

# The University of Chicago Genetic Services Laboratories



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## 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  $\beta$ -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

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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