HLA genetics in LADA

Original article:
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Summary and Comment:
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Summary

The major susceptibility genes for type 1 diabetes, HLA-DRB1 and HLA-DQB1, were genotyped by sequence-specific polymerase chain reaction in 387 patients with latent autoimmune diabetes in adults (LADA) and in 327 non-diabetic controls.

The main susceptibility haplotypes in LADA were identical to those in classical type 1 diabetes. The highest risk genotypes were associated with a younger age at diagnosis, while genotypes containing protective haplotypes were associated with an older age at diagnosis. Differential susceptibility was associated with DR4 subtypes: DRB*0401 conferred susceptibility to LADA, whereas DRB1*0403 conferred significant protection.

The authors concluded that differences in HLA-encoded susceptibility could not explain the differences observed in clinical presentation between classical type 1 diabetes and LADA.

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Comment

Type 1 diabetes is a polygenic chronic disease that results from the progressive destruction of insulin-secreting islet β-cells by a cell-specific autoimmune response. Development of selective β-cell autoimmunity derives from the absence or disruption of both central (thymus-dependent) and peripheral self-tolerance toward islet β-cells. Genetic and still undefined environmental factors interact to determine the development and onset of type 1 diabetes.

Three major autoantigens have been identified in the disease: the secreted hormone insulin (as well as its non-secreted precursor proinsulin); the 65 kDa isoform of glutamic acid decarboxylase, GAD65; and the insulinoma-associated tyrosine phosphatase, IA-2. Proinsulin is the most specific β-cell antigen but also the primary autoantigen tackled by the effector autoreactive lymphocytes.

Type 1 diabetes represents around 15% of all cases of diabetes and its peak incidence ranges between 10 and 14 years of age. The term LADA was first introduced to describe patients with a slowly progressive form of autoimmune diabetes that could be treated initially without insulin [1]. The acronym is also used to distinguish LADA from type 1 diabetes with immediate need for insulin, and from type 2 diabetes where insulin is not required at all or not for years after diagnosis. This form of autoimmune diabetes has also been designated as slowly progressive insulin-dependent diabetes or as type 1.5 diabetes. Diagnosis of LADA relies on three criteria: adult age at diagnosis (≥30 years), the presence of β-cell autoantibodies, and a delay of several months (at least 6 months) from initial diagnosis before the need for insulin to control hyperglycemia. Since islet autoantibodies against insulin and phosphatase IA-2 are rare in late-onset diabetes, the diagnosis of LADA is mainly based upon the detection of GAD autoantibodies. However, given that GAD autoantibodies are also detected in classical type 1 diabetes, their use to define LADA lacks specificity. Consequently, a debate has now begun with regard to the necessity, as well as the medical benefit, for designating LADA as a unique etiological entity [2, 3].

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Type 1 diabetes is a polygenic disease, but the major genetic contribution (±50%) comes from the histocompatibility HLA region on chromosome 6 (IDDM1). Cross-sectional studies have previously shown that age at diagnosis of type 1 diabetes is inversely correlated to the frequency of highest risk HLA phenotypes (DR3/DQ2 and/or DR4/DQ8) [4, 5]. Before their present study, the authors showed that the genetic sus-

ceptibility (±10%) conferred by the variable number of tandem repeats located upstream of the INS/IGF2 genes (IDDM2) cannot be distinguished from that observed in type 1 diabetes [6]. A previous genetic study also found similar HLA susceptibility genes in type 1 diabetes and LADA [7]. Thus, the similarity of the genetic predisposition associated with the two major susceptibility loci of type 1 diabetes strongly suggests that adult-onset autoimmune diabetes is just an age-related extension of the same pathogenic process responsible for type 1 diabetes in children. However, a series of other extra-HLA genes linked to type 1 diabetes (CTLA4, PTPN22, IL2RA, IL10) have not yet been investigated in LADA.

There remains a very important question about the pathogenesis of LADA: either it involves long-standing cell-specific autoimmunity with slow β-cell destruction over many years, or it corresponds to the onset of islet autoimmunity in adulthood with a short preclinical phase. At present, no one is able to answer this important question, although some arguments support the idea that type 1 diabetes could be a relapsing-remitting autoimmune disease, at least in some cases (like multiple sclerosis) [8]. If such a view were proved correct, LADA might in fact simply correspond to a late-stage form of type 1 diabetes. Therefore other studies are clearly needed to firmly demonstrate that LADA is a clinical entity different from classical type 1 diabetes. Nevertheless, as recently stated [9], if β-cell destruction is slowly progressive in LADA, this implies a wider therapeutic window for preventive strategies including immune-based therapies.

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