Abstract

The Genetics of Diabetes Mellitus

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Besides a great variety of genetic or non genetic types of so called secondary diabetes there remain two main types of idiopathic or genuine diabetes which may either be described as juvenile onset versus maturity onset type or as insulin dependent versus non insulin dependent type diabetes. With both classifications some uncertainty remains with the proper assignment of individual cases. Nevertheless, no doubt remains that the two types of diabetes, also described as type I versus type II diabetes, are genetically or etiologically independent.

Insulin dependent diabetes (IDDM)

Only this type of diabetes is statistically associated with special HLA antigens. Corresponding to ethnic differences of HLA antigen frequencies the frequency of IDDM shows marked variations between different populations. The discovery of the HLA association has established the concept of heterogeneity of diabetes and has supported the theories of IDDM as an autoimmune disease. It has, however, not yet led to a clarification of the formal genetics of this type of diabetes. Single dominant and single recessive inheritance can be ruled out. The determination of HLA antigens does not allow any clinical, genetic or prognostic statement in single cases. Genetic counselling is only possible on the basis of empiric data. In caucasian populations the risk for children of patients with IDDM also to become diabetic is low: only about 1 ~ 2 % up to the age of 25 years. The frequency of non insulin dependent diabetes is not increased among relatives of insulin dependent diabetics.

Non insulin dependent diabetes (NIDDM)

Since many patients who do not need insulin for survival are treated by insulin for better control of blood glucose insulin treatment per se does not allow to classify a diabetic as being insulin dependent. The genetic control of this type of diabetes is much higher than that of IDDM. By a special method of age correction it has been calculated than 35~40% of all first degree relatives of patients with NIDDM would also become diabetic if they would live long enough (about 85 years of age). The incidence is lower among relatives of obese diabetics, indicating that other than genetic factors play an etiologic role in these patients. This observations strongly indicates a heterogeneity even within the non insulin dependent type of diabetes. A special subtype of NIDDM is the so called MODY or Tattersall syndrome which is clinically defined as a benigne type of non insulin dependent diabetes with onset in childhood or early adulthood. This type of diabetes is regularly inherited as an autosomal dominant
trait. For the purpose of genetic counselling of young people it is inevitable to rule out this type of diabetes before the low risk figures of IDDM can be taken as a basis for recommendations. The so called chlorpropamid alcohol flush test was recently described as a marker for MODY and related dominantly inherited types of diabetes, but, unfortunately, these observations were not reproducible by other groups, including our own.

The lack of reliable genetic markers and thereby the difficulties to assign individual cases to genetic entities remain the predominant problem and challenge in the field of genetics of diabetes mellitus.