including deletion(s),^{8,9} duplication(s), translocation(s),¹⁰ and the presence of a marker chromosome.^{11,12} These reports utilized technologies for detecting CNVs limited to resolutions of 5–10 Mb for standard karyotyping, 3–5 Mb for FISH probes, or 80–200 Kb for BAC clones.¹³ Advances in high resolution array-comparative genomic hybridization (array CGH) have improved detection capabilities into the range of 1 Kb,¹⁴ increasing dramatically the ability to detect small, potentially symptomatic CNVs.

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CASE REPORT

CCDD Phenotype Associated with a Small Chromosome 2 Deletion

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ABSTRACT

Purpose: Some individuals are born with congenital limitation of ocular motility, often associated with ptosis and retraction of the globe. Many of these disorders are now known as the congenital cranial dysinnervation disorders (CCDDs). While several genes have been associated with CCDD phenotypes, there are still patients for whom the genetic basis has not been identified. **Methods:** Clinical evaluation and neuroimaging, sequencing of candidate genes, and array comparative genomic hybridization (array CGH). **Results:** The patient was a four-year-old girl with mild dysmorphism; bilateral mild ptosis; substantial limitation of abduction OS with milder limitations of abduction OD, adduction OS, and vertical gaze OS; and retraction OS > OD on attempted adduction. No mutations were detected in the *HOXA1*, *KIF21A*, *SALLA*, *TUBB3*, and *CHN1* genes. Array CGH revealed a 8 Kb *de novo* deletion on chromosome 2 (2q24.3) that encompassed a portion of only one gene, the Xin Actin-binding Repeat containing 2 (Gene Symbol *XIRP2*; NM_001079810). This gene encodes a protein that is involved in muscle development and protecting actin filaments from depolymerization. It interacts functionally with 10 other proteins playing a similar role in muscle development. **Conclusions:** This patient's chromosomal abnormality affected only one gene that currently seems involved only in muscle development. All other genes currently associated with the CCDDs affect neurologic development. Genetic information from this patient implies that genes involved in development and maintenance of extraocular muscles can cause congenital ocular motility disorders as well.

Keywords: Congenital cranial dysinnervation disorder, Duane retraction syndrome, dysmorphism, ptosis, *XIRP2*

INTRODUCTION

Ophthalmologists recognized over 60 years ago that certain children were born with congenital ocular motility abnormalities associated with limited eye movements and occasionally retraction of the globe.^{1,2} Duane retraction syndrome (DRS) was one of the first described of these congenital ocular motility disorders and classically consists of absent abduction with globe

retraction and narrowing of the palpebral fissure on attempted adduction.^{2,3} In the past, DRS and similar congenital ocular motility abnormalities were assumed to be due to a developmental abnormality of muscles, a phenomenon termed congenital fibrosis of the extraocular muscles (CFEOM).⁴ However, more recently, this category of disorders has been recategorized as the congenital cranial dysinnervation disorders (CCDD) because all genes currently linked

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RESEARCH REPORT

Microdeletions involving Chromosomes 12 and 22 Associated with Syndromic Duane Retraction Syndrome

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ABSTRACT

Background: Duane retraction syndrome (DRS) is the most common of the congenital cranial dysinnervation disorders (CCDDs). CCDDs can be monogenic or chromosomal in origin. Identification of the genetic cause(s) in patients and families with DRS facilitates definitive diagnosis and provides insights into these developmental errors.

Materials and Methods: This study described a young girl with DRS on the left and several additional developmental abnormalities. Clinical examination including neuroimaging, sequencing of candidate genes associated with DRS, and array comparative genomic hybridization (array CGH) were performed.

Results: The proband had unilateral DRS type 3 on the left with somewhat low-set ears, mild motor delay with normal intelligence, and an asymmetric neck without a palpable right sternocleidomastoid muscle. Spine X-rays revealed a Klippel-Feil syndrome (KFS) and an MRI showed a webbed neck. She also had spina bifida at C8-T1 and a submucosal cleft palate. The parents of the proband were related with no other family member affected similarly. Sequencing of *SALL4*, *CHN1*, *HOXA1*, and *TUBB3* did not show any mutation. Array CGH revealed de novo deletions of 21 Kb on chromosome 12q24.31 and 11 Kb on chromosome 22q13.31, each encompassing only one gene, ring finger protein 34, E3 ubiquitin protein ligase (RNF34) and peroxisome proliferator-activated receptor alpha (*PPARA*) respectively.

Conclusions: This patient presents an unusual phenotype associated with a unique combination of two chromosomal microdeletions.

Keywords: Array CGH; cleft palate; congenital cranial dysinnervation disorder; Duane retraction syndrome; dysmorphism; Klippel-Feil anomaly; spina bifida

INTRODUCTION

Development of the normal human ocular motility system is a complex process involving numerous genes acting in concert at the correct time and place.¹ Congenital cranial dysinnervation disorders (CCDDs) are the group of congenital, static disturbances of ocular motility that result when *in utero* development of this system is disturbed.^{2,3} The

occurrence of CCDDs has now been reported in the setting of monogenic disorders causing cell cycle disruptions (e.g. abnormal brainstem development in the *HOXA1* spectrum disorders),⁴ abnormal apoptosis (e.g. death of oculomotor nucleus neurons with *PHOX2A* mutations),⁵ and abnormalities of signal transduction and transcription (e.g. CFEOM1 and CFEOM3 due to *KIF21A* and *TUBB3* mutations).^{6,7} Other CCDDs seem likely to be the result

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RESEARCH REPORT

Duane retraction syndrome in a patient with Duchenne muscular dystrophy

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ABSTRACT

Purpose: We describe the clinical features of a boy with bilateral Duane retraction syndrome (DRS), Duchenne muscular dystrophy (DMD), and other medical problems.

Methods: The child was followed-up for five years; his chart was reviewed, including the results of a muscle biopsy and genetic testing. Multiplex ligation-dependent probe amplification (MLPA) was used to interrogate deletions/duplications in the *dystrophin* gene.

Results: The proband had bilateral DRS with otherwise normal ocular motility; he also had developmental delay, mild mental retardation, and seizures. Clinical diagnosis of DMD included progressive proximal weakness, highly elevated creatine kinase levels, and a muscle biopsy showing significant dystrophic changes including contracted, degenerative, and regenerative fibers, and negative dystrophin immunostaining. MLPA documented duplication of exons 3 and 4 of the *dystrophin* gene.

Conclusions: This boy is the third patient to be reported with DRS and DMD, the second with bilateral DRS and the only one with other neurologic features. Mutated *dystrophin* is present in extraocular muscles and in the central nervous system (CNS) in DMD, leaving open the question of whether this co-occurrence is the result of the genetic muscle abnormality, CNS effects caused by *dystrophin* mutations, or chance.

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KEYWORDS

Duane retraction syndrome; Duchenne muscular dystrophy; dystrophin; eye movements; muscular dystrophy

Introduction

Duane retraction syndrome (DRS) is a common congenital ocular motility abnormality occurring in 1/1000 births. It is usually isolated and sporadic, and more common among females.¹ Three monogenic DRS syndromes have been described due to autosomal dominant mutations in *sal-like 4* (*SALL4*)² and *chimerin 1* (*CHN1*)³ and autosomal recessive mutations in *Homo sapiens homeobox A* (*HOXA1*).⁴ In addition, extraocular muscles (EOM) disturbances including globe retraction and horizontal motility restriction have been reported in ocular motility problems due to mutations in *kinesin family member 21A* (*KIF21A*)⁵ and *tubulin, beta 3 class III* (*TUBB3*)⁶ and in numerous chromosomal copy number variations.^{7–9}

Recently, the term congenital fibrosis of the extraocular muscles (CFEOM) has been recategorized as the congenital cranial dysinnervation disorders (CCDD) because all genes currently linked to congenital ocular motility abnormalities disturb neurologic development,^{1,10} and not muscle development. In fact, it is a curious observation that most muscular dystrophies spare the EOM so that eye movements remain full throughout life, and histologic specimens of EOM do not exhibit the pattern of necrosis, fibrosis, and regeneration

seen in most skeletal muscles in either human or animal models of these disorders.¹¹

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy worldwide, affecting one in 3600 boys.¹² DMD results from mutations in the *dystrophin* gene, spanning 2.4 million base-pairs on chromosome Xp21.2 and consists of 79 exons encoding a 427 kDa protein. Dystrophin protein anchors the actin cytoskeleton to the extracellular matrix and plays a role in protecting the muscle from mechanical injury.¹³ In most cases, *dystrophin* mutations that preserve the reading frame result in the milder Becker phenotype whereas mutations that disrupt the reading frame result in the more severe Duchenne phenotype.¹⁴ The clinical presentation of boys with DMD includes delayed motor milestones, proximal weakness, hypertrophied calves, and markedly elevated creatine kinase (CK) levels. Ocular motility is almost always clinically unaffected although the mutated *dystrophin* gene is also expressed in EOM.¹⁵

Two previous patients have been reported with DMD and DRS,^{15,16} forming an exception to the general rule that DMD is not associated with clinically significant disturbances of ocular motility. The patient described here is the third such example, but he differs from both previous reports in important ways as described.

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LETTER TO THE EDITOR

TO THE EDITOR

Duane Retraction Syndrome Associated with a Small X Chromosome Deletion

Keywords: Abducens cranial nerve, congenital cranial dysinnervation disorders, cleft palate, *dystrophin* gene, Duchenne muscular dystrophy

This report describes the genetic evaluation of a girl with bilateral Duane retraction syndrome (DRS), cleft palate, and mildly reduced hearing who was found by high-resolution array-comparative genomic hybridization (array CGH) to have a chromosomal anomaly involving a single gene known to be involved in muscle development.

The study was approved by the Institutional Review Board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia, and informed consent was obtained. Patients' medical records were reviewed, including multiple examinations by both the Ophthalmology and Otolaryngology Departments at King Abdulaziz University Hospital over a period of almost 15 years. Data extracted included family history, complete ophthalmologic and neurologic examinations, laboratory results, and neuroimaging. Genes associated with syndromic DRS (*SALL4*, *CHN1*, *TUBB3*, *HOXA1*, and *KIF21A*) were sequenced; the complete coding regions of the *SALL4*, *CHN1*, *TUBB3*, and *HOXA1* genes and exons 8, 20, and 21 considered hotspot for mutations in the *KIF21A* gene were sequenced according to protocols described previously.¹

The Affymetrix Cytogenetics Whole-Genome 2.7M array (Affymetrix Inc., Santa Clara, CA, USA) was used to detect known and novel chromosomal aberrations across the entire genome. The array CGH assay was performed according to the manufacturer's instructions as detailed elsewhere.¹ Data were analyzed using the Affymetrix Chromosome Analysis Suite, v1.2, software. In the absence of internationally recognized criteria for analysis of high-resolution array CGH results, we devised preliminary criteria for a copy number variant (CNV) to be considered potentially pathologic, including: (1) it was not reported in the Database of Genomic Variants (DGV; <http://projects.tcag.ca/variation/>) among normal controls; (2) it was not present in 150 healthy controls of similar ethnicity; (3) it included an area of the genome encompassing one or more functional genes; and (4) it segregated with the phenotype and was not present in unaffected family members. The threshold for gain or loss was adjusted to 10kb. We used the National Center for Biotechnology Information Human Genome Assembly Build 35.

The proband was a 16-year-old girl with bilateral type 3 DRS. Her parents were first cousins. Her father was reportedly asymptomatic, but her mother had congenital strabismus that was treated with strabismus surgery during childhood. Three of her mother's seven siblings reportedly had congenital strabismus as well. These individuals could not be examined, but none had features of DRS by report. The proband had four unaffected siblings and a brother with congenital left superior oblique palsy.

