A POLYMORPHIC LOCUS NEAR THE HUMAN INSULIN GENE ASSOCIATED WITH INSULIN-DEPENDENT DIABETES MELLITUS

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ABSTRACT

There is a polymorphic locus near the beginning of the human insulin gene on chromosome 11 whose size is extremely variable. This locus, the insulin gene hypervariable region (HVR), is composed of tandem repeats of a family of related oligonucleotides. Its size varies because of variation in the number of repeats. Population studies indicate that the sizes of the HVR fall into three heterodisperse classes, designated 1, 2 and 3 in order of increasing size and whose frequency varies between racial groups. The common Class 1 allele and the homozygous Class 1 genotype are significantly more frequent (p < 0.001) in Caucasians with insulin-dependent diabetes mellitus (IDDM) than in patients with non-insulin-dependent diabetes or non-diabetic controls. The Class 1 HVR allele may be a marker for an allele of a gene which predisposes to IDDM. Although the identity of this diabetogenic locus has yet to be determined, possible candidates include: 1) a gene encoding a beta-cell specific autoantigen; 2) one which determines the susceptibility of the beta cell to viral infection or its response to such infection; and 3) a gene which influences beta cell regeneration.

INTRODUCTION

Diabetes mellitus comprises a heterogeneous group of disorders whose etiology seems to be multifactorial with both genetic and environmental factors contributing to its development (1-3).

Type I or insulin-dependent diabetes mellitus (IDDM) is characterized by severe deficiency of insulin secretion due to profound beta cell destruction. These patients require therapy with exogenous insulin to
avoid severe hyperglycemia and ketosis. Although this disorder occurs at any age, its onset is most common in the young and circulating islet cell antibodies are detected in as many as 80-85% of these patients at the onset of their disease. In most cases of IDDM, a positive association with the Class II major histocompatibility complex (MHC) antigens, HLA-DR3 and -DR4, suggests that genetic factors on the short arm of human chromosome 6 (which carries the MHC) contribute to the development of manifest diabetes. However, monozygotic twin studies by Pyke and his colleagues (4) show that genetic factors alone are not sufficient to produce diabetes since as many as 44% of twins in a large series (147 pairs) were discordant for diabetes. Moreover, among Caucasians approximately 50% of non-diabetics are HLA-DR3 or -DR4 and yet only about 0.1% of the population develops IDDM. These observations support the concept that additional genetic determinants and/or environmental factors such as viruses, drugs or toxic chemicals may be required to precipitate the development of IDDM in individuals having HLA-DR3 and/or HLA-DR4 antigens. This type of diabetes is found primarily in Caucasians of northern Europe or their descendents. In the United States, which has a mixed racial population, about 5,500,000 patients are projected to have diabetes mellitus and the prevalence of IDDM in this group is about 10% (5). By contrast, in Scandinavia 20% of the diabetic population have IDDM. In Asia and Africa this form occurs in less than 1% of the diabetic patients.

Type II or non-insulin-dependent diabetes mellitus (NIDDM) is less well-characterized and probably represents an even more heterogeneous group of patients than Type I. These are patients with a less severe form of diabetes who do not require insulin therapy for survival. They show no association with HLA antigens and have no demonstrable circulating islet cell antibodies. This type of diabetes develops more frequently in older individuals, of all racial groups, manifesting itself most commonly after the age of 40 years and particularly when obesity is developing or progressing in parallel with advancing age. Concordance for NIDDM in identical twins approaches 100%, indicating that there is a significant genetic factor in the etiology of this form of diabetes (4). The clinical and biochemical features of NIDDM suggest that components of the insulin-producing beta cell as well as of the insulin responsive