Butyrylcholinesterase K variant is associated with type 2 diabetes in UK caucasians

Y. Hashim, D. Shepherd, S. Wiltshire, A. Clarke, R.R. Holman

Diabetologia (2000); **43**: Suppl 1: A51

Background and Aims: Apolipoprotein E (ApoE) ε4, Butyrylcholinesterase (BCHE)-K variant and alpha 2-macroglobulin (a2M)-18 5 bp deleletion variants are increased in patients with Alzheimer's disease (AD), particularly those with a positive family history. ApoE, BCHE is found in amyloid deposits in AD and in the pancreatic islet amyloid deposits in type 2 diabetics. Increasing cerebral and islet amyloidosis is concomitant with increasing severity of both diseases. a2M, a serum pan-protease inhibitor mediates the clearance and degradation of A-beta, the major component of amyloid beta deposits. We therefore, examined the ε4, BCHE-K and a2M variants for association with diabetes, the associated phenotype and the epistatic interactions between the three genes.
Materials and Methods: We examined UKPDS non-obese, ICA and GADA negative type 2 Caucasian diabetics; (i) with more severe β-cell deficiency with high fasting plasma glucose (FPG) > 12 mmol/L (n = 65) and a positive family history of diabetes (FH); (ii) less severe β-cell deficiency, FGP < 8 mmol/L with variable FH (iii) randomly selected diabetics (n = 185); (iv) randomly selected diabetics from the Diabetes in Family Study (n = 43) and a positive FH; (v) non diabetic matched controls (n = 350). the APoE promoter -491 and -219, the ApoE gene residues 112 and 158 and the a2M -18 5 bp deletion variants were all genotyped by automated Fluorescent-restriction fragment length polymorphism using ABI 377. BCHE-K variant was genotyped using standard ARFLP assay.
Results: No deviation from Hardy-Weinberg equilibrium were observed for any of the variants. The prevalence of all six variants did not differ significantly between all diabetics (iiv) and controls (v). However, the frequency of BCHE-K variant differed significantly between groups (ii) and (v) (Fishers Exact test, P = 0.0075) and between groups (iii) and (v) (Chi-square, P = 0.027). No association with the severe β-cell deficient (i) group or with a positive family history [(i) or (iv)] were found for any of the variants. Epistatic interactions between the variants in the three genes in these diabetics remains to be evaluated by linkage disequilibrium algorithms, as do further phenotypic analyses.
Conclusion: BCHE-K variant is significantly associated with diabetes and in particular with less severe β-cell deficiency.