

## NEW LIGHT ON GENETICS OF DIABETES IN INDIA

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Diabetes mellitus is predominantly a genetic disorder whose ultimate expression and clinical variability is governed by various environmental factors. However the exact genetic mechanisms involved are far from clear and for this reason diabetes had been referred to as a "geneticist's nightmare" (1).

Though diabetes is a heterogeneous syndrome, the modern classification divides diabetes into 2 major types namely IDDM and NIDDM types. This is based on clinical, biochemical, immunological and genetic studies (2). Most earlier studies have been done in Caucasian races. It is well known that there are differences in the clinical profile of diabetes in different ethnic groups. Till recently there has been very little work on the genetics of diabetes in India. Recent work has led to a better understanding of the hereditary mechanisms determining susceptibility to diabetes in India.

In the etiology of IDDM there is no doubt that genetic as well as environmental factors are involved. The genetic susceptibility is linked with the major histocompatibility system, the HLA System. Several groups have reported a possible association between HLA System and IDDM (3-6). In most studies published so far, mostly Caucasian patients have been HLA-typed. HLA B 8 and B 15 have been found to be positively associated with IDDM in N. Europeans. On the other hand HLA B 18 shows a maximal increase in Southern

Europeans (4). Perhaps the strongest association of IDDM is with HLA DR 3 and DR 4.

### I. GENETICS OF IDDM IN INDIA

#### HLA Studies in Indian populations :

Srikanta, Mehra, Vaidya, Malaviya and Ahuja (7) reported on the HLA antigens in Type I diabetes mellitus in North India. The frequencies of HLA BW 21 was significantly increased and that of B 7 was significantly reduced, HLA B 8, B 15, B 18 which are associated with IDDM in Caucasians did not demonstrate any significant association with IDDM in this series of patients. The HLA patterns quoted in N. India are also different from that noted in Japan, which is the HLA BW 22 J 1, (BW 54). A recent study from S. India by Kirk et al (8) has shown still more interesting findings. The HLA profile in IDDM in S. India is quite different from that reported from N. India. In S. India, HLA B 8 is associated with IDDM, which is similar to the findings in the Caucasian IDDM. However unlike the Caucasians, there was no association with B 15. These studies appear to provide evidence for genetic differences in susceptibility to IDDM between Indians and Caucasians and also between the North and South Indian populations. They also corroborate the earlier studies of Hammond and Asmal (9) who

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Received for publication on 7-5-1984.

reported the HLA profile in Indian IDDM patients in S. Africa. It was noted that while the Dravidian (S. Indian) IDDM population in S. Africa showed an increased prevalence of HLA B 8, this was not seen in the Aryan (N. Indian) population.

These reports on HLA are among the first to appear in races other than Caucasian and the Japanese. They are also the first reports on the HLA profile of IDDM patients in India.

Serjeantson, Ryan, Ram and Zimmet (10) reported an interesting study of HLA and non insulin dependent diabetes (NIDDM) in Fiji Indians. There was a significant increase in BW 61 in NIDDM Fiji patients of Indian origin. This study is interesting because it is the one of the few reports of an HLA association with NIDDM type of diabetes. In Caucasians, there is no HLA association with NIDDM. The authors claim that they have identified yet another genetically distinct group in the Indian population: that of an HLA associated NIDDM (type 2) diabetes. The results remain to be confirmed, because in our own studies on the HLA patterns in Indians living in India, no such association has been noted between HLA and NIDDM. The only other report of an HLA association with NIDDM has been in a study of S. African Blacks of the Xhosa tribe in whom an association between HLA A 2 and NIDDM was noted (11).

#### **Studies on Properdin (BF) System :**

The properdin (BF) system which is associated with the alternate complement pathway, is situated close to the HLA region on chromosome 6. There have been reports of associations between the BF system and IDDM in Caucasian races. Recent studies have shown an association between the BF system and IDDM in

Indian populations. These studies have again shown genetic differences between the IDDM in North and South India.

