OBSERVATIONS

Identification of Two New Mutations in the Glucokinase Gene That Result in Maturity-Onset Diabetes of the Young

Glucokinase catalyzes glucose to glucose-6-phosphate conversion in the pancreatic β-cell and is a key regulator of insulin secretion (1). The glucokinase gene (*GCK*) on chromosome 7p15.3–15.1 has 12 exons. *GCK* heterozygous inactivating mutations result in mild fasting hyperglycemia termed maturity-onset diabetes of the young type 2 (MODY2) or MODY-GCK (MIM # 125851) (2). The mutations result in diminished insulin secretion (3) and possibly decreased hepatic glucose uptake and glycogen synthesis (4). Several hundred inactivating mutations throughout exons 2 to 10 have been described (5). We report two previously undescribed mutations.

Both patients were assessed at the Pediatric Diabetes Education Centre, Stollery Children's Hospital, Edmonton, Canada. Glucose and A1C were measured by standard methodology in the hospital's clinical laboratory. *GCK* mutation analysis was performed by Ambry Genetics (Aliso Viejo, CA). Genomic DNA was isolated from blood samples; exons 1a and 2–10 were sequenced following PCR amplification.

Patient 1, a 14-year-old East Indian male, presented with random glucose 9.7 mmol/l, fasting glucose 7.0 mmol/l, and A1C 7.2% (4.3–6.1%). GAD65 antibody level was 0 nmol/l (≤0.02). He was asymptomatic. His mother had a previous diagnosis of gestational diabetes with two pregnancies and mild type 2 diabetes not requiring pharmacotherapy (fasting glucose 6.7 mmol/l, A1C 6.4%). Two of her four siblings were also reported to have type 2 diabetes. *GCK* analysis on Patient 1 and his mother revealed the heterozygous presence of a c.244 A→G variant in exon 3, resulting in alanine replacing threonine at amino acid position 82 (p.T82A). The patient's two younger sisters were found to have the same mutation. The older sister, age 12 years, had fasting glucose 7.5 mmol/l and A1C 6.7%. The younger sister, age 5 years, had fasting glucose 5.8 mmol/l and A1C 6.3%. The mutation was not detected in the father who had normal fasting glucose and A1C.

Patient 2, a 12-year-old Serbian female, presented with a 2-year history of mild hyperglycemia. An oral glucose tolerance test revealed fasting glucose 6.6 mmol/l and 2-h glucose 7.7 mmol/l. Capillary glucose sampling showed fasting levels between 5.8 and 7.9 mmol/l and random or 2-h postprandial levels up to 9.6 mmol/l. Her A1C was 6.8%. GAD65 antibody level was 0 nmol/l. She was asymptomatic. Her mother was diagnosed with diabetes at 10 years old but did not require pharmacotherapy therapy as a child. As an adult, she was labeled with type 2 diabetes and started on metformin. Her recent A1C was 7.1%. There was also a history of diabetes in two maternal aunts. *GCK* analysis on Patient 2 and her mother revealed the heterozygous presence of a c.83delA variant in exon 2 with a single nucleotide deletion and resulting frameshift mutation. This mutation was not detected in the father, who had normal random glucose and A1C.

Both patients continue to have nonprogressive mild hyperglycemia over the last year without pharmacotherapy. We have identified two previously undescribed mutations in *GCK* resulting in the phenotypic presentation of MODY-GCK.

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