She was the product of a normal pregnancy and delivery, but was born with a cleft palate that was successfully repaired at the age of 1 year. Her hearing was modestly reduced bilaterally with flat tympanograms, but she did not require hearing aids. She achieved normal developmental milestones, although her speech from early childhood through her teenage years was modestly abnormal with poorly formed words and multiple word substitutions, possibly as the result of her hearing difficulties. Cognitive function was grossly normal, and she did not display any autistic features.

At age 16 years, the proband's visual acuity measured 20/30 OU with excellent color vision and normal appearing optic discs and posterior poles bilaterally. She had a small esotropia and right hypertropia in forced primary position and, in general, assumed a small face turn and head tilt to the left. She had bilateral DRS type 3 with almost complete absence of abduction and modest deficits of adduction associated with marked retraction of each eye on attempted adduction (Figure 1). An upshoot of the nonfixing adducting eye could be elicited during attempted horizontal gaze if the eyes were slightly above midline. Additionally, a downshoot of the left eye would occur if attempting right gaze slightly below the horizontal midline. Convergence was relatively poor. A magnetic resonance imaging scan of the brain and orbits performed at age 11 years was entirely normal, including extraocular muscles (EOMs), except that the abducens nerves were not well seen, possibly because of motion artifact in the CSF anterior to pons.

No sequence variations were detected in the screened regions of *SALL4*, *CHN1*, *HOXA1*, *TUBB3*, and *KIF21A* genes. Array CGH documented a 12-kb deletion in chromosome X extending from 32,568,156 to 32,580,298 and encompassing part of only the *dystrophin* gene (Gene Symbol *DMD*; NC_000023.11) extending from exon 14 to intron 16. The deletion involves repeat 2 and repeat 3 encoding the central rod domain of the DMD gene that comprises of 24 spectrin-like repeats folded in triple coiled-coil structure. The DMD gene reading frame checker at the Leiden Muscular Dystrophy database (www.dmd.nl), which predicts the effect of exon deletion/duplication on the reading frame indicated that deleting the exon 14 through exon 15 leads to an in-frame deletion. Further analysis using the eDystrophin database (<http://edydrophin.genouest.org/>), which predicts the consequences of the in-frame mutations at the protein level, indicated that the deletion of exons 14-15 (c.1603-?_1812+?del; p.Val535_Ala640del) partially affects the lipid-binding domain 1 of the DMD protein and may not allow the protein reconstituting a triple-coiled coil at the new junction of the two sides of the deletion, leading to hybrid or fractional repeat, and the filamentous structure may not be maintained. The copy number state was equal to 1, indicating that this deletion was likely to be heterozygous. The confidence value calculated by the Chromosome Analysis Suite software was 88%, with a marker count of 16 spanning the deleted area. This deletion was absent in the proband's mother and father and was therefore likely to be de novo. It was not present in the DGV or in 150 unrelated healthy individuals of similar ethnicity.

The patient described here is a young woman with bilateral syndromic DRS. She also had a cleft palate and moderately poor hearing bilaterally. DRS, cleft palate, and partial deafness occur in

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The genetics of nonsyndromic bilateral Duane retraction syndrome



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PURPOSE	To assess the importance of monogenic mutations and chromosomal copy number variants (CNVs) in the occurrence of nonsyndromic bilateral Duane retraction syndrome (bilateral nsDRS).
METHODS	The medical records of 12 patients with bilateral nsDRS were reviewed. Genes associated with DRS and associated congenital cranial dysinnervation disorders (<i>SALL4</i> , <i>CHN1</i> , <i>HOXA1</i> , <i>TUBB3</i> , and <i>KIF21A</i>) were sequenced in the standard fashion in each patient. Array comparative genomic hybridization (array CGH) was performed using Affymetrix CytoGenetics Whole-Genome 2.7M array, and the results were analyzed using Affymetrix Chromosome Analysis Suite v1.2. CNVs were assessed as unlikely to be pathologic if they were also present in the Database of Genomic Variants (DGV) or our local database of array CGH results in 150 normal individuals of Middle Eastern ethnicity.
RESULTS	No patient had a sequence mutation in <i>SALL4</i> , <i>CHN1</i> , <i>HOXA1</i> , <i>TUBB3</i> , or <i>KIF21A</i> . These 12 patients each had 36–42 chromosomal deletions and/or duplications (mean with standard deviation, 26.25 ± 6.77), but all of these CNVs were present either in the DGV or in our local database of normal individuals of similar ethnicity and, therefore, are considered nonpathogenic.
CONCLUSIONS	The results reported here suggest that bilateral nsDRS is not usually associated with mutations in these genes or with chromosomal CNVs. Current evidence suggests other factors such as epigenetic and/or teratogenic abnormalities may be a potential cause of bilateral nsDRS. (<i>J AAPOS</i> 2016;20:396–400)

Duane retraction syndrome (DRS) was one of the first described congenital ocular motility disorders and classically consists of deficient abduction with globe retraction and narrowing of the palpebral fissure on attempted adduction.^{1,2} DRS represents congenital defective innervation of the lateral rectus muscle by the ipsilateral abducens nerve with subsequent aberrant innervation of that muscle by a branch of the ipsilateral oculomotor nerve, resulting in varying degrees of co-contraction of the lateral and medial rectus muscles on attempted adduction.^{2,3} DRS is usually unilateral, isolated, and sporadic, without an identifiable monogenic cause, but it occurs bilaterally in

13%–24% of DRS patients,^{4–6} with or without other congenital anomalies.^{5,7,8}

Three monogenic DRS syndromes have been reported, including Duane–radial ray syndrome (DRRS; OMIM 607323), caused by autosomal dominant mutations in the spaltlike transcription factor 4 (*SALL4*) gene^{9,10}; Duane retraction syndrome 2 (DURS2; OMIM 604356), due to autosomal dominant mutations of chimerin 1 (*CHN1*)^{11,12}; and the Bosley–Salih–Alorainy syndrome (BSAS; OMIM 601536), caused by autosomal recessive mutations of homeobox A1 (*HOXA1*).^{13–15} In addition, patients with ocular motility abnormalities due to autosomal dominant kinesin family member 21A (*KIF21A*) or tubulin, beta 3 class III (*TUBB3*) mutations may have ocular motility deficits that include features similar to DRS.^{16,17} The genetic causes of DRS are not always monogenic in origin, because a number of syndromic DRS patients have now been reported in association with a variety of different chromosomal copy number variations (CNVs).¹⁸ Epigenetic and teratogenic causes have been hypothesized in the absence of a recognized genetic abnormality.¹⁹

There have been rare reports of nonsyndromic bilateral Duane retraction syndrome (bilateral nsDRS) from monogenic mutations in the context of affected families, but it is unclear how common this phenomenon is. We evaluated 12 patients with bilateral nsDRS for possible monogenic and chromosomal etiologies.

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- Full article provided in chapter 3

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- Full article provided in appendix chapter 8

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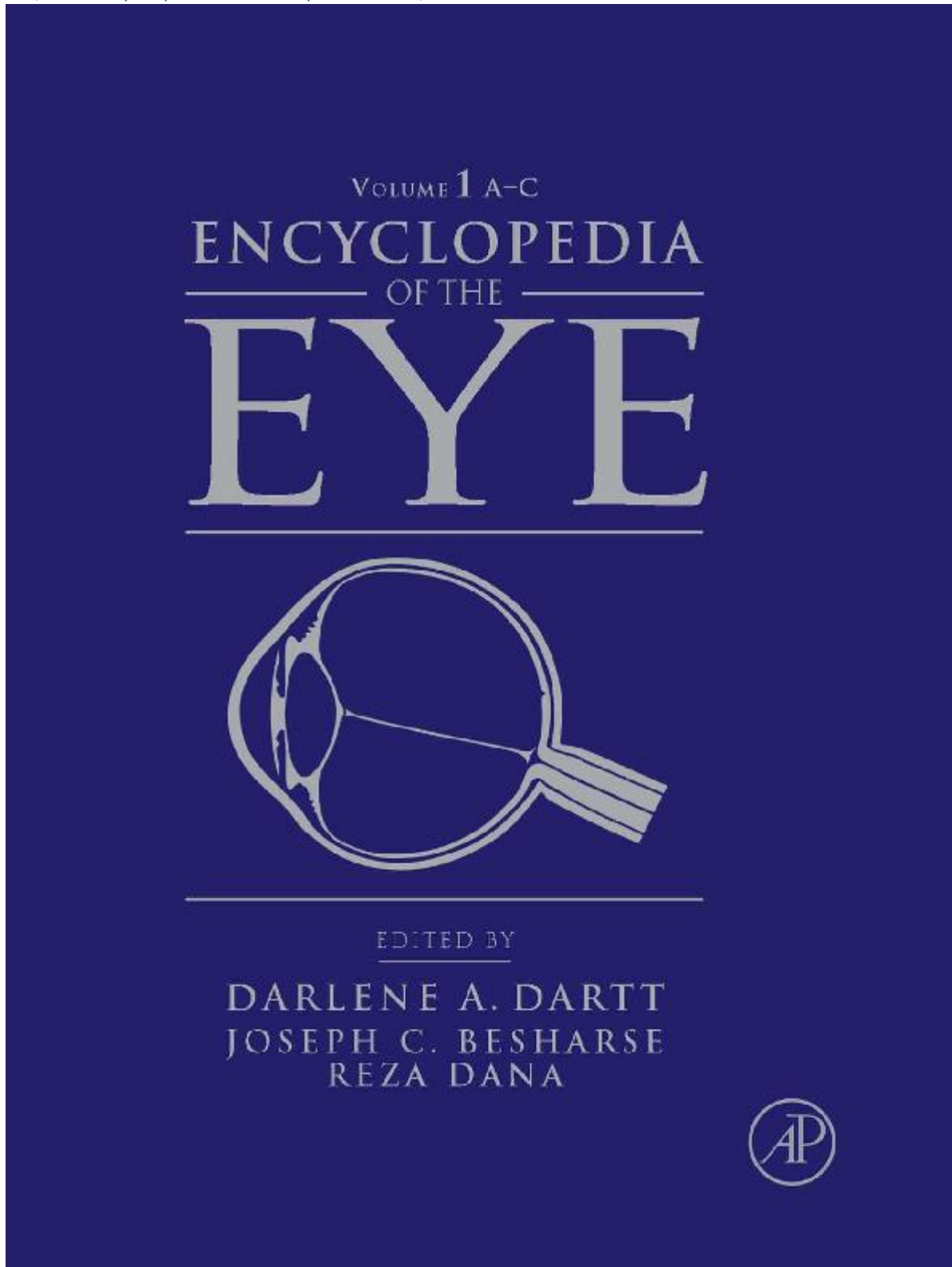
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Neurological features of congenital fibrosis of the extraocular muscles type 2 with mutations in PHOX2A

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Congenital fibrosis of the extraocular muscles type 2 (CFEOM2) is a complex strabismus syndrome that results from mutations in the homeodomain transcription factor PHOX2A. To define the clinical and neuroimaging features of patients with this autosomal recessive syndrome, we studied 15 patients with genetically defined CFEOM2. All patients underwent full neurological, neuro-ophthalmological and orthoptic assessments. Twelve patients had pupillary pharmacological testing and nine had 3.0 tesla MRI of the brain, brainstem and orbits. Patients were born with severe bilateral ptosis and exotropia with almost complete bilateral absence of adduction, elevation, depression and intorsion. Variable abduction was present prior to strabismus surgery in 14 patients, and central ocular motility reflexes (smooth pursuit, saccades, vestibulo-ocular reflex and optokinetic reflex) were intact except for convergence. Pupillary light and near reflexes were not present, but irises were anatomically normal and responded to pupillary pharmacology. Neuroimaging of brain and brainstem was remarkable for the anatomical absence of cranial nerve (CN) 3 and probably CN 4 bilaterally. Therefore, the CFEOM2 phenotype and neuroimaging are both consistent with the congenital absence of CNs 3 and 4. Additional features included presence of most central ocular motility reflexes, a central lack of pupillary responsiveness of uncertain aetiology and modest phenotypic variability that does not correlate with specific PHOX2A mutations. Clinical presentation, neuroimaging and *Phox2a*^{-/-} animal models all support the concept that CFEOM2 is a primary neurogenic abnormality with secondary myopathic changes.

