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NLM Citation: Sloan JL, Carrillo N, Adams D, et al. Disorders of Intracellular Cobalamin Metabolism. 2008 Feb 25 [Updated 2021 Dec 16]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Disorders of Intracellular Cobalamin Metabolism

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Created: February 25, 2008; Revised: December 16, 2021.

Summary

Clinical characteristics

Disorders of intracellular cobalamin metabolism have a variable phenotype and age of onset that are influenced by the severity and location within the pathway of the defect. The prototype and best understood phenotype is *cblC*; it is also the most common of these disorders. The age of initial presentation of *cblC* spans a wide range:

- In utero with fetal presentation of nonimmune hydrops, cardiomyopathy, and intrauterine growth restriction
- Newborns, who can have microcephaly, poor feeding, and encephalopathy
- Infants, who can have poor feeding and slow growth, neurologic abnormality, and, rarely, hemolytic uremic syndrome (HUS)
- Toddlers, who can have poor growth, progressive microcephaly, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures
- Adolescents and adults, who can have neuropsychiatric symptoms, progressive cognitive decline, thromboembolic complications, and/or subacute combined degeneration of the spinal cord

Diagnosis/testing

The diagnosis of a disorder of intracellular cobalamin metabolism in a symptomatic individual is based on clinical, biochemical, and molecular genetic data. Evaluation of the methylmalonic acid (MMA) level in urine and blood and plasma total homocysteine (tHcy) level are the mainstays of biochemical testing. Diagnosis is confirmed by identification of biallelic pathogenic variants in one of the following genes (associated complementation groups indicated in parentheses): *MMACHC* (*cblC*), *MMADHC* (*cblD*-combined and *cblD*-homocystinuria), *MTRR* (*cblE*), *LMBRD1* (*cblF*), *MTR* (*cblG*), *ABCD4* (*cblJ*), *THAP11*(*cblX*-like), *ZNF143*(*cblX*-like), or a hemizygous variant in *HCFC1* (*cblX*, which can show a *cblC* complementation class).

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Management

Treatment of manifestations: Critically ill individuals must be stabilized, preferably in consultation with a metabolic specialist, by treating acidosis, reversing catabolism, and initiating parenteral hydroxocobalamin. Treatment of thromboembolic complications (e.g., HUS and thrombotic microangiopathy) includes initiation of hydroxocobalamin (OHCbl) and betaine or an increase in their doses. Long-term management focuses on improving the metabolic derangement by lowering plasma tHcy and MMA concentrations and maintaining plasma methionine concentrations within the normal range. Gastrostomy tube placement for feeding may be required; infantile spasms, seizures, congenital heart malformations, and hydrocephalus are treated using standard protocols.

Prevention of primary manifestations: Early institution of injectable hydroxocobalamin improves survival and may reduce but not completely prevent primary manifestations. To prevent metabolic decompensations, patients are advised to avoid situations that result in catabolism, such as prolonged fasting and dehydration, and always remain on a weight-appropriate dose of hydroxocobalamin.

Surveillance: During the first year of life, infants may need to be evaluated once or twice a month by a metabolic specialist to assess growth, nutritional status, feeding ability, and developmental and neurocognitive progress. Toddlers and school-age children should be evaluated at least twice a year to adjust medication dosing (hydroxocobalamin, betaine) during growth and evaluate nutritional status. Teens and adults may be seen on a yearly basis. Routine ophthalmologic, neurologic, and cardiac evaluations may also be appropriate.

Agents/circumstances to avoid: Prolonged fasting (longer than overnight without dextrose-containing intravenous fluids); dietary protein intake below the recommended dietary allowance for age or more than that prescribed by a metabolic specialist; methionine restriction including use of medical foods that do not contain methionine; and the anesthetic nitrous oxide.

Evaluation of relatives at risk: If the pathogenic variants in the family are known, at-risk sibs may be tested prenatally to allow initiation of treatment in utero or as soon as possible after birth.

If the newborn sib of an affected individual has not undergone prenatal testing, molecular genetic testing can be performed in the first week of life if the pathogenic variants in the family are known. Otherwise, evaluation of urine organic acids and plasma amino acids, measurement of total plasma homocysteine, serum methylmalonic acid analysis, and acylcarnitine profile analysis can be used for the purpose of early diagnosis and treatment.

Genetic counseling

The majority of disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. The disorder of intracellular cobalamin metabolism caused by pathogenic variants in *HCFC1* is inherited in an X-linked manner. The risk to sibs depends on the genetic status of the mother. If the mother of the proband has an *HCFC1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit the pathogenic variant will be heterozygous and will usually not be affected (no affected females have been described to date).

Once the pathogenic variant(s) have been identified in an affected family member, carrier testing for at-risk relatives, molecular genetic prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

Disorders of Intracellular Cobalamin Metabolism: Included Phenotypes
• *cblC* • *cblD*-combined • *cblD*-homocystinuria • *cblE* • *cblF* • *cblG* • *cblJ* • *cblX*

Diagnosis

The disorders of intracellular cobalamin metabolism result from deficient synthesis of the coenzymes derived from vitamin B_{12}:

- Adenosylcobalamin (AdoCbl) – the coenzyme for methylmalonyl-CoA mutase enzyme
- Methylcobalamin (MeCbl) – the coenzyme for the enzyme methionine synthase (MTR) (Figure 1)

This *GeneReview* describes inborn errors of cobalamin metabolism, including disorders with combined methylmalonic acidemia and homocystinuria caused by AdoCbl and MeCbl deficiency (Table 1 – B) as well as disorders associated with homocystinuria (MeCbl deficiency) (Table 1 - C). For disorders associated with isolated methylmalonic acidemia (AdoCbl deficiency) (Table 1 – A) see Isolated Methylmalonic Acidemia.

Note: All the disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner except for *cblX* (associated with pathogenic variants in *HCFC1*), which is inherited in an X-linked manner.

Table 1. Disorders of Intracellular Cobalamin Metabolism by Biochemical Phenotype

Biochemical Phenotype	Complementation Group [1]	Gene
A. Methylmalonic acidemia (AdoCbl deficiency) [2]	*cblA*	*MMAA*
	cblB	*MMAB*
	cblD-methylmalonic aciduria	*MMADHC* [3]
B. Combined methylmalonic acidemia and homocystinuria [4] (AdoCbl and MeCbl deficiency)	*cblC* [5]	*MMACHC* [6] *PRDX1* [7] *HCFC1* [8] (*cblX*) *THAP11* [7] *ZNF143* [9]
	cblD-combined	*MMADHC* [3]
	cblF	*LMBRD1*
	cblJ	*ABCD4* [10]

Table 1. continued from previous page.

