Balanced chromosome translocations and abnormal phenotypes

A report of 5 cases

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Summary

Five cases in which phenotypic abnormalities were found in association with apparent balanced chromosomal translocations are described. In 3 patients, one of the parents was found to be a carrier of the same translocation. In a further patient, the translocation was shown to be *de novo* and in the remaining patient the father was not available for chromosome studies. In a review of the literature the breakpoints in 36 familial balanced translocations were compared with 40 *de novo* translocations (including the present cases) all associated with phenotypic abnormalities. No common translocation was found in these groups, but it was observed that chromosomes 4 and 5 were significantly more involved in *de novo* translocations than in familial translocations. The possible aetiology and implications for prenatal diagnoses are discussed.

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Reciprocal translocations represent one of the most common chromosomal aberrations in man, their frequency amounting to approximately 1 in 1 000 births.[1]

Carriers of balanced reciprocal chromosome translocations are usually phenotypically normal but cases have been reported where individuals with apparent balanced translocations presented with mental retardation and phenotypic abnormalities.

Five cases with apparently balanced chromosome translocations detected because of abnormal phenotypes are reported. In a review of the literature the chromosomal breakpoints in a further 33 familial balanced translocations are compared with 39 *de novo* translocations, all associated with phenotypic abnormalities.

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Patients and methods

In a routine referral of patients to the Department of Cytogenetics at Tygerberg Hospital, 5 patients with phenotypic abnormalities were found to have balanced chromosome translocations.

In all cases chromosome preparations were made from peripheral blood lymphocyte cultures and in some cases from fibroblast cultures and were Q-banded[2] and G-banded[3] according to methods described at the Paris conference on Standardization in Human Genetics.[4]

A review of the literature showed 72 cases with balanced chromosome translocations and phenotypic abnormalities which could be tabulated with the present 5 cases according to the origin of the translocation: (*i*) familial; or (*ii*) *de novo*.

Case reports

Case 1

A male infant was delivered by caesarean section at 38 weeks' gestation because of fetal distress and prolonged labour. The baby weighed 1 750 g at birth, and the Apgar score was 5 and 10 after 1 and 5 minutes respectively. The father and mother were 37 and 31 years old at the time of the birth. There was a history of a previous miscarriage, but no further family history of abnormalities.

Two weeks after birth the infant was referred for genetic evaluation because of a suspected chromosomal abnormality.

Clinical features. The baby was long (exact length unknown) and had long hands, fingers and toes. The head circumference was below the 3rd percentile. The face was small with a prominent forehead and flat low-placed ears without ear lobes, narrow palpebral fissures and micrognathia. He failed to thrive and died shortly after a surgical repair of a pyloric stenosis at the age of 6 months.

Cytogenetic studies. The karyotype of the infant revealed the following apparently balanced translocation: 46,XY,t (3;5) (3pter → 3q23:;5pter → 5qter::3q23 → 3qter). The father's karyotype was: 46,XY/46,XY,t (3;5) (3pter → 3q23:;5pter → 5qter::3q23 → 3qter) with the translocation found in 32% of the cells analysed. The mother's karyotype had a different balanced translocation: 46,XX,t (7;18) (7qter → 7p12:;18qter → 18pter::7p12 → 7pter).

Case 2

An uneventful full-term pregnancy resulted in the birth of a female infant weighing 2 100 g, the only child of phenotypically normal parents. The father was 28 and the mother 27 years old at the time of birth. There was a history of use of marijuana by the father. At the age of 3 years the patient presented with psychomotor retardation.

Clinical features. Her length, weight and head circumference were normal for her age. She was mentally retarded, behaved abnormally and made little contact with her surroundings. Otherwise she was phenotypically normal. Several special examinations, including viral studies, thyroid studies and studies for metabolic abnormalities were performed but were not informative.

Cytogenetic studies. The child's karyotype revealed the following balanced translocation: 46,XX,t (1;4) (1qter → 1p32::4q31 → 4qter;4pter → 4q31::1p32 → 1pter). The mother had a normal karyotype but the father was not available for a chromosome analysis.

Case 3

This baby, weighing 3 100 g, was born by caesarean section at 40 weeks' gestation because of placenta praevia diagnosed at 35 weeks' gestation. He is the youngest son of normal parents and has 2 other normal siblings. The father and mother were 35 and 33 years old at the time of the birth. The baby developed slight neonatal jaundice, which was treated by phototherapy. Three febrile convulsions were recorded up to the age of 3 years, at which time he presented with psychomotor retardation.