Keywords: brain imaging; brain development; ocular motor nerve; congenital ophthalmoplegia

Abbreviations: CCDDs = congenital cranial dysinnervation disorders; CFEOM2 = congenital fibrosis of the extraocular muscles type 2; CN = cranial nerve; EOM = extraocular muscle

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Introduction

Congenital strabismus in humans can result from mutations in a number of genes, including *ROBO3* (Jen *et al.*, 2004), *PHOX2A* (Nakano *et al.*, 2001), *SALL4* (Al-Baradie *et al.*, 2002), *HOXA1* (Tischfield *et al.*, 2005) and *KIF21A* (Yamada *et al.*, 2003) that are essential to the normal development of brainstem motor neurons or

axons. We now refer to these syndromes as congenital cranial dysinnervation disorders (CCDDs) (Gutowski *et al.*, 2003).

The first insight into the genetics of the CCDDs came from studies of congenital fibrosis of the extraocular muscles type 2 (CFEOM2; OMIM 602078), in which affected

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RESEARCH REPORT

Retinal Dysfunction in Patients with Congenital Fibrosis of the Extraocular Muscles Type 2

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ABSTRACT

Introduction: Congenital fibrosis of the extraocular muscles type 2 (CFEOM2) is a distinct non-syndromic form of congenital incomitant strabismus secondary to orbital dysinnervation from recessive mutations in the gene *PHOX2A*. The phenotype includes bilateral ptosis, very large angle exotropia, ophthalmoplegia, and poorly-reactive pupils. Other than amblyopia, afferent visual dysfunction has not been considered part of CFEOM2; however, we have repeatedly observed non-amblyopic subnormal vision in affected patients. The purpose of this study was to document this recurrent feature of the phenotype.

Methods: A retrospective case series (2002-2012).

Results: Eighteen patients (four families) were identified; all affected individuals had confirmed homozygous recessive *PHOX2A* mutations except one individual for whom genetic testing was not done because of multiple genetically confirmed family members. Age at assessment ranged from 5-62 years old (median 10 years old). All patients had decreased best-corrected visual acuity not completely explainable by amblyopia in both the preferred and non-preferred eye. In those patients who had further ancillary testing, visual fields (five patients) and electroretinography (10 patients) confirmed abnormalities not ascribable to amblyopia.

Conclusions: In addition to a distinct form of congenital incomitant strabismus, the phenotype of CFEOM2 includes subnormal vision consistent with retinal dysfunction. This could be the direct result of *PHOX2A* mutations or a secondary effect of orbital dysinnervation.

Keywords: Congenital cranial dysinnervation disorder; congenital fibrosis of the extraocular muscles; *PHOX2A*; retina

INTRODUCTION

Although congenital fibrosis of the extraocular muscles (CFEOM) was originally considered a primary disorder of extraocular muscle formation, CFEOM is now recognized as one of several rare forms of congenital incomitant strabismus secondary to orbital dysinnervation that are collectively known as congenital cranial dysinnervation disorders (CCDDs).¹ The main clinical features of CFEOM type 2 (CFEOM2; Mendelian inheritance in

Man [MIM] #602078) are bilateral ptosis and absent adduction, supraduction, and infraduction, creating the appearance of bilateral oculomotor nerve palsies.² Abduction is present although often incomplete, and pupils generally are variable in size and shape and non-reactive to light and accommodative targets although they respond appropriately to pupillary pharmacologic agents and accommodative ability seems intact.³ Neuroimaging shows absent oculomotor nerves bilaterally.³

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BRAIN
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A novel syndrome caused by the E410K amino acid substitution in the neuronal β -tubulin isotype 3

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Missense mutations in *TUBB3*, the gene that encodes the neuronal-specific protein β -tubulin isotype 3, can cause isolated or syndromic congenital fibrosis of the extraocular muscles, a form of complex congenital strabismus characterized by cranial nerve misguidance. One of the eight *TUBB3* mutations reported to cause congenital fibrosis of the extraocular muscles, c.1228G>A results in a *TUBB3* E410K amino acid substitution that directly alters a kinesin motor protein binding site. We report the detailed phenotypes of eight unrelated individuals who harbour this *de novo* mutation, and thus define the 'TUBB3 E410K syndrome'. Individuals harbouring this mutation were previously reported to have congenital fibrosis of the extraocular muscles,

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Publication list for Chapter 5

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- Full article provided in chapter 5

Oystreck, D. T., Alorainy, I. A., Morales, J., Chaudhry, I. A., Elkhamary, S. M., & Bosley, T. M. (2014). Ocular motility abnormalities in orbitofacial neurofibromatosis type 1. *J AAPOS*, 18(4), 338-343.

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CLINICAL STUDY

Orbitofacial neurofibromatosis: clinical characteristics and treatment outcome

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DT Oystreck² and TM Bosley^{1,2}

Abstract

Purpose To report clinical observations and surgical management in a large series of patients with orbitofacial neurofibromatosis type 1 (OFNF).

Patients and methods Patients were identified and medical records reviewed for demographic data, ophthalmologic examinations, surgical interventions, and procedure outcome to create a retrospective, non-comparative case series of patients with OFNF seen at one medical centre over a 23-year period.

Results Sixty patients with OFNF (31 females and 29 males; mean age, 14 years) were followed for an average of 5.7 years. Presenting signs and symptoms included eyelid swelling in all patients, ptosis in 56 (93.3%), proptosis in 34 (56.6%), dystopia or strabismus in 30 (50%), and decreased visual acuity in 50 (83.3%). Surgical intervention included ptosis repair in 54 (90%; mean 1.6 surgical procedures), facial and orbital tumour debulking in 54 (90%; mean 2.3 surgeries), and canthoplasty in 28 (46.6%) patients. Eleven patients required enucleation or exenteration of a blind eye.

Conclusion Patients with OFNF often require multiple procedures to preserve vision, prevent additional disfigurement, and achieve cosmetic rehabilitation. Patients need regular ophthalmological monitoring given the potential for progressive visual and cosmetic consequences.

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Keywords: neurofibromatosis type 1; orbitofacial neurofibromatosis; pleomorphic neurofibromas; sphenoid dysplasia; optic pathway glioma

Introduction

Neurofibromatosis type 1 (NF1; von Recklinghausen disease; OMIM 162200) is a fairly frequent (1 in 3000 live births), autosomal dominant, neurocutaneous disorder that has considerable clinical variability and the potential for multisystem involvement.¹ Although most commonly benign, neurofibromas (NFs) have the potential of malignant transformation² and can have devastating functional and cosmetic effects. In orbitofacial NF1 (OFNF), which occurs in 1-22% of patients, NFs may cause progressive, disfiguring tumours of the orbital, facial, and temporal areas.^{3,4} In this study, we review the experience with surgical management of OFNF in patients seen at the King Khaled Eye Specialist Hospital (KKESH), a tertiary eye care referral centre in Riyadh, Saudi Arabia, and the largest eye facility in the Middle East.

Patients and methods

Patients with OFNF treated at KKESH over a 23-year period were identified and their medical records reviewed to catalogue demographic information, presenting signs and symptoms, ophthalmologic examination data, diagnostic studies performed, and surgical interventions rendered. All patients had NF1 on the basis of clinical criteria established by the National Institute of Health,^{5,6} and the diagnosis of OFNF was confirmed histologically in all surgical cases.^{1,3} Pathological specimens ranged from small tissue biopsy sample obtained at the time of ptosis correction to bulky tumours up to 25 cm in aggregate.

Visual acuity (VA) was recorded for each eye at least at the time of diagnosis and at the last eye examination. Involvement of

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Original Contribution

Congenital Myasthenic Syndrome Due to Homozygous *CHRNE* Mutations: Report of Patients in Arabia

Mustafa A. Salih, MD, Darren T. Oystreck, MMedSci, OC(C), Yasser H. Al-Faky, MD, FRCS, Mohammed Kabiraj, MD, Mohamed I. A. Omer, FRCP, Elamin M. Subahi, FRCP, David Beeson, PhD, Khaled K. Abu-Amero, PhD, Thomas M. Bosley, MD

Abstract: We describe the clinical characteristics of 3 siblings from 1 family with congenital myasthenic syndrome due to homozygous mutations of the gene coding for the epsilon subunit of the acetylcholine receptor (*CHRNE*). Onset of symptoms occurred in the first few months of life with ptosis, restricted ocular motility, mild proximal weakness, and difficulty swallowing. Multiple hospital admissions were required due to recurrent pulmonary infections. There was no decremental conduction on repetitive nerve stimulation, but jitter was increased on single fiber electromyographic. Since early childhood, our patients have done well without pulmonary or bulbar symptoms and with partial improvement on pyridostigmine therapy. Response of ptosis to diagnostic ice pack test was striking. Although these siblings have a clinical history and examination findings typical of homozygous *CHRNE* mutations, the clinical presentation of congenital myasthenia subtypes is variable, and accurate genotyping is essential in choosing the appropriate treatment.

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The congenital myasthenic syndromes (CMS) are rare and comprise a group of inherited disorders (1) in which the safety margin of the neuromuscular junction transmission is compromised (2,3). CMS may be misdiagnosed as a congenital muscular dystrophy or myopathy leading to delayed or incorrect treatment (1).

The diagnosis of CMS is based on clinical symptomatology and absence of antiacetylcholine receptor (AChR) antibodies plus at least 1 of the following: electromyographic (EMG) evidence of neuromuscular transmission defect, response to pyridostigmine, and molecular genetic confirmation (3). Depending on the mutated gene, symptoms and signs may not be present in utero or in the neonatal period (1,4), potentially complicating diagnosis. Molecular diagnosis is critical because incorrect treatment in CMS can be life threatening (4).

We describe 3 brothers with CMS from a consanguineous family. These patients have homozygous mutations of the gene encoding the epsilon subunit of the AChR (*CHRNE*) (5,6). They illustrate important features of the history and examination of this CMS variant, including the potential value of the ice pack test reported previously in autoimmune myasthenia.

CASE REPORT

Three siblings from a consanguineous family with 5 children were the product of normal pregnancies (with normal in utero movement) and were asymptomatic in the immediate postpartum period. However, by the age of 2–3 months, the oldest boy (Patient 1) developed bilateral ptosis, decreased feeding, choking, and failure to thrive. He had several hospital admissions and on 4 occasions was admitted to the neonatal intensive care unit because of respiratory failure. The middle brother (Patient 2) and the younger brother (Patient 3) had less severe symptoms beginning at approximately 4 months of age, although they

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Ocular Neostigmine Drops for Diagnosing Myasthenia Gravis

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Abstract

Introduction: A variety of tests have been devised for the diagnosis of myasthenia gravis (MG). The best known of these (Tensilon test, using intravenous edrophonium chloride) may cause serious complications (bradycardia and syncope) dictating cardiac monitoring during the procedure. Ocular neostigmine drops, a simple procedure, may significantly reduce the risk of diagnostic testing for possible MG.

