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The genetics of diabetes mellitus, including the South African perspective

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Summary

By and large, essential diabetes mellitus is thought to be 50% inherited and 50% environmental. In insulin-dependent diabetes mellitus (IDDM) there is a strong link with the HLA system with regard to the inheritance of 'susceptible' diabetic genes, especially the DR3 and DR4 alleles. In IDDM environmental factors act in a predisposed individual to initiate an immune response with resultant beta-cell damage and destruction. Non-insulin-dependent diabetes mellitus (NIDDM) has no clear HLA link, but has been shown in studies of twins to have a stronger genetic basis than IDDM. In NIDDM environmental factors (race, ethnicity, diet, obesity) have an important influence on the clinical expression of the disease and the severity of complications in a genetically predisposed individual. The non-insulin-dependent diabetes of the young (NIDDY) variant and the phenomenon of chlorpropamide-primed alcohol-induced flushing both underline the heterogeneity of NIDDM. Because of the heterogeneous nature and multifactorial inheritance pattern of diabetes mellitus, accurate genetic counselling is not possible as yet. However, data to date suggest that it is unwise to advise prospective parents not to procreate, since the overall risk of the development of clinical diabetes mellitus is extremely low.

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The inheritance pattern of diabetes mellitus continues to defy specific characterization — the terms 'a geneticist's nightmare'¹ and 'geneticist's graveyard'² have been used in this context. It is now widely accepted that diabetes is a heterogeneous disorder with multifactorial inheritance. Heterogeneity implies that different genetic and/or environmental aetiological factors can result in similar clinical disorders, and multifactorial implies the action of two or more genes situated at different loci in a more or less additive fashion. Although evidence suggests that the two major forms of clinical diabetes are genetically distinct and tend to breed true within families,³⁻⁶ the following discussion will attempt to show how both heterogeneity and multifactorial inheritance are interwoven and contribute to both type I (insulin-dependent diabetes mellitus (IDDM)) and type II (non-insulin-dependent diabetes mellitus (NIDDM)) and its variants. A discussion of the specific genetic syndromes associated with glucose intolerance is beyond the scope of this article.

IDDM

The discovery of the histocompatibility antigen (HLA) system provided new insight into the genetic heterogeneity of IDDM and scientifically confirmed that in cases of IDDM, irrespective of age of onset, the major genetic susceptibility to diabetes is conferred by genes in the HLA chromosomal region.^{7,8}

The HLA system, which constitutes the major histocompatibility complex in man, is located on the short arm of the sixth chromosome and constitutes approximately 1/1 000th of the total genome.⁹ This genetic system consists of the HLA A, B and C loci which are found on all nucleated cell surfaces, whereas the more recently established HLA D and DR genes (loci) are found predominantly on B lymphocytes. The HLA system is extremely polymorphic at each locus, and between 6 and 30 alleles exist at each one of these loci, and there act to produce a slightly different surface antigen. Between these various loci (A, B, C, D and DR) there exists linkage disequilibrium, implying that some HLA genes and antigens occur more frequently in some individuals than would be expected from their frequencies.¹⁰

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The first HLA association with IDDM described was an increased prevalence in HLA B15,¹¹ while later studies included the HLA B8 association.^{7,12} At present the HLA association with IDDM as determined by population studies indicates that the main susceptibility is conferred by two alleles within the HLA D locus — allele DR3, which is closely linked to HLA B8 and B18, and allele DR4, which is linked to B15 and B40. The coexistence of DR3 and DR4 in the same individual greatly increases susceptibility to IDDM.² It is now clear that the alleles Dw3-DR3 and Dw4-DR4 represent the strongest and therefore primary association with type I diabetes, while the associations with HLA A, B and C antigens are almost certainly secondary and are due to linkage disequilibrium within the HLA system.^{13,14} At present there appear to be at least two susceptibility genes (S1 and S2), associated with the following HLA specificities: S1: Dw3-DR3-B8-Cw7-A1; S2: Dw4-DR4-B15-Cw3-A2. Owing to linkage disequilibrium within the HLA system, the factors which constitute the S1 axis and S2 axis are frequently inherited as haplotypes in diabetic families. The D-region specificities form the primary associations and possess the highest relative risk for the development of IDDM.^{15,16} It is of great interest that in subjects who possess HLA B7 linked to alleles Dw2-DR2 there is an extremely low risk of developing IDDM, suggesting the possibility of 'protective' genes in addition to the previously discussed 'susceptible' genes.^{10,17,18} However, recent studies would suggest that this phenomenon is secondary to the primary positive association with HLA Dw3 and Dw4.¹⁹

