THE GENETICS OF TYPE I AND TYPE II DIABETES:

ANALYSIS BY RECOMBINANT DNA METHODOLOGY

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ABSTRACT

Susceptibility to IDDM is linked to the HLA-D locus on the short arm of chromosome 6, a region believed to be involved in the process of communication between cells which determines immune responses. Presumably an HLA molecule encoded by this region, unable to present a particular antigenic pathogen to the immune system, is inherited. The HLA-DR locus is quite complex, however. The gene which codes for this defective molecule may be identified by a combination of use of monoclonal antibodies and cloned gene probes which specifically hybridize to various portions of this region. Investigators are searching for HLA-DR4 containing chromosomes in IDDM which show similar patterns of restriction enzyme polymorphism. Hopefully, complete structural analysis of these related sequences will provide information about the mechanisms which confer susceptibility to develop IDDM.

A strong genetic component is involved in NIDDM evidenced by a high concordance in monozygotic twins. Nevertheless, there is much evidence of genetic heterogeneity. At the present time no clear cut genetic marker has been defined. The human insulin gene has been cloned and by Southern blot hybridization analysis of peripheral leukocyte DNA, the insulin gene locus is being evaluated as a possible contributor to the genetic defect. Population studies at the present time have not identified any particular polymorphic insulin allele associated with NIDDM. Population studies are complicated by heterogeneity of NIDDM, racial and ethnic differences, and heterogeneity of insulin alleles. Linkage analysis in family studies will provide an alternative approach to population studies to determine what role if any the insulin gene plays in the
The familial aggregation of diabetes has long been noted (see ref. 1 for review). In relatives of diabetics, the prevalence ranges from 10-30%, while it is variously estimated to be between 0.1-3% in the general population. But familial aggregation of a trait may be caused either by genetic or environmental factors. One approach to dissecting the contribution of these factors is the study of concordance in twins. Pyke and associates observed that overall identical twins always show a higher concordance rate than dizygotic twins, irrespective of their age of diagnosis. Furthermore, they noted that identical twins of younger onset are often discordant for diabetes while identical twins of older onset are usually concordant. In a study of 200 pairs of monozygotic twins, the concordance of Type I or insulin dependent diabetes (IDDM) was 80 of 147 twin pairs (54%). In contrast, 48 of 53 Type II or non-insulin dependent diabetes (NIDDM) pairs (91%) were concordant for diabetes. Thus, while genetic factors are important in both types of diabetics, a strong environmental component makes genetic analysis of IDDM more complex.

I. THE GENETICS OF INSULIN DEPENDENT DIABETES (IDDM)

The relationship between the HLA locus and IDDM

Which genes are involved in IDDM and NIDDM? At the First International Workshop of the Genetics of Diabetes held in 1976, Nerup et al. presented evidence that there was a relationship between certain histocompatibility alleles and IDDM, suggesting that inheritance is related to one or more genes on the short arm of chromosome 6. Since that time numerous studies have confirmed that IDDM and NIDDM are genetically separate disease entities.

The association between the HLA system and IDDM was first noted in population studies. Individuals with disease were HLA typed at the A, B, and C loci. There are two classes of HLA antigens, class I or HLA-A, B, C antigens found on the cell membranes of all nucleated cells and class II or HLA-D antigens which are found only on some cell types. These two classes differ in their biochemical structure and biological function. The HLA-A, B, C antigens are recognized serologically, and consist of two polypeptide chains, a heavy chain carrying the HLA-A, B, or C antigenic determinant and a light invariant chain, beta-2 microglobulin which is controlled by a gene outside the HLA system. When non-diabetic controls of similar race were typed at the same loci, it was noted that certain HLA types occurred more frequently in the diabetic population. Results