Method: To investigate its efficacy, the miotic effect of neostigmine was explored using 30 rabbits. One drop of sterile neostigmine solution (2.5 mg/ml) was instilled into the right eye (RE) of each rabbit using the left eye (LE), which received sterile normal saline, as control. Serial assessments of pupillary size were done. One drop of neostigmine was instilled daily for 7 days to investigate its safety. Six patients (aged 4.5–55y, median=42y, mean=36.4y) with MG had the same test and were observed for increase of the palpebral fissure height (documented by photography).

Results: At baseline there was no significant difference in the mean [SD] pupillary size of the rabbits between the RE (7 mm [1.07]) and LE (7 mm [1.07]), $p=0.63$. Significant miotic effect was observed in the RE compared to the LE at 30, 60 and 90 minutes (respectively, 4.8 mm [1.86] vs 7.0 mm [1.09], $p=0.0001$; 4.8 mm [1.86] vs 7.0 mm [1.09], $p=0.0001$; and 3.2 [0.76] vs 7.0 [0.0], $p=0.013$). Administration of one drop of neostigmine daily for 7 days caused no ocular inflammation. All six patients with MG had an observable increase of the palpebral fissure height (documented by photography) of at least 2 mm, 30 minutes after neostigmine instillation. The response was dramatic in the three patients with no prior treatment for MG.

Conclusion: Ocular neostigmine drops is a safe, simple and efficient diagnostic test for MG.

Keywords: Myasthenia gravis; Diagnosis; Ocular neostigmine drops; Tensilon test; Edrophonium chloride

Introduction

Myasthenia gravis (MG) is an acquired autoimmune disorder caused by autoantibodies directed against epitopes on or around the acetylcholine receptor (AChR) in the muscle membrane [1]. The condition is characterized clinically by variable ptosis, ocular motility abnormalities, and weakness of voluntary muscles in other parts of the body [1]. Nearly all patients present with extraocular muscles involvement, causing ptosis and diplopia, and in 20–40% of patients, weakness remains limited to these muscles (ocular MG) [1-3]. The diagnosis may be difficult to make on clinical grounds especially in juvenile cases when weakness is restricted to few muscles such as in ocular MG [4], and a variety of supportive diagnostic tests have been devised [5].

Perhaps the best known of these is the Tensilon test [5-8], using intravenous edrophonium chloride, which is an acetylcholinesterase (AChE) inhibitor with very short action. Unfortunately, edrophonium causes cholinergic side effects that may include increased oral and bronchial secretions, bradycardia, abdominal cramps, sweating, bradycardia, heart block, hypotension, and red, watery, painful eyes. These are often uncomfortable for the patient, and although serious complications of bradycardia and syncope are rare [9] the test is now commonly performed with cardiac monitoring and atropine available as an anti-cholinergic agent. Other relative contraindications for performance of edrophonium are cardiac dysrhythmias and bronchial asthma. A second quick bedside test is by applying an ice pack locally

to a ptotic eyelid for 2-5 minutes and observing for any improvement of ptosis or eye movement deficit [10-12]. The ice pack test is simple, inexpensive, and has a reported sensitivity of 93–97% and specificity of 97–98% [13]. This adjunctive diagnostic test is particularly helpful if the edrophonium test is contraindicated or not available. However, the procedure is unlikely to be tolerated by young children [14].

Other supportive tests require laboratory and electrophysiologic facilities. Serologic tests include assessing AChR antibodies which are found in 80% of adults with MG [15], 70% of peripubertal juvenile MG but only 50% of prepubertal MG [16,17]. Antibodies to muscle-specific kinase (MuSK) are rare in juvenile MG [18].

Electrodiagnosis of MG includes repetitive nerve stimulation [RNS] (looking for a decrement of greater than 10% of the fifth compared to the first-evoked compound muscle action potential [CMAP] in

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Clinical Observation

Variable Ptosis after Botulinum Toxin Type A Injection with Positive Ice Test Mimicking Ocular Myasthenia Gravis

Ahmad M. Alaraj, MD, Darren T. Oystreck, MMedSci, Thomas M. Bosley, MD

Abstract: We describe a patient who received cosmetic botulinum toxin type A injections to the brow and subsequently developed unilateral ptosis that was variable during examination and was transiently improved after the ice pack test. Ptosis gradually resolved spontaneously over approximately 3 months. This is the third patient to have variable ptosis documented after botulinum toxin type A injection to the brow and the second to have a positive ice test. The ice test is not completely specific for myasthenia gravis but may, at times, improve ptosis resulting from other defects at the neuromuscular junction. Wound botulism now is much more common because of illicit drug use, and the ice test also might be positive in this setting.

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Botulinum toxin injections (Botox; Allergan, Inc, Irvine, CA) (Dysport; Medicis Aesthetics, Inc, Scottsdale, AZ) (Myobloc; Elan, Inc, San Francisco, CA) are the most common minimally invasive facial procedures performed in the United States and probably worldwide (1,2). We describe a patient with unilateral ptosis following cosmetic botulinum toxin type A injections to the brow that mimicked myasthenia gravis (MG), including having a positive ice test (3,4). This patient highlights the issues regarding diagnostic difficulties in the setting of ptosis following botulinum toxin type A injection and regarding the specificity of the ice test for myasthenic ptosis.

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Alaraj et al. *J Neuro-Ophthalmol* 2013; 33: 169-171

CASE REPORT

A 52-year-old woman presented with a 1-week history of a drooping right upper eyelid. She denied diplopia, pain, dysphagia, dysarthria, dyspnea, generalized weakness, or any other focal neurologic symptoms, and initially, she did not mention receiving cosmetic botulinum toxin injections. Medical history was significant for diabetes mellitus and hypertension, and her medications were glibenclamide and amlor. Family history was unremarkable.

Visual acuity was 20/20 in the right eye and 20/40 in the left eye. She had 3 mm of right upper eyelid ptosis (Fig. 1A) with fatigability of the right levator on sustained upgaze and a positive Cogan lid twitch sign. The left upper eyelid was normal, as was examination of the pupils. Ocular motility was full, and funduscopy was normal. The remainder of her neurologic examination was unremarkable without dysarthria or midline or appendicular weakness. A 5-minute ice test was performed resulting in transient improvement in ptosis of >2 mm (Fig. 1B).

General physical examination and chest x-ray were normal. Acetylcholine receptor antibody titer was within the normal limits. On a follow-up visit, the patient admitted receiving cosmetic botulinum toxin type A injection to the right eyebrow 3 days before the onset of right ptosis. There was complete resolution of ptosis over 12 weeks (Fig. 1C).

DISCUSSION

Our patient developed unilateral upper lid ptosis shortly after cosmetic botulinum toxin type A injections to the ipsilateral brow and forehead. Initial clinical examination mimicked MG with variable lid position, Cogan lid twitch sign, and transient resolution of ptosis after cooling of the involved lid with an ice pack (3,4). The patient did not have diplopia, limited ocular motility, or any other systemic signs or symptoms of generalized MG, and acetylcholine receptor

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VIDEO Neurologic features of horizontal gaze palsy and progressive scoliosis with mutations in *ROBO3*

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Abstract—Objective: To review the neurologic, neuroradiologic, and electrophysiologic features of autosomal recessive horizontal gaze palsy and progressive scoliosis (HGPPS), a syndrome caused by mutation of the *ROBO3* gene on chromosome 11 and associated with defective decussation of certain brainstem neuronal systems. **Methods:** The authors examined 11 individuals with HGPPS from five genotyped families with HGPPS. Eight individuals had brain MRI, and six had electrophysiologic studies. **Results:** Horizontal gaze palsy was fully penetrant, present at birth, and total or almost total in all affected individuals. Convergence, ocular alignment, congenital nystagmus, and vertical smooth pursuit defects were variable between individuals. All patients developed progressive scoliosis during early childhood. All appropriately studied patients had hypoplasia of the pons and cerebellar peduncles with both anterior and posterior midline clefts of the pons and medulla and electrophysiologic evidence of ipsilateral corticospinal and dorsal column-medial lemniscus tract innervation. Heterozygotes were unaffected. **Conclusions:** The major clinical characteristics of horizontal gaze palsy and progressive scoliosis were congenital horizontal gaze palsy and progressive scoliosis with some variability in both ocular motility and degree of scoliosis. The syndrome also includes a distinctive brainstem malformation and defective crossing of some brainstem neuronal pathways.

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Dretakis and Kondoyannis were the first to recognize the autosomal recessive syndrome of horizontal gaze palsy and progressive scoliosis (HGPPS; OMIM 607313).¹ The most complete neurologic description to date² was the 1975 review of a Hakka Chinese family, noting the absence of horizontal gaze in the examined patients and the development of severe, progressive scoliosis during childhood.

We confirmed the autosomal recessive character of this syndrome in six affected individuals of two unrelated consanguineous families and localized the problem to chromosome 11q23–25.³ Recently, we studied 10 unrelated consanguineous HGPPS families and identified 10 different mutations in the human *ROBO3* gene,⁴ a gene homologous to roundabout genes in other species that are important in the regulation of axonal midline crossing during brain development.^{5,6} We found electrophysiologic evidence of uncrossed corticospinal and dorsal column-

medial lemniscus pathways. Therefore, patients with HGPPS have a profound anatomic maldevelopment of the brainstem, including failure of at least two long neuronal tracts to decussate, violating a fundamental principle of vertebrate neuroanatomy.

We describe neurologic, neuroradiologic, and electrophysiologic observations in 11 affected members of five genotyped HGPPS families.

Methods. Patients. We interviewed five consanguineous families (figure 1) and examined 11 affected individuals (seven male and four female subjects aged 2 months to 22 years) over a period of up to 5 years (table 1). Four of these families were previously reported⁴ (Family A = Family 2; Family B = Family 1; Family C = Family 3; Family D = Family 4), and all affected individuals harbored homozygous mutations in *ROBO3* (3325 + 1 G in Family A, G361E in Family B, R703P in Family C, and S705P in Family D). The remaining family (E) had the same frameshift mutation in *ROBO3* as Family A and proved to be distantly related. All individuals signed informed consent approved by Institutional Review Boards at all participating institutions.

Clinical evaluation. All patients had a complete neuro-ophthalmologic and neurologic examination, including videotaping of eye movements. Near and distance visual acuity and near point of accommodation were measured in most patients. Orthoptic assessment was performed on 10 individuals (not C-1), with observations dependent on age and ability to cooperate. Fusional status

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Khan, A. O., Oystreck, D. T., Al-Tassan, N., Al-Sharif, L., & Bosley, T. M. (2008). Bilateral synergistic convergence associated with homozygous ROB3 mutation (p.Pro771Leu). *Ophthalmology*, 115(12), 2262-2265.⁶¹

Bilateral Synergistic Convergence Associated with Homozygous ROB3 Mutation (p.Pro771Leu)

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Objective: To document the phenotype and determine the genotype of a child with synergistic convergence.

Design: Interventional case report.

Participants: Patient and nuclear family (7 members total).

Methods: Ophthalmologic, neurologic, and radiologic examination of the proband; venous blood sampling for candidate gene testing of the proband; venous blood sampling for confirmatory testing in other family members.

Main Outcome Measures: Clinical and radiologic observations in proband and candidate gene results.

Results: The proband, a 9-year-old girl, substituted convergence for horizontal gaze (synergistic convergence) since birth. She also had conjugate pendular nystagmus, asynchronous blinking, and high myopia. No family member had ophthalmologic or medical symptoms. Neuroradiologic imaging revealed hindbrain dysplasia and modest scoliosis. Sequencing of *ROB3*, the gene associated with horizontal gaze palsy and progressive scoliosis, revealed a novel missense mutation (p.Pro771Leu) that altered an evolutionarily conserved amino acid. Screening the family for this mutation confirmed that both parents were carriers and identified 2 sisters as carriers and 2 brothers as noncarriers.

