THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Testing for MODY

Clinical features: The most prevalent monogenic diabetes phenotype, accounting for approximately 1% of all causes of diabetes, is MODY (maturity onset diabetes of the young) [1]. MODY is characterized by dominant inheritance of early-onset non-autoimmune diabetes that occurs in adolescence and young adulthood. However a residual insulin secretion may be still maintained for some years after diagnosis and exogenous insulin is generally not required at the time of diagnosis. These patients are typically misdiagnosed as Type 1 or Type 2 diabetes, however two or more consecutive generations of diabetes and the absence of metabolic features (significant obesity or features of insulin resistance) is more suggestive of MODY [2]. MODY is a heterogeneous group of disorders caused by mutations in genes important to pancreatic β-cell development, function, and regulation, glucose sensing and in the insulin gene itself [3]. The most common forms of MODY are due to mutations in the *HNF1A* and *HNF4A* genes, which encode for transcription factors important to pancreatic development and beta cell function, and in the glucokinase gene, *GCK* [3]. Mutations in at least 7 other genes can cause inherited diabetes with a MODY phenotype [7-14]. Recent reports have described the identification of mutations in *ABCC8* and *KCNJ11* in MODY patients suggesting that mutations in these genes can be associated with a large spectrum of diabetes phenotypes and may exhibit incomplete penetrance in some generations [4, 5]. A molecular diagnosis of MODY has important implications for treatment and identifies at-risk family members.

Our MODY Panel includes sequencing and deletion/duplication analysis of the genes listed below, as well as analysis for the mitochondrial mutations m.3243A>G, m.8296A>G, and m.14709T>C.

MODY Panel						
ABCC8	APPL1	BLK	CEL	GCK	HNF1A	HNF4A
HNF1B	INS	KCNJ11	KLF11	NEUROD1	PAX4	PDX1

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. 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.

MODY Panel (sequence and deletion/duplication analysis of included genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3000
CPT codes:	See test page
Turn-around time:	4-6 weeks

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. All abnormal results are reported by telephone.

Additional Resources:

The Kovler Diabetes Center at the University of Chicago provides additional research and resources for patients with monogenic forms of diabetes, including a MODY registry. Find out more at: http://monogenicdiabetes.uchicago.edu/mody-registry/

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

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