Biochemical Phenotype	Complementation Group [1]	Gene
C. Homocystinuria [4] (MeCbl deficiency)	*cblD*-homocystinuria	*MMADHC* [3]
	cblE	*MTRR*
	cblG	*MTR*

Note: The terms methylmalonic acidemia and methylmalonic aciduria are synonymous, as are the terms hyperhomocysteinemia and homocystinuria.
1. The nomenclature for inherited disorders of intracellular cobalamin metabolism is based on cellular complementation analysis that defines cobalamin groups A-J (*cblA - cblJ*). The name of each disorder is prefixed with "cbl" (for cobalamin) followed by a unique capital letter for its complementation group determined by somatic cell analysis (e.g., *cblC* represents complementation group C).
2. cblA, *cblB*, and *cblD*-methylmalonic aciduria are discussed in detail in Isolated Methylmalonic Acidemia and briefly under Differential Diagnosis.
3. Coelho et al [2008]
4. The homocystinuria seen in disorders of intracellular cobalamin metabolism is associated with low/normal methionine in contrast to the homocystinuria seen in cystathionine beta-synthase deficiency, which is associated with high methionine (see Figure 1).
5. Individuals with *cblX* can show a *cblC* complementation class.
6. A rare complex variant of *MMACHC* and adjacent gene *PRDX1* has been described [Guéant et al 2018]; see Molecular Genetics.
7. Quintana et al [2017]
8. Yu et al [2013]
9. Pupavac et al [2016]
10. Coelho et al [2012]

The diagnosis of a disorder of intracellular cobalamin metabolism in a symptomatic individual is based on clinical, biochemical, and molecular genetic data. With the availability of molecular genetic testing, complementation group analysis is no longer frequently used.

Suggestive Findings

A disorder of intracellular cobalamin metabolism **should be suspected** in individuals with the following physical and laboratory findings.

Physical findings

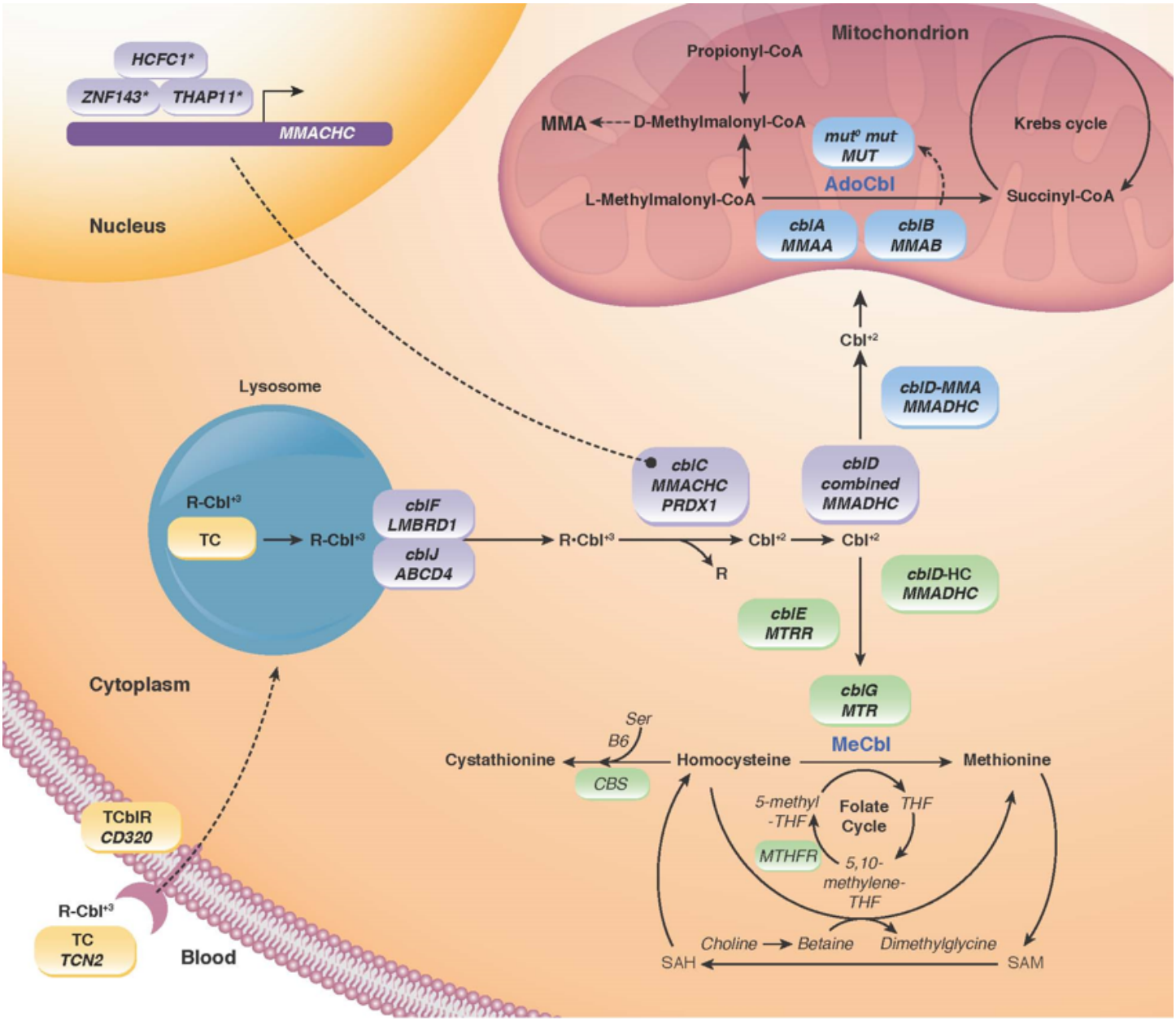
- **In utero.** Nonimmune hydrops, cardiomyopathy, intrauterine growth restriction
- **Newborns.** Microcephaly, poor feeding, encephalopathy
- **Infants.** Poor feeding and slow growth, hypotonia, developmental delay, seizures including infantile spasms, infantile maculopathy. Rarely, hemolytic uremic syndrome and obtundation.
- **Toddlers.** Poor growth, progressive microcephaly, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, hypotonia, seizures
- **Adolescents and adults.** Neuropsychiatric symptoms, progressive cognitive decline, thromboembolic complications, subacute combined degeneration of the spinal cord

Laboratory findings

- Macrocytic anemia with normal B_{12} levels, thrombocytopenia, and/or neutropenia
- Hyperammonemia and/or metabolic acidosis in infancy (rare)

Newborn with abnormal newborn screening based on elevated C3 propionylcarnitine or decreased methionine (See ACMG ACT Sheets for C3 and methionine.)