Conclusions: This is the second reported patient with synergistic convergence and the first associated with a documented pathologic genotype. Unlike the previously reported case (which occurred in the setting of the cranial dysinnervation disorder congenital fibrosis of the extraocular muscles), our patient presumably has a supranuclear cause.

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Synergistic convergence is a rare abnormal extraocular muscle motility pattern consisting of bilateral adduction during attempted lateral gaze in the absence of convergence spasm. It has been described previously in an adult with clinical and radiologic evidence for congenital fibrosis of the extraocular muscles type 1 (CFEOM1, On-Line Mendelian Inheritance in Man [MIM] 135700).¹ In that patient, synergistic convergence was presumably infranuclear in origin, related to the aberrant orbital innervation that is part of the congenital cranial dysinnervation disorders.² We describe the phenotype and document the genotype for a second patient with synergistic convergence. Unlike the previously reported case, our patient probably has a supranuclear etiology caused by a novel homozygous mutation in *ROB3* [MIM *608630], the gene associated with horizontal gaze palsy and progressive scoliosis (HGPPS) [MIM 60731].^{3,4}

Materials and Methods

Institutional review board approval was granted for this project. The patient had complete ophthalmologic, neurologic, and orthoptic examinations. Magnetic resonance imaging of the brain was obtained on

a 3.0 Tesla Siemens Magnetom Allegra scanner (Siemens Medical Systems, Erlangen, Germany), including axial 3-dimensional Fourier transform constructive interference in steady-state of the brainstem. Family members were observed but not thoroughly examined; they had no ophthalmologic or general medical symptoms.

A 5-mL venous blood sample was collected from the patient for diagnostic sequencing of coding exons in the candidate genes *KIF21A* (MIM *608283), *HCVX1* (MIM *142955), and *ROB3*. Sequencing was done using polymerase chain reaction on a MegaBace 1000 capillary sequencer (Global Medical Instrumentation, Ramsey, MN; exact primers and conditions available on request). Carrier testing for the apparent *ROB3* mutation was performed on the proband's parents and 4 siblings. Controls were 50 healthy Saudi individuals (100 chromosomes) who donated their DNA for polymorphism research. When a sequence variant was identified, it was tested for in one control (2 chromosomes). If the variant was not found in the one control, it was tested for in the 100 normal chromosomes.

Results

The proband, a 9-year-old girl who was the fifth child of a first-cousin marriage, was seen because of congenital, nonprogressive, abnormal eye movements. Birth history and medical history

Amouri, R., Nehdi, H., Bouhlal, Y., Kefi, M., Larnaout, A., & Hentati, F. (2009). Allelic *ROBO3* heterogeneity in Tunisian patients with horizontal gaze palsy with progressive scoliosis. *J Mol Neurosci*, 39(3), 337-341.⁶²

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Allelic *ROBO3* Heterogeneity in Tunisian Patients with Horizontal Gaze Palsy with Progressive Scoliosis

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Abstract Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder characterized by the congenital absence of horizontal gaze, progressive scoliosis, and failure of the corticospinal and somatosensory axon tracts to decussate in the medulla. HGPPS is caused by mutations of the *ROBO3* gene, which encodes a protein that shares homology with the roundabout family of transmembrane receptors that are important in axon guidance and neuronal migration. To date, over 15 mutations have been found in consanguineous families of Greek, Italian, Turkish, Pakistani, Saudi Arabian, and Indian descent. To detail clinical, cerebral magnetic resonance imaging (MRI) and genetic findings of ten HGPPS patients from four unrelated Tunisian families. Four unrelated consanguineous Tunisian families with a total of ten patients suffering from horizontal gaze palsy with progressive scoliosis. Genetic linkage analysis and direct sequencing of the *ROBO3* gene. All patients shared similar clinical gaze movement abnormalities and variable degrees of scoliosis. Four distinct homozygous mutations were identified. This study extends the molecular spectrum of the *ROBO3* gene and the geographic origin of patients with *ROBO3* gene mutations, and underlines the homogeneity of the motor ocular syndrome whatever type of mutation is encountered.

Keywords Autosomal recessive disorder · Genetic mutation · Horizontal gaze palsy · Progressive scoliosis

Introduction

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder characterized by the absence of conjugate lateral eye movements with preserved vertical gaze and progressive scoliosis from birth (Bosley et al. 2005). A striking brainstem malformation, with markedly diminished size and a bifid appearance of the medulla oblongata (“butterfly medulla”), is found in patients with HGPPS (Jen et al. 2004; MacDonald et al. 2004). The unusual appearance of the medulla and abnormal functional results suggest that sensorimotor projections do not cross the midline in HGPPS (Jen et al. 2004; MacDonald et al. 2004).

The gene responsible for HGPPS has been identified as *ROBO3*. This gene encodes a protein that shares homology with the roundabout family of transmembrane receptors important in axon guidance and neuronal migration (Jen et al. 2004). Over ten different mutations located in different domains of the encoded protein have been identified and are thought to diminish the function of this receptor (Jen et al. 2004). To date, the patients reported are essentially from consanguineous families of Greek, Italian, Turkish, Pakistani, Saudi Arabian, and Indian descent. One patient from non-consanguineous parents of Irish and German descent was reported as a compound heterozygote (Jen et al. 2004).

In this study, we report the clinical, cerebral MRI and genetic findings of ten HGPPS affected patients from four unrelated Tunisian families.

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- Full PDF is provided in chapter 2 appendix

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A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome

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Multinucleate cellular syncytial formation is a hallmark of skeletal muscle differentiation. Myomaker, encoded by *Myrk* (*Tmem8c*), is a well-conserved plasma membrane protein required for myoblast fusion to form multinucleated myotubes in mouse, chick, and zebrafish. Here, we report that autosomal recessive mutations in *MYMK* (OMIM 615345) cause Carey-Fineman-Ziter syndrome in humans (CFZS; OMIM 254940) by reducing but not eliminating *MYMK* function. We characterize *MYMK*-CFZS as a congenital myopathy with marked facial weakness and additional clinical and pathologic features that distinguish it from other congenital neuromuscular syndromes. We show that a heterologous cell fusion assay *in vitro* and allelic complementation experiments in *myrk* knockdown and *myrk*^{int/int} zebrafish *in vivo* can differentiate between *MYMK* wild type, hypomorphic and null alleles. Collectively, these data establish that *MYMK* activity is necessary for normal muscle development and maintenance in humans, and expand the spectrum of congenital myopathies to include cell-cell fusion deficits.

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NEW OBSERVATIONS REGARDING THE RETINOPATHY OF GENETICALLY CONFIRMED KEARNS–SAYRE SYNDROME

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Purpose: To report novel retinal findings in Kearns–Sayre syndrome and correlate degree of retinopathy with other clinical findings.

Methods: Observational case series of patients from Saudi Arabia with retinal and neuroophthalmologic examinations, medical chart review, and mitochondrial genetic evaluation.

Results: The three unrelated patients had progressive external ophthalmoplegia and pigmentary retinopathy bilaterally. Muscle biopsy in two of the cases revealed mitochondrial myopathy. All three had abnormal findings on neuroimaging and modestly reduced visual acuity in both eyes with a variable pigmentary retinopathy. One of the patients had bilateral subretinal fibrosis with a full-thickness macular hole in the right eye. All three patients had single, large-scale mitochondrial DNA (mtDNA) deletions (5.0–7.6 kb in size) with blood mtDNA heteroplasmy levels ranging from below 20% to 57%. Severity of pigmentary retinopathy did not correlate with severity of progressive external ophthalmoplegia, but did correspond grossly with electroretinographic abnormalities, just as the degree of ocular motility restriction and ptosis in each patient correlated with the size of their extraocular muscles on neuroimaging. In addition, the size of the single, large-scale mtDNA deletion and level of mtDNA heteroplasmy corresponded with degree of ocular motility restriction but not with severity of retinopathy.

Conclusion: Subretinal fibrosis and macular hole are novel retinal observations which expand clinical profile in Kearns–Sayre syndrome. Genetic testing for mtDNA deletions and heteroplasmy in blood, muscle biopsy, careful ocular and retinal examination including electroretinography, and imaging are indispensable tests for this condition.

RETINAL CASES & BRIEF REPORTS 12:349–358, 2018

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Saudi Arabia; ††The Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom; and †††The Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland.

Kearns–Sayre syndrome (KSS)¹ is a rare mitochondrial (mt) cytopathy which is generally recognized by the triad of progressive external ophthalmoplegia, pigmentary retinopathy, and onset

Oystreck, D. T., Khan, A. O., Vila-Coro, A. A., Oworu, O., Al-Tassan, N., Chan, W. M., Engle, E.C., Bosley, T. M. (2009). Synergistic divergence: a distinct ocular motility dysinnervation pattern. *Invest Ophthalmol Vis Sci*, 50(11), 5213-5216.³⁷

Synergistic Divergence: A Distinct Ocular Motility Dysinnervation Pattern

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PURPOSE. To summarize the clinical, neuroimaging, and genetic observations in a group of patients with unilateral synergistic divergence (SD).

METHODS. Five unrelated patients with unilateral SD underwent ophthalmic and orthoptic examinations; three of them also had magnetic resonance imaging of the brain and orbits. Three patients underwent genetic evaluation of genes known to affect ocular motility: *KIF21A*, *PHOX2A*, *HOXA1*, and *ROBO3*.

RESULTS. The patients did not meet the clinical criteria for CFEOM types 1, 2, or 3. Each patient had severe adduction weakness on the affected side and large-angle exotropia in primary gaze that increased on attempted contralateral gaze because of anomalous abduction. Magnetic resonance imaging revealed a much smaller medial rectus muscle in the involved SD orbit. Oculomotor cranial nerves were present in the one patient imaged appropriately. Genetic sequencing in three patients revealed no mutations in *KIF21A*, *PHOX2A*, *HOXA1*, or *ROBO3*.

CONCLUSIONS. SD should be classified as a distinct congenital ocular motility pattern within congenital cranial dysinnervation disorders. It may be caused by denervation of the medial rectus with dysinnervation of the ipsilateral lateral rectus by the oculomotor nerve precipitated by genetic abnormalities (some currently identified) or by local environmental, teratogenic, or epigenetic disturbances. (*Invest Ophthalmol Vis Sci*. 2009;50:5213-5216) DOI:10.1167/iov.08-2928

Synergistic divergence (SD) is a congenital ocular motility pattern characterized by paradoxical abduction during attempted horizontal gaze to the contralateral side.¹ This rare

condition is generally unilateral and is always associated with limited adduction of the affected eye. The pathophysiology of anomalous abduction remains unclear but has been variously attributed to mechanical factors, anomalous innervation of the ipsilateral medial and lateral recti muscles,^{2,3} and even anomalous cross innervation between the two lateral recti.⁴ SD is usually an isolated ocular motility abnormality, but it has been described several times in conjunction with ocular motility phenotypes consistent with congenital fibrosis of the extraocular muscles types 1 (CFEOM1)⁵ and 3 (CFEOM3).⁶

This report summarizes clinical, radiologic, and genetic observations in a group of patients with unilateral SD.

METHODS

Five unrelated patients of Middle Eastern ethnicity had complete orthoptic and ophthalmic examinations, including dilated funduscopy. Ocular motility was assessed visually and by videotaping. Fusion was measured using the Worth 4-Dot Test and the Lang Stereo Test.

Standard brain MR pulse sequences were acquired in one patient by a 1.5-Tesla scanner (Signa; GE Medical Systems, Waukesha, WI) and in two patients by a 3.0-Tesla scanner (Magnetom Allegra; Siemens Medical Systems, Germany), including sagittal T₁-weighted spin-echo, coronal fluid-attenuated inversion recovery, axial dual echo, and axial proton density inversion recovery sequences in all patients and axial 3D FT constructive interference in steady state (CISS) of the brain stem in one patient. One patient had brain computed tomography performed on another scanner (Sensation 4; Siemens Medical Systems).

