Clinical Features
Heterozygous inactivating mutations in GCK [OMIM#138079] have been described in patients with maturity onset diabetes of the young type 2 (GCK-MODY) [OMIM#125851], which is characterized by mild fasting hyperglycemia (1). Hyperglycemia is present at birth but often only detected later in life, when individuals undergo routine screening tests (1). Affected individuals rarely, if ever, show progression of disease, or develop the microvascular or macrovascular complications typically associated with diabetes (1). These patients typically therefore can be managed by diet alone, and treatment with oral medications or insulin can actually cause poorer outcomes as patients have an altered counter-regulatory response to hypoglycemia (2). Homozygous inactivating GCK mutations are associated with permanent neonatal diabetes mellitus (PNDM) (1). In addition, heterozygous activating mutations in GCK have also been observed, which lead to hypoglycemia (1).

Molecular Genetics
GCK encodes for the enzyme glucokinase, which has a central role in the regulation of blood glucose and acts as a “glucose sensor” in pancreatic β-cells (3). Mutations in GCK associated with GCK-MODY typically result in a modest decrease in glucokinase activity, which in turn leads to mild fasting hyperglycemia (4).

Inheritance
GCK-MODY is inherited in an autosomal dominant manner. The majority of mutations are inherited, although de novo mutations have also been described. Recurrence risk for children of an affected individual is 50%.

Test methods
We offer mutation analysis of all coding exons and intron/exon boundaries of GCK by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis of the GCK gene is performed by oligonucleotide array-CGH which identifies copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

GCK sequencing
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $850
CPT codes: 81405
Turn-around time: 4 weeks

GCK deletion/duplication analysis
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81404
Turn-around time: 4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Results
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS