Variation at the insulin VNTR locus but not the CTLA-4 locus is associated with age of onset and need for insulin therapy in latent autoimmune diabetes in adults (LADA)


Diabetologia (2001); 44: Suppl 1: A75

**Background and Aims:** Subjects with Latent autoimmune diabetes in adults (LADA) have islet cell antibodies (ICA) and glutamic acid decarboxylase antibodies (GADA) typical of Type 1 diabetes. Disease presentation is more typical of Type 2 diabetes. Decreased disease severity in LADA patients may be related to reduced genetic susceptibility. To determine if there is an association of the Type 1 diabetes susceptibility genes, the insulin VNTR (11p15.5) and CTLA-4 (2q33) with LADA, the allele frequencies in LADA and Type 2 diabetic patients were compared. Genetic variation at the insulin VNTR and CTLA-4 loci was studied in relation to phenotypic characteristics.

**Materials and Methods:** Patients examined included 373 LADA, 530 Type 2 diabetic patients from the UKPDS and 330 non-diabetic subjects from the Diabetes in Families (DIF) study. Patients were genotyped by PCR-RFLP for the −23HphI A/B polymorphism in the insulin gene (which is in linkage disequilibrium with the VNTR class I/III alleles) and for the A49G transition in exon 1 of CTLA-4.

**Results:** The VNTR class I alleles were significantly associated with LADA compared to Type 2 diabetic patients (p < 0.0001). Division of patients by age at diagnosis showed a significant association of the VNTR class I alleles in those presenting younger: p < 0.0001 (25-<35 years), and p < 0.0001 (35-<45 years). The frequency of the VNTR class III alleles was increased in the older age groups (45-<55 and 55-65 years). In those diagnosed between 55 and 65 years, the class III allele frequency was similar to that in the non-diabetic subjects. There was an association of VNTR class I alleles with age at diagnosis (p = 0.026), BMI (p = 0.009) and need for insulin therapy within 6 years of diagnosis (p = 0.03). There was no association of the CTLA-4 polymorphism with LADA.

**Conclusions:** Genetic susceptibility from the insulin VNTR locus is associated with a younger age at diagnosis and a more severe phenotype in LADA patients suggesting a similarity between younger LADA and Type 1 diabetic patients.