Five milliliters of peripheral blood was collected in EDTA tubes from three patients and high-molecular-weight DNA was extracted with a blood kit (Puregene; Qiagen, Hilden, Germany), quantified spectrophotometrically, and stored at -20°C in aliquots until required. *PHOX2A* (MIM *602753),⁷ *HOXA1* (MIM *142955),⁸ and *KIF21A* (MIM *608283)⁹ (Mendelian Inheritance in Man, provided in the public domain by the National Institutes of Health, Bethesda, MD; <http://www.ncbi.nlm.nih.gov/Omim/>) coding exons and exon-intron boundaries were amplified using polymerase chain reactions (PCR) with *Taq* DNA polymerase (Hotstar; Qiagen). Two patients also had *ROBO3* (MIM *608630)¹⁰ sequenced. All resulting amplicons for *PHOX2A*, *HOXA1*, and *ROBO3*, and the amplicons for *KIF21A* exons 8, 20, and 21 were direct sequenced on a sequence analyzer (3730; Applied Biosystems, Inc. [ABI], Foster City, CA). The remaining *KIF21A* amplicons were analyzed by denaturing high-performance liquid chromatography (DHPLC; Transgenomic, Inc., Omaha, NE). All screening conditions were as previously published, and primers are available on request. Study protocol adhered to the tenets of the Declaration of Helsinki, and patients signed consent forms approved by the King Khaled Eye Specialist Hospital, Riyadh, or the Children's Hospital, Boston.

RESULTS

Birth, general medical history, and family history were unremarkable, although two patients were from consanguineous families (a typical prevalence in the Middle East). Figure 1 illustrates the eye movements of patients 1, 2, and 3, whereas Table 1 presents clinical details. All patients were male, and all

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REPORT

HOXB1 Founder Mutation in Humans Recapitulates the Phenotype of *Hoxb1*^{-/-} Mice

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Members of the highly conserved homeobox (*HOX*) gene family encode transcription factors that confer cellular and tissue identities along the antero-posterior axis of mice and humans. We have identified a founder homozygous missense mutation in *HOXB1* in two families from a conservative German American population. The resulting phenotype includes bilateral facial palsy, hearing loss, and strabismus and correlates extensively with the previously reported *Hoxb1*^{-/-} mouse phenotype. The missense variant is predicted to result in the substitution of a cysteine for an arginine at amino acid residue 207 (Arg207Cys), which corresponds to the highly conserved Arg5 of the homeodomain. Arg5 interacts with thymine in the minor groove of DNA through hydrogen bonding and electrostatic attraction. Molecular modeling and an in vitro DNA-protein binding assay predict that the mutation would disrupt these interactions, destabilize the HOXB1:PBX1:DNA complex, and alter HOXB1 transcriptional activity.

Congenital facial paralysis (CFP) has been classified among the congenital cranial dysinnervation disorders (CCDDs).¹⁻³ CFP could be inherited, and autosomal-dominant loci have been mapped for isolated CFP (HCFP1 locus) and for CFP with variable hearing loss (HCFP2 locus).⁴⁻⁶ CFP can also occur together with complex congenital eye-movement disorders, and in particular as a component of Moebius syndrome (MIM 157900). Moebius syndrome was defined at the Moebius Syndrome Foundation Research Conference in 2007 as congenital, nonprogressive facial weakness with limited abduction of one or both eyes (inability to move the eye fully outward or toward the ear).⁷ Additional features can include hearing loss and other cranial nerve dysfunction, as well as motor, orofacial, musculo-skeletal, neurodevelopmental, and social problems.^{1,8,9} Moebius syndrome is most frequently sporadic, and with the exception of rare *HOXA1* (MIM 142955) or *TUBB3* (MIM 602661) mutations that cause atypical

Moebius syndromes, its genetics remain undefined.^{10,11} Sorting out its genetics has been complicated, in part, by the not-infrequent misdiagnosis of Moebius syndrome in children who have CFP but do not have limited abduction of the eye.

In an effort to identify causative mutations for Moebius syndrome and CFP, we in the Jabs and Engle laboratories enrolled probands diagnosed with these and related disorders and their family members in ongoing genetic studies. The Jabs study was approved by the institutional review boards at The Johns Hopkins University and Mount Sinai School of Medicine, and the Engle study was approved by the institutional review board of Boston Children's Hospital. Written informed consent was obtained from participating family members or from their guardians. All investigations were conducted in accordance with the principles of the Declaration of Helsinki.

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Ophthalmic features of ataxia telangiectasia-like disorder

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INTRODUCTION	Ataxia telangiectasia (AT) is a recessive neurodegenerative disease due to a faulty repair mechanism for breaks in double-stranded DNA (<i>ATM</i> mutation). Ophthalmic features of AT include conjunctival telangiectasia, strabismus, saccadic dysfunction with head thrusts, and convergence insufficiency. Ataxia telangiectasia-like syndrome (ATLD) is a more recently recognized condition due to homozygous mutation in <i>MRE11</i> , a gene also involved in the cellular repair response to double-stranded DNA breaks; ophthalmic features of ATLD are not well described. The purpose of this article is to describe the ophthalmic features of ATLD.
METHODS	Full ophthalmologic and orthoptic evaluations were obtained in 13 individuals: 10 previously reported ATLD patients, an additional related ATLD patient, and 3 nonaffected relatives. All individuals were from three unrelated consanguineous Saudi Arabian families harboring an <i>MRE11</i> mutation (W210C). Age range was from 2 to 40 years of age.
RESULTS	No affected patient had structural ocular abnormality (eg, conjunctival telangiectasia), manifest strabismus at distance, or duction limitation. All but one (the youngest) had saccadic dysfunction (without head thrusts). Most patients had abnormal convergence. Older patients had nystagmus with abnormalities in smooth pursuit and vestibular ocular reflex. All patients had cerebellar atrophy by neuroimaging and slowly progressive ataxia. The unaffected heterozygous relatives had unremarkable ophthalmic and neurologic examinations.
CONCLUSIONS	Saccadic dysfunction without head thrusts and convergence abnormality are common in ATLD secondary to homozygous W210C <i>MRE11</i> mutation. Older patients have nystagmus with abnormalities in smooth pursuit and vestibular ocular reflex. Eye movement control systems apparently deteriorate with time in this rare neurological disease. Ophthalmic features of AT that were not observed in any of our ATLD patients include conjunctival telangiectasia, head thrusting, and manifest strabismus at distance. (<i>J AAPOS</i> 2008;12:186-189)

Ataxia telangiectasia (AT; [On-line Mendelian Inheritance in Man (OMIM) 208900, <http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>]) is a rare (1/40,000 for the USA) genomic instability syndrome due to a faulty repair response to double-stranded DNA breaks (homozygous *ATM* mutation) and is characterized by progressive cerebellar ataxia, dysarthria, sensitivity to ionizing radiation, cancer predisposition, and immunodeficiency with recurrent infections.^{1,2} Homozygous *ATM* mutation causes loss of function of the

ATM protein, a nuclear protein kinase integral for the cellular repair response to breaks in double-stranded DNA.^{1,2} Ocular features of AT, more prominent with increasing patient age, include conjunctival telangiectasia, strabismus, saccadic dysfunction with head thrusts, and convergence insufficiency.³

Ataxia telangiectasia-like disorder (ATLD; [OMIM 604391]) is a more recently recognized genomic instability syndrome due to a defect in a different component of the complex cellular response to double-stranded DNA breaks (homozygous *MRE11* mutation affecting the Mre11-Rad50-Nbs1 complex).^{1,4-7} There have been only 16 previously documented cases—4 from the United Kingdom,² 2 from Italy,⁶ and 10 from Saudi Arabia.⁷ In comparison to AT, ATLD has a later onset of neurological features, slower progression, and milder symptoms—including no reports to date of cancer predisposition or immunodeficiency.^{1,4-7} Virtually all ATLD patients carry *MRE11* mutations that express some level of corresponding protein (unlike the situation in AT, where most patients have *ATM* mutations that result in no detectable protein).^{1,4} Descriptions of ophthalmic features in ATLD are limited.^{4,7}

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Ophthalmic Features of Joubert Syndrome

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Purpose: Joubert syndrome (Online Mendelian Inheritance in Man 213300) is a rare autosomal recessive congenital malformation of the brainstem and cerebellar vermis. Diagnosis is based on characteristic clinical features (e.g., hypotonia, episodic hyperpnea, developmental delay, progressive ataxia) and is confirmed by distinctive neuroradiologic findings (e.g., the "molar tooth" sign). Variable ophthalmic features have been mentioned in prior reports; however, most do not detail eye findings and the few that do were before the publication of suggested diagnostic criteria. The objective of the current study is to describe the ophthalmic phenotype in a cohort of patients with Joubert syndrome for whom the diagnosis was made using current diagnostic criteria.

Design: Prospective case series.

Participants: Eight children diagnosed clinically with radiologic confirmation.

Methods: Ophthalmic examination and visual electrophysiology.

Main Outcome Measures: Ocular and oculomotor examination (as allowed by patient cooperation), electroretinography, flash visual-evoked potential (fVEP).

Results: Patients' ages ranged from 7 months to 10 years. Saccadic dysfunction was observed in all cooperative patients (8/8); compensatory head thrusts or turns were present in all except the youngest patient (7 months of age). Most patients (5/8) had primary-position nystagmus (see-saw in 3/5). Abnormal pursuit (3/7) and a dystrophic retinal appearance (3/8) were also seen. One patient had bilateral asymmetric ptosis with unilateral lid elevation during ipsilateral abduction. Electroretinography findings were normal for all 8 patients. Seven patients underwent fVEP; 6 were abnormal (asymmetric) and one was not interpretable because of study artifact.

Conclusions: Ophthalmologists should be aware that saccadic dysfunction (typically with head thrusts) and primary position nystagmus (typically see-saw) in a developmentally delayed child suggest the diagnosis of Joubert syndrome, especially if a dystrophic retinal appearance is also present. Our findings of asymmetric fVEPs and see-saw nystagmus suggest an abnormality in optic nerve decussation, consistent with the concept that impaired axonal guidance occurs in patients with Joubert syndrome.

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Joubert syndrome (Online Mendelian Inheritance in Man 213300) is a rare autosomal recessive disorder that is diagnosed clinically and confirmed radiologically.¹⁻⁵ The syndrome was named after Marie Joubert, who in 1969 described 4 patients with episodic tachypnea, developmental delay, ataxia, abnormal eye movements, and absence of the cerebellum.¹ In the same year, Dekaban² described 2 similar siblings who also had a retinal dystrophy. Since then, approximately 200 cases of Joubert syndrome have been published⁶ and diagnostic criteria have been proposed^{3,7}; however, because of the syndrome's rarity the diagnosis of Joubert syndrome can easily be overlooked.^{3,6} Hypotonia, ataxia, and global developmental delay are universal clinical findings.^{3,7} Episodic hyperpnea is common in infancy, and typical facial features are common in childhood (high rounded eyebrows, broad nasal bridge, anteverted nostrils, low-set ears).^{3,7,8} Neuroimaging shows absence of the cerebellar vermis and the "molar tooth sign"—an abnormal configuration of the superior cerebellar peduncles that connect the cerebellum to the midbrain.^{3,5,7} The absence of decussation of both the superior cerebellar peduncles and the corticospinal tracts at the medullary pyramids suggests

that patients with Joubert syndrome have a defect of axon guidance.^{9,10} A variety of other coexisting congenital abnormalities have been reported infrequently, including meningoencephalocele, microcephaly, polydactyly, kidney abnormality, soft tissue tumor of the tongue, liver disease, and duodenal atresia.⁷ The term "Joubert disease and related disorders" is sometimes used when associated findings suggest a unique distinct syndrome.³

Both ocular and oculomotor abnormalities have been reported to occur in patients with Joubert syndrome¹⁻¹⁵; however, most previous reports do not detail eye findings and the few that do¹¹⁻¹⁵ were before the publication of suggested diagnostic criteria.^{5,7} The purpose of this study is to describe the ophthalmic phenotype of Joubert syndrome in children who were diagnosed using suggested diagnostic criteria.

