CAN THE HIGH RISK OF TYPE I DIABETES IN FINLAND BE EXPLAINED BY FAMILIAL AGGREGATION AND BY HLA HAPLOTYPE DISTRIBUTION?

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Finland is the country which has the highest incidence of Type I (insulin dependent) diabetes in the world. The age-adjusted annual incidence in 1977 to 1984 was 30 per 100,000 in the age group 0-15 years (1). Finland is also one of the countries in the world where the incidence of Type I diabetes is rapidly increasing. The latest data from 1986 to 1987 indicate that the incidence is now about 40 per 100,000 which means about 350 new cases per year.

In September 1986 a nationwide epidemiologically based study into Type I diabetes called "DiMe" study was started in Finland which has a population of 4.5 million. The aim of the "DiMe" study is to find out more about the genetic and environmental factors involved in Type I diabetes and their interaction in order to plan the appropriate preventive measures for the future. All families with a newly diagnosed Type I diabetic child aged 0-14 years were invited to take part in the nationwide study which began in September 1986. As of April 1988, 430 new cases have been reported from the 33 collaborating hospitals. More than 90% of the families have agreed to participate.

GENETIC STUDY

The major genetic susceptibility to Type I diabetes is conferred by genes in the HLA region which is located on the short arm of chromosome 6 in the distal portion of the 6p21.3 band (for review see 2). Linkage between the HLA system and the genes coding for susceptibility to Type I diabetes has clearly been demonstrated (3).

Therefore, HLA antigens and HLA genes can be taken as markers for Type I diabetes. Whether one uses conventional serological methods for determining HLA antigens or one uses the recently developed techniques of RFLP (restriction fragment length polymorphism) analysis or oligonucleotide typing or whether one determines the aminoacid sequence of the HLA genes themselves it remains the HLA haplotype which carries the disease susceptibility allele that is important.

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The aim of the genetic part of the DiMe study was to collect HLA genotype and haplotype data from all participating newly diagnosed Type I diabetic children and their first degree relatives i.e. parents and siblings.

FAMILIAL AGGREGATION

The majority (87.7%) of the first 400 Finnish families with a newly diagnosed Type I diabetic child reported to the DiMe study by March 1988 were simplex families or so called sporadic cases where only one child had diabetes, and 49 (12.3%) were multiplex families or so called familial cases where at least one other first degree relative had also Type I diabetes (Table 1). Of these 400 families 19 had more than one Type I diabetic child; 18 had 2 and one family had 3 Type I diabetic children. Of the newly diagnosed DiMe probands 14 had a Type I diabetic sibling diagnosed before the DiMe study started in September 1986 and were therefore secondary cases, one DiMe proband was a tertiary case and up till now 5 of the "healthy" siblings of the newly diagnosed DiMe probands also developed Type I diabetes during the study.

At the time of the present analysis in 292 of the participating families the information on family history of Type I diabetes in first and also in second degree relatives was complete and computerized. Twelve fathers and 9 mothers had Type I diabetes which means that 7.2% of the diabetic children had an affected parent, 9.6% had an affected grandparent and 37.7% had at least one second or third degree relative with Type I diabetes.

HLA HAPLOTYPE DISTRIBUTION

Out of the 43 HLA genotyped multiplex families participating in the DiMe study 60% were families with one diabetic child and one diabetic parent and 30% were families with 2 affected children. Those HLA haplotypes which had been transmitted from the affected parent to the affected child were studied in more detail.

Due to the dominant "en bloc" inheritance of the HLA antigens parent and child are by definition haplo-identical. The haplotype which the affected child has inherited from the affected parent has to carry the disease susceptibility gene for Type I diabetes except in the rare event of recombination.

There were 19 such haplotypes of which 11 (58%) were DR4 positive and 5 (26%) DR3 positive. These percentages were very similar to the gene frequencies found in the newly diagnosed Type I diabetic probands of the DiMe study, i.e. 50% for DR4 and 20% for DR3.

Table 2 shows which B locus antigens were found together with DR4, DR3 and DR1 on these 19 haplotypes. Whereas, as expected, 3 out of 5 of the DR3 positive haplotypes carried B8 as expected only 3 out of 11 DR4 positive haplotypes carried Bw62. Four of the DR4 positive haplotypes carried the B locus antigen Bw56 which was a completely unexpected finding. All these DR4, Bw56 positive haplotypes carried the A locus antigen A2 and the C locus antigen Cw1. This A2, Cw1, Bw56, DR4 haplotype has not been reported to be increased in Type I diabetes in any other study or in any other ethnic group.

Bw56 is a subgroup of the broad antigen Bw22 which also consists of Bw55 which is the major subgroup of Bw22 in Caucasoid populations and of Bw54 which is only found in Mongoloid populations. Bw54 has been described to be increased in Japanese Type I diabetic patients (4).