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.

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

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.
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:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region (%)</th>
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</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
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<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
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<tr>
<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>
<td>86.8-98.5</td>
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<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
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</table>

*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>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD4</td>
<td>PXMP1L, PMP69, P70R, EST352188</td>
<td>603214</td>
<td>Methylmalonic aciduria and homocystinuria, cblJ type</td>
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<tr>
<td>ACSF3</td>
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<td>614245</td>
<td>Combined malonic and methylmalonic aciduria</td>
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<td>ADK</td>
<td>AK</td>
<td>102750</td>
<td>Hypermethioninemia due to adenosine kinase deficiency</td>
<td>AR</td>
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<tr>
<td>AHCY</td>
<td>SAHH</td>
<td>180960</td>
<td>Hypermethioninemia with S-adenosylhomocysteine hydrolase deficiency</td>
<td>AR</td>
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<tr>
<td>AMN</td>
<td>amnionless</td>
<td>605799</td>
<td>Megaloblastic anemia 1, Norwegian type</td>
<td>AR</td>
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<tr>
<td>CBLIF</td>
<td>TCN3, IF, IFMH, INF</td>
<td>609342</td>
<td>Intrinsic factor deficiency</td>
<td>AR</td>
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<tr>
<td>CBS</td>
<td>HIP4</td>
<td>613381</td>
<td>Homocystinuria due to cystathionine beta-synthase deficiency</td>
<td>AR</td>
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<tr>
<td>CD320</td>
<td>8D6, 8D6A</td>
<td>606475</td>
<td>Methylmalonic aciduria, transient, due to transcobalamin receptor defect</td>
<td>AR</td>
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<tr>
<td>CUBN</td>
<td>MGA1, IFCR, gp280</td>
<td>602997</td>
<td>Megaloblastic anemia 1, Finnish type</td>
<td>AR</td>
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<tr>
<td>GNMT</td>
<td></td>
<td>606628</td>
<td>Glycine N-methyltransferase deficiency</td>
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</table>

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked
<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCFC1</td>
<td>HFC1, MRX3, HCFC-1, HCFC1, CFF, VCAF, MGC70925, PPP1R89</td>
<td>300019</td>
<td>Methylmalonic acidemia and homocysteinemia, cblX type; intellectual disability, X-linked 3</td>
<td>XL</td>
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<tr>
<td>LMBRD1</td>
<td>C6orf209, FLJ11240, bA810I22.1, cbIF</td>
<td>612625</td>
<td>Methylmalonic aciduria and homocystinuria, cblF type</td>
<td>AR</td>
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<tr>
<td>MAT1A</td>
<td>MAT, SAMS, MAT1A, SAMS1</td>
<td>610550</td>
<td>Methionine adenosyltransferase I/III deficiency</td>
<td>AD and AR</td>
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<td>MCEE</td>
<td>GLOD2</td>
<td>608419</td>
<td>Methylmalonyl-CoA epimerase deficiency</td>
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<td>MMAA</td>
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<td>MMAB</td>
<td>cblB, CFAP23</td>
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<td>Methylmalonic aciduria, cblB type</td>
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<td>MMACHC</td>
<td>DKFZP564I122, cblC</td>
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<td>Methylmalonic aciduria and homocystinuria, cblC type</td>
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<td>MMADHC</td>
<td>C2orf25, CL25022, cblD</td>
<td>611935</td>
<td>Methylmalonic aciduria and homocystinuria, cblD type</td>
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<tr>
<td>MMUT</td>
<td>MCM</td>
<td>609058</td>
<td>Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency, mut (0) type</td>
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<td>MTHFR</td>
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<td>607093</td>
<td>Homocystinuria due to deficiency of N(5,10)-methylene tetrahydrofolate</td>
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<tr>
<td>MTR</td>
<td>cblG</td>
<td>156570</td>
<td>Homocystinuria-megaloblastic anemia, cblG complementation type</td>
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<td>MTRR</td>
<td>cblE</td>
<td>602568</td>
<td>Homocystinuria-megaloblastic anemia, cblE complementation type</td>
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<td>PCCA</td>
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<td>232000</td>
<td>Propionic acidemia</td>
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<td>PCCB</td>
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<td>232050</td>
<td>Propionic acidemia</td>
<td>AR</td>
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<td>SUCLA2</td>
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<td>603921</td>
<td>Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)</td>
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<td>SUCLG1</td>
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<td>611224</td>
<td>Mitochondrial dna depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)</td>
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<td>TCN1</td>
<td>TCI, TC1</td>
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<td>Transcobalamin I deficiency</td>
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<td>TCN2</td>
<td>D22S676, D22S750, TC2</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

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

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