Materials and Methods

In a series of 8 consecutive patients, the diagnosis of Joubert syndrome was made on the basis of clinical criteria and confirmatory neuroimaging.^{3,7} Institutional review board approval was granted for complete ophthalmologic evaluation of this cohort.

Salih, M. A., Abu-Amero, K. K., Alrasheed, S., Alorainy, I. A., Liu, L., McGrath, J. A., Van Maldergem, L., Al-Faley, Y.H., AlSuhaibani, A.H., **Oystreck, D.T.**, Bosley, T. M. (2011). Molecular and neurological characterizations of three Saudi families with lipoid proteinosis. *BMC Med Genet*, 12, 31.⁶⁷

RESEARCH ARTICLE

Open Access

Molecular and neurological characterizations of three Saudi families with lipid proteinosis

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Abstract

Background: Lipid proteinosis is a rare autosomal recessive disease characterized by cutaneous and mucosal lesions and hoarseness appearing in early childhood. It is caused by homozygous or compound heterozygous mutations in the *ECM1* gene. The disease is largely uncharacterized in Arab population and the mutation(s) spectrum in the Arab population is largely unknown. We report the neurologic and neuroradiologic characteristics and *ECM1* gene mutations of seven individuals with lipid proteinosis (LP) from three unrelated consanguineous families.

Methods: Clinical, neurologic, and neuro-ophthalmologic examinations; skin histopathology; brain CT and MRI; and sequencing of the full *ECM1* gene.

Results: All seven affected individuals had skin scarring and hoarseness from early childhood. The two children in Family 1 had worse skin involvement and worse hoarseness than affected children of Families 2 and 3. Both children in Family 1 were modestly mentally retarded, and one had typical calcifications of the amygdalae on CT scan. Affected individuals in Families 2 and 3 had no gross neurologic, neurodevelopmental, or neuroimaging abnormalities. Skin histopathology was compatible with LP in all three families. Sequencing the full coding region of *ECM1* gene revealed two novel mutations in Family 1 (c.1300-1301delAA) and Family 2 (p.Cys269Tyr) and in Family 3 a previously described 1163 bp deletion starting 34 bp into intron 8.

Conclusions: These individuals illustrate the neurologic spectrum of LP, including variable mental retardation, personality changes, and mesial temporal calcification and imply that significant neurologic involvement may be somewhat less common than previously thought. The cause of neurologic abnormalities was not clear from either neuroimaging or from what is known about *ECM1* function. The severity of dermatologic abnormalities and hoarseness generally correlated with neurologic abnormalities, with Family 1 being somewhat more affected in all spheres than the other two families. Nevertheless, phenotype-genotype correlation was not obvious, possibly because of difficulty quantifying the neurologic phenotype and because of genetic complexity.

Background

Lipid proteinosis (LP; MIM 247100) is a rare autosomal recessive disease characterized by cutaneous and mucosal lesions and hoarseness appearing in early childhood [1] that is caused by homozygous or compound heterozygous mutations in the *ECM1* gene located on chromosome 1q21 [2]. This gene encodes a protein that is an important structural component of basement membrane and extracellular matrix [3,4], and loss of

protein-protein interactions due to *ECM1* gene mutations is the likely cause of dermatologic abnormalities including warty skin, scarring, and mucosal thickening [5]. These changes also affect the nasopharynx, tongue, and vocal cords, resulting in severe fibrosis and the hoarseness characteristic of the disorder.

Approximately one third of affected individuals are reported to have mild mental retardation [6], and neuropsychological problems may be more common [7-9]. Other reported neurologic abnormalities include complex partial seizures, memory loss, and emotional difficulties, often beginning in teenage years and progressing from that time onward [6,8]. Calcification of the mesial

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The neurology of carbonic anhydrase type II deficiency syndrome

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Carbonic anhydrase type II deficiency syndrome is an uncommon autosomal recessive disease with cardinal features including osteopetrosis, renal tubular acidosis and brain calcifications. We describe the neurological, neuro-ophthalmological and neuroradiological features of 23 individuals (10 males, 13 females; ages at final examination 2–29 years) from 10 unrelated consanguineous families with carbonic anhydrase type II deficiency syndrome due to homozygous intron 2 splice site mutation (the 'Arabic mutation'). All patients had osteopetrosis, renal tubular acidosis, developmental delay, short stature and craniofacial disproportion with large cranial vault and broad forehead. Mental retardation was present in approximately two-thirds and varied from mild to severe. General neurological examinations were unremarkable except for one patient with brisk deep tendon reflexes and two with severe mental retardation and spastic quadriplegia. Globes and retinae were normal, but optic nerve involvement was present in 23/46 eyes and was variable in severity, random in occurrence and statistically correlated with degree of optic canal narrowing. Ocular motility was full except for partial ductional limitations in two individuals. Saccadic abnormalities were present in two, while half of these patients had sensory or accommodative strabismus, and seven had congenital nystagmus. These abnormalities were most commonly associated with afferent disturbances, but a minor brainstem component to this disorder remains possible. All internal auditory canals were normal in size, and no patient had clinically significant hearing loss. Neuroimaging was performed in 18 patients and repeated over as long as 10 years. Brain calcification was generally progressive and followed a distinct distribution, involving predominantly basal ganglia and thalamic and grey–white matter junction in frontal regions more than posterior regions. At least one child had no brain calcification at age 9 years, indicating that brain calcification may not always be present in carbonic anhydrase type II deficiency syndrome during childhood. Variability of brain calcification, cognitive disturbance and optic nerve involvement may imply additional genetic or epigenetic influences affecting the course of the disease. However, the overall phenotype of the disorder in

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RESEARCH ARTICLE

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Molecular and neurological characterizations of three Saudi families with lipid proteinosis

Mustafa A Salih¹, Khaled K Abu-Amero^{2*}, Saleh Alrasheed³, Ibrahim A Alorainy⁴, Lu Liu⁵, John A McGrath⁶, Lionel Van Maldergem⁷, Yasser H Al-Fakey², Adel H AlSuhailbani², Darren T Oystreck², Thomas M Bosley^{2,8}

Abstract

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Methods: Clinical, neurologic, and neuro-ophthalmologic examinations; skin histopathology; brain CT and MRI; and sequencing of the full *ECM1* gene.

Results: All seven affected individuals had skin scarring and hoarseness from early childhood. The two children in Family 1 had worse skin involvement and worse hoarseness than affected children of Families 2 and 3. Both children in Family 1 were modestly mentally retarded, and one had typical calcifications of the amygdalae on CT scan. Affected individuals in Families 2 and 3 had no gross neurologic, neurodevelopmental, or neuroimaging abnormalities. Skin histopathology was compatible with LP in all three families. Sequencing the full coding region of *ECM1* gene revealed two novel mutations in Family 1 (c.1300-1301delAA) and Family 2 (p.Cys269Tyr) and in Family 3 a previously described 1163 bp deletion starting 34 bp into intron 8.

Conclusions: These individuals illustrate the neurologic spectrum of LP, including variable mental retardation, personality changes, and mesial temporal calcification and imply that significant neurologic involvement may be somewhat less common than previously thought. The cause of neurologic abnormalities was not clear from either neuroimaging or from what is known about *ECM1* function. The severity of dermatologic abnormalities and hoarseness generally correlated with neurologic abnormalities, with Family 1 being somewhat more affected in all spheres than the other two families. Nevertheless, phenotype-genotype correlation was not obvious, possibly because of difficulty quantifying the neurologic phenotype and because of genetic complexity.

Background

Lipoid proteinosis (LP; MIM 247100) is a rare autosomal recessive disease characterized by cutaneous and mucosal lesions and hoarseness appearing in early childhood [1] that is caused by homozygous or compound heterozygous mutations in the *ECM1* gene located on chromosome 1q21 [2]. This gene encodes a protein that is an important structural component of basement membrane and extracellular matrix [3,4], and loss of

protein-protein interactions due to *ECM1* gene mutations is the likely cause of dermatologic abnormalities including warty skin, scarring, and mucosal thickening [5]. These changes also affect the nasopharynx, tongue, and vocal cords, resulting in severe fibrosis and the hoarseness characteristic of the disorder.

Approximately one third of affected individuals are reported to have mild mental retardation [6], and neuropsychological problems may be more common [7-9]. Other reported neurologic abnormalities include complex partial seizures, memory loss, and emotional difficulties, often beginning in teenage years and progressing from that time onward [6,8]. Calcification of the mesial

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CASE REPORT

Ophthalmologic Observations in a Patient with Partial Mosaic Trisomy 8

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ABSTRACT

Background: To carefully assess the phenotype and genotype of a patient with partial mosaic trisomy 8 with particular attention to ophthalmologic features.

Methods: Ophthalmologic and neuro-ophthalmologic examination; neuroimaging; conventional karyotyping; and array comparative genomic hybridization (CGH).

Results: The proband was the only affected child of a non-consanguineous family. At birth she was noted to have facial dysmorphism including telecanthus, low set ears, prominent nares, and an everted lower lip. She had an accommodative esotropia with otherwise normal globes, optic nerves, retinae, and orbits. She also had delayed motor milestones and mild mental retardation associated with agenesis of the corpus callosum. Both karyotyping and array CGH documented mosaic partial trisomy of chromosome 8 that included all of the "q" arm and part of the proximal "p" arm.

Conclusions: This girl had a number of the classic features of mosaic trisomy 8, including an accommodative esotropia with none of the other ocular and orbital anomalies described in patients with mosaic trisomy 8. This report constitutes an initial effort to create a virtual database of patients with mosaic chromosome 8 in which careful phenotype-genotype correlation employing high resolution array CGH may help identify clues regarding the genetic etiology of ophthalmologic features of this syndrome.

Keywords: Accommodative esotropia, agenesis of corpus callosum, dysmorphism, mosaic trisomy 8

INTRODUCTION

Complete trisomy 8 is usually an early lethal condition. Trisomy 8 mosaicism is a less severe disorder with a distinct phenotypic presentation including retarded psychomotor development; moderate to severe mental retardation sometimes associated with corpus callosum agenesis; limb and skeletal anomalies including deep palmar and longitudinal plantar furrows, clinodactyly, and limitation of joint motion; facial

dysmorphism with hypertelorism, broad nasal root, and eye abnormalities; and congenital heart defects.^{1,2}

Mosaic trisomy 8 has not been reported in Saudi Arabia previously, and the incidence of the disorder is not known in the region. We describe a Saudi child with a rare cytogenetic presentation of mosaic trisomy 8 involving the entire "q" arm and part of the "p" arm³ who survived past the neonatal period with a number of developmental and dysmorphic features including an esotropia.

