Blueprint Genetics

MODY Panel

Test code: EN0601

Is ideal for patients with a clinical suspicion of maturity onset diabetes of the young (MODY).

The panel covers genes associated with autosomal dominant forms of the disease.

About MODY

Maturity-onset diabetes of the young (MODY) is an autosomal dominant inherited form of diabetes and accounts for 1–2% of individuals with diabetes. MODY is a rare clinically and genetically heterogeneous form of diabetes characterized by young age of onset (generally 10-45 years of age), with development of non-insulin dependent diabetes prior to 25 years of age. Additionally, blood vessel abnormalities of the retinas (retinopathy) and kidneys, and congenital abnormalities due to diabetes complications have also been noted. Individuals with MODY typically have no reported history of obesity or metabolic syndrome accompanying hyperglycemia. Many people with MODY are misdiagnosed with type 1 or type 2 diabetes. MODY is the most common form of monogenic diabetes with an estimated prevalence at 1:10,000 in adults and 1:23,000 in children. Approximately 80% of cases are misdiagnosed as type 1 or type 2 diabetes, complicating prevalence and incidence estimations. Genetic testing is generally pursued only in those with classic features of MODY. However, only 50% of subjects with genetically diagnosed MODY meet classic criteria. Establishing a diagnosis of MODY significantly impacts clinical management. Heterozygous mutations in *HNF1A*, *HNF4A*, and *GCK* account for >90% of all MODY with a known genetic cause. Patients with *HNF1A* and *HNF4A* mutations have slowly progressing beta-cell dysfunction, and treatment with low-dose sulfonylurea results in stable or improved glycemic control and improved quality of life related to diabetes care compared with insulin or metformin therapy. GCK-MODY has a unique phenotype of mild, nonprogressive hyperglycemia, with HbA1c typically <7% (53 mmol/mol). It is not associated with increased risk of microvascular and macrovascular complications seen in other forms of diabetes. Generally, treatment does not change HbA1c. Molecular diagnosis of GCK-MODY allows pharmacologic therapy to be discontinued and decreases the frequency of medical surveillance. (PMID: 24026547).

Availability

Results in 3-4 weeks

Gene set description

Genes in the MODY Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCC8	Hyperinsulinemic hypoglycemia, Diabetes, permanent neonatal, Hypoglycemia, leucine-induced, Diabetes mellitus, transient neonatal, Pulmonary arterial hypertension (PAH)	AD/AR	170	641
APPL1	Maturity-onset diabetes of the young, type 14	AD	2	2
BLK	Maturity onset diabetes of the young	AD	5	9
CEL	Maturity-onset diabetes of the young, type 8	AD	4	13
GCK	Hyperinsulinemic hypoglycemia, familial, Diabetes mellitus, permanent neonatal, Maturity-onset diabetes of the young, type 2	AD/AR	178	837
HNF1A	Maturity onset diabetes of the young, Renal cell carcinoma, nonpapillary clear cell, Liver adenomatosis	AD	78	528

HNF1B	Renal cell carcinoma, nonpapillary chromophobe, Renal cysts and diabetes syndrome	AD	35	234
HNF4A	Congenital hyperinsulinism, diazoxide-responsive, Maturity onset diabetes of the young, Fanconi renotubular syndrome 4 with maturity-onset diabetes of the young	AD	32	147
INS	Diabetes mellitus, permanent neonatal, Hyperproinsulinemia, familial, with or without diabetes, Maturity onset diabetes of the young	AD	33	78
KCNJ11	Hyperinsulinemic hypoglycemia, Diabetes, permanent neonatal, Diabetes mellitus, transient neonatal, Maturity-onset diabetes of the young 13, Paternally-inherited mutations can cause Focal adenomatous hyperplasia	AD/AR	63	178
KLF11	Maturity onset diabetes of the young	AD	1	4
NEUROD1	Maturity onset diabetes of the young	AD	3	18
PAX4	Diabetes mellitus	AD	3	10
PDX1	Pancreatic agenesis, Neonatal diabetes mellitus, Maturity-onset diabetes of the young, type 4, Lactic acidemia due to PDX1 deficiency	AD/AR	10	28
RFX6	Pancreatic hypoplasia, intestinal atresia, and gallbladder aplasia or hypoplasia, with or without tracheoesophageal fistula, Martinez-Frias syndrome, Mitchell-Riley syndrome	AR	10	31

*Some regions of the gene are duplicated in the genome. Read more.

