

## **The Variable Number of Tandem Repeats Upstream of the Insulin Gene is a Susceptibility Locus for Latent Autoimmune Diabetes in Adults.**

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The etiopathological relationship between latent autoimmune diabetes in adults (LADA) and classical type 1 (insulin dependent) diabetes remains unclear. Variation at the insulin gene variable number of tandem repeats (VNTR) minisatellite influences susceptibility to type 1 diabetes, but studies in LADA have been small and inconsistent. We examined the role of insulin gene variation (using flanking variants as surrogates for VNTR subtypes) in the largest case-control study of LADA to date (400 case and 332 control subjects). Highly significant associations were identified with disease, with dominant protective effects of the T allele at -23HphI (odds ratio [OR] 0.42 [95% CI 0.31-0.58],  $P = 2.4 \times 10^{-8}$ ), A allele at +1,404Fnu4HI (0.50 [0.36-0.70],  $P = 3.2 \times 10^{-5}$ ), and C allele at +3,580MspI (0.55 [0.35-0.85],  $P = 0.0046$ ). As with type 1 diabetes, the -23HphI variant (a surrogate for the subdivision of VNTR into class I and III alleles) most clearly defined susceptibility in LADA. However, there was no association with age at diagnosis or requirement for insulin therapy 6 years post diagnosis. This study establishes that variation within the insulin gene region does influence susceptibility to LADA, with the direction and magnitude of effect indistinguishable from that previously reported for type 1 diabetes. In conclusion, differences in VNTR-encoded susceptibility do not explain the differences in clinical presentation that distinguish classical type 1 diabetes and LADA.