- Detection by newborn screening (NBS) depends on the C3 and C3/C2 ratio cutoff values used by reference laboratories and the availability of detection of low methionine [Chace et al 2001, Weisfeld-Adams et al 2010, Huemer et al 2015b]. *cblD*-homocystinuria, *cblE*, and *cblG* do not have elevated C3 and



*HCFC1, ZNF143, THAP11 are recently described genes that are transcriptional coactivators thought to regulate *MMACHC* expression; the exact mechanisms are unknown.

MMA = methylmalonic acid; Cbl = cobalamin; Cbl III = 3+ state (oxidized) cobalamin; Cbl II=reduced cobalamin; AdoCbl = 5′-adenosylcobalamin; MeCbl = methylcobalamin; CBS = cystathionine β-synthase; MTHFR = methylene- tetrahydrofolate reductase; TC = transcobalamin; TCblR = transcobalamin receptor; SAM = s-adenosylmethionine; SAH = s-adenosylhomocysteine

Figure 1. Intracellular metabolism of cobalamin. The intracellular cobalamin metabolism and related pathways – including the complementation groups and corresponding genes – are shown.

Endocytosis of **cobalamin** bound to its blood carrier transcobalamin (TC) occurs through the transcobalamin receptor (TCblR). Inside the lysosome, **cobalamin** is released from transcobalamin and then transported into the cytoplasm where it undergoes enzyme-mediated reduction (Cbl III to Cbl II) and then mitochondrial adenosylation to form adenosylcobalamin (AdoCbl) or cytosolic methylation to form methylcobalamin. The color-coded boxes around the cobalamin-processing enzymes indicate their role in causing: (1) isolated AdoCbl deficiency and associated increase in MMA (blue); (2) isolated MeCbl deficiency and hyperhomocysteinemia (green); (3) both AdoCbl and MeCbl deficiencies causing elevations in MMA and homocysteine (purple).

are often not identified on newborn screening. In some US states, detection of low methionine and the use of an NBS tool (clir.mayo.edu; registration required) in combination with measurement of homocysteine has sucessfully identified individuals with *cblE* and *cblG* [Wong et al 2016].
- Since NBS potentially allows early detection of certain disorders of intracellular cobalamin metabolism, some affected individuals may be diagnosed before the onset of symptoms.

Establishing the Diagnosis

The diagnosis of a disorder of intracellular cobalamin metabolism **is established** in a proband with specific biochemical testing results (see Biochemical Testing and Table 2) and confirmed by identification of biallelic pathogenic variants in one of the genes listed in Table 3 – with the exception of *HCFC1*, in which a hemizygous pathogenic variant is confirmatory. For equivocal molecular genetic testing results, enzymatic testing on skin fibroblasts can be used.

Biochemical Testing

The identification of disorders of intracellular cobalamin metabolism relies on the following testing (Table 2):

- **Urine organic acid (UOA) analysis** to screen for elevation of methylmalonic acid (MMA). Other secondary metabolites such as 3-hydroxypropionate, methylcitrate, and tiglylglycine may be seen transiently in symptomatic affected individuals.
- **Serum methylmalonic acid analysis** is more quantitative than urine organic acid analysis.
- **Total plasma homocysteine (tHcy) analysis** is the preferred method of detecting plasma homocysteine.

  Note: Delays in separating serum from plasma after obtaining a blood sample can artificially increase total homocysteine by as much as 10% an hour [Ubbink 2000, Refsum et al 2004].
- **Plasma amino acid (PAA) analysis.** Hypomethioninemia, seen in disorders with defective MeCbl synthesis, helps differentiate disorders of intracellular cobalamin metabolism from other causes of homocystinuria, such as cystathionine beta-synthase deficiency, in which methionine level is elevated (see Differential Diagnosis, **Cystathionine beta-synthase deficiency**).

  Other findings that can be seen on PAA analysis:
  - Hyperhomocysteinemia and mixed disulfides (which are also excreted in the urine)
  - Cystathionine (which is also excreted in the urine) in individuals with *cblC*
- **Serum vitamin B_{12} levels** to exclude vitamin B_{12} deficiency

  Note: *cblF* and *cblJ* disorders are the exceptions and have been reported to have low B_{12} levels at diagnosis.
- **Plasma acylcarnitine analysis** to detect elevation of propionylcarnitine (C3) or confirm the elevated propionylcarnitine following newborn screening

Table 2. Metabolite Concentrations in Disorders of Intracellular Cobalamin Metabolism

		Methylmalonic Acid		Plasma Total Homocysteine (tHcy)	Plasma Methionine
		Urine	Blood		
Biochemical Phenotype	**Complementation Group**	**Normal Values**			
		<4 mmol/mol/Cr [1]	<0.27 µmol/L [1]	3-13 µmol/L	11-37 µmol/L
		Values by Biochemical Phenotype			

Table 2. continued from previous page.

		Methylmalonic Acid		Plasma Total Homocysteine (tHcy)	Plasma Methionine
		Urine	Blood		
Combined AdoCbl & MeCbl deficiency	*cblC* [1]	100s to low 1,000s of mmol/mol Cr when ill or at presentation; generally ranging from 10s to 100s mmol/mol Cr during treatment	100s of µmol/L at presentation and when ill; 1-10 µmol/L when well & treated [2]	>100 when ill; 20-80 µmol/L when well & treated [2]	Low to normal
	cblD-combined [3]	Can be >1,000 mmol/mol Cr	NR	>100 µmol/L in some cases	Low to normal
	cblF [4]	200 mmol/mol/Cr when untreated; normal during treatment	Normal when treated	Increased when untreated; normal when treated	Normal
	cblJ [5]	Increased	Increased	Increased	Low to normal
	cblX [6, 7, 8]	Increased	Increased	Normal to increased	Low to normal
MeCbl deficiency	*cblD*-homocystinuria [3]	Normal	Normal	>100 µmol/L in some cases	Low to normal
	cblE	Normal [9]	Normal	>100 µmol/L when ill	Low [10]
	cblG	Normal	Normal	Increased	Low [10]

NR = not reported
1. Standard values have not been exclusively derived from children or neonates. Some laboratories report urine methylmalonic acid (MMA) concentrations in mg/g/Cr (normal: <3 mg/g/Cr) and serum concentrations in nmol/L (normal: <271 nmol/L). The molecular weight of MMA is 118 g/mol.
2. Authors' experience with >50 affected individuals
3. Values refer to *cblD*-combined and *cblD*-homocystinuria.
4. Alfadhel et al [2011]
5. Kim et al [2012]
6. Yu et al [2013]
7. Pupavac et al [2016]
8. Quintana et al [2017]
9. Mild elevation uncommon [Tuchman et al 1988]
10. Watkins & Rosenblatt [2014]

