HLA, WHAT NEXT ?

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'Simple' HLA typing has long gone and now it's a relic of the past. And, linking diabetes to HLA-B8 or - B15 or B35 or - B21 or - DR3, or even properdin factor BfSl in Indians[1], is fast reaching antiquity. But diabetes has always been a challenge to geneticist, never ceasing to give nightmares to an ever continuing stream of researchers. Some of the very recent reports on genetic markers in Indian diabetics are being briefed here.

The last remaining domain of HLA-DP, DQ DR and DX regions for both alpha and beta genes was investigated using Southern blot hybridisation methods and gene probes, in 58 Insulin dependent diabetics (IDDM) and 43 unrelated controls living in Madras. An increased allelic frequency of a DQ alpha 4.6 Kb fragment was found in diabetics (32%) compared to controls (11.5%). Interestingly, 19% of diabetics and none of the controls were homozygous for this allele (relative risk=11). All those with the DQ alpha 4.6 Kb allele also possessed the DR alpha 4.5 Kb allele, which was homozygous in 86% of diabetics against only 47% of controls. There was no association of DX alpha alleles with IDD from Madras[2].

In a further study of the same population, an increased frequency of the Taq 1 DQ beta restriction fragment length polymorphism (RFLP) designated as (T20mega/T6) was found in diabetics) relative risk = 10.6). A combination of DYT2-omega/T6 with either DQ alpha RFLP or homozygous DQ alpha 4.6 allele was present in 55% of the diabetics and none of the controls (relative risk=101). These combinations and DQ related genetic markers seem unique to South Indian population with IDDM[3].

Exit HLA, enter insulin gene and its receptor gene studies. A never ending quest for decoding genes has turned the focus of attention from chromosome 6 to chromosomes 11 and 19.

In an early study, DNA from 38 Non insulin dependent diabetics (NIDD) and 39 controls of a Punjabi population was analysed using Southern blot technology, and insulin gene and insulin receptor gene probes. A Bgl II polymorphism was found with insulin receptor probe, which however did not differentiate diabetics (47%) from controls (56%). Though there was no difference in genotype distribution for insulin gene, the size distribution of the alleles was however different-diabetics more frequently had allele sites between 870 and 1 Kb (59% vs. 16% controls). Specific insulin related alleles may be associated with NIDDM in Punjabis[4].

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Later, using cDNA probe and restriction enzymes Bgl II and Bam H I, insulin receptor gene polymorphisms were analysed in 79 Punjabi Sikh NIDDs and 55 controls. Neither Bgl II polymorphism (3.6 Kb band) nor Bam H I polymorphism (7.5 Kb band) was different in diabetics from controls, whereas Caucasian diabetics had a relatively higher incidence of Bam H I polymorphism. These findings imply that insulin receptor gene or a closely linked locus on chromosome 19 may not contribute to diabetes in Punjabi diabetics[5].

A similar study of 45 South Indian NIDDs and 43 controls, of whom 44% had diabetics among their first degree relatives was organised from Madras. Three insulin receptor RFLPs were studied with Bgl II, Rsa I and Bam H I in in these NIDDs, but there was no association. However, using insulin gene probe and Pvu II a class 3 allele was seen in 36% of NIDDs and in only 9.5% of the controls[6].

Perhaps one day in the near future, the offending genetic marker for diabetes may hopefully be defined.

References

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