Genetics of Diabetes Mellitus: A Review of Indian Population Studies

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SUMMARY

Most of the published genetic studies in Indian diabetics are reviewed and tabulated, for better understanding by the physicians in the developing countries. Rapidly emerging new concepts in this aspect of diabetes will be of great significance to developing countries in early diagnosis of diabetics and for implementing primary preventive programmes in the near future.

In India IDDs, there is a strong link with the HLA system implying the inheritance of 'susceptible' diabetic genes, especially the DR3 and DR4 alleles, and possibly environmental (?) factors act in a predisposed individual to initiate an immune response to cause beta-cell damage and destruction.

On the other hand, NIDDM has no clear HLA link and environmental factors (race, ethnicity, sex, age, diet, activity, obesity and life style) have an important influence on the clinical expression of the disease and the severity of complications in a genetically (?) predisposed individual.

By and large, genetic studies on diabetics suggest that diabetes is about 50 per cent inherited, and other 50 per cent acquired or environmental. Because of the heterogeneous nature and multifactorial inheritance pattern of diabetes, accurate genetic counseling 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 in offspring is extremely low.

INTRODUCTION

Diabetes mellitus has rightly retained its dubious distinction as the 'geneticist's nightmare', since James Neel's description in 1962 (1). Aetiogenesis of this disease is never fully understood, and physicians continue to face the dilemma of answering parents anxiously questioning whether their diabetic daughters or sons will ever by able to marry and have children?

Moreover, practicing physicians from developing countries need to show more interest in genetics while dealing with diabetics in their countries, because a large part of the research to identify markers essential in early diagnosis of diabetes, is being carried out in emigrant 'old world' populations. The obvious reason is that these populations, wherever they are living, are known to have high ethnic susceptibility to diabetes mellitus. Such international studies will certainly be of paramount importance to us in planning primary preventive measures in the near future.

This review, being a compilation of the recent publication on genetic research in diabetes specific to Indian populations, supplements what has already been summarized in earlier Indian reviews by Mehra in 1986 (2) and Rao in 1987 (3).

FAMILY STUDIES

Ever since a probable genetic link with blood group A or ' chlorpropamide-alcohol flush', for type II diabetes was known, similar studies were also done within India and in migrant Indians (4). One of those reports was from Patiala, where the investigators have noted association of diabetes mellitus with A, AB and Rh-positive blood groups in a large series of 520 'adult' diabetics (5). Many more studies indicating genetic linkage through biochemical markers and on the offspring of conjugal diabetics followed from different parts of the country.

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 # This review topic was presented at the National Seminar on Recent Trends in Diabetes Mellitus, held on March 24, 1990, at the Institute of Genetics, Osmania University, Hyderabad.

Table 1: Class I HLA Antigens in Indian Populations

AUTHOR	YEAR	NUMBER		HLA		RR
IDDM						
Mehra	1986	105	NI	A	1	1.1
Mehra	1986	47	EI	A	1	1.2
Mehra	1986	105	NI	A	3	1.0
Mehra	1986	47	EI	A	3	0.5
Mehra	1986	105	NI	Aw	19	0.9
Mehra	1986	47	EI	Aw	19	0.6
Omar	1984	68		Aw	19	2.2
Srikanta	1981	54	NI	A	28	+ve
Srikanta	1981	54	NI	B	7	-ve
Mehra	1986	105	NI	B	7	1.2
Mehra	1986	47	EI	B	7	0.8
Hammond	1980	44		B	8	+ve
Srikanta	1981	54	NI	B	8	Nil
Omar	1984	68		B	8	3.2
Kirk	1985		SI	B	8	+ve
Mehra	1986	105	NI	B	8	4.8
Mehra	1986	47	EI	B	8	0.5
Bodansky	1987	17	NI	B	8	+ve
Hammond	1980	44		B	15	-ve
Srikanta	1981	54	NI	B	15	Nil
Mehra	1986	105	NI	B	15	3.2
Mehra	1986	47	NI	B	15	2.0
Bodansky	1987	17	NI	B	15	-ve
Srikanta	1981	54	NI	B	18	nil
Srikanta	1987	54	NI	Bw	21	+ve
Mehra	1986	105	NI	B	21	4.9
Mehra	1986	47	EI	B	21	0.3
Srikanta	1981	54	NI	B	35	+ve
Mehra	1986	105	NI	B	35	0.6
Mehra	1986	47	EI	B	35	1.3
NIDDM						
Kirk	1985		SI	A	nil	
Omar	1985	84	NI	Aw	24	+ve
			SI	Aw	24	0.1
Kirk	1985		SI	B		nil
Omar	1985	84		B	15	+ve
			NI	B	15	4.8
Omar	1985	84		Bw	16	+ve
Omar	1988	84		Bw	61	1.7