The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#)

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database (ClinVar); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD). The list of associated, gene specific phenotypes are generated from CGD or Mitomap databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
ABCC8	Chr11:17415959	c.4412-13G>A	NM_000352.3	rs1008906426
ABCC8	Chr11:17427028	c.3399+13G>A	NM_000352.3	rs182340196
ABCC8	Chr11:17449501	c.2041-12C>A	NM_000352.3	
ABCC8	Chr11:17449510	c.2041-21G>A	NM_000352.3	rs746714109
ABCC8	Chr11:17449514	c.2041-25G>A	NM_000352.3	
ABCC8	Chr11:17452526	c.1672-20A>G	NM_000352.3	
ABCC8	Chr11:17465872	c.1333-1013A>G	NM_000352.3	

ABCC8	Chr11:17470268	c.1177-53_1177-51delGTG	NM_000352.3	rs1271038564
ABCC8	Chr11:17498513	c.-190C>G	NM_000352.3	
BLK	Chr8:11422122	c.*505G>T	NM_001715.2	
GCK	Chr7:44186044	c.1022+18G>A	NM_033507.1	rs150914617
GCK	Chr7:44193073	c.49-15_49-11delCCCCTinsGGGAGGG	NM_033507.1	
GCK	Chr7:44229009	c.-457C>T	NM_000162.3	rs548039601
GCK	Chr7:44229109	c.-557G>C	NM_000162.3	
HNF1A	Chr12:121416034	c.-538G>C	NM_000545.5	
HNF1A	Chr12:121416110	c.-462G>A	NM_000545.5	
HNF1A	Chr12:121416281	c.-291T>C	NM_000545.5	rs534474388
HNF1A	Chr12:121416285	c.-287G>A	NM_000545.5	
HNF1A	Chr12:121416285		NM_000545.5	
HNF1A	Chr12:121416289	c.-283A>C	NM_000545.5	
HNF1A	Chr12:121416314	c.-258A>G	NM_000545.5	rs756136537
HNF1A	Chr12:121416354	c.-218T>C	NM_000545.5	
HNF1A	Chr12:121416385	c.-187C>A/T	NM_000545.5	
HNF1A	Chr12:121416385		NM_000545.5	
HNF1A	Chr12:121416385		NM_000545.5	rs970766228
HNF1A	Chr12:121416391		NM_000545.5	
HNF1A	Chr12:121416437		NM_000545.5	
HNF1A	Chr12:121416446		NM_000545.5	rs780586155
HNF1A	Chr12:121416453	c.-119G>A	NM_000545.5	rs371945966
HNF1A	Chr12:121416475	c.-97T>G	NM_000545.5	
HNF1A	Chr12:121416508		NM_000545.5	
HNF4A	Chr20:42984253	c.-192C>G	NM_175914.4	
HNF4A	Chr20:42984264	c.-181G>A	NM_175914.4	
HNF4A	Chr20:42984271	c.-174T>C	NM_175914.4	
HNF4A	Chr20:42984276	c.-169C>T	NM_175914.4	
HNF4A	Chr20:42984299	c.-146T>C	NM_175914.4	
HNF4A	Chr20:42984309	c.-136A>G	NM_175914.4	
HNF4A	Chr20:43036000	c.291-21A>G	NM_000457.4	

