MODY Panel

PANEL GENE LIST

*ABCC8, APPL1, BLK, *CEL, GCK, GLUD1, HADH, HNF1A, HNF1B, HNF4A, INS, KCNJ11, *KLF11, NEUROD1, PAX4, PDX1 (IPF1), RFX6, WFS1*

**whole gene deletions/duplications only*

CLINICAL FEATURES

Maturity-onset diabetes of the young (MODY) is a monogenic form of insulin-independent diabetes that follows an autosomal dominant pattern of inheritance and typically presents before the age of 25 years. MODY accounts for approximately 1-2% of diabetes mellitus and can be difficult to differentiate from the more common forms of diabetes. Differentiating factors include lack of autoantibodies usually observed with type 1 diabetes and lack of obesity often observed with type 2 diabetes. Genetic testing can establish an accurate diagnosis and identify a genetic etiology, which has important implications for individualized management of symptoms and prognostic information for family members.[1,2]

Variants in the *HNF1A* gene cause MODY3, which accounts for approximately 20-50% of MODY cases. The phenotype associated with MODY3 is highly variable, with patients' blood glucose levels ranging from normal to high. Typically, individuals with MODY3 manifest in adolescence or early adult life with beta-cell failure and progressive hyperglycemia, putting patients at risk for microvascular and macrovascular complications. Hyperglycemic control can be maintained for many years with sulfonylurea, although individuals with MODY3 often will ultimately progress to insulin treatment. Variants in the *HNF4A* gene cause MODY1, which accounts for approximately 5% of MODY cases and has a similar presentation to MODY3. Heterozygous variants in the *PDX1* gene cause MODY4, which also has a similar presentation but is a very rare cause of MODY.[1,2]

MODY2 is caused by inactivating variants in the *GCK* gene, accounting for another 20-50% of MODY cases. Typically, patients with MODY2 have mild to moderate fasting hyperglycemia and are often asymptomatic. The majority of individuals with MODY2 are managed with diet alone and rarely need pharmacological intervention.[1,2]

Approximately 5% of MODY cases are due to variants in the *HNF1B* gene, which causes MODY5. MODY5 is characterized by renal disease and insulin resistance.[5] Individuals with MODY5 have reduced pancreatic size, and females may have urogenital abnormalities. Sulfonylurea treatment is ineffective for controlling hyperglycemia, and insulin treatment is usually necessary.[1,2]

Variants in the genes *NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11, APPL1* (MODY6- 14), as well as *RFX6* and *WFS1* are rare and have been reported in few families. Therefore, each gene accounts for a small portion of MODY cases, likely less than 1%.[7,8,9,12-14] Variants in the *ABCC8, INS*, and *KCNJ11* genes are also associated with familial hyperinsulinemia and permanent neonatal diabetes mellitus.7,8 The GLUD1 and HADH genes are associated with familial hyperinsulinism, which is characterized by dysregulated insulin secretion from pancreatic beta-cells.[10,11] The inappropriate release of insulin into the blood leads to persistent hyperinsulinaemic hypoglycemia (HH).[11]

GENETICS

Autosomal Dominant.

Bi-allelic variants in the *GCK* and *PDX1* genes cause the rare autosomal recessive phenotype of permanent neonatal diabetes.[3] Bi-allelic variants in the *ABCC8, HADH* and *KCNJ11* genes cause autosomal recessive familial hyperinsulinemia, also referred to as hyperinsulinemic hypoglycemia.[7,8,11]

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TEST METHODS

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Due to homology with pseudogene(s), only sequence for exons 2-7, 10 and 11 (up to codon Val596) of the *CEL* gene is analyzed. The VNTR in the 3' end of exon 11 and any possible gene rearrangements in this genomic region will not be evaluated. For the *CEL* and *KLF11* genes, only whole gene deletions and duplication may be detected. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

CLINICAL SENSITIVITY

MODY accounts for 1-2% of individuals with diabetes mellitus. Among individuals with MODY, approximately 20-50% have a variant in the *GCK* gene (MODY2) and 20-50% have a variant in the *HNF1A* gene (MODY3). Variants in the *HNF4A* (MODY1) gene and *HNF1B* (MODY5) gene each account for approximately 5% of MODY.[1,2,6] Variants in the remaining genes causing MODY are rare, and each likely accounts for less than 1% of MODY cases.[7,8,9,12-14] The *GLUD1* and *HADH* genes are responsible for approximately 5% and 1% of familial hyperinsulinism, respectively.[10,11]

Gene	Protein	Inheritance	Disease Associations
HNF4A	HEPATOCYTE NUCLEAR FACTOR 4-ALPHA	AD	MODY 1
GCK	GLUCOKINASE	AD/AR	MODY 2, permanent neonatal diabetes
HNF1A	HEPATOCTYE NUCLEAR FACTOR 1-ALPHA	AD	MODY 3
PDX1 (aka IPF1)	PANCREAS/DUODENUM HOMEOBOX PROTEIN 1	AD/AR	MODY 4, permanent neonatal diabetes, pancreatic agenesis 1
HNF1B	HEPATONUCLEAR FACTOR 1- BETA	AD	MODY 5
NEUROD1	NEUROGENIC DIFFERENTIATION 1	AD	MODY 6
KLF11	KRUPPEL-LIKE FACTOR 11	AD	MODY 7
CEL	CARBOXYL-ESTER LIPASE	AD	MODY 8
PAX4	PAIRED BOX GENE-4	AD	MODY 9

INS	INSULIN	AD	MODY 10, permanent neonatal diabetes mellitus, familial hyperinsulinemia
BLK	TYROSINE KINASE, B LYMPHOCYTE SPECIFIC	AD	MODY 11
ABCC8	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 8	AD / AR	MODY 12, permanent neonatal diabetes, familial hyperinsulinemia
KCNJ11	POTASSIM CHANNEL, INWARDLY RECTIFTYING, SUBFAMILY J, MEMBER 11	AD / AR	MODY 13, permanent neonatal diabetes, familial hyperinsulinemia
APPL1	ADAPTOR PROTEIN PHOSPHOTYROSINE INTERATION, PH DOMAIN, AND LEUCINE ZIPPER-CONTAINING PROTEIN 1	AD	MODY 14
GLUD1	GLUTAMATE DEHYDROGENASE 1	AD	Familial hyperinsulinism/ Hyperinsulinismhyperammonemia (HH)
HADH	3-HYDROXYACYL-CoA DEHYDROGENASE	AR	Familial hyperinsulinism / HH
RFX6	REGULATORY FACTOR X, 6	AR / AD (reduced penetrance)	Mitchell-Riley syndrome, MODY
WFS1	WOLFRAMIN ER TRANSMEMBRANE GLYCOPROTEIN	AR / AD	Wolfram syndrome, nonsyndromic hearing loss, nonsyndromic diabetes mellitus

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