(RR=relative risk; NI=North, SI=South, EI=East Indians)

An interesting report in 1985, indicated that if all the offsprings of conjugal diabetes were to be followed till the age of 60 years , 63 percent of them might be expected to develop diabetes (6). One of the recent reports from these investigators from Madras-offspring of one diabetic parent (OPDR-A) and offspring of one diabetic parent with a first-degree family history of diabetes on the non-diabetic parental side (OPDR-B), were studied for familial aggregation of non-insulin-dependent diabetes mellitus (NIDDM). Prevalence of NIDDM was 36 per cent and 54 per cent in the OPDR-A and OPDR-B families respectively, and the susceptibility to diabetes was reported same whether the father or the mother had diabetes, and there was a male predominance among the diabetic offspring (7). Further, offspring of conjugal diabetic parents were also shown to elicit lower as well as delayed first and peak phases of insulin seretion compared to the control values, which could also serve as genetic markers (8).

All these reports, while confirming the heterogeneity in the inheritance pattern of diabetes mellitus in Indians, also suggested racial or ethnic differences in the genetics of diabetes.

HLA SYSTEM

A well-justified euphoria albeit short lived had arrived in India with the HLA system in the early part of the present decade. This coincided with the international organ transplantation boom. One of the earliest HLA studies from the All India Institute of Medical Sciences (AIIMS), New Delhi, was in fifty-four North Indian type I diabetics. The frequencies of HLA-BW21, BW35, and -A28 were reported increased and that of HLA-B7 was reduced, whereas HLA-B8, -B15 (commoner with western IDD populatins), and -B18 were not found associated with IDDM in this series of patients (9,10). In a later study of the properdin system (Bf) present near HLA on the short arm of chromosome 6, a rare factor BfSI was found to be associated with insulin-dependent diabetes (IDDM) in north India (11).

These results have promoted further studies from the southern parts of the country, to identify race specificity in HLA antigen distribution in normal populations as well as disease states. From Madras, Vellore and Coimbatore in South India, HLA-A and B as well as the clas III antigens-properdin system (Bf), complement system (C2, C4A, C4B) and glyoxalase (GLO) present on chromosome 6 were tested in diabetics. Significant increase in HLA-B8, of BfF and decrease of C4 A6 was reported in IDDs. Though no significant variation in HLA, Bf, C2 or GLO frequencies was found in NIDDs, there was a significant decrease in C4B 1 and an increase in C4B 2. These HLA and Bf associations in south Indian IDDs were different from those reported previously from North India (12,13).

Table 2
Class II HLA Antigens in Indian Populations

AUTHOR	YEAR	NUMBER		HLA		RR
IDDM						
Bhatia	1985	88	NI	DR	2	0.2
Mehra	1986	39	EI	DR	2	0.3
Omar	1984	35		DR	3	3.1
Bhatia	1985	88	NI	DR	3	10.5
Mehra	1986	39	EI	DR	3	3.0
Bodansky	1987	17	NI	DR	3	+ve
Omar	1984	35	NI	DR	4	8.3
Bhatia	1985	88	NI	DR	4	1.1
Mehra	1986	39	EI	DR	4	0.4
Omar	1984	35		DR3/DR4		7.3
Bodansky	1987	17	NI	DR3/DR4		+ve
NIDDM						
Omar	1988	104		DR		nil

Later following sophistication in HLA typing and access to better facilities, detailed studies on HLA system were done by DR locus typing. At AIIMS, eighty eight north Indian patients with IDDM and 113 unaffecting individuals were typed for HLA-DR antigens from -DR1 to -Dr7, the frequency of HLA-DR3 was found significantly increased in the patients, with a relative risk (RR) of 10.52 being much higher than that in the Western IDDM population. HLA - DR2 showed a significant negative association as in Western reports (RR=0.18), but DR4 had no relationship with IDDM. These results further emphasized the differences in HLA-IDDM associations among different ethnic groups (14).