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Individuals with the distinctive laboratory findings of a specific disorder of intracellular cobalamin metabolism described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas symptomatic individuals with nonspecific supportive clinical and laboratory findings in whom the diagnosis of a disorder of intracellular cobalamin metabolism has not been considered are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of a disorder of intracellular cobalamin metabolism, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis of *MMACHC* first in individuals with biochemical findings of combined AdoCbl and MeCbl deficiency as it is by far the most commonly associated gene (Figure 2). If only one pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. If single-gene testing is nondiagnostic, a multigene panel is the next step.
- **A multigene panel** for inherited disorders of intracellular cobalamin metabolism that includes the genes listed in Table 3 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For this disorder a multigene panel that also includes deletion/duplication analysis can be considered if sequence analysis has not identified two pathogenic variants in an individual with strong biochemical evidence for a disorder of intracellular cobalamin metabolism.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by the wide of array of possible nonspecific clinical findings or an individual has atypical phenotypic features of a disorder of intracellular cobalamin metabolism, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

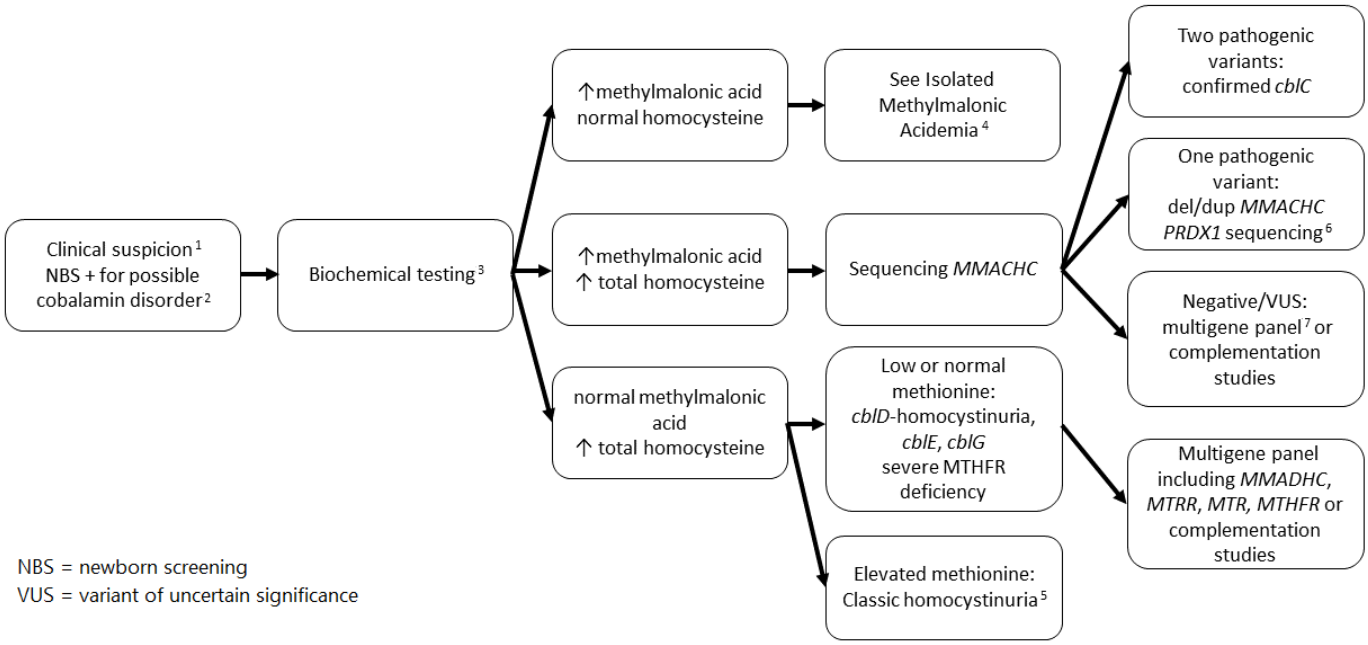


Figure 2. Testing algorithm to confirm the diagnosis of a disorder of intracellular cobalamin metabolism in a proband

Footnotes:

1. While diagnostic testing is being performed, contact genetics/metabolic team and initiate treatment **immediately**.

2. The following results on NBS could be due to a cobalamin disorder: ↑C3, ↑C3/C2, ↓Met.

3. The following biochemical testing should be performed: plasma total homocysteine, serum methylmalonic acid, plasma amino acids, plasma acylcarnitine profile, serum vitamin B_{12}, urine organic acids. B_{12} deficiency must be ruled out; in babies positive on newborn screening, maternal serum vitamin B_{12} levels should be measured to rule out maternal B_{12} deficiency. Note: Individuals with *cblF* and *cblJ* can have B_{12} deficiency as part of their condition. In rare cases, metabolites can normalize with vitamin B_{12} therapy; molecular genetic testing should be used for diagnosis.

4. Methylmalonic acidemia

5. Homocystinuria

6. Variants in *PRDX1* can be seen in individuals with only one *MMACHC* pathogenic variant [Guéant et al 2018].

7. Multigene panel should include *ABCD4*, *HCFC1*, *LMBRD1*, *MMADHC*, *THAP11*, and *ZNF143*.

Table 3. Molecular Genetic Testing Used in Disorders of Intracellular Cobalamin Metabolism

Gene [1]	Complementation Group / Disorder	Proportion of Disorders of Intracellular Cobalamin Metabolism Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
MMACHC	*cblC*	80%	96%-98% [5, 6, 7]	Unknown [8, 9]
MMADHC	*cblD*-combined; *cblD*-homocystinuria	<5%	22/22 [10]	Unknown [8]
MTRR	*cblE*	<5%	21/22 [11]	Unknown [8]
LMBRD1	*cblF*	<5%	23/24 [12]	One reported [13]
MTR	*cblG*	<5%	64/74 [11]	Unknown [8]
ABCD4	*cblJ*	<<1%	12/12 [14]	Unknown [8]

Table 3. continued from previous page.

