Hepatocyte Nuclear Factor 1-Alpha (MODY 3) gene mutations in type 2 diabetics of different ethnicity

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HNF1a mutations cause dominantly inherited Maturity onset Diabetes of the Young Type 3 (Mody 3), that classically presents at age less than 25 yrs. It can occasionally present as Type 2 diabetes in adults, when the phenotype has been reported as predominantly non-obese with marked beta-cell deficiency causing insulin requiring diabetes. The aim was to determine how frequently HNF1a mutations are observed in type 2 diabetics of different racial origins, white Causcasians, Afro-Carribean , Asian-Indian and Chinese and the nature of associated phenotype We examined 3 subgroups of non-obese ICA- and GADA-negative diabetic white Caucasian subjects, (i) severe beta cell deficient (FPG = <12 mmol/l) (n=68) (ii) mild hyperglycaemic (FPG = <8mmol/l) (n=27); (iii) gestational diabetics (n=38); (iv) randomly selected diabetic subjects (n=75). We examined 25 randomly chosen diabetics and 25 normoglycaemic control subjects from the remaining three racial groups, in whom diabetes present at younger age of onset. We screened for mutations with sequencing and SSCP with mutations verified by RFLP-based assays. Two promoter mutations were found in the mildly hyperglycaemic groups, one being a heterozygous 2bp deletion in a putative C/EBP binding site and a missense mutation in exon 4 (G301A) and exon 7 (C492T) in diabetic patients who had a similar, mild phenotype. One classical Type 2 diabetic had an exon 7 (C498A) missense mutation. Mody 3 mutations were not found in supposedly high-risk, markedly hyperglycaemic patients but more often in patients with glucokinase-like phenotype (p= 0.0019). Four novel, non-conservative missense mutations were identified In Afro-caribbean and Chinese diabetics that alter the structure and size of the amino acid. This prevalence does not account for the early age of onset of diabetes in the ethnic groups. HNFIα mutations appear to occur at low prevalence in several ethnic groups.