Cobalamin/Propionate/Homocysteine Metabolism-Related Disorders Panel

Disorders of cobalamin (vitamin B_{12})/propionate/homocysteine metabolism result from defects in the vitamin B_{12} metabolic pathway. Abnormal biochemical findings may include elevated propionylcarnitine levels and/or propionyl/acetylcarnitine ratio in plasma and increased methylmalonic acid in blood; vitamin B_{12} levels may be normal or elevated. The clinical features of these disorders are highly variable, with multiple systems affected, and age of disease onset ranges from the perinatal period to adulthood. Molecular testing is used to confirm suspected cobalamin/propionate/homocysteine metabolism-related disorders in individuals with clinical symptoms and/or biochemical findings.

Featured ARUP Testing

Cobalamin/Propionate/Homocysteine Metabolism Related Disorders Panel, Sequencing and Deletion/Duplication 2011157

Method: Massively Parallel Sequencing

- Use to confirm suspected cobalamin (vitamin B_{12})/propionate/homocysteine metabolism-related disorder in individuals with clinical symptoms and/or biochemical findings
- Do not use to assess vitamin B_{12} concentrations
- If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information

Genetics

Genes

See Genes Tested table for genes included in the panel.

Etiology

Pathogenic germline variants in genes associated with the cobalamin metabolic pathway cause disorders of cobalamin (vitamin B_{12})/propionate/homocysteine metabolism.

Prevalence

The table below details the prevalence of several disorders of cobalamin metabolism. The true prevalence of the disorders of cobalamin metabolism is unknown.

Disorder	Prevalence
Isolated methylmalonic acidemia	1/50,000-100,000
Methylmalonic aciduria and homocystinuria, cblC type	1/200,000 (overall)
Homocystinuria due to cystathionine beta-synthase deficiency	1/200,000 to 1/344,000 (worldwide)
Propionic acidemia	1/105,000-130,00 (in the U.S.)
Other disorders included in this panel	Rare

Inheritance

Autosomal recessive for all genes tested, except for *HCFC1* (X-linked) and *MAT1A* (autosomal dominant or autosomal recessive)

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large (single exon-level or larger) deletions and duplications.

- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

Variable, dependent on condition

Analytic Sensitivity

For MPS:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

Limitations

- A negative result does not exclude a heritable form of cobalamin metabolism disorders.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following regions are not sequenced due to technical limitations of the assay:
  - *ABCD4* (NM_001353592, NM_001353599, NM_001353600, NM_001353609) partial exon(s) 17 (Chr14:74753377-74753383)
  - *ABCD4* (NM_001353594, NM_001353601, NM_001353606, NM_001353608) partial exon(s) 16 (Chr14:74753377-74753383)
  - *ABCD4* (NM_001353607) partial exon(s) 15(Chr14:74753377-74753383)
  - *ABCD4* (NM_001353610) partial exon(s) 14(Chr14:74755363-74755398)
  - *ABCD4* (NM_020325) partial exon(s) 18(Chr14:74753377-74753383)
  - *CBS* (NM_001321072) exon(s) 1
  - *IVD* (NM_001354597) exon(s) 1
  - *IVD* (NM_001354598, NM_001354600) exon(s) 12,13
  - *IVD* (NM_001354601) exon(s) 12
  - *IVD* (NM_001354599, NM_001354600) partial exon(s) 2(Chr15:40699947-40700010)
  - *PCCA* (NM_001352609) exon(s) 22
  - *SUCLA2* (NM_003850) partial exon(s) 8(Chr13:48528275-48528320)
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in the *ADK, AHCY*, and *GNMT* genes
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:

- *AMN* (NM_030943) 10; *CBS* (NM_001321072) 1; *IVD* (NM_001354597) 1; *IVD* (NM_001354598, NM_001354600) 12-13; *IVD* (NM_001354601) 12; *PCCA* (NM_001352609) 22

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ABCD4	603214	Methylmalonic aciduria and homocystinuria, cblJ type	AR
ACSF3	614245	Combined malonic and methylmalonic aciduria	AR
ADK	102750	Hypermethioninemia due to adenosine kinase deficiency	AR
AHCY	180960	Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	AR
AMN	605799	Imerslund-Grasbeck syndrome 2	AR
CBLIF	609342	Intrinsic factor deficiency	AR
CBS	613381	Homocystinuria, B6-responsive and nonresponsive types Thrombosis, hyperhomocysteinemia	AR
CD320	606475	Methylmalonic aciduria, transient, due to transcobalamin receptor defect	AR
CTH	607657	Cystathioninuria	AR
CUBN	602997	Imerslund-Grasbeck syndrome 1 Proteinuria, chronic benign	AR
HCFC1	300019	Methylmalonic acidemia and homocysteinemia, cblX type; intellectual disability, X-linked 3	XL
IVD	607036	Isovaleric acidemia	AR
LMBRD1	612625	Methylmalonic aciduria and homocystinuria, cblF type	AR
MAT1A	610550	Hypermethioninemia, persistent, autosomal dominant, due to methionine adenosyltransferase I/III deficiency Methionine adenosyltransferase deficiency, autosomal recessive	AD/AR
MCEE	608419	Methylmalonyl-CoA epimerase deficiency	AR
MLYCD	606761	Malonyl-CoA decarboxylase deficiency	AR
MMAA	607481	Methylmalonic aciduria, vitamin B_{12} responsive, cblA type	AR
MMAB	607568	Methylmalonic aciduria, vitamin B_{12} responsive, cblB type	AR
MMACHC	609831	Methylmalonic aciduria and homocystinuria, cblC type	AR
MMADHC	611935	Mmethylmalonic aciduria and homocystinuria, cblD type	AR
MMUT	609058	Methylmalonic aciduria, mut (0) type	AR
MTHFR	607093	Homocystinuria due to deficiency of (5,10)-methylenetetrahydrofolate	AR
MTR	156570	Homocystinuria-megaloblastic anemia, cblG complementation type	AR
MTRR	602568	Homocystinuria-megaloblastic anemia, cblE complementation type	AR

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

Gene	MIM Number	Disorder	Inheritance
PCCA	232000	Propionic acidemia	AR
PCCB	232050	Propionic acidemia	AR
SUCLA2	603921	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	AR
SUCLG1	611224	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	AR
TCN2	613441	Transcobalamin II deficiency	AR

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

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