Cobalamin/Propionate/Homocysteine Metabolism Related Disorders Panel

Disorders of cobalamin (vitamin B12)/propionate/homocysteine metabolism result from defects in the vitamin B12 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.

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 propionylacetylcarnitine ratio are usually detected in plasma, and increased methylmalonic acid is detected in blood, despite normal or elevated vitamin B12 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 B12-responsive, cblA type – 1/50,000-100,000
- Methylmalonic aciduria, vitamin B12-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, B9-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)

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 B12)/propionate/homocysteine metabolism-related disorder in individuals with clinical symptoms and/or biochemical findings. Should not be ordered to assess vitamin B12 level.
For tests to consider before ordering genetic testing, see Related Tests.
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_0033850) 11

Analytical Sensitivity
For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region&lt;sup&gt;a&lt;/sup&gt; (%)</th>
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<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
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<td>Deletions 1-10 bp</td>
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<td>84.3-98.2</td>
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<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
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<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
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<td>Insertions 11-23 bp</td>
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<sup>a</sup> 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
<th>Inheritance</th>
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<tbody>
<tr>
<td>ABCD4</td>
<td>PXMP1L, PMP69, P70R, EST352188</td>
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<td>Methylmalonic aciduria and homocystinuria, cblJ type</td>
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<td>Hypermethioninemia due to adenosine kinase deficiency</td>
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<td>AHcy</td>
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<td>Hypermethioninemia with S-adenosylhomocysteine hydrolase deficiency</td>
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<td>CBLF</td>
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<td>Intrinsic factor deficiency</td>
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<td>CBS</td>
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<td>Homocystinuria due to cystathionine beta-synthase deficiency</td>
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<td>Gene</td>
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<td>CD320</td>
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<td>Methylmalonic aciduria, transient, due to transcobalamin receptor defect</td>
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<td>CUBN</td>
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<td>GNMT</td>
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<td>LMBRD1</td>
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<td>Methionine adenosyltransferase I/III deficiency</td>
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<td>Methionine adenosyltransferase I/III deficiency</td>
<td>AD and AR</td>
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<td>MTHFR</td>
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<td>Methylmalonic aciduria due to deficiency of N(5,10)-methylene tetrahydrofolate</td>
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<td>MTR</td>
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<td>232000</td>
<td>Propionic acidemia</td>
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<td>Transcobalamin II deficiency</td>
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</tbody>
</table>

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

REFERENCES


RELATED TESTS

Acylcarnitine Quantitative Profile, Plasma 0040033
Method: Tandem Mass Spectrometry

Amino Acids Quantitative by LC-MS/MS, Plasma 2009389
Method: Quantitative Liquid Chromatography/Tandem Mass Spectrometry

Organic Acids, Urine 0098389
Method: Gas Chromatography/Mass Spectrometry

Vitamin B12 with Reflex to Methylmalonic Acid, Serum (Vitamin B12 Status) 0055662
Method: Quantitative Chemiluminescent Immunoassay/Quantitative High Performance Liquid Chromatography-Tandem Mass Spectrometry

Vitamin B12 and Folate 0070160
Method: Quantitative Chemiluminescent Immunoassay

Methylmalonic Acid, Serum or Plasma (Metabolic Disorders) 2005255
Method: Quantitative Liquid Chromatography-Tandem Mass Spectrometry

Methylmalonic Acid (MMA) Quantitative, Urine 0083918
Method: Quantitative High Performance Liquid Chromatography-Tandem Mass Spectrometry

Homocysteine, Total 0099869
Method: Quantitative Enzymatic