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ORIGINAL ARTICLE

Neurologic Injury in Isolated Sulfite Oxidase Deficiency

Thomas M. Bosley, Ibrahim A. Alorainy, Darren T. Oystreck, Ali M. Hellani, Mohammed Z. Seidahmed, Mohamed El Faki Osman, Mohamed A. Sabry, Mohamed S. Rashed, Eiman A. Al-Yamani, Khaled K. Abu-Amero, Mustafa A. Salih

ABSTRACT: Background: We review clinical, neuroimaging, and genetic information on six individuals with isolated sulfite oxidase deficiency (ISOD). **Methods:** All patients were examined, and clinical records, biochemistry, neuroimaging, and sulfite oxidase gene (SUOX) sequencing were reviewed. **Results:** Data was available on six individuals from four nuclear families affected by ISOD. Each individual began to seize within the first week of life. Neurologic development was arrested at brainstem reflexes, and severe microcephaly developed rapidly. Neuroimaging within days of birth revealed hypoplasia of the cerebellum and corpus callosum and damage to the supratentorial brain looking like severe hypoxic-ischemic injury that evolved into cystic hemispheric white matter changes. Affected individuals all had elevated urinary S-sulfocysteine and normal urinary xanthine and hypoxanthine levels diagnostic of ISOD. Genetic studies confirmed SUOX mutations in four patients. **Conclusions:** ISOD impairs systemic sulfite metabolism, and yet this genetic disease affects only the brain with damage that is commonly confused with the clinical and radiologic features of severe hypoxic-ischemic encephalopathy.

RÉSUMÉ: Lésions neurologiques dans le déficit isolé en sulfite oxydase. Contexte : Nous avons revu l'information clinique, de neuroimagerie et génétique de 6 individus atteints d'un déficit isolé en sulfite oxydase (DISD). **Méthode :** Tous les patients ont été examinés et leurs dossiers ont été revus, incluant la biochimie, la neuroimagerie et le séquençage du gène de la sulfite oxydase (SUOX). **Résultats :** Les données de 6 individus, faisant partie de 4 familles nucléaires différentes, atteintes de SUOX, étaient disponibles. Chaque individu a commencé à présenter des crises convulsives au cours de la première semaine de vie. Le développement neurologique était limité à la présence de réflexes du tronc cérébral et une microcéphalie sévère s'installait rapidement. La neuroimagerie effectuée dans les premiers jours après la naissance a montré une hypoplasie du cervelet et du corps calleux et des dommages sus-tentoriels ressemblant à une lésion hypoxique-ischémique sévère qui évoluait vers des changements d'aspect kystique de la substance blanche hémisphérique. Les individus atteints avaient tous un taux urinaire élevé de S-sulfocystéine et un taux urinaire normal de xanthine et d'hypoxanthine, caractéristiques du DISD. Les études génétiques ont confirmé une mutation de SUOX chez 4 patients. **Conclusions :** Le DISD perturbe le métabolisme systémique du sulfite et pourtant cette maladie génétique n'atteint que le cerveau. Le dommage à ce niveau est souvent confondu avec les manifestations cliniques et radiologiques d'une encéphalopathie hypoxique-ischémique sévère.

Can J Neurol Sci. 2014; 41: 42-48

Isolated sulfite oxidase deficiency (ISOD; MIM #272300) is an autosomal recessive syndrome involving homozygous or compound heterozygous mutations in the sulfite oxidase gene (SUOX; MIM #606887) on chromosome 12q13.2-13.3. Typically, an affected infant develops seizures and feeding difficulties within the first week of life, often with axial hypotonia and limb hypertonia. Initial neuroimaging usually shows diffuse edema affecting supratentorial structures, and cystic changes later appear in the hemispheric white matter¹. Neurologic development is generally halted at the level of brainstem reflexes, and the child remains vegetative and rapidly develops microcephaly. Death frequently occurs within the first years of life. A somewhat milder form of the disease has been reported^{2,3}, and some individuals survive into childhood. A related autosomal recessive disorder, molybdenum cofactor deficiency (MOCOD; MIM #252150), has similar clinical and radiologic features⁴ but is due to other mutated genes affecting sulfur and uric acid metabolism⁵.

The first clue to the etiology of ISOD was recognition that sulfite oxidase (SO), a soluble mitochondrial enzyme, was underactive in affected individuals⁶. Isolated sulfite oxidase deficiency patients experience an accumulation of sulfite, S-sulfocysteine, taurine, and thiosulfate and a decreased concentration of plasma cysteine⁷. They have elevated urinary

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Genetics

Genome-Wide Association Study Identifies a Susceptibility Locus for Comitant Esotropia and Suggests a Parent-of-Origin Effect

Sherin Shaaban,^{*,1-4} Sarah MacKinnon,⁵ Caroline Andrews,^{1,1,6} Sandra E. Staffieri,^{7,8} Gail D. E. Maconachie,⁹ Wai-Man Chan,^{1,6} Mary C. Whitman,^{2,5,10} Sarah U. Morton,¹¹ Seyhan Yazar,^{12,13} Stuart MacGregor,¹⁴ James E. Elder,^{8,15} Elias I. Traboulsi,¹⁶ Irene Gottlob,⁹ Alex W. Hewitt,^{7,13,17} Strabismus Genetics Research Consortium, David G. Hunter,^{5,10} David A. Mackey,^{7,13,17} and Elizabeth C. Engle^{1-3,5,6,18}

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Oystreck D.T. The orthoptic evaluation. In: Lambert SR, Lyons CJ, eds. Taylor & Hoyt's Pediatric Ophthalmology and Strabismus, 5th ed: Elsevier, 2017.¹¹

Oystreck, D. T., Engle, E. C., & Bosley, T. M. (2011). Recent progress in understanding congenital cranial dysinnervation disorders. *J Neuroophthalmol*, 31(1), 69-77.²⁶

- Full article provided in chapter 9

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- Full article provided in chapter 9

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- Full article provided in chapter 9

Oystreck, D. T. (2018). Ophthalmoplegia and Congenital Cranial Dysinnervation Disorders. *Journal of Binocular Vision and Ocular Motility*, 68(1), 31-33.⁷⁵

- Full article provided in chapter 9

Evidence for Objective 1

1

Demographic data & Summary information:

Name:		M / F
I.D.	D.O.B.:	Ethnic origin:
Residence:		Institutions examined at:

- New patient to KKESH
- Previously assessed at KKESH
- Included in past studies

Studies included in:**Previous classification given:****Previous genetic analysis:****Signs & Symptoms:**

1. Visual symptoms:
2. Observations by family members:
3. Neurological or systemic conditions:

Family History:

4. Parent's relation:
5. Other affected family members (pedigree analysis & classifications given)

RP 0424 strabismus form

Evidence for Objective 1



Children's Hospital Boston - Center for Strabismus Research
PHYSICIAN INFORMATION SHEET



Project Title:

**Genetic studies of Strabismus,
Congenital Cranial Dysinnervation Disorders (CCDD's)
and their associated anomalies.**

--- *Standardized Data Collection Form* ---

Section I.	Examining Physician Contact Details
Section II.	Participant Background Information
Section III.	Visual Acuity & Refraction Status
Section IV.	Anomalous Head Posture
Section V.	Lid Position
Section VI.	Ocular Alignment (Strabismus)
Section VII.	Resting Eye Position
Section VIII.	Ocular Motility
Section IX.	Other Associated Features
Section X.	Our Contact Details

Page Number 1

Evidence for Objective 1

ID: AEA-001

Mobius datasheet

ID: AEA-001 Sex: F Age: 22

Photos: Video: # Family members examined: 4

Previous strabismus surgery history: # Family members affected: 1 - IDENTICAL TWINS NOT AFFECTED

Gold weight ^{nil} R+L lids
+ Dra. Stage tubes in upper inner canthi

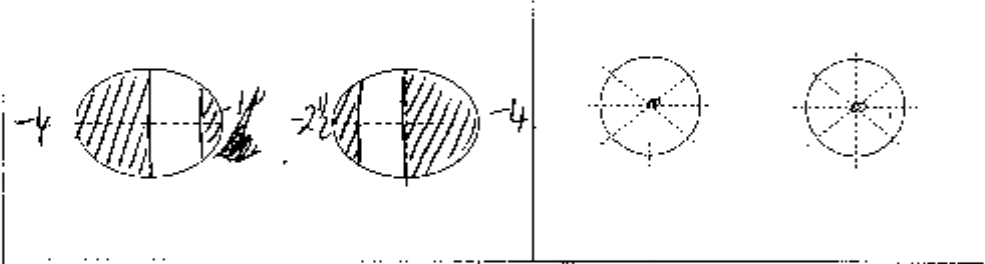
Ocular alignment: Have 9x records: Y/N

PCT N 3gls L X(CT) 25°
E 0.10 + DTD
0 3gls 4x incyclo 0.0700

Anomalous head postures: ~~not tilt~~ ~~Shoulder~~

Ocular motility summary:

Resting globe position:



RE LE

Ocular motility - Right gaze (retraction; synergistic movements)

near adduction

Ocular motility - Left gaze (retraction; synergistic movements)

Good Adduction

Ocular motility - upgaze (retraction; synergistic movements)

Normal

Ocular motility - downgaze (retraction; synergistic movements)


normal

Evidence for Objective 1

Oystreck D.T. The orthoptic evaluation. In: Lambert SR, Lyons CJ, eds. Taylor & Hoyt's Pediatric Ophthalmology and Strabismus, 5th ed: Elsevier, 2017.¹¹

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AU-9, page 75-10	DKN defined, pls check.	<input type="checkbox"/>
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AU-11, page 75-13	Edit OK? (Was "Trail")	<input type="checkbox"/>
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Evidence for objective 5

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REVIEW



Congenital cranial dysinnervation disorders: a concept in evolution

*Thomas M. Bosley^a, Khaled K. Abu-Amero^{a,b}, and Darren T. Oystreck^{a,c}***Purpose of review**

We review the congenital and genetic diagnoses that are currently included in the congenital cranial dysinnervation disorders (CCDDs).

Recent findings

Recent literature contains new genotypic and phenotypic descriptions of Duane retraction syndrome, Moebius syndrome, and other CCDDs. New genes which when mutated can result in CCDD have been identified, permitting a better understanding of associated phenotypes. More information is available regarding neurodevelopmental and clinical effects of various gene mutations associated with individual CCDDs. For certain CCDDs, the phenotype of a particular individual may not completely predict the genotype, and conversely, the genotype may not always predict the phenotype.

Summary

The CCDD concept has focused attention on specific congenital disturbances of human ocular motility and on the fact that these disorders are typically neurogenic in origin. The past decade has seen rapid evolution within this field with the last 2 years yielding additional information about existing diagnoses, genes, and phenotypes that may result in better classification of these disorders and new genotype-phenotype correlations in the future.

Keywords

brainstem development, congenital cranial dysinnervation disorders, cranial nerves, ocular motility, strabismus

INTRODUCTION

Ophthalmologists recognized over 60 years ago that certain children were born with congenital ocular motility abnormalities associated with restricted eye movements and fibrotic extraocular muscles [1]. This observation led to the assumption that the primary problem was a congenital abnormality of muscle development and thus to the concept of 'congenital fibrosis of the extraocular muscles' (CFEOM) [2]. Duane retraction syndrome (DRS) [3] and Moebius syndrome (MBS) [4] were recognized early on, and a number of other sporadic and familial congenital ocular motility syndromes were added as time passed.

Evidence accumulated over time that most or all of these syndromes had a neurogenic cause. Therefore, in 2002 an alternative concept of 'congenital cranial dysinnervation disorders (CCDD)' was proposed that shifted the focus away from muscle development [5]. Developments in the last decade have supported the CCDD concept, with all currently identified genes that cause CCDDs when mutated affecting brainstem and/or cranial

nerve development. It is likely that we have not yet identified all syndromes that would fall under the CCDD rubric, although presumably the ones not yet identified are less common (or at least harder to characterize) than those already recognized.

THE CONGENITAL CRANIAL DYSINNERVATION DISORDERS CONCEPT

The CCDD concept encompasses most congenital, static abnormalities of ocular motility and some additional abnormalities primarily involving lid

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