INS	Chr11:2181023	c.*59A>G	NM_000207.2	rs397515519
INS	Chr11:2181242	c.188-15G>A	NM_000207.2	rs574629011
INS	Chr11:2181258	c.188-31G>A	NM_000207.2	rs797045623
INS	Chr11:2181774	c.187+241G>A	NM_000207.2	
INS	Chr11:2182419	c.-39A>C	NM_000207.2	
INS	Chr11:2182532	c.-152C>A	NM_000207.2	
INS	Chr11:2182532	c.-152C>G	NM_000207.2	
INS	Chr11:2182533	c.-153C>G	NM_000207.2	rs915076855
INS	Chr11:2182543	c.-187_-164del	NM_000207.2	
KCNJ11	Chr11:17409692	c.-54C>T	NM_000525.3	
KCNJ11	Chr11:17409772	c.-134G>T	NM_000525.3	rs387906398
NEUROD1	Chr2:182545307	c.-162G>A	NM_002500.4	rs537184640
RFX6	Chr6:117198947	c.224-12A>G	NM_173560.3	

Test Strengths

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level
- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

Genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)

- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test performance

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed paraffin embedded tissue), saliva and dry blood spots (filter cards). These sample types were selected in order to maximize the likelihood for high-quality DNA yield. The diagnostic yield varies depending on the assay used, referring healthcare professional, hospital and country. Plus analysis increases the likelihood of finding a genetic diagnosis for your patient, as large deletions and duplications cannot be detected using sequence analysis alone. Blueprint Genetics' Plus Analysis is a combination of both sequencing and deletion/duplication (copy number variant (CNV)) analysis.

Performance of Blueprint Genetics high-quality, clinical grade NGS sequencing assay for panels.

	Sensitivity % (TP/(TP+FN)	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	99.2% (7,745/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA

Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Size range (0.1-47 Mb)	100% (25/25)	
The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics		
Mean sequencing depth	143X	
Nucleotides with >20x sequencing coverage (%)	99.86%	

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

		Specificity
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2084 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.9%(12/13)	99.98%
Heteroplasmic (<5%)	88.7% (47/53)	99.93%

Insertions and deletions by sequence analysis n=42 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%
Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	>0.9999
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%
Heteroplasmic (15%)	100.0% (17/17)	100.0%
Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	
rho zero cell line (=no mtDNA), mean sequencing depth	12X	

Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding and regulatory variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the 'Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases including, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation

software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with <20X sequencing depth if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the crucial details of the analysis process.

Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis is orthogonal confirmation. Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing when they do not meet our stringent NGS quality metrics for a true positive call. Reported heterozygous and homo/hemizygous copy number variations with a size <10 and <3 target exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen and confirmed less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references, abstracts and variant databases used to help ordering providers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification. We do not recommend using variants of uncertain significance (VUS) for family member risk stratification or patient management. Genetic counseling is recommended.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Our internal database and our understanding of variants and related phenotypes increases with every case analyzed. Our laboratory is therefore well-positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the MODY Panel

ICD-10	Disease
E11.9	Maturity-onset diabetes of the young

Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- Amed S et al. Maturity-Onset Diabetes of the Young (MODY): Making the Right Diagnosis to Optimize Treatment. Can J Diabetes. 2016 Oct;40(5):449-454.
- American Diabetes Association
- Anık A et al. Maturity-onset diabetes of the young (MODY): an update. J Pediatr Endocrinol Metab. 2015 Mar;28(3-4):251-63.
- Canadian Diabetes Association
- Diabetes Australia
- Diabetes UK
- GeneReviews - Classification of Diabetes Mellitus
- National Institute of Diabetes and Digestive and Kidney Diseases
- Naylor RN et al. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. Diabetes Care. 2014;37(1):202-9.
- Timsit J et al. Searching for Maturity-Onset Diabetes of the Young (MODY): When and What for? Can J Diabetes. 2016 Oct;40(5):455-461.