Gene [1]	Complementation Group / Disorder	Proportion of Disorders of Intracellular Cobalamin Metabolism Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
HCFC1	*cblX*	<1%	14/17 [15]	Unknown [8]
THAP11	Not yet defined-*cblX*-like	<1%	Single case report [16]	Unknown [8]
ZNF143	Not yet defined-*cblX*-like	<1%	Single case report [17]	Unknown [8]

Genes are listed in order of complementation group number.
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Liu et al [2010]
6. Lerner-Ellis et al [2009]
7. A rare complex variant of *MMACHC* and adjacent genes has been described [Guéant et al 2018].
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.
9. One consanguineous individual has been found to have biallelic *MMACHC* whole-gene deletions [Author, unpublished observation].
10. Stucki et al [2012]
11. Watkins et al [2002], Huemer et al [2015b]. One deep intronic pathogenic variant has been reported [Zavadáková et al 2005, Homolova et al 2010] (detailed in Molecular Genetics).
12. Rutsch et al [2009]
13. A deletion spanning exon 2 was reported by Miousse et al [2011].
14. Coelho et al [2012]
15. Yu et al [2013]
16. Quintana et al [2017]
17. Pupavac et al [2016]

Complementation Group Analysis

Complementation analysis is a method used historically to diagnose the specific defects of intracellular cobalamin metabolism using cultured skin fibroblasts [Watkins & Rosenblatt 1986]. Because of the availability of molecular genetic testing this method is now performed infrequently, but it may still be useful for individuals with equivocal molecular results.

Clinical Characteristics

Clinical Description

Disorders of intracellular cobalamin metabolism have a variable phenotype (Table 4) and age of onset that are influenced by the severity and location within the pathway of the defect.

Table 4. Clinical Manifestations of Disorders of Intracellular Cobalamin Metabolism

	Manifestations	Combined AdoCbl and MeCbl Deficiency					MeCbl Deficiency		
		cblC [1]	*cblD* [2]	*cblF* [3]	*cblJ* [4]	*cblX* [5]	*cblD* [2]	*cblE* [6]	*cblG* [6]
Perinatal	Intrauterine growth retardation	X [7]		X					
	Microcephaly	X				X		X	X
	Hydrops fetalis	X							
	Dysmorphic features	+/- [8]		+/-		X			
	Congenital heart disease	X [9]		X	X				
	Fetal dilated cardiomyopathy	X							
	Hydrocephalus	X					X		
	Brain malformations	+/-				X			
	Cardiomyopathy w/left ventricular noncompaction	X							
Infantile & childhood	Acute metabolic decompensation	X	X			X			
	Lethargy	X		X	X			X	X
	Progressive encephalopathy	X	X				X		
	Seizures	X	X	X		X	X	X	X
	Ataxia	X	X						
	Hypotonia	X	X	X	X		X	X	X
	Developmental delay / intellectual disability	X	X	X		X	X	X	X
	Demyelinating neuropathy	X							
	Dystonia						X		
	Microcephaly	X						X	X
	Subdural hematoma	X [10]							
	Feeding difficulties	X	X	X	X			X	X
	Failure to thrive	X	X	X					
	Nystagmus	X [11]	X				X	X	
	Retinal degeneration	X [11]			X				
	Maculopathy	X							
	Optic atrophy	X [11]							X
	Megaloblastic anemia, cytopenias	X	X	X	X	X	X	X	X
	Recurrent infections			X					
	Stomatitis, glossitis	X		X					
	Hemolytic uremic syndrome	X [12]						X	X [13]
	Cerebral atrophy	X						X	X
	Transient ischemic attack				X				
	Dysmorphic features	X				X			
	Self-injurious behaviors					X			

Table 4. continued from previous page.

	Manifestations	Combined AdoCbl and MeCbl Deficiency					MeCbl Deficiency		
		cblC [1]	*cblD* [2]	*cblF* [3]	*cblJ* [4]	*cblX* [5]	*cblD* [2]	*cblE* [6]	*cblG* [6]
	Infantile spasms	X				X			X
	Hyperammonemia	X				X			
	Skin pigmentation abnormalities				X				
Adolescent & adulthood	Progressive encephalopathy	X							
	Leukoencephalopathy	X [14]							
	Psychosis	X [15]	X						
	Dementia	X [15]							
	Neuropsychiatric symptoms	X [15]						X	
	Executive dysfunction	X [14]						X	
	Subacute combined degeneration of the spinal cord	X [15]							X [16]
	Glomerulopathy	X [17]						X	
	Thromboembolic microangiopathy	X [18]							
	Deep venous thrombosis	X [15]						X	
	Pulmonary thromboembolism	X [19]							
	Stroke	X [20]							
	Marfanoid features	X [21]							

1. Nogueira et al [2008]
2. Suormala et al [2004], Coelho et al [2008], Miousse et al [2009]
3. Gailus et al [2010], Alfadhel et al [2011]
4. Coelho et al [2012], Kim et al [2012]
5. Yu et al [2013]
6. Watkins & Rosenblatt [2014]
7. Frattini et al [2010]
8. Cerone et al [1999]
9. Profitlich et al [2009]
10. Francis et al [2004]
11. Gaillard et al [2008]
12. Kind et al [2002], Sharma et al [2007]
13. Labrune et al [1999]
14. Boxer et al [2005]
15. Powers et al [2001], Roze et al [2003]
16. Carmel et al [1988]
17. Brunelli et al [2002]
18. Van Hove et al [2002], Guigonis et al [2005]
19. Brandstetter et al [1990]
20. Geraghty et al [1992]
21. Heil et al [2007]

Combined Methylmalonic Acidemia and Homocystinuria

cblC and cblD-combined types. *cblC*, the most common of the disorders of intracellular cobalamin metabolism, is the best understood clinically and is described here as a prototype for combined methylmalonic acidemia and homocystinuria. In *cblC*, age of onset ranges from prenatal to adult. The infantile presentation is the most frequently recognized.

- **Perinatal manifestations.** Intrauterine growth restriction (IUGR) has been seen in infants with *cblC* [Nogueira et al 2008, Frattini et al 2010] and *cblF* [Alfadhel et al 2011]. Other manifestations can include the following [Francis et al 2004, Smith et al 2006, Profitlich et al 2009]:
  - Microcephaly
  - Congenital heart malformation
  - Dilated cardiomyopathy
  - Hydrocephalus
  - Mild dysmorphic features (long face, high forehead, smooth philtrum, and low-set ears) [Cerone et al 1999]
- **Infantile presentation.** This severe presentation is progressive and may be lethal unless treated. The absence of an acute metabolic presentation or the presence of a normal newborn screen result does not rule out the diagnosis of a disorder of intracellular cobalamin metabolism [Harding et al 2003, Ahrens-Nicklas et al 2015]. Infants may present with the following:
  - Failure to thrive, poor feeding, and hypotonia in the first weeks of life
  - An acute metabolic derangement (high anion gap metabolic acidosis, ketonuria, and hyperammonemia)
  - Hemolytic uremic syndrome (HUS) that may be fatal if treatment with daily hydroxocobalamin (OHCbl) is not initiated promptly [Kind et al 2002, Sharma et al 2007, Carrillo-Carrasco & Venditti 2012]

  Untreated infants may have multiorgan involvement, neurologic deterioration, seizures (i.e., infantile spasms), and encephalopathy.