All the above HLA studies in IDDM have been documented in Whites, but the frequencies of different HLA antigens vary considerably in different populations; in some, HLA specificities are exclusively found in certain racial groups only. There is an increased association of type I diabetes in Japan with HLA B12,²⁰ Bw54²¹ and Dw4-DR4, but not B8 and DR3.²² There is increasing evidence that associations with DR3 and DR4 also exist in Black American insulin-dependent diabetics.²³ South African Whites are similar to European Whites with regard to HLA-antigen frequency distribution, but South African Blacks (Xhosa) are different in that they lack HLA A11 but possess HLA Aw43, which is absent in Whites.²⁴ Study of Xhosa IDDM subjects showed no increase in HLA B8 or B15 or decrease in B7 (as seen in Whites with IDDM), but there was a significant increase in HLA BW35. In the Black (Xhosa) NIDDM patients a significant increase in HLA A2 was found, which is the first known link between type II diabetes and the HLA system.²⁵

Heterogeneity in IDDM has also been demonstrated by studies of identical twins which have shown only a 50% concordance rate when the age of onset of diabetes in the index (initially diagnosed) twin was below 45 years. This finding suggests that there is a large group of subjects with IDDM in whom environmental factors are of major importance, although the predisposition to diabetes can be genetically determined.^{26,27} By determining this heterogeneity one may identify groups at risk for vascular complications, as was seen in a study of monozygotic twins in which the concordant pairs with IDDM were found to have more frequent and more severe complications than the discordant pairs.²⁸ However, recent evidence suggests no link at all between an HLA association and microvascular complications of IDDM.²⁹ Although there have been recent reports of an increased prevalence of blood group B in female type I diabetics,³⁰ and that fast acetylator phenotypes are more susceptible to diabetic neuropathy,³¹ neither of these factors appear to influence predisposition to microvascular disease in any way.

At present there is no doubt that the major susceptibility to type I diabetes is determined by one or more genes linked to the major histocompatibility complex, and present evidence favours the existence of two separate susceptibility genes in strong linkage disequilibrium with either HLA DR3 or DR4 alleles. However, it is evident from both HLA and twin studies that the

pathogenesis of IDDM does not have an exclusively genetic basis, but that environmental factors (viral, immunological) may under certain circumstances interact with the genes controlling susceptibility and resistance to beta-cell damage, and thereby trigger the mechanism to initiate an immune response in a predisposed individual, resulting in ultimate destruction of the pancreatic islet beta-cell membrane.

NIDDM

Several facts support the heterogeneity of NIDDM. No HLA association with type II diabetes has yet been found,¹² but recent reports suggest a possible association in the South African Xhosa.²⁵ The most compelling evidence for genetic transmission is provided by studies of twins. The first extensive study with monozygotic twin pairs²⁶ showed 71 pairs to be concordant and 35 pairs to be discordant, while a second study involving 185 pairs of monozygotic twins showed 110 pairs to be concordant and 75 pairs to be discordant.³² When the pairs in both studies were classified according to the age of onset of the disease, only 50% were concordant; in these the age of onset in the index patient was below 45 years, whereas 100% of those in whom diabetes developed in the index twin after the age of 50 years were concordant. It therefore appears that among twin pairs with NIDDM the concordance rate approached 100%, whereas in those pairs with IDDM concordance was approximately 50%.

