Cobalamin/Propionate/Homocysteine Metabolism-Related Disorders Panel

Indications for Ordering

Confirm suspected cobalamin (vitamin B₁₂)/propionate/homocysteine metabolism-related disorder in individual with clinical symptoms and/or biochemical findings

Test Description

• Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  ○ Reported variants are confirmed by Sanger sequencing
• Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization array

Tests to Consider

Primary test

Cobalamin/Propionate/Homocysteine Metabolism Related Disorders Panel, Sequencing (25 Genes) and Deletion/Duplication (24 Genes) 2011157

Related tests

• Acylcarnitine Quantitative Profile, Plasma 0040033
• Amino Acids Quantitative by LC-MS/MS, Plasma 2009389
• Organic Acids, Urine 0098389
• Vitamin B₁₂ with Reflex to Methylmalonic Acid, Serum (Vitamin B₁₂ Status) 0055662
• Vitamin B₁₂ and Folate 0070160
• Methylmalonic Acid, Serum or Plasma (Metabolic Disorders) 2005255
• Methylmalonic Acid (MMA) Quantitative, Urine 0083918
• Homocysteine, Total 0099869

Familial Mutations, Targeted Sequencing 2001961

• Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence

• Methylmalonic aciduria from all causes – 1/48,000-61,000 in North America
• For individual disorders, see table

Age of onset – wide range, from neonatal period to adulthood

Symptoms

• Systems
  ○ Cardiovascular
  ○ Gastrointestinal
  ○ Hematological
  ○ Immunological
  ○ Neurological
  ○ Neuromuscular/skeletal
  ○ Ocular
  ○ Renal
  ○ Respiratory
  ○ Skin
• Other symptoms
  ○ Dysmorphia
  ○ Failure to thrive

Genetics

Genes – see table

Variants – variants in multiple genes appear to cause overlapping and highly variable phenotypes

• Other genetic and/or biochemical/dietary factors may influence severity of clinical phenotype
Results

Clinical sensitivity – unknown

Results

- Positive
  - Two pathogenic variants detected on opposite chromosomes in a gene with autosomal recessive (AR) inheritance
    - Confirms diagnosis of cobalamin/propionate/homocysteine metabolism-related disorder
  - One pathogenic variant detected in an X-linked gene in males or one pathogenic variant detected in an autosomal dominant gene in males or females
    - Confirms diagnosis of cobalamin/propionate/homocysteine metabolism-related disorder
  - One pathogenic variant detected in an AR gene
    - Individual is a carrier
  - One pathogenic variant detected in an X-linked gene in females
    - Individual is a carrier

- Negative – no pathogenic variant detected
  - Reduces, but does not exclude, a diagnosis of cobalamin/propionate/homocysteine metabolism-related disorder
  - Inconclusive – variants of uncertain clinical significance may be identified

Limitations

- Not determined or evaluated
  - Variants in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Breakpoints for large deletions/duplications
  - Deletions/duplications will not be detected in HCFC1 gene
  - Small deletions or insertions may not be detected
  - Diagnostic errors can occur due to rare sequence variations
  - Lack of detectable gene variant does not exclude a diagnosis of cobalamin/propionate/homocysteine metabolism-related disorder

