

UKPDS 19: heterogeneity in NIDDM: separate contributions of IRS-1 and beta 3-adrenergic-receptor mutations to insulin resistance and obesity respectively with no evidence for glycogen synthase gene mutations. UK Prospective Diabetes Study.

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Insulin receptor substrate-1 (IRS-1), beta 3-adrenergic-receptor (beta 3-AR) and glycogen synthase (GS) genes are candidate genes for non-insulin-dependent diabetes mellitus (NIDDM), insulin resistance, dyslipidaemia and obesity. We studied white Caucasian subjects with NIDDM, 227 being randomly selected, 49 NIDDM within the top two percentiles of insulin resistance; 54 with dyslipidaemia in the top quintile of triglyceride/insulin and the bottom quintile of HDL, and 166 non-diabetic control subjects. We examined the association of the simple tandem repeat DNA polymorphisms (STRPs) near the IRS-1 and GS genes, and the prevalence of mutations at codons of IRS-1 513 and 972, beta 3-AR 64 and GS 464 using restriction fragment length polymorphism (RFLP). The STRP alleles in IRS-1 were significantly different between NIDDM and control subjects ($p = 0.015$). The IRS-1 972 mutation was significantly different between the four groups with increased prevalence in the insulin resistant and dyslipidaemia subjects (18 and 26% compared with 11% in control subjects; $p < 0.0005$). Those with or without IRS-1 mutations had similar clinical characteristics and impaired insulin sensitivity. beta 3-AR 64 mutation was not significantly different between the four groups but those with the mutation were more obese, with a test for linear association between number of alleles and degree of obesity in an analysis of variance showing a significant association ($p = 0.029$). The GS 464 mutation was not detected in any of the diabetic or control subjects and the population association study using GS STRP showed no difference in allelic frequencies between NIDDM patients and control subjects. A mutation in lipoprotein lipase at codon 291, associated in the general population with low HDL cholesterol, was not at increased prevalence in the NIDDM patients with dyslipidaemia. In conclusion, IRS-1 972 had an increased prevalence in subjects with insulin resistance, with or without dyslipidaemia. beta 3-AR 64 was associated with increased obesity

but not with insulin resistance or dyslipidaemia. These separate contributions to different features of NIDDM are an example of the polygenic inheritance of this heterogeneous disorder.