Cobalamin/Propionate/Homocysteine Metabolism-Related Disorders Panel

Indications for Ordering

Confirm suspected cobalamin (vitamin B_{12})/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 and Deletion/Duplication 2011157

Related tests

- Acylcarnitine Quantitative Profile, Plasma 0040033
- Amino Acids Quantitative by LC-MS/MS, Plasma 2009389
- Organic Acids, Urine 0098389
- Vitamin B_{12} with Reflex to Methylmalonic Acid, Serum (Vitamin B_{12} Status) 0055662
- Vitamin B_{12} 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

Test Interpretation

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

Gene Symbol	Gene Name	Transcript	OMIM #	Disorder	Inh.	Prevalence
ABCD4	ATP-binding cassette, sub-family D (ALD), member 4	NM_005050	603214	Methylmalonic aciduria and homocystinuria, cblJ type	AR	Unknown
ACSF3	Acyl-CoA synthetase family member 3	NM_174917	614245	Combined malonic and methylmalonic aciduria	AR	Unknown
AMN	Amnionless homologue (mouse)	NM_030943	605799	Megaloblastic anemia-1, Norwegian type	AR	Unknown; population-specific founder mutations
CBS	Cystathionine-beta-synthase	NM_000071	613381	Homocystinuria due to cystathionine-beta-synthase deficiency	AR	1/1,800 in Qatar 1/6,400 in Norway 1/17,800 in Germany
CD320	CD320 molecule	NM_016579	606475	Methylmalonic aciduria due to transcobalamin receptor defect	AR	<1/million
CUBN	Cubilin	NM_001081	602997	Megaloblastic anemia-1, Finnish type	AR	Unknown; population-specific founder mutations
HCFC1	Host cell factor C1 (VP16-accessory protein)	NM_005334	300019	Intellectual disability, X-linked 3 (methylmalonic acidemia and homocysteinemia, cblX type)	XL	<1/million
GIF	Gastric intrinsic factor	NM_005142	609342	Intrinsic factor deficiency	AR	Unknown; population-specific founder mutations
LMBRD1	LMBR1 domain containing 1	NM_018368	612625	Methylmalonic aciduria and homocystinuria, cblF type	AR	<1/million
MAT1A	Methionine adenosyltransferase I, alpha	NM_000429	610550	Methionine adenosyltransferase deficiency	AR AD	1/22,000 in Spain 1/26,000 in Portugal
MCEE	Methylmalonyl CoA epimerase	NM_032601	608419	Methylmalonyl-CoA epimerase deficiency	AR	1/50,000-100,000
MMAA	Methylmalonoic aciduria (cobalamin deficiency) cblA type	NM_172250	607481	Methylmalonic aciduria, vitamin B12-responsive, cblA type	AR	1/50,000-100,000
MMAB	Methylmalonic aciduria (cobalamin deficiency) cblB type	NM_052845	607568	Methylmalonic aciduria, vitamin B12-responsive, cblB type	AR	1/50,000-100,000
MMACHC	Methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria	NM_015506	609831	Methylmalonic aciduria and homocystinuria, cblC type	AR	1/67,000
MMADHC	Methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria	NM_015702	611935	Methylmalonic aciduria, and homocystinuria, cblD type	AR	1/50,000-100,000
MTHFR	5,10-methylenetetrahydrofolate reductase (NAD(P)H)	NM_005957	607093	Homocystinuria due to MTHFR deficiency	AR	Unknown

Gene Symbol	Gene Name	Transcript	OMIM #	Disorder	Inh.	Prevalence
MTR	5-methyltetrahydrofolate L homocysteine S methyltransferase (methionine synthase)	NM_000254	156570	Homocystinuria-megaloblastic anemia, cblG type	AR	Unknown
MTRR	5-methyltetrahydrofolate-homocysteine methyltransferase reductase (methionine synthase reductase) (cbl E)	NM_002454	602568	Homocystinuria-megaloblastic anemia, cblE type	AR	Unknown
MUT	Methylmalonyl CoA mutase	NM_000255	609058	Methylmalonic aciduria, mut (0) type	AR	1/50,000-100,000
PCCA	Propionyl CoA carboxylase, alpha polypeptide	NM_000282	232000	Propionic acidemia	AR	1/50,000-100,000 1/1,000-2,000 in the Inuit, Greenland 1/5,000 in Saudi Arabia
PCCB	Propionyl CoA carboxylase, beta polypeptide	NM_000532	232050	Propionic acidemia	AR	
SUCLA2	Succinate-CoA ligase, ADP-forming, beta subunit	NM_003850	603921	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	AR	<1/million
SUCLG1	Succinate-CoA ligase, gdp-forming, alpha subunit	NM_003849	611224	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	AR	<1/million
TCN1	Transcobalamin I (vitamin B12 binding protein, R binder family)	NM_001062	189905	Transcobalamin I deficiency	AR	<1/million
TCN2	Transcobalamin II	NM_000355	613441	Transcobalamin II deficiency	AR	<1/million
AD, autosomal dominant; AR, autosomal recessive; Inh., inheritance; XL, X-linked						