With regard to the vascular complications of NIDDM, a study involving 44 monozygotic twin pairs who were concordant and who had been diabetic for 10 years showed remarkable similarity in respect of the presence and absence of retinopathy. If one twin developed severe retinopathy so would the other, whereas if one remained free from complications so would the other, despite the fact that they might have lived apart in different cities and adopted different lifestyles. This suggests that *genetic* factors are important in the development of diabetic retinopathy.³³

The influence of ethnic group on the incidence of diabetes is well known, together with the fact that distinctive forms of diabetes occur in various ethnic groups. Although the American Pima Indians are ethnically related to and share the same environment as the Navajo, the former have an incidence of diabetes 40 times that of the latter; the discrepancy is due in part to a more sedentary lifestyle, greater food intake and consequent obesity of the Pima Indians.³⁴ In contrast, in Alaska the Athabaskan Indians and Eskimos, who are ethnically different but live under similar, severe environmental conditions, have an equal (low) incidence of diabetes.³⁵ Although the prevalences of microvascular complications in diabetics of different races is strikingly different, the threshold for development of microvascular disease is similar in Whites and Pima Indians because of the latter's evolution to the metabolic genotype of the 'inappropriate' Western dietary pattern.^{36,37} In South Africa, Natal Indians are less prone to ketosis than are South African Blacks (Xhosa), but the former have more vascular complications.³⁸ It is interesting that the incidence of diabetes among Natal Indians has been shown to be 4 times higher than that among Whites, although the former were less overweight and had a lower intake of kilojoules, sugar and fat.³⁹

The best-delineated heterogeneity as regards NIDDM was described in 1974⁴⁰ in a distinct group of patients who had developed NIDDM at a young age (non-insulin-dependent diabetes of the young — NIDDY). The diabetes was metabolically mild, showed no evidence of ketonuria and was easily controlled without the use of insulin. The inheritance pattern was suggestive of autosomal dominance; evidence for this emanated from family studies which showed that: (i) diabetes was directly transmitted through three generations; (ii) 85% of the affected patients had an affected parent; and (iii) 50% of the siblings were diabetic.^{41,42} A similar pattern of inheritance was found in another group of

NIDDDY patients known as Mason diabetics after their family surname.³² To date there has been no HLA link with NIDDDY,^{42,43} although one study suggests a possible link in a family under observation.⁴⁴

A recent development which may further exemplify the heterogeneity within NIDDDM is the phenomenon of chlorpropamide-primed alcohol-induced flushing (CPAF). Originally studies were carried out on Mason diabetics and their families, all of whom were primed with 1 tablet (250 mg) of chlorpropamide followed by 10 ml of sherry 12 hours later. These results showed CPAF in 90% of the NIDDDY patients, in at least 1 parent of each patient, and in 50% of their siblings and offspring — indicating a mendelian dominant inheritance pattern. It was therefore postulated that CPAF was a marker for the development of NIDDDY.⁴⁵ However, further studies in late-onset NIDDDM patients revealed that 60% of them were CPAF-positive and that this trait was particularly prevalent in subjects with a strong family history of NIDDDM.⁴⁶ Type II diabetic patients with CPAF are reported to have milder diabetes as regards degenerative vascular complications, and severe diabetic retinopathy was found to be 7 times more common in CPAF-negative than in CPAF-positive non-insulin-dependent diabetics.⁴⁷ This evidence, and that previously discussed in relation to retinopathy in twin studies,³³ suggests that the tendency to develop retinopathy and its progression are largely influenced by genetic background. Recent evidence suggests that patients with NIDDDM who exhibit the CPAF phenomenon are significantly less likely to develop large-vessel disease; hence flushing is probably related to the pathogenesis not only of small-vessel but also of large-vessel disease.⁴⁸

CPAF can be simulated by the infusion of enkephalin analogues, and the resulting reaction can be blocked by administration of the opiate-antagonist naloxone. The administered enkephalin produced marked flushing only in those people who also showed CPAF. This suggests that the genesis of CPAF may involve an increased sensitivity to enkephalins, the endogenous opiates. These observations have led to the hypothesis that a link may exist between CPAF-positive NIDDDM and opiate-like neurotransmitters which could influence the secretion of insulin with a resultant effect on hepatic glucose output.⁴⁹ However, other groups have failed to confirm these findings and it is currently not clear whether CPAF predisposes to diabetes.