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>Transcript</th>
<th>OMIM #</th>
<th>Disorder</th>
<th>Inh.*</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD4</td>
<td>ATP-binding cassette, sub-family D (ALD), member 4</td>
<td>NM_005050</td>
<td>603214</td>
<td>Methylmalonic aciduria and homocystinuria, cblI type</td>
<td>AR</td>
<td>Unknown</td>
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<td>ACSF3</td>
<td>Acyl-CoA synthetase family member 3</td>
<td>NM_174917</td>
<td>614245</td>
<td>Combined malonic and methylmalonic aciduria</td>
<td>AR</td>
<td>Unknown</td>
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<td>AMN</td>
<td>Amnionless homologue (mouse)</td>
<td>NM_030943</td>
<td>605799</td>
<td>Megaloblastic anemia-1, Norwegian type</td>
<td>AR</td>
<td>Unknown; population-specific founder mutations</td>
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<tr>
<td>CBS</td>
<td>Cystathionine-beta-synthase</td>
<td>NM_000071</td>
<td>613381</td>
<td>Homocystinuria due to cystathionine-beta-synthase deficiency</td>
<td>AR</td>
<td>1/1,800 in Qatar 1/6,400 in Norway 1/17,800 in Germany</td>
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<tr>
<td>CD320</td>
<td>CD320 molecule</td>
<td>NM_016579</td>
<td>606475</td>
<td>Methylmalonic aciduria due to transcobalamin receptor defect</td>
<td>AR</td>
<td>&lt;1/million</td>
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<tr>
<td>CUBN</td>
<td>Cubilin</td>
<td>NM_001081</td>
<td>602997</td>
<td>Megaloblastic anemia-1, Finnish type</td>
<td>AR</td>
<td>Unknown; population-specific founder mutations</td>
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<td>HCFC1</td>
<td>Host cell factor C1 (VP16-accessory protein)</td>
<td>NM_005334</td>
<td>300019</td>
<td>Intellectual disability, X-linked 3 (methylmalonic acidemia and homocysteinemia, cblK type)</td>
<td>XL</td>
<td>&lt;1/million</td>
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<td>GIF</td>
<td>Gastric intrinsic factor</td>
<td>NM_005142</td>
<td>609342</td>
<td>Intrinsic factor deficiency</td>
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<td>Unknown; population-specific founder mutations</td>
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<td>LMBRD1</td>
<td>LMBRD1 domain containing 1</td>
<td>NM_018368</td>
<td>612625</td>
<td>Methylmalonic aciduria and homocystinuria, cblI type</td>
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<td>&lt;1/million</td>
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<tr>
<td>MAT1A</td>
<td>Methionine adenosyltransferase I, alpha</td>
<td>NM_000429</td>
<td>610550</td>
<td>Methionine adenosyltransferase deficiency</td>
<td>AR</td>
<td>1/22,000 in Spain 1/26,000 in Portugal</td>
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<td>MCEE</td>
<td>Methylmalonyl-CoA epimerase</td>
<td>NM_032601</td>
<td>608419</td>
<td>Methylmalonyl-CoA epimerase deficiency</td>
<td>AR</td>
<td>1/50,000-100,000</td>
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<td>MMAA</td>
<td>Methylmalonic aciduria (cobalamin deficiency) cblA type</td>
<td>NM_172250</td>
<td>607481</td>
<td>Methylmalonic aciduria, vitamin B12-responsive, cblA type</td>
<td>AR</td>
<td>1/50,000-100,000</td>
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<td>MMAB</td>
<td>Methylmalonic aciduria (cobalamin deficiency) cblB type</td>
<td>NM_052845</td>
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<td>Methylmalonic aciduria, vitamin B12-responsive, cblB type</td>
<td>AR</td>
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<td>MMACHC</td>
<td>Methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria</td>
<td>NM_015506</td>
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<td>Methylmalonic aciduria and homocystinuria, cblC type</td>
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<td>MMADHC</td>
<td>Methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria</td>
<td>NM_015702</td>
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<td>Methylmalonic aciduria, and homocystinuria, cblD type</td>
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<td>1/50,000-100,000</td>
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<td>MTHFR</td>
<td>5,10-methylenetetrahydrofolate reductase (NAD(P)H)</td>
<td>NM_005957</td>
<td>607093</td>
<td>Homocystinuria due to MTHFR deficiency</td>
<td>AR</td>
<td>Unknown</td>
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<td><em>MTR</em></td>
<td>S-methyltetrahydrofolate L homocysteine S methyltransferase (methionine synthase)</td>
<td>NM_000254</td>
<td>156570</td>
<td>Homocystinuria-megaloblastic anemia, cblG type</td>
<td>AR</td>
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<td><em>MTRR</em></td>
<td>S-methyltetrahydrofolate-homocysteine methyltransferase reductase (methionine synthase reductase) (cbl E)</td>
<td>NM_002454</td>
<td>602568</td>
<td>Homocystinuria-megaloblastic anemia, cblE type</td>
<td>AR</td>
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<td><em>MUT</em></td>
<td>Methylmalonyl CoA mutase</td>
<td>NM_000255</td>
<td>609058</td>
<td>Methylmalonic aciduria, mut (0) type</td>
<td>AR</td>
<td>1/50,000-100,000</td>
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<td><em>PCCA</em></td>
<td>Propionyl CoA carboxylase, alpha polypeptide</td>
<td>NM_000282</td>
<td>232000</td>
<td>Propionic acidemia</td>
<td>AR</td>
<td>1/50,000-100,000 1/1,000-2,000 in the Inuit, Greenland 1/5,000 in Saudi Arabia</td>
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<td><em>PCCB</em></td>
<td>Propionyl CoA carboxylase, beta polypeptide</td>
<td>NM_000532</td>
<td>232050</td>
<td>Propionic acidemia</td>
<td>AR</td>
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<td><em>SUCLA2</em></td>
<td>Succinate-CoA ligase, ADP-forming, beta subunit</td>
<td>NM_003850</td>
<td>603921</td>
<td>Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)</td>
<td>AR</td>
<td>&lt;1/million</td>
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<td><em>SUCLG1</em></td>
<td>Succinate-CoA ligase, gdp-forming, alpha subunit</td>
<td>NM_003849</td>
<td>611224</td>
<td>Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)</td>
<td>AR</td>
<td>&lt;1/million</td>
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<td><em>TCN1</em></td>
<td>Transcobalamin I (vitamin B12 binding protein, R binder family)</td>
<td>NM_001062</td>
<td>189905</td>
<td>Transcobalamin I deficiency</td>
<td>AR</td>
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<td><em>TCN2</em></td>
<td>Transcobalamin II</td>
<td>NM_000355</td>
<td>613441</td>
<td>Transcobalamin II deficiency</td>
<td>AR</td>
<td>&lt;1/million</td>
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</tbody>
</table>

* Inh.* = inheritance; AD = autosomal dominant; AR = autosomal recessive; XL= X-linked