There were also studies reporting on HLA typing including non-diabetic family members from New Delhi. The HLA haplotype segregation and autoantibody spectrum in 7 IDD multiplex families of North Indian origin, were published in 1986. In a total of 17 diabetic sibs, 7 shared both haplotypes and 3 shared one haplotype with the proband, and no HLA-non-identical sibs were observed. Thus the mode of inheritance in this study was found compatible with an autosomal recessive model (15).

Summarizing HLA antigen studies from India, Ahuja indicated heterogeneity of allele of B locus and properdin factor based on racial differences, while confirming specificity of DR3-DR4 for IDDM (16).

RESTRICTION FRAGMENT LENGTH POLYMORPHISM (RFLP)

By now, much of the heat generated by the HLA system has cooled off, as it was increasingly evident that a specific genetic marker for diabetes was still eluding the purview of the geneticists. Yet the quest continued with more sophistication and advanced technology. DNA genotyping for HLA system was introduced and the nature of HLA-DR3 and -D4 associations have been explored using Southern blot techniques and radioactive HLA-D region probes. During the last five years , most of the genetic research of Indian diabetics was done at the London Hospital by Hitman, with collaboration from the Diabetes Research Centre (DRC), Madras (for South Indians) and Ealing Hospital, London (for North Indian populations living in Southall).

In publication of 1987 by DRC group, restriction fragment length polymorphisms (RFLPs) of the HLA-DR beta, -DQ alpha, -DG beta, and –DX alpha genes have been examined in South Indian diabetic patients and controls. As the linkage arrangements in South Indians were shown to be different for DR2 ,DR4, and DRw6 from those commonly seen in Europeans, investigators were hopeful of localizing the primary disease-promoting gene in IDDM. These authors have also suggested that there was at least one probable DQ beta allele in the pathogenesis of IDDM and proceeded with further details on HLA-DQ locus in later reports(17).

Following identification close markers for IDDM in Western Caucasoid subjects from DQ region (both alpha and beta genes) RFLPs, 58 unrelated Dravidian IDDs and 43 controls form DRC, Madras were similarly analysed. An increased frequency of the Taq 1 DQ beta RFLPs-designate`d as T2 omega/T6 (RR = 10.6), and of homzygotes for Taq 1 DQ alpha 4.6 kb (RR=11), was found in the patients.

Table 3:
RFLP studies in Indian Populations

AUTHOR	YEAR	NUMBER		HLA	RR
IDDM					
Fletcher	1988		NI	DR4/DQB/DXa	5.1
Fletcher	1988		NI	DRw6/DQB	0.1
Fletcher	1988		NI	DR3/DRB	12.1
Hitman	1988	58	NI	DQ Taq 1 DQa 4.6 Kb	11.0
				DQ T2 Omega/T6	10.6
				(both)	101.0
NIDDM					
Hitman	1987	164	NI	DR/DQ/DXa	nil
				Insulin gene	nil
				Insulin receptor gene	nil

The highest relative risk for IDDM was obtained by comparing patients with control subjects who either co-inherited DQ T2 omega/T6 with certain DQ alpha RFLPs or were DQ alpha 4.6 kb homozygotes. The combinations of both of them accounted for 55.5 per cent of IDDs and in none of the controls (RR=101) (18).

Hitman and Mohan in 1988 compared British and South Indian RFLP studies and reported that the same DR4 related polymorphism was found in IDDM subjects in both populations, whereas HLA-DR3 preferential allelic associations were different. Best differentiation between diabetics and controls was found in a combination of HLA-DQ region alpha and beta polymorphisms which were totally different for the two populations. Suggesting that at least one gene involved in the susceptibility of IDDM is located within the HLA-DQ region related to HLA-DR4, authors have maintained that the location of -DR3 related gene still remained elusive and that it might be the -DR beta gene encoding -DR3 itself. In both populations, it is combination of two HLA-D region haplotype which is strongly associated with IDDM, suggesting a possibility of trans-complementation with formation of mixed isotopic dimers (19).

TROPICAL DIABETES

Lastly , Tropical Calcific Pancreatitis, classified under Malnutrition Related category (MRDM) by WHO, merits brief discussion here. In earlier HLA studies at AIIMS on 10 ‘pancreatic’ diabetics from Kerala in 1986, HLA-A2 was noted in 44.4 per cent of cases compared to 15.7 percent of controls. Neither -B nor -DR showed any significant associations in this small study series. In a later study on ninety-nine first-degree relatives of fibrocalculous pancreatic diabetes (FCPD), familial aggregation of the disease with evidence for vertical transmission in some families was reported (20). Recently, in a RFLP report of 52 FCPDs and 76 NIDDs from Madras, FCPD was shown to share susceptibility genes with NIDDM (class 3 allele of insulin gene, RR=7.9), and IDDM (HLA DQβ gene). For the first time, these authors suggested a genetic component to FCPD also, in common with NIDDM related insulin gene locus (21).

