Maturity-Onset Diabetes of the Young and Neonatal Diabetes Panel, Sequencing

Maturity-onset diabetes of the young (MODY) typically occurs in adolescents or young adults <35 years of age. Affected individuals often have mild stable fasting hyperglycemia, weak response to pharmacologic therapy, a personal or family history of neonatal diabetes or neonatal hypoglycemia, and an autosomal dominant pattern of inheritance. Neonatal diabetes (ND) is defined by persistent hyperglycemia in infants <6 months of age. Molecular testing is recommended to guide treatment for MODY and ND.

Featured ARUP Testing

MODY and Neonatal Diabetes Panel, Sequencing 3001593

Method: Massively Parallel Sequencing

Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary.

Disease Overview

Symptoms/Associated Disorders

Maturity-Onset Diabetes of the Young[1]:

- Early-onset diabetes in adolescents or young adults
- Absence of pancreatic islet autoantibodies
- Endogenous insulin production 5 years after onset
- Low insulin requirement
- Lack of ketoacidosis when insulin is omitted
- Lack of obesity or acanthosis nigricans
- Normal triglyceride and high-density lipoprotein levels

Neonatal Diabetes:

- Persistent hyperglycemia (>150-200 mg/dL) in infants <6 months of age
- Mean age of diagnosis: 7 weeks
- May present with intrauterine growth restriction, glucosuria, ketonuria, hyperketonemia, severe dehydration, and failure to thrive
- Decreased fecal elastase and increased fat in stool in infants with pancreatic hypoplasia

Etiology

Pathogenic variants in several overlapping genes for MODY and ND

- Pathogenic variants in *GCK* (30-50%),[2] *HNF1A* (30-65%),[3,4] *HNF4A* (5-10%),[3] and *HNF1B* (<5%)[5] are causative for at least 70% of MODY.
- Pathogenic variants in *GCK* (4%),[4,6] *INS* (20%),[7,8] *ABCC8* (19%),[9] and *KCNJ11* (30%)[10] are causative for 73% of ND.

Epidemiology/Prevalence

- Prevalence of MODY is estimated at 1-3%[7,11] in the U.S.
- Prevalence of ND is rare. The incidence has been reported between 1 in 160,000 in Austria to 1 in 215,000 in Slovakia.[12,13]

Inheritance

- Autosomal dominant (AD) for the main causative genes for MODY: *GCK, HNF1A, HNF4A,* and *HNF1B*
- AD and autosomal recessive (AR) for main causative genes for ND
  - AD: *INS, ABCC8,* and *KCNJ11*
  - AR: *GCK*

Penetrance

Dependent on the causative gene

- Pathogenic *HNF1A* variants are causative for 30-60% of MODY and have a 63% penetrance by age 25, 79% penetrance by 35, and 96% penetrance by age 55.
- Pathogenic variants in *KCNJ11* and *ABCC8* have shown reduced penetrance for ND.

Test Description

Clinical Sensitivity

At least 70% for MODY and 73% for ND (see Etiology above)

Limitations

- A negative result does not exclude a diagnosis of MODY or ND.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of the test result may be impacted if the patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Most regulatory region and deep intronic variants
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *CEL* (NM_001807) 1, 8, 9, 11
    - *ABCC8* (NM_001351295) partial exon 14 (Chr11:17449973-17450018)
  - The following may not be detected:
    - Deletions/duplications/insertions of any size by massively parallel sequencing
    - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
    - Low-level somatic variants

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ABCC8	600509	NIDDM	AD
		Diabetes mellitus, permanent neonatal 3, with or without neurologic features	AD, AR
		Diabetes mellitus, transient neonatal 2	AD
		Hyperinsulinemic hypoglycemia, familial, 1	AD, AR
		Hypoglycemia of infancy, leucine sensitive	AD
APPL1	604299	MODY, type 14	AD
CEL	114840	MODY, type 8	AD
EIF2AK3	604032	Wolcott-Rallison syndrome	AR
FOXP3	300292	Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked	XLR
GATA4	600576	Neonatal and childhood diabetes	AD
GATA6	601656	Pancreatic agenesis and congenital heart defects	AD
GCK	138079	NIDDM, late onset	AD
		Hyperinsulinemic hypoglycemia, familial, 3	AD
		MODY, type 2	AD
		Diabetes mellitus, permanent neonatal 1	AR
HNF1A	142410	NIDDM 2	AD
		IDDM 20	AD
		MODY, type 3	AD
HNF1B	189907	NIDDM	AD
		Renal cysts and diabetes syndrome	AD
HNF4A	600281	NIDDM	AD
		Fanconi renotubular syndrome 4, with MODY	AD
		MODY, type 1	AD
INS	176730	IDDM2	AD

NIDDM, noninsulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; XLR, X-linked recessive

Gene	MIM Number	Disorder	Inheritance
		Diabetes mellitus, permanent neonatal	AD, AR
		Hyperproinsulinemia	AD
		MODY, type 10	AD
KCNJ11	600937	Diabetes mellitus, transient neonatal, 3	AD
		Diabetes, permanent neonatal 2, with or without neurologic features	AD
		Hyperinsulinemic hypoglycemia, familial 2	AR
		MODY, type 13	AD
NEUROD1	601724	MODY, type 6	AD
NEUROG3	604882	Diarrhea 4, malabsorptive, congenital	AR
PDX1	600733	MODY, type 4	AD
		Pancreatic agenesis 1	AR
RFX6	612659	Mitchell-Riley syndrome	AR
SLC19A2	603941	Thiamine-responsive megaloblastic anemia syndrome	AR
WFS1	606201	NIDDM	AD
		Wolfram-like syndrome, AD	AD
		Wolfram syndrome 1	AR
ZFP57	612192	Diabetes mellitus, transient neonatal, 1	AD

NIDDM, noninsulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; XLR, X-linked recessive

References

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Related Information

Diabetes Mellitus - Type 1, Type 2, and Gestational

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