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. Age of disease onset ranges from the perinatal period to adulthood. Multiple organ systems are affected. Molecular testing is used to confirm suspected cobalamin/propionate/homocysteine metabolism-related disorder in individuals with clinical symptoms and/or biochemical findings.

Tests to Consider

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

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Confirm suspected cobalamin (vitamin B_{12})/propionate/homocysteine metabolism-related disorder in individuals with clinical symptoms and/or biochemical findings. Should not be ordered to assess vitamin B_{12} level.

For tests to consider before ordering genetic testing, see Related Tests.

Disease Overview

Findings

- Cardiovascular
- Gastrointestinal
- Hematological
- Immunological
- Neurological
- Neuromuscular/skeletal
- Ocular
- Renal
- Respiratory
- Dysmorphic features
- Failure to thrive
- Metabolic decompensation

Etiology

- Defects of absorption, transport, and intracellular metabolism of cobalamin/propionate/homocysteine lead to accumulation of methylmalonic acid, methionine, and/or homocysteine in blood and urine.
- Elevated propionylcarnitine level and/or propionyl/acetylcarnitine ratio are usually detected in plasma, and increased methylmalonic acid is detected in blood, despite normal or elevated vitamin B_{12} levels.

Prevalence

- Methylmalonic aciduria from all causes – 1/48,000-61,000 in North America
- Isolated methylmalonic acidemia – 1/50,000-100,000
- Combined malonic/methylmalonic aciduria – ~1/30,000
- Methylmalonic aciduria, vitamin B_{12}-responsive, cblA type – 1/50,000-100,000
- Methylmalonic aciduria, vitamin B_{12}-responsive, cblB type – 1/50,000-100,000
- Methylmalonic aciduria and homocystinuria, cblC type – up to 1/67,000
- Methylmalonic aciduria, and homocystinuria, cblD type – 1/50,000-100,000
- Methylmalonic aciduria, mut (0) type – 1/50,000-100,000
- Methylmalonyl-CoA epimerase deficiency – 1/50,000-100,000
- Homocystinuria due to cystathionine beta-synthase deficiency – 1/1,800 in Qatar; 1/6,400 in Norway; 1/17,800 in Germany
- Methionine adenosyltransferase deficiency – 1/22,000 in Spain; 1/26,000 in Portugal
- Homocystinuria, B_6-responsive and nonresponsive types, combined – 1/58,000-1,000,000
- Propionic acidemia – 1/50,000-100,000; 1/1,000-2,000 in Inuit in Greenland; 1/5,000 in Saudi Arabia
- Rare for other disorders included in the panel

Inheritance

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

Genotype-Phenotype Correlation

- Variants in multiple genes cause overlapping and highly variable phenotypes.
- Other genetic and/or biochemical/dietary factors may influence severity of clinical phenotype.
- Clinical features and age of onset are highly variable.

Test Description

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

Variable, dependent on condition

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 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
  - Non-coding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1 kb in the targeted genes by array
  - 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:
    - *ABCD4* (NM_005050) 1; *HCFC1* (NM_005334) 26; *MTHFR* (NM_001330358) 1; *PCCB* (NM_001178014) 4; *SUCLA2* (NM_003850) 11

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical 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	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	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	Alias Symbol(s)	MIM Number	Disorder	Inheritance
ABCD4	PXMP1L, PMP69, P70R, EST352188	603214	Methylmalonic aciduria and homocystinuria, cblJ type	AR
ACSF3		614245	Combined malonic and methylmalonic aciduria	AR
ADK	AK	102750	Hypermethioninemia due to adenosine kinase deficiency	AR
AHCY	SAHH	180960	Hypermethioninemia with S-adenosylhomocysteine hydrolase deficiency	AR
AMN	amnionless	605799	Megaloblastic anemia 1, Norwegian type	AR
CBLIF (GIF)	TCN3, IF, IFMH, INF	609342	Intrinsic factor deficiency	AR
CBS	HIP4	613381	Homocystinuria due to cystathionine beta-synthase deficiency	AR
CD320	8D6, 8D6A	606475	Methylmalonic aciduria, transient, due to transcobalamin receptor defect	AR
CUBN	MGA1, IFCR, gp280	602997	Megaloblastic anemia 1, Finnish type	AR
GNMT		606628	Glycine N-methyltransferase deficiency	AR
HCFC1	HFC1, MRX3, HCF-1, HCF1, CFF, VCAF, MGC70925, PPP1R89	300019	Methylmalonic acidemia and homocysteinemia, cblX type; intellectual disability, X-linked 3	XL
LMBRD1	C6orf209, FLJ11240, bA810I22.1, cblF	612625	Methylmalonic aciduria and homocystinuria, cblF type	AR
MAT1A	MAT, SAMS, MATA1, SAMS1	610550	Methionine adenosyltransferase I/III deficiency	AD and AR
MCEE	GLOD2	608419	Methylmalonyl-CoA epimerase deficiency	AR
MMAA	cblA	607481	Methylmalonic aciduria, B_{12} responsive, cblA type	AR
MMAB	cblB, CFAP23	607568	Methylmalonic aciduria, cblB type	AR
MMACHC	DKFZP564I122, cblC	609831	Methylmalonic aciduria and homocystinuria, cblC type	AR
MMADHC	C2orf25, CL25022, cblD	611935	Mmethylmalonic aciduria and homocystinuria, cblD type	AR
MMUT (MUT)	MCM	609058	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency, mut (0) type	AR
MTHFR		607093	Homocystinuria due to deficiency of N(5,10)-methylenetetrahydrofolate	AR