  Maculopathy and progressive retinopathy develop in most individuals with infantile *cblC*.
  - The initial manifestations are "wandering eye movements," ocular fixation difficulties, and nystagmus.
  - Fundoscopic changes (which can be detected by careful examination as early as the first month of life) are characterized by abnormal macular pigmentation, "bull's-eye" macula, or macular coloboma; the retinal disease evolves over time into pigmentary retinopathy and optic nerve atrophy [Brooks et al 2016].
  - Note: Adolescent and adult (late-onset) presentations of *cblC* and other inborn errors of cobalamin metabolism do not typically have the ophthalmologic complications. Optic atrophy and other eye findings such as nystagmus and strabismus have been described in *cblG* [Poloschek et al 2005, Huemer et al 2015a].
- **Childhood presentation (first years of life).** Failure to thrive, poor head growth, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures are typical. Renal thrombotic microangiopathy, HUS, pulmonary hypertension, and diffuse lung disease can also be seen [Kömhoff et al 2013, Beck et al 2017, Liu et al 2017].
- **Adolescent and adult presentation.** Individuals with this presentation usually have predominant **neurologic and neuropsychiatric** manifestations including the following:
  - Neuropsychiatric symptoms (behavioral and personality changes, social withdrawal, visual and auditory hallucinations, delirium, psychosis) [Huemer et al 2014]
  - Progressive cognitive decline (regression, deterioration in school or work performance, impaired dexterity and memory, speech difficulties, dementia, and lethargy) that is frequently described in the absence of other manifestations [Powers et al 2001, Boxer et al 2005, Ben-Omran et al 2007, Thauvin-Robinet et al 2008]

- Brain MRI may reveal leukodystrophy ranging from isolated periventricular white matter hyperintensities to diffuse white matter loss [Rossi et al 2001, Longo et al 2005].
- Subacute combined degeneration of the spinal cord [Bodamer et al 2001, Ben-Omran et al 2007, Tsai et al 2007]. In some cases, improvement has been reported after initiation of treatment [Thauvin-Robinet et al 2008].

Other presenting concerns in adolescents and adults have included renal thromobotic microangiopathy, HUS, pulmonary hypertension, and pulmonary thrombotic events [Huemer et al 2014].

***cblX* and related types: disorders of transcriptional regulation.** Newly identified disorders of intracellular cobalamin metabolism can have the biochemical features of *cblC* but are often clinically distinct with a more severe neurologic phenotype. These disorders include the X-linked disorder *cblX* and a similar phenotype (found in two individuals) associated with biallelic pathogenic variants in either *THAP11* or *ZNF143* [Yu et al 2013, Pupavac et al 2016, Quintana et al 2017].

Individuals have presented with signs from the prenatal period (IUGR, congenital malformations) to age five months (developmental delay, seizures). The developmental delay has been characterized as severe with significant intellectual disability and is associated with early-onset intractable seizures including infantile spasms. Microcephaly, brain malformations, and dysmorphic features were noted in some individuals. Other clinical features include nonketotic hyperglycinemia [Scalais et al 2017] and congenital malformations [Gérard et al 2015].

Some expected metabolite abnormalities were mild enough to be difficult to detect. Abnormal metabolites responded to B_{12} therapy, but clinical manifestations did not.

***cblF* and *cblJ* types: disorders of lysosomal cobalamin transport**

- ***cblF.*** Individuals with *cblF* often present during infancy with symptoms similar to *cblC* – IUGR, poor postnatal growth, feeding difficulties, and developmental delay – but can also have stomatitis with or without glossitis and congenital heart malformations [Alfadhel et al 2011]. Additional features such as cleft palate, unilateral renal agenesis, hepatic ductopenia, and intraventricular hemorrhage have also been described [Gailus et al 2010, Constantinou et al 2016].
- ***cblJ.*** Only five individuals with *cblJ* have been reported. Three presented neonatally with poor growth, feeding problems, respiratory distress, bone marrow suppression, and cardiac defect [Coelho et al 2012, Fettelschoss et al 2017] and two in early childhood with hyperpigmentation and premature graying; one of the two had a transient ischemic attack [Kim et al 2012, Takeichi et al 2015]. Retinopathy was described in one individual in early childhood [Fettelschoss et al 2017].
- Note: *cblF* and *cblJ* can in some cases be distinguished from *cblC* and *cblD*-combined because the former present with low serum B_{12} levels.

Isolated Homocystinuria (*cblE, cblG, cblD*-Homocystinuria)

Methylcobalamin deficiency secondary to methionine synthase reductase deficiency (*cblE*), methionine synthase deficiency (*cblG*), and *cblD*-homocystinuria are rare syndromes that are not identified on newborn screening, resulting in a delayed diagnosis [Huemer et al 2015a].

cblE. Most children with *cblE* present in the first two years of life with severe growth failure, megaloblastic anemia, and neurologic manifestations; isolated megaloblastic anemia and HUS [Palanca et al 2013] may also be seen. Presentation in adolescence with atypical glomerulopathy has also been described [Paul et al 2013].

cblG. Individuals with *cblG* characteristically present in the first year of life with neurologic manifestations and megaloblastic anemia; however, phenotypic variability ranges from infantile to adult presentation. Neurologic manifestations may include weakness, hypotonia, seizures, mental status changes, and adult-onset

leukoencephalopathy. Other unusual presentations of adult-onset *cblG* include megaloblastic anemia and progressive weakness (initially diagnosed as multiple sclerosis) [Carmel et al 1988], neuropsychiatric illness [Hill et al 2004], and thromobotic microangiopathy and atypical HUS [Vaisbich et al 2017]. Optic nerve atrophy, nystagmus, and strabismus have been described [Poloschek et al 2005, Huemer et al 2015a].

***cblD*-homocystinuria.** Individuals with *cblD*-homocystinuria (isolated methylcobalamin deficiency) had cognitive impairment, neurologic signs, and megaloblastic anemia [Suormala et al 2004]. Thromboembolic complications including clinically significant thrombophilia causing renal artery thrombosis [Watkins & Rosenblatt 1989], HUS, and pulmonary hypertension [Labrune et al 1999] have also been described.

