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)

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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.