Genetic heterogeneity of autoimmune diabetes: age of presentation in adults is influenced by HLA DRB1 and DQB1 genotypes (UKPDS 43). UK Prospective Diabetes Study (UKPDS) Group.

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AIMS/HYPOTHESIS: Juvenile-onset, insulin-dependent diabetes is associated with islet cell antibodies and with specific "high-risk" HLA-DRB1 and HLA-DQB1 genotypes. Patients with Type II (non-insulin-dependent) diabetes mellitus can have islet-related antibodies, but the genotypic associations at different ages of onset have not been evaluated. Our aim was to determine (i) the prevalence of DRB1 and DQB1 genotypes in patients at diagnosis of Type II diabetes at different ages from 25 to 65 years compared with the general population, and (ii) whether the presence of islet cell antibodies (ICA) or glutamic acid decarboxylase antibodies (GADA) or both by age is associated with different DRB1 and DQB1 genotypes. METHODS: The antibodies to islet cells and those to glutamic acid decarboxylase were measured in 1712 white Caucasian diabetic subjects at diagnosis of diabetes and they were genotyped for HLA DRB1*03 and DRB1*04 and the high-risk DRB1*04-DQB1* 0302 haplotype. To assess over-representation of high-risk alleles for Type I (insulin-dependent) diabetes mellitus, the prevalence of high-risk alleles in diabetic patients was expressed relative to the prevalence of low-risk alleles, non-DR3/non-DR4, that provided a reference denominator in both the diabetic patients and in 200 non-diabetic control subjects. The prevalence of ICA or GADA or both in patients with different HLA genotypes was assessed in those diagnosed in four age groups, 25-34 years, 35-44 years, 45-54 years and 55-65 years. RESULTS: In Type II diabetic patients presenting at ages 25-34, 35-44 and 45-54 years, there was an increased prevalence of DR3/DR4 compared with the general population with approximately 6.5-fold, 2.9-fold, 2.1-fold over-representation, respectively ($p < 0.0001$, < 0.01, < 0.05) but this was not found in those aged 55-65 years old. In the group aged 25-34 years, 32 % of patients with ICA or GADA or both had DRB1*03/DRB1*04-DQB1*0302 compared with 10% in those aged 55-65 years and expected 3% prevalence. Conversely, only 14% of those aged 25-34 years with antibodies had non-DR3/non-

DR4, compared with 35 % in those aged 55-65 years. There was thus pronounced age heterogeneity in DRB1 and DQB1 predisposition to Type II diabetes. The antibodies displaced DRB1 or DQB1 genotypes in the multivariate model for requiring insulin therapy by 6 years of follow-up. CONCLUSION/HYPOTHESIS: The age of presentation of Type I diabetes in adulthood was in part dependent on the DRB1/DQB1 genotype. Islet cell antibodies and glutamic acid decarboxylase antibodies were strongly associated with DRB1*03/DRB1*04-DQB1*0302 in early adulthood but showed little relation with specific HLA genotypes after the age of 55 years.