In South Africa the population with NIDDDY differs quite considerably from those described above, in that: (i) NIDDDY is common in both fat and lean subjects in the Natal Indian population; (ii) in both Indian and Cape Coloured (of mixed descent) patients NIDDDY is associated with severe vascular complications; (iii) there is no association with CPAF;³⁹ and (iv) autosomal dominant inheritance has not been established. However, a recent study involving the Natal Indian NIDDDY population showed that the trait was highly heritable and probably of an autosomal dominant mode.⁵⁰

Genetic counselling

In a given family the increased risk of the development of diabetes in comparison with the general population is only in relation to that specific type of diabetes that has occurred in the family, and does not pertain to all subsets of diabetes.⁵¹

The potential for HLA antigens as prenatal markers of diabetes may soon be used in the counselling of siblings of known insulin-dependent diabetics. In the case of parents with an affected child with IDDM who wish to ascertain the risks to future offspring, prenatal HLA typing of fetal cells obtained by amniocentesis can be carried out.⁵² The finding of fetal cells HLA-identical to those of the diabetic sibling would sharpen the predictive accuracy, but because of incomplete penetrance and/or heterogeneity^{53,54} only a 50% risk can be offered, and one

TABLE I. RISK FOR SIBLINGS OF PATIENTS WITH ONSET OF INSULIN-DEPENDENT-DIABETES (IDD) BEFORE 16 YEARS OF AGE (ADAPTED FROM RUBINSTEIN *ET AL.*⁵²)

Parent 1	Parent 2	% empirical risk*	% specific risk† — No. of D haplotypes shared with first affected		
			2	1	0
Normal	Normal	13	50	2	0,1
IDD	Normal	25	50	50	2
IDD	IDD	50	50	50	50

*When HLA typing is not determined.
†When HLA D typing is available.

would be loath to recommend therapeutic abortion under these circumstances (Table I).

As regards HLA antigens as markers in IDDM, it is known that less than 1% of healthy DR3- or DR4-positive subjects are likely to develop diabetes, but in the presence of a strong family history of IDDM these genes may indicate a susceptibility to the disease. The siblings of a diabetic with IDDM have, overall, a 27 times increased risk of developing the disease by the age of 16 years. An HLA-non-identical sibling has virtually zero risk, a haploid-identical sibling has a 37 times increased risk, and an HLA-identical sibling has a 90 times increased risk of developing IDDM.²

The rest of the statistics available are for the most part empirical recurrence risks (data concerning the actually observed recurrences of these disorders in a large number of families), and have at present been reported for White populations only. If a child has IDDM, the average risk to his siblings of developing IDDM is 5 - 10%. If a parent has IDDM the risk to the offspring of developing overt diabetes during the 1st decade of life is generally reported as 1 - 2% or less. For NIDDDM the risk to first-degree relatives is \pm 5 - 10% for clinical diabetes and 15 - 25% for their having an abnormal glucose tolerance test result, whereas the risk to children of an affected parent with NIDDDM is 5 - 15%.⁵⁵ Since NIDDDY appears to be an autosomal dominant disorder, the offspring and siblings run a risk of inheritance of 50% (Table II).

Taking all factors into account, it is unwise to advise prospective parents not to procreate because one of them is diabetic. Even if both parents are affected, the majority of conjugal diabetic marriages are those of two individuals with NIDDDM, where fertility is often reduced; the prevalence of overt diabetes in the offspring ranges from 5% to 10% in most series,⁵⁵ and if affected the offspring will usually develop NIDDDM later in life.⁵⁶ There is increasing evidence that congenital malformations, which account for 6 - 8% of all deaths in infants of diabetic mothers, may be attributed to poor metabolic control during the period of conception and the early

TABLE II. RISK OF DIABETES IN RELATIVES OF DIABETICS

	% risk
Type I diabetes (IDDM)	
Siblings of diabetics	5 - 10
Children of diabetic father or mother	1 - 2
Type II diabetes (NIDDDM)	
Siblings of diabetics	5 - 10
Children of diabetic father or mother	5 - 15
NIDDDY	50

weeks of pregnancy.⁵⁷ It is therefore essential to advise any prospective diabetic mother to obtain 'tight' blood glucose control before planning to conceive. This state of normoglycaemia may have to be obtained by multiple daily insulin injections or the use of continuous subcutaneous insulin infusion and dedicated home blood glucose monitoring — procedures best carried out under the supervision of a specialized diabetic unit.

In conclusion, the most reassuring aspect of the present data is the overall low risk of the development of clinical diabetes in first-degree relatives, this especially pertaining to IDDM.

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