Genotype-Phenotype Correlations

Genotype-phenotype correlations observed include the following:

cblC

- Infantile-presentation (early-onset), severe disease is associated with the *MMACHC* pathogenic variants c.271dupA or c.331C>T in the homozygous or compound heterozygous state.
- Noninfantile presentation (late onset) is usually associated with *MMACHC* pathogenic variants c.394C>T and *MMACHC* c.482G>A [Morel et al 2006, Nogueira et al 2008, Lerner-Ellis et al 2009, Wang et al 2009, Almannai et al 2017]. It may also be associated with *MMACHC* variant c.271dupA if individuals are compound heterozygotes for c.394C>T, c.347T>C, c.440 G>C, or c.482G>A [Morel et al 2006].

***cblD*.** The location of pathogenic variants within *MMADHC* correlates with the type of enzyme deficiency:

- **AdoCbl deficiency.** Typically, pathogenic nonsense and frameshift variants are found in exons 3 and 4, encoding the region of the protein necessary for AdoCbl synthesis.
- **MeCbl deficiency.** Pathogenic missense variants are found in exons 6 and 8, encoding the C-terminal region of the protein necessary for MeCbl synthesis.
- **AdoCbl and MeCbl deficiency.** Pathogenic variants occur in exon 5, exon 8, and intron 7, encoding the middle of the protein [Stucki et al 2012].

***cblE*,** caused by the *MTRR* c.1361C>T (p.Ser545Leu) Iberian pathogenic variant, has a milder phenotype than other reported pathogenic variants in *MTRR* with no evident neurologic involvement [Zavadáková et al 2002].

Clear genotype-phenotype correlations have not been described for *cblF*, *cblG*, *cblJ*, or *cblX*.

Prevalence

The true prevalence of the disorders of intracellular cobalamin metabolism is unknown.

- The incidence of *cblC* has been estimated at 1:200,000 births. Newborn screening suggested an incidence closer to 1:100,000 in New York State and 1:67,000 in California, where an incidence of 1:46,000 was estimated in the Hispanic population [Cusmano-Ozog et al 2007, Weisfeld-Adams et al 2010].
- Fewer than 40 cases have been described for *cblE* and *cblG*, and fewer than 20 cases each for *cblD*, *cblF*, *cblJ*, and *cblX* and its related types.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ABCD4*, *LMBRD1*, *MMACHC*, *MMADHC*, *MTR*, *MTRR*, *THAP11*, or *ZNF143*.

HCFC1 pathogenic variants can cause intellectual disability with or without congenital malformations, in the absence of the characteristic biochemical manifestations of cobalamin disorder [Huang et al 2012, Koufaris et al 2016].

Differential Diagnosis

The following disorders may cause clinical manifestations and laboratory abnormalities similar to those seen in disorders of intracellular cobalamin metabolism.

Disorders causing both methylmalonic acidemia and homocystinuria

- **Vitamin B_{12} deficiency.** Individuals with vitamin B_{12} deficiency can have methylmalonic acidemia and homocystinuria, as can the newborns of mothers who have vitamin B_{12} deficiency. To establish the diagnosis of vitamin B_{12} deficiency, it is necessary to measure serum vitamin B_{12} concentrations in both affected newborns and their mothers.

  B_{12} deficiency can occur in a breastfed infant of a vegan mother and in an infant born to a mother with subclinical pernicious anemia. The mother may not necessarily have a very low serum concentration of vitamin B_{12}. Maternal vitamin B_{12} deficiency can result in elevated methylmalonic acid level in an infant with findings that range from severe encephalopathy [Higginbottom et al 1978, Dror & Allen 2008] to elevated propionylcarnitine detected by newborn screening (NBS) [Chace et al 2001].

  Intramuscular replacement therapy to normalize vitamin B_{12} serum concentration reverses the metabolic abnormality.

- **Imerslund Gräsbeck syndrome** (OMIM 261100). Features of this autosomal recessive disorder may include poor cobalamin absorption, abnormal renal tubular protein reabsorption, and urinary tract malformations. The disorder is caused by biallelic pathogenic variants in one of two genes that encode intrinsic factor receptor components: *CUBN* (encoding cubulin) and *AMN* (encoding amnionless) [Gräsbeck 2006].

- **Transcobalamin II deficiency** (OMIM 275350). Transcobalamin II (TCII) is required for the movement of cobalamin from intestinal enterocytes into cells throughout the body. Transcobalamin II deficiency, a rare autosomal recessive condition associated with biallelic pathogenic variants in *TCN2*, is characterized by the infantile onset of megaloblastic anemia, failure to thrive, neurologic disease, and immunologic disease. Serum cobalamin concentrations are generally normal with a reduced (untreated) unsaturated B_{12} binding capacity and a reduced level of transcobalamin II (the latter detected by an immunoassay) [Kaikov et al 1991, Watkins & Rosenblatt 2014].

- **Transcobalamin receptor deficiency,** also known as methylmalonic acidemia, TCblR type (OMIM 613646). Transcobalamin receptor deficiency is a defect in the cellular uptake of cobalamin bound to TCII. Inheritance is autosomal recessive and associated with biallelic variants in *CD320*, often a common in-frame deletion. This disorder may be a common defect in cobalamin metabolism based on the allele frequency in population databases (MAF 0.009), but few affected individuals have been identified and the clinical phenotype is not well described [Quadros et al 2010]. Affected individuals may be identified on NBS; metabolites may normalize with cobalamin therapy and some individuals are reported to be asymptomatic [Hannah-Shmouni et al 2018; Authors, unpublished observations].

Disorders causing primarily isolated homocystinuria

- **Cystathionine beta-synthase (CBS) deficiency** (classic homocystinuria) is a disorder of homocysteine catabolism with a Marfan syndrome-like phenotype, soft skin, lens dislocation, developmental delays / cognitive impairment, and thromboembolism. CBS deficiency is progressive with onset typically in childhood. Biochemically it is characterized by elevated serum concentration of methionine and decreased

serum concentration of cysteine. Inheritance is autosomal recessive and associated with biallelic variants in *CBS*.

- **Methylenetetrahydrofolate reductase (MTHFR) deficiency** (OMIM 236250) is a defect in folate-dependent methylation pathways that results in diminished conversion of homocysteine to methionine. The biochemical hallmark is moderate homocystinuria with low to normal plasma methionine levels. In contrast to methionine biosynthetic defects like *cblE* and *cblG*, megaloblastic anemia does not occur. The clinical course is characterized by varying severity, cognitive impairment, and white matter disease [Fenton et al 2001]. Inheritance is autosomal recessive and associated with biallelic variants in *MTHFR*.
- **Mild homocystinuria** can result from folate deficiency or vitamin B_{12} deficiency.