The BF haplotype associated with IDDM in Caucasian populations is the BFS. Kirk, Ranford, Viswanathan, Mohan, Ramchandran, Snehalatha, Chetty and John (12) reported an association between the properdin system and insulin dependent diabetes in S. India. Seventyseven IDDM patients belonging to the four southern states of India namely Tamil Nadu, Andhra Pradesh, Karnataka and Kerala were studied. All patients were ketosis prone IDDM. There was a significant increase among IDDM patients, when compared with controls, in the BFF phenotype. This increase in the BFF phenotype was reflected also in a significant difference in the BFS gene frequency between IDDM patients and controls. There were no significant differences between controls and NIDDM. The relative risk for the BFF phenotype in IDDM was 4.1.

In contrast to the previous reported results for North Indian IDDM patients (13) there was no significant association of the BFS 1 haplotype with either IDDM or NIDDM patients in the S. Indian population studied. This suggests that the susceptibility allele(s) for IDDM in South India arose independently from the susceptibility allele(s) in North India. Alternatively, it is possible that a different etiological factor with a distinctive genetic susceptibility is present in the South Indians.

Table 1 summarises the HLA and BF associations with IDDM in India compared to the Caucasians.

#### **Studies on genetics of NIDDM patients in India :**

Few studies have been reported on the genetics of NIDDM patients in India. Viswanathan (14) published the results of

**Table 1**  
**HLA AND PROPERDINE (BF)**  
**HAPLOTYPES ASSOCIATED WITH**  
**IDDM IN CAUCASIANS AND INDIANS**

Race	HLA	BF System
Caucasian	HLA B <sub>8</sub> B <sub>15</sub> DR 3 DR 4	BFS
N. Indian	BW 21	BFS <sub>1</sub>
S. Indian	B <sub>8</sub>	BFF

a 20 years follow up study on relatives of diabetic patients. This study suggests that the genetic factor appears to be stronger in Indian diabetics compared to other races. When one parent had diabetes 11.3% of all offspring had diabetes and when both parents were diabetic 25.1% of all offsprings had diabetes. When those above 40 years were analysed (in the offspring of two diabetic parents) as many as 55.6% had overt diabetes. This study was based on a questionnaire method. Obviously if all offspring were tested, the figure would be very much higher. These prevalence rates for diabetes in the offspring of conjugal diabetics are the highest reported in any population studied, suggesting that in Indian diabetics, the genetic factor is quite strong.

Mohan, Ramachandran and Viswanathan (15) reported their preliminary observations on a unique long term project on Primary Prevention of Diabetes. Detailed pedigree charts of offspring of over 2000 "Conjugal" diabetic couples and equal number of offspring of 'One Parent' diabetic and 'No Parent diabetic' couples have been registered at the Diabetes Research Centre, Madras. The study includes glucose tolerance tests, insulin and C-peptide assay in the offspring with a view to detect early biochemical markers. In the next phase of

the project which is now underway at the Centre, steps are being taken to prevent the influence of environmental diabetogenic factors.

**New genetic markers for diabetes: Studies on offspring of diabetic parents.**

Two recent studies on offspring of diabetic parents by the author and his colleagues have shown evidence for new genetic markers for diabetes.

Snehalatha et al(16) reported a study of C-peptide levels in offspring of conjugal diabetics. Earlier studies on offspring of conjugal diabetics (genetic prediabetics) have focussed mainly on immunoreactive insulin levels (IRI). IRI levels have been reported to be low, normal or high by various authors (17-19). Since insulin undergoes a significant amount of extraction in the liver, measurement of C-peptide is now considered a more specific index of pancreatic beta cell reserve. The author and his colleagues estimated C-peptide levels in offsprings of conjugal diabetics (OCDP) who had normal glucose tolerance and found that OCDP in general had a lower C-peptide reserve. Thus they concluded that a low C-peptide level may serve as an early genetic marker of diabetes( 16).

In another interesting study, the serum uric acid levels were estimated in offspring of conjugal diabetics (OCDP) (20). It was seen that OCDP had a higher uric acid levels compared to controls of diabetics. An earlier report by Hermann et al (21) studying prediabetics had also suggested that uric acid levels are raised in prediabetic stage. Two other observations suggest that uric acid may be in some way linked to diabetes. Firstly, gout occurs with increased frequency in diabetics. Secondly alloxan which is used to produce diabetes in experimental animals is a derivative of uric acid. In view of the

above findings the author's finding of high uric acid levels in offspring of conjugal diabetics merits further study.

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