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

Gene	Alias Symbol(s)	MIM Number	Disorder	Inheritance
MTR	cblG	156570	Homocystinuria-megaloblastic anemia, cblG complementation type	AR
MTRR	cblE	602568	Homocystinuria-megaloblastic anemia, cblE complementation type	AR
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
TCN1	TCI, TC1	189905	Transcobalamin I deficiency	AR
TCN2	D22S676, D22S750, TC2	613441	Transcobalamin II deficiency	AR

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

Additional Resources

Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014; 9 130. PubMed

Cusmano-Ozog K, Levine S, Martin M, et al. Cobalamin C disease identified by newborn screening: the California experience. In: Program and abstracts for the SIMD annual meeting Mol Genet Metab. 2007:227-65. [Accessed: Nov 2018]

Manoli I, Sloan JL, Venditti CP. Isolated Methylmalonic Acidemia. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Revision: Dec 2016; Accessed: Feb 2020]

Martins E, Marcão A, et al. Methionine Adenosyltransferase I/III Deficiency in Portugal: High Frequency of a Dominantly Inherited Form in a Small Area of Douro High Lands. JIMD Rep. 2012; 6 107-12. PubMed

Rosenblatt D, Watkins D. Methylmalonic acidemia without homocystinuria. Orphanet. Mar 2012; [Last Update: Mar 2012; Accessed: Nov 2018]

Sacharow SJ, Picker JD, Levy HL. Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: May 2017; Accessed: Feb 2020]

Skovby F, Gaustadnes M, Mudd SH. A revisit to the natural history of homocystinuria due to cystathionine beta-synthase deficiency. Mol Genet Metab. 2010 Jan;99(1):1-3. PubMed

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Sloan JL, Johnston JJ, Manoli I, Chandler RJ, Krause C, Carrillo-Carrasco N, Chandrasekaran SD, Sysol JR, O'Brien K, Hauser NS, Sapp JC, Dorward HM, Huizing M; NIH Intramural Sequencing Center Group, Barshop BA, Berry SA, James PM, Champaigne NL, de Lonlay P, Valayannopoulos V, Geschwind MD, Gavrilov DK, Nyhan WL, Biesecker LG, Venditti CP. Exome sequencing identifies ACSF3 as a cause of combined malonic and methylmalonic aciduria. Nat Genet. 2011 Aug 14;43(9):883-6. PubMed

Weisfeld-Adams JD, Morrissey MA, Kirmse BM, et al. Newborn screening and early biochemical follow-up in combined methylmalonic aciduria and homocystinuria, cblC type, and utility of methionine as a secondary screening analyte. Mol Genet Metab. 2010; 99 (2): 116-23. PubMed

Related Tests

Amino Acids Quantitative by LC-MS/MS, Plasma 2009389

Method: Quantitative Liquid Chromatography/Tandem Mass Spectrometry

Methylmalonic Acid, Serum or Plasma (Metabolic Disorders) 2005255

Method: Quantitative Liquid Chromatography-Tandem Mass Spectrometry

Homocysteine, Total 0099869

Method: Quantitative Enzymatic

Organic Acids, Urine 0098389

Method: Gas Chromatography-Mass Spectrometry (GC-MS)

Methylmalonic Acid (MMA) Quantitative, Urine 0083918

Method: Quantitative High Performance Liquid Chromatography-Tandem Mass Spectrometry

Vitamin B12 and Folate 0070160

Method: Quantitative Chemiluminescent Immunoassay

Vitamin B12 with Reflex to Methylmalonic Acid, Serum (Vitamin B12 Status) 0055662

Method: Quantitative Chemiluminescent Immunoassay/Quantitative High Performance Liquid Chromatography-Tandem Mass Spectrometry

Acylcarnitine Quantitative Profile, Plasma 0040033

Method: Tandem Mass Spectrometry

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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