Susceptibility for latent autoimmune diabetes in adults (LADA) is determined by variation at the *IDDM2* (insulin-gene) locus in white Caucasian patients from UK repositories

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Background and Aims: Latent autoimmune diabetes in adults (LADA) is a slowly-progressing form of autoimmune diabetes developing in adults that masquerades as clinical Type 2 diabetes (T2D). LADA is characterised by the presence of islet cell autoantibodies that occur in classical juvenile-onset Type 1 diabetes (T1D), although insulin dependence is not inevitable. Common disease pathology but a less aggressive clinical progression between LADA and classical T1D could arise from increased protection/reduced susceptibility from shared risk genes. Our aim was to determine whether the fine structure of the known association between islet autoimmunity and insulin-gene variation in T1D is also observed in LADA. In T1D, VNTR alleles detected by certain haplotypes in the insulin gene region were originally reported to confer differential susceptibility to disease. The following haplotypes were defined by the -23*HphI*, +1428*FokI* and +3580*MspI* sites: class I ID- and class I other (IC+/ID+), class III IIIA/'Protective' (PH) and IIIB/'Very Protective' (VPH) haplotypes. We tested for association of these T1D-defined haplotypes with LADA.
Materials and Methods: 442 antibody-positive, LADA patients aged >25 years at diagnosis (238 from UKPDS, 138 from Warren 2 consortium, 42 from Exeter Young-onset T2D study and 24 from Diabetes in Families study) and 353 non-diabetic subjects (ND) recruited in the Diabetes in Families study were genotyped for the -23*HphI* (class I/III VNTR detection), +1404*Fnu4HI* (+1428*FokI* surrogate, PH/VPH detection) and +3580*MspI* (ID- haplotype detection) variants by Amplifluor™ technology. Genotypic and haplotypic association tests were performed using standard contingency tables and haplotype trend regression, respectively. Haplotype frequencies were estimated using the estimation-maximisation (EM) algorithm, as implemented in the HelixTree™ software package.
Results: Single-point analyses revealed dominant protective effects at all three sites; T allele (class III) at -23*HphI* (OR = 0.43 [0.32-0.58], $p < 0.001$), A allele at +1404*Fnu4HI* (OR = 0.51 [0.37-0.69], $p < 0.001$) and C allele at +3580*MspI* (OR = 0.55 [0.37-0.83], $p = 0.004$). Variable levels of linkage disequilibrium (LD) (r^2 0.06-0.89) were observed between pairs of SNPs in the different sample groups. Four major 3-point haplotypes were observed with frequencies higher than 1%, corresponding to the class I ID-, class I other (IC+/ID+), PH and VPH. Haplotype frequency distributions differed significantly between LADA and ND (haplotype trend regression, $p = 5 \times 10^{-6}$). The haplotype frequencies in LADA vs ND were as follows: class I ID-, 40% vs 33%; class I other, 41% vs 37%; PH: 14% vs 22% and VPH: 4% vs 8%.
Conclusion: Class I haplotypes predispose to disease in LADA, whereas class III haplotypes confer a protective effect suggesting that susceptibility at the insulin gene region is similar to that reported for T1D.