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 14 genes listed below.

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

Gene	Inheritance	Disease Phenotype and Molecular Genetics
GCK [OMIM#138079]	AD	Heterozygous inactivating *GCK* mutations are the most frequent monogenic cause of diabetes in asymptomatic children with persistent hyperglycemia or glycosuria (MODY2) [6].
HNF1A [OMIM#142410]	AD	Heterozygous mutations in the *HNF1A* (MODY-3) and *HNF4A* genes (MODY-1) are both associated with MODY. Overall, *HNF1A* mutations are the most common cause of MODY, with mutations having been described in multiple populations including Caucasian, Asian, and African populations [7]. Hyperglycemia in patients with MODY-1 and MODY-3 is progressive overtime, and typically results in the need for treatment with oral medications or insulin. *HNF1A* encodes a transcription factor HNF-1α and plays a role in regulation of the insulin gene and genes encoding proteins involved in glucose transport and metabolism [8]. The *HNF4A* gene encodes HNF-4α, an orphan nuclear receptor that regulates expression of HNF-1α [7].
HNF4A [OMIM#600281]	AD	
HNF1B [OMIM#189907]	AD	Heterozygous mutations in *HNF1B* are associated with a distinct form of MODY (MODY-5) that is characterized by renal cysts in addition to diabetes [9]. *HNF1B* encodes a transcription factor HNF-1β and plays a role in regulation of the insulin gene and genes encoding proteins involved in glucose transport and metabolism [7].
PDX1 [OMIM#600733]	AD	Mutations in the *PDX1* gene are a rare cause of MODY. In a consanguineous family in which an infant with pancreatic agenesis was homozygous for a 1-bp deletion in the *PDX1* gene, Stoffers et al. [10] found that members heterozygous for this mutation had early-onset type 2 diabetes mellitus, which they designated MODY4 (OMIM#606392). The expression of diabetes in these families may occur at later ages than in families with other types of MODY.
NEUROD1 [OMIM#601724]	AD	Heterozygous loss-of-function *NEUROD1* mutations are a rare cause of MODY (OMIM# 606394) [10]. Diabetes mellitus caused by heterozygous

		mutations in *NEUROD1* has been reported in three families [11] and was subsequently designated as MODY6.
KLF11 [OMIM#603301]	AD	Heterozygous *KLF11* point mutations are a rare cause of MODY (OMIM#610508) [12].
CEL [OMIM#114840]	AD	Heterozygous *CEL* frameshift deletions in the variable number of tandem repeats (VNTR) caused MODY (OMIM#609812) in two families with autosomal dominantly inherited diabetes and exocrine pancreas dysfunction [13].
PAX4 [OMIM#167413]	AD	Heterozygous *PAX4* mutations are a rare cause of MODY (OMIM#612225) [14].
INS [OMIM#176730]	AD	Heterozygous *INS* mutations are a rare cause of MODY (OMIM#613370) [15, 16].
BLK [OMIM#191305]	AD	Heterozygous *BLK* mutations are a rare cause of MODY (OMIM#613375) [17].
APPL1 [OMIM#616511]	AD	Heterozygous loss of function variants in *APPL1* have been described in two families with MODY14 [18].
ABCC8 [OMIM#600509]	AD	Recently, Johansson et al. identified a missense mutation in a patient with diabetes diagnosed at 25 years of age MODY patients suggesting that mutations in these genes can be associated with a large spectrum of diabetes phenotypes and can be not totally penetrant [19].
KCNJ11 [OMIM# 600937]	AD	Heterozygous *KCNJ11* mutations have been recently identified by Bonnefond et al. in a patient with MODY [5] confirming the wide spectrum of diabetes related phenotypes due to mutations in *KCNJ11.*

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 14 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3000
CPT codes:	81406, 81407
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.

References:

1. McDonald, T.J. and S. Ellard, *Maturity onset diabetes of the young: identification and diagnosis.* Ann Clin Biochem.

2. Murphy, R., S. Ellard, and A.T. Hattersley, *Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes.* Nat Clin Pract Endocrinol Metab, 2008. **4**(4): p. 200-13.
3. Ellard, S., C. Bellanne-Chantelot, and A.T. Hattersley, *Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young.* Diabetologia, 2008. **51**(4): p. 546-53.
4. Bowman, P., et al., *Heterozygous ABCC8 mutations are a cause of MODY.* Diabetologia. **55**(1): p. 123-7.
5. Bonnefond, A., et al., *Whole-exome sequencing and high throughput genotyping identified KCNJ11 as the thirteenth MODY gene.* PLoS One. **7**(6): p. e37423.
6. Schnyder, S., et al., *Genetic testing for glucokinase mutations in clinically selected patients with MODY: a worthwhile investment.* Swiss Med Wkly, 2005. **135**(23-24): p. 352-6.
7. Fajans, S.S., G.I. Bell, and K.S. Polonsky, *Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young.* N Engl J Med, 2001. **345**(13): p. 971-80.
8. Stoffel, M. and S.A. Duncan, *The maturity-onset diabetes of the young (MODY1) transcription factor HNF4alpha regulates expression of genes required for glucose transport and metabolism.* Proc Natl Acad Sci U S A, 1997. **94**(24): p. 13209-14.
9. Lindner, T.H., et al., *A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta.* Hum Mol Genet, 1999. **8**(11): p. 2001-8.
10. Stoffers, D.A., et al., *Early-onset type-II diabetes mellitus (MODY4) linked to IPF1.* Nat Genet, 1997. **17**(2): p. 138-9.
11. Malecki, M.T., et al., *Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus.* Nat Genet, 1999. **23**(3): p. 323-8.
12. Neve, B., et al., *Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function.* Proc Natl Acad Sci U S A, 2005. **102**(13): p. 4807-12.
13. Raeder, H., et al., *Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction.* Nat Genet, 2006. **38**(1): p. 54-62.
14. Plengvidhya, N., et al., *PAX4 mutations in Thais with maturity onset diabetes of the young.* J Clin Endocrinol Metab, 2007. **92**(7): p. 2821-6.
15. Edghill, E.L., et al., *Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood.* Diabetes, 2008. **57**(4): p. 1034-42.
16. Molven, A., et al., *Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes.* Diabetes, 2008. **57**(4): p. 1131-5.
17. Borowiec, M., et al., *Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction.* Proc Natl Acad Sci U S A, 2009. **106**(34): p. 14460-5.
18. Prudente, S., et al., *Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus.* Am J Hum Genet, 2015. **97**(1): p. 177-85.
19. Johansson, S., et al., *Exome sequencing and genetic testing for MODY.* PLoS One. **7**(5): p. e38050.