EMIGRANT INDIAN STUDIES : SOUTH AFRICA

As early as in 1990, the HLA antigens in 44 Asian Indians with IDDM were reported form South Africa, and the frequency of HLA-B8 was found increased, while that of HLA-B15 was not (22). This was an earlier indication that racial heterogeneity existed in HLA associations with diabetes. By 1984, more reports followed on the HLA status-in a series of 68 South African Indian IDDs and 760 controls and DR specificities determined in 35 patients and 235 controls, diabetics showed a significant increase in the frequencies of HLA-B8 (RR=3.2), and Aw24 (RR=2.2) antigens. HLA-DR3 was found to be much more common in IDDs (RR=3.1), but DR3/DR4 heterozygosity was associated with a much greater relative risk of 7.25. In patients of North Indian origin a strong association with DR4 was seen (RR=8.3) (23).

No association between NIDDM and HLA antigens has been noted in whites, but a positive relation was reported in a 1985 study on 84 South African Indian NIDDs and in 760 healthy Indian controls. Though increased frequencies of Aw24 , B15 and Bw61 seen in these patients was not significant among Indians of North Indian origin, there was a significant association between B15 and NIDDM (RR=4.8). in Indians of South Indian origin, no clear association with any specific HLA antigens was seen, although there was a slight increase in the frequency of Aw24 (24).

Further positive relations between the HLA system and NIDDM was described in 184 Indian patients and 1444 control subjects and by HLA-DR antigen typing in 104 patients and 330 control subjects. There was a significant increase in the frequency of HLA -Bw61 in patients, although the degree of association was not very strong (RR=1.7). However, no relation could be established at the DR locus. It was suggested that the relatively high frequency of the Bw61 allele in South African Indians could, in the presence of some environmental factor like obesity, confer increased susceptibility to NIDDM (25).

UNITED KINGDOM

In a report published in 1987, a total of 17 Asian children with type 1 diabetes from the industrial West Yorkshire in the United Kingdom, were ascertained. It was interesting to note that in this series of cases, there was a very strong familial occurence as seven of the diabetic children were from three multiplex families and two fathers from these families and diabetes. There were significant

increases in HLA-B8 and HLA-DR3 and increases in HLA-DR4 and HLA-DR3/DR4, while HLA-Following these reports, a recent study of 1988 on HLA class II DNA polymorphisms indicated that HLA-DR4 in North India 'type 1' diabetic patients was significantly associated with DQ beta and DX alpha DNA polymorphisms (RR=5.12), which was also identical to those found in DR4-positive White Caucasoid patients. Similarly, a DQ beta polymorphism with very low relative risk (RR=0.10) for 'type 1' diabetes in North Indian diabetic subjects was also markedly reduced in White Caucasoid patients. However, this latter pattern was associated with DR2 in White Caucasoid subjects, and with DRw6 in North Indians. In addition, a DR3- associated DR beta polymorphism was also reported to be increased in North Indian diabetic patients (RR=12.1). These authors have contended that the DQ subregion may be a primary site of genetic influence on susceptibility to 'type 1' diabetes, based on these findings (28).

After 1985, following identification of insulin gene and insulin receptor gene on chromosome 11 and 19 respectively, RFLPs of these genes and HLA system were studied in NIDD and non-diabetic Punjabi Sikhs (n=164), using insulin receptor, insulin, and HLA-D alpha chain gene probes. Insulin receptor gene RFLPs were defined using Southern blot techniques and the restriction enzyme Bgl II and Bam H1. In Punjabi Sikhs and British Caucasoids neither of the RFLPs distinguished NIDD subjects from controls. In the Sikhs no association with NIDDM was seen with the hypervariable region of the insulin gene or with HLA-DR/DQ/DX alpha chain restriction fragment length polymorphisms. Therefore authors concluded that despited the high prevalence of NIDDM in Asians, no genetic markers could be found for this disease using the available cloned gene probes (27).

ACKNOWLEDGEMENTS

Publications reviewed in this article are made available through 'Diabetes Databank' established at the Nizam's Institute of Medical Sciences, Hyderabad, supported by funds from the Department of Science and Technology, New Delhi.

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