Genotype and beta cell response to therapy in a large type 2 diabetic cohort

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Background and Aims: Identification of common genetic variants able to predict therapeutic response to currently available agents would revolutionise clinical care delivery. In the present study, we have examined two genetic variants implicated in type 2 diabetes susceptibility, in participants from the UKPDS study to establish whether genotype was related to response to therapy.
Materials and Methods: The UKPDS was a large, multi-centre, prospective, randomised, intervention trial of 5102 patients with newly diagnosed type 2 diabetes. Following a dietary run-in, patients unable to achieve fasting plasma glucose (fpg) <6 mmol/l (n=4209) were randomised to either diet alone (n=1138), aiming to remain free of diabetic symptoms and maintaining a fpg of < 15 mmol/l; or to sulphonylurea therapy (n=1573) or a basal insulin supplement (n=1156), with intent to maintain a fpg < 6 mmol/l. Overweight patients could also be randomised to metformin (n=342). Genotyping, by allelic discrimination, of the *PPARG* Pro12Ala variant and *INS* VNTR class (inferred by genotyping the -23 *HphI* variant) was carried out on DNA available from 4139 participants. HOMA derived beta cell function was calculated in the 2472 participants with complete data. Two measures of treatment response were examined; (i) change in %B in the first year following randomisation, analysed using multiple regression, after adjustment for a range of factors including therapy allocation, sex, ethnicity and GAD antibody status and ii) time to halving of %B (or requirement for insulin therapy) from one year after randomisation, analysed using a Cox proportional hazards model, again after adjustment.
Results: *PPARG* Pro12Ala genotypes were distributed as Pro/Pro, 82.4%; Pro/Ala, 16.7%; Ala/Ala, 0.9%. Distribution of the *INS* VNTR was: Class I/I, 48.4%; Class I/III, 38.7%; Class III/III, 12.9%. All alleles were in Hardy Weinberg equilibrium. With respect to genotype, no significant change in beta cell function was observed in either a univariate regression model (*PPARG*, n=1804; *INS* VNTR, n=1805) or in a multivariate model adjusted for therapy allocation, gender, ethnicity, beta cell function at randomisation, antibody status, BMI and lipids (*PPARG*, n=1471; *INS* VNTR, n=1469). In a Cox proportional hazards model, adjusted for the same covariates, there was no significant effect of genotype on time to halving of %B (*PPARG*, n=1383; *INS* VNTR, n=1384). When these same measures were examined in groups stratified by randomised therapy, again no differences in %B were seen by genotype. For example, there was no difference in mean change in %B between genotypes in overweight patients randomised to diet (*PPARG* Pro/Pro -12.2%, Pro/Ala -13.5%, Ala/Ala -17.8%, p>0.15, adjusted; *INS* VNTR Class I/I -14.3%, Class I/III -10.7%, Class III/III -11.9%, p>0.15, adjusted).
Conclusions: In the current study, there was no relationship between beta cell responses to diet, sulphonylurea or metformin therapy and common genetic variation in the *PPARG* or *INS* genes