

## **Insulin VNTR and HLA DRB1/DQB1 loci affect age of presentation of autoimmune diabetes in adults**

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Glutamic acid decarboxylase antibodies (GADA) and islet cell antibodies (ICA) are present in 12% of Type 2 diabetes-diagnosed patients. In early adult presentation, patients with antibodies are non-obese but older patients are obese and less often require insulin therapy. Genetic variations may explain the heterogeneity. Allelic variation at both the HLA and insulin VNTR loci account for 40% of genetic risk in juvenile-onset Type 1 diabetic British Caucasians. We typed 255 antibody positive patients for the predisposing HLA, DR3, DR4, and DQB1 alleles by PCR-artificial RFLP and 306 antibody positive patients by PCR-RFLP at the insulin gene -23 HphI site which is in strong linkage disequilibrium with the insulin VNTR. The presence of class III alleles protects against Type 1 diabetes. For analysis, patients were grouped into decades by age at diagnosis (years): 25-34, 35-44, 45-54, 55-65. The high risk DR3/DR4 genotype was present in 38% of patients with onset at 25-34 years vs. 14% in those with onset at 55-65 years. The nonDR3/nonDR4 genotype increased in frequency as age at diagnosis increased, from 14% to 34% ( $\chi^2$  trend test:  $p=0.006$ ). The frequency of the VNTR class III alleles (B genotypes) for protection against Type I diabetes increased from 13% at 25-34 years to 40% at 55-65 years. ( $\chi^2$  trend test:  $p=0.016$ ) compared to 51% in healthy controls and 27% in type 1 insulin dependent diabetic patients diagnosed under 17 years of age. The younger age of onset is associated with a greater genetic load for diabetes, and conversely older age of onset with less genetic load.