Prevalence of glucokinase (GCK) mutations in people with elevated fasting glucose levels: implications for clinical trials

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Background: There is considerable interest in large scale screening programmes and prospective studies to determine which factors influence whether individuals progress to diabetes. Within these programs there are likely to be individuals with permanent “fixed” defects in glucose sensing who are unlikely to progress to diabetes. Glucokinase (GCK) inactivating mutations cause a subtype of maturity-onset diabetes of the young (GCK-MODY) with elevated fasting plasma glucose (FPG) levels (5.5-8.0 mmol/L) but with normal 2 hour plasma glucose increments (2HPGI) after a 75g oral glucose tolerance test (OGTT) (<4.5 mmol/L). Since the population prevalence of GCK mutations is unknown the number of individuals in these programmes with a “fixed” glucose sensing defect due to a GCK mutation is unknown. The aims of our study were to determine the prevalence of GCK mutations in a cohort selected for impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) and to establish if these individuals could be distinguished from non-GCK-MODY subjects on clinical criteria alone.

Methods: We screened 662 people with FPG levels 5.5-7.7 mmol/L inclusive for GCK mutations by DHPLC analysis (98% sensitivity, 4% false-positive rate). Their mean (SD) FPG was 5.9 (0.7) mmol/L, 2HPGI 2.67 (2.3) mmol/L body mass index (BMI) 28.6 (4.5) kg/m² and age 52.1 (9.9) years. The assay was validated by testing 58 different heterozygous GCK mutations. Samples showing an abnormal chromatogram were sequenced on an ABI3700.

Results: Five pathogenic mutations and 11 non-functional polymorphisms were identified. The 5 individuals with GCK mutations were indistinguishable from the rest with mean (SD) FPG 6.2 (0.8) mmol/L, 2HPGI 3.5 (1.5) mmol/L, BMI 29.8 (5.2) kg/m² and age 48.2 (8.9) years.

Conclusion: The prevalence of <1% of GCK mutations in our cohort suggests that FPG screening may not greatly enhance identification of GCK-MODY individuals in this age group. Our data demonstrate that it is not possible to identify patients with GCK-MODY on clinical criteria alone in cohorts selected on the basis of IGT and/or IFG.