Clinical features. His head circumference, length and weight were normal for his age. He had a strange appearance and a broad face. Little contact could be made with him and there was little emotional reaction. He could not talk and made choreiform movements with his hands and feet. Results of thyroid studies, amino-acid chromatography and radiographs of the skull and skeleton were normal. The diagnosis of global mental retardation of unknown origin was made.

Cytogenetic studies. The child's karyotype revealed the following balanced translocation: 46,XY,t (5;14) (5pter → 5q13::14q24 → 14qter; 14pter → 14q24::5q13 → 5qter). The karyotypes of both parents were normal.

Case 4

This patient was the second child of normal parents and had 2 normal siblings. The father and mother were 38 and 31 years old at the time of the birth. There was no family history of any abnormalities. Apart from an appendicectomy at 6 weeks' gestation the pregnancy was uncomplicated. The baby was born at term and weighed 4 600 g. Three days after birth she developed megencephaly and convulsions. At 7 months a ventriculogram showed small lateral ventricles, agenesis of the corpus callosum and megencephaly. At the age of 1 year she was placed in an institution for the mentally retarded. At the age of 14 years she was still being treated for grand mal epilepsy.

Clinical features. The patient was severely mentally retarded and had a broad face, broad forehead and a low anterior and posterior hairline. Her head circumference was normal. The eyes had a slight antimongoloid slant, the ears were big, low-placed and posteriorly rotated and the philtrum was short. She had a carp mouth, a short broad neck, a severe lumbar scoliosis and overriding of the second toe by the first toe on the right foot.

Cytogenetic studies. A chromosomal analysis of the patient revealed the following balanced translocation: 46,XX,t (5;7) (5pter → 5q12::7pl?4 → 7pter;7qter → 7pl?4::5q12 → 5qter). The mother was found to be the carrier of this translocation. The father had a normal karyotype. The siblings have not yet been karyotyped.

Case 5

This patient presented at the age of 10 years with several features of the Goltz syndrome. She was the second child of normal parents and had 4 normal siblings. No other history could be obtained.

Clinical features. The patient was growth-retarded and mildly mentally retarded. She had a triangular face with sparse hair and relatively big pointed ears, a broad, flat nasal bridge, a short philtrum, prognathism, and partial anodontia. Her chest was asymmetrical with bilateral accessory nipples. The right hand showed syndactyly of fingers II and III with partial absence of II and clinodactyly of finger IV. Clinodactyly was present bilaterally in fingers V. The left leg was shorter than the right leg. The left foot was hypoplastic with absence of the toes. There was also nail dystrophy. The skin showed areas of hypo- and hyperpigmentation in a linear distribution and telangiectasis in the skin folds. The left calf showed an area of fat herniation. Histologically the pigmented skin lesions showed slight hyperkeratosis with acanthosis and focal chronic inflammatory cell infiltrate.

Cytogenetic studies. The patient's karyotype revealed the following balanced translocation: 46,XX,t (1;10) (1qter → 1p32::10q22 → 10qter;10pter → 10q22::1p32 → 1pter). The mother was found to be the carrier of the translocation. The father and 3 siblings had normal karyotypes; the 4th sibling has not been tested.

Discussion

Including these 5 cases, 76 cases have been reported in the literature with balanced, non-Robertsonian chromosomal translocations in association with mental retardation and/or phenotypic abnormalities.

Out of the total of 76 patients, 36 had familial translocations,[5–23] and 19 of these were reported to be mentally retarded. The father was the carrier of the translocation in 22 cases and the mother in 14.

Three patients presented with autosomal dominant syndromes,[24] namely the Möbius syndrome,[11] Crouzon's disease,[12] and the Greig syndrome.[22] Two other patients presented with Pierre Robin's syndrome[12,21] and one with the Goltz syndrome (case 5), which has been described as X-linked dominant.[24] One patient with a t (14;18) had the 18q-phenotype.[16]

Forty of these 76 cases had *de novo* balanced translocations[5,6,9,12–14,16,21,25–35] and 25 (62,5%) of them were reported to be mentally retarded. One patient with a t (5;16) presented with the 16q-syndrome[16] and 1 with a t (3;15) (q29;q11) with the Prader-Willi syndrome.[12] Another patient had the Franceschetti syndrome[35] which has been described as an autosomal dominant condition.[24] Of the 76 patients, 44 were reported to be mentally retarded.

