THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

GCK Analysis for Maturity Onset Diabetes of the Young Type 2 (GCK-MODY)

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 ofer 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. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

GCK sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$850
CPT codes:	81404, 81405
Turn-around time:	4 weeks

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

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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

1. Osbak KK, Colclough K, Saint-Martin C et al. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. Hum Mutat 2009: 30: 1512-1526.
2. Guenat E, Seematter G, Philippe J et al. Counterregulatory responses to hypoglycemia in patients with glucokinase gene mutations. Diabetes Metab 2000: 26: 377-384.
3. Negahdar M, Aukrust I, Johansson BB et al. GCK-MODY diabetes associated with protein misfolding, cellular self-association and degradation. Biochim Biophys Acta 2012: 1822: 1705-1715.
4. Froguel P, Zouali H, Vionnet N et al. Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. N Engl J Med 1993: 328: 697-702.

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