The breakpoints of the 36 familial and 40 *de novo* translocations were mapped to the chromosomes (Fig. 1). No common translocation was found, but it was observed that chromosomes 4 and 5 were significantly more involved in *de novo* translocations when compared to familial translocations.

Various screening studies of selected populations have been undertaken and the conclusion was that apparently balanced translocations are five times more common among mentally retarded people than among the general population of newborn infants.[9,12,13,16,36–38]

Theories put forward to explain the association between balanced chromosomal rearrangements and phenotypic abnormalities are:

1. A coincidental finding.[19,20]
2. Genes at the breakpoint may be altered in such a way that a dominant mutation is simulated.[5,21] This explains anomalies found in association with *de novo* translocations, but does not explain those found in familial cases.
3. The occurrence of a small deletion at the site of the chromosome break,[32,39] or a duplication,[9] so that the rearrangement is actually unbalanced.[15,16,26]
4. A position effect.[5,6,9,17,22,26,27,31,35,36,39,40]
5. Physical gene disruption with consequent loss of function at the breakpoint of a chromosomal translocation may lead to functional homozygosity of a recessive gene located at one of the sites of the respective translocation chromosomes.[21]

A problem arises for the genetic counsellor when such a rearrangement is found in a second trimester amniocentesis, especially if the translocation is *de novo* or if there is an affected sibling with the same balanced translocation.

Conclusion

Although this is a large selected group of patients no definite conclusions could be made with this study.

To prove or disprove the association between apparent balanced translocations and phenotypic abnormalities high-

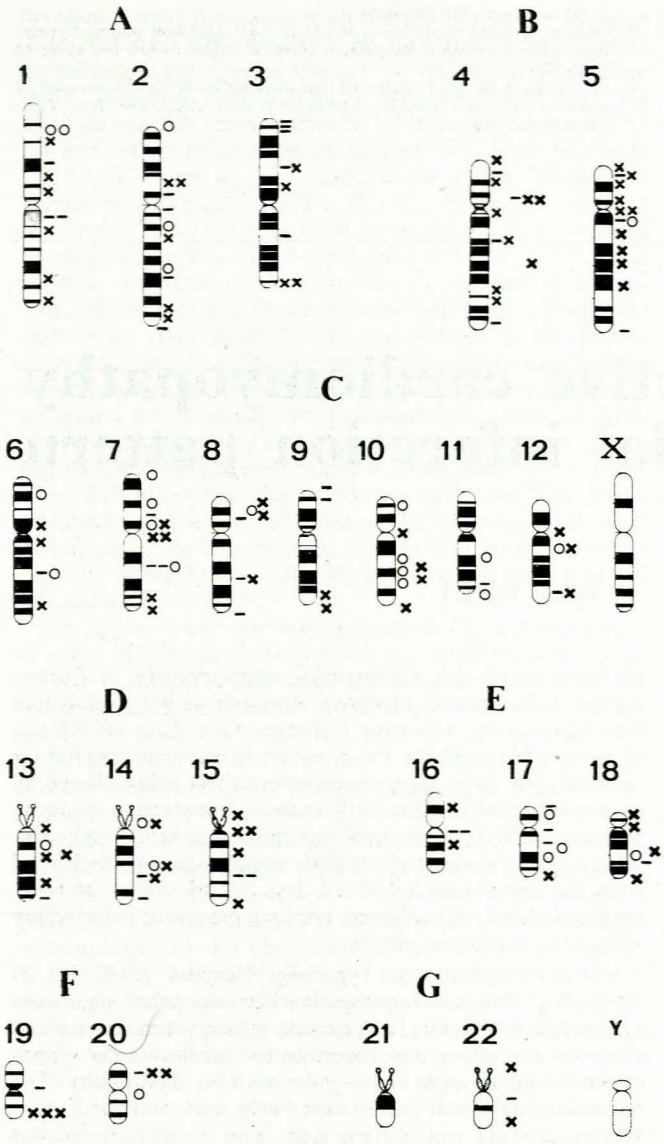

Fig. 1. Breakpoints of 36 familial[5-23] and 40 *de novo* translocations[5,6,9,12-14,16,21,25-35] mapped on a diagrammatic G-banded karyotype (x = *de novo* translocation breakpoints; o and — = familial translocation breakpoints (o = maternal origin, — = paternal origin)).

resolution chromosome banding should be done on all cases to detect microscopic deletions or duplications. Where possible studies should be done of enzymes mapped to the breakpoint regions.

Children with Mendelian disorders who display some unusual features, children with two Mendelian disorders and all new cases of common recessive disorders should be examined chromosomally.[21]

There is no doubt, however, that most children with balanced translocations will develop normally, and until the issue has been clarified only fetuses found to have unbalanced chromosomal translocations should be considered for abortion.

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Hypertrophic obstructive cardiomyopathy with pseudo-myocardial infarction pattern

A case report

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Summary

A 60-year-old woman with mild hypertension and presumed ischaemic heart disease was followed up over a very long period on account of angina pectoris. Acute myocardial infarction (MI) was suspected on the basis of the history, ECG findings and serum enzyme values, but disproved by radio-isotope investigation. Echocardiography demonstrated features of hypertrophic obstructive cardiomyopathy (HOCM), a diagnosis supported by cardiac catheterization and endomyocardial biopsy (EMB). Histological features of HOCM were absent from left ventricular EMB specimens despite a significant intraventricular gradient, but the right ventricular EMB demonstrated extensive changes of HOCM despite a small intraventricular gradient. Cardiac catheterization excluded previous MI and coronary artery disease. A further interesting feature was the development of congestive cardiac failure, which necessitated modification of her drug therapy.)

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Case report

This 60-year-old, obese, white woman had been treated for hypertension and angina pectoris for some 20 years. There was also a history of hypercholesterolaemia and thyrotoxicosis necessitating a subtotal thyroidectomy in 1965. Her father had died from diabetes mellitus. The patient was taking a great number of drugs which included atenolol, isosorbide dinitrate orally and sublingually, dipyridamole, clofibrate, aspirin, a diuretic and a sedative. Approximately 1 week before admission to the Intensive Coronary Care Unit (ICCU) at Tygerberg Hospital she was admitted to a private hospital for 'sciatica', and there experienced severe chest pain followed by syncope. The ECG taken at that time was reported as showing 'nonspecific T-wave changes' and the serum lactate dehydrogenase level was reputedly slightly raised. She was discharged from the private hospital after 2 days but a few days later was awoken suddenly with a severe crushing precordial pain slightly relieved by sublingual nitrates.

She was admitted to Tygerberg Hospital ICCU on 29 November 1984. On interrogation her only other significant symptoms were grade II dyspnoea, lethargy and palpitations not related to effort. Assessment of the cardiovascular system elicited a regular right radial pulse with no abnormality. The remaining peripheral pulses were fairly weak and the jugular venous pressure was not elevated. The blood pressure was 120/80 mmHg with significant postural decrease. There was evidence of left ventricular (LV) cardiomegaly; the apex beat was forceful and in the 6th intercostal space in the anterior axillary line. The 1st and 2nd heart sounds were normal but there was a prominent LV 4th heart sound. A grade 3/6 midsystolic murmur was clearly audible at the mitral area with some radiation up the left parasternal region and axilla. She had grade I hypertensive retinopathy. Side-room investigations were all negative. A chest radiograph delineated slight LV cardiomegaly. A resting ECG recorded while the patient was experiencing chest pain revealed sinus rhythm of 100/min, a P-R interval of 0,12 second, mean QRS axis of +10°, and LV hypertrophy by voltage criteria with anterolateral 2-3 mm horizontal ST-segment depression due to either a 'strain pattern' or possible acute nontransmural myocardial infarction (MI). Furthermore, there was very poor R-wave progression in the anteroseptal leads indicative of a pseudo-infarction pattern of LV hypertrophy or myocardial ischaemia. No atrial enlargement could be seen. A resting ECG, done after relief of chest pain by sublingual isosorbide dinitrate, indicated far less ST-segment depression anterolaterally.

The clinical diagnosis was of a possible acute nontransmural anterolateral MI with mitral incompetence secondary to papillary muscle dysfunction. Heparinization was instituted, as were maintenance nitrates, nifedipine 10 mg 3 times daily, and atenolol 50 mg/d. Later during the day the patient suddenly

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