Disorders causing primarily methylmalonic acidemia

- Disorders associated with isolated methylmalonic acidemia include methylmalonic acidemia due to pathogenic variants of methylmalonyl-CoA mutase (*MUT*), *cblA* (*MMAA*), and *cblB* (*MMAB*); SUCLA2 deficiency; *cblD*-MMA (*MMADHC*); "benign methylmalonic acidemia" [Sniderman et al 1999, Martens et al 2002]; Reye-like syndrome [Chang et al 2000]; and combined malonic and methylmalonic acidemia (CMAMMA; OMIM 614265) caused by *ACSF3* pathogenic variants [Alfares et al 2011, Sloan et al 2011].
- For a more detailed description of other entities with isolated methylmalonic acidemia, see Isolated Methylmalonic Acidemia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a disorder of intracellular cobalamin metabolism, the following evaluations are recommended.

In an unstable individual:

- Serial metabolic evaluations of blood gases, electrolytes, glucose, ammonia, liver function, total and direct bilirubin, renal function, lactate dehydrogenase, plasma amino acids (methionine), plasma methylmalonic acid (MMA), and total plasma homocysteine (tHcy) to guide acute management until the individual stabilizes
- Complete blood count (CBC) with differential to evaluate for megaloblastic anemia or cytopenias
- Peripheral blood smear to evaluate for the presence of schistocytes, in the presence of other manifestations of hemolytic uremic syndrome (HUS)

Once the individual becomes stable:

- Clinical assessment of growth parameters, head circumference, ability to feed, developmental status, and neurologic status
- Laboratory assessment of nutritional status (electrolytes, albumin, prealbumin, plasma amino acids [with careful attention to methionine levels], vitamin levels [including thiamine and 25-hydroxyvitamin D], and trace minerals) and renal function; complete blood count to monitor for cytopenias
- Echocardiogram to screen for cardiac defects and cardiomyopathy [Profitlich et al 2009, Tanpaiboon et al 2013]
- EEG and brain MRI in symptomatic individuals
- Ophthalmologic examination
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A set of guidelines for the diagnosis and management of *cblC*, *cblD*, *cblE*, *cblF*, *cblG*, *cblJ*, and MTHFR deficiency have been published [Huemer et al 2017].

Early treatment with hydroxocobalamin injections improves survival and biochemical, hematologic, and microangiopathic symptoms in individuals with *cblC*. Both newborn screening (NBS) and early treatment are recommended by current guidelines [Huemer et al 2015b, Huemer et al 2017].

Institution of therapy during acute illness results in rapid improvement of clinical, biochemical, and hematologic manifestations in individuals with early- and late-onset *cblC* [Bartholomew et al 1988, Rosenblatt et al 1997, Bodamer et al 2001, Tomaske et al 2001, Kind et al 2002, Van Hove et al 2002, Fowler et al 2008].

At the Time of Diagnosis

Goals of treatment are to reduce toxic metabolites and avoid low methionine levels.

- Parenteral hydroxocobalamin (OHCbl) is the mainstay of therapy and should be instituted **immediately** when a disorder of intracellular cobalamin metabolism is suspected clinically or following positive NBS for propionylcarnitine.
- Cyanocobalamin should not be used as it will not be effective in individuals with *cblC*.
- Avoid treating individuals with a low-protein diet and medical foods designed for the treatment of individuals with isolated MMA because they contain no methionine, which can further reduce methionine level.
- Those with elevated total plasma homocysteine (tHcy) should also receive betaine (250 mg/kg/day) and folate or folinic acid. Betaine has a short effective half-life and should be given in divided doses (optimally divided into 3 or 4 doses per day). It can also be titrated to response while monitoring tHcy and plasma methionine.

Acute Metabolic Decompensation

Although less common in the disorders of intracellular cobalamin metabolism than in isolated methylmalonic acidemia, severe acidotic/ketotic crises due to profound methylmalonic acidemia can occur, in particular at presentation or if untreated. Such critically ill individuals should be managed in consultation with a metabolic specialist. MedicAlert® bracelets and emergency treatment protocols outlining fluid and electrolyte therapy should be available for all affected individuals.

Treatment includes volume replacement with isotonic solutions containing high (10%-12.5%) glucose to reverse catabolism, correction of metabolic acidosis with sodium bicarbonate, and prompt reintroduction of feedings – preferably enterally, but parenterally if enteral route cannot be established. Parenteral hydroxocobalamin should be given immediately in the setting of an acute decompensation.

Thromboembolic Complications

Thromboembolic complications as a cause of mortality in *cblC* are likely associated with increasing plasma concentrations of tHcy [Carrillo-Carrasco & Venditti 2012]. The proper management of thromboembolic complications, such as HUS and thrombotic microangiopathy, should include initiation (or dosage increase) of OHCbl and betaine [Van Hove et al 2002, Sharma et al 2007].

Long-Term Management

The goals of long-term management include improving the metabolic derangement by lowering plasma tHcy and methylmalonic acid (MMA) concentrations and maintaining plasma methionine concentrations within the normal range. These are accomplished by the following.

Parenteral hydroxocobalamin (OHCbl). The most experience derives from the treatment of individuals with *cblC*. Infants are usually started at a daily dose of 1.0 mg (~0.3 mg/kg/day) of OHCbl given intramuscularly or subcutaneously (SQ). Parenteral OHCbl (not the cyanocobalamin form or oral form) is the only effective preparation. Placement of a SQ catheter could be used to minimize cutaneous punctures [Maines et al 2017]; prefilled injections may increase compliance.

Weight-appropriate adjustment of OHCbl to 0.3 mg/kg/day to maintain the dosing in infancy is recommended and can be attained by the ability to concentrate OHCbl up to 30 mg/mL [Carrillo-Carrasco et al 2012]. Further titration of the dose may be empirically adjusted as needed for worsening clinical manifestations [Van Hove et al 2002] or for metabolic control of plasma tHcy, MMA, or methionine [Carrillo-Carrasco et al 2009]. Biochemical as well as clinical improvement has been demonstrated after increasing doses of OHCbl [Matos et al 2013], although clinical trials are needed to demonstrate long-term clinical outcomes [Dionisi-Vici et al 2013].

Betaine. Oral betaine (starting at ~250 mg/kg/day) is recommended in those with elevated plasma total homocysteine as it facilitates conversion of homocysteine to methionine through betaine homocysteine methyltransferase.

Folate and folinic acid. Folic acid and folinic acid can potentially augment remethylation and may help improve plasma tHcy and methionine concentrations. Folinic acid may be preferred as it crosses the blood-brain barrier more efficiently than folic acid. The adult dose of folate is 1.0 mg by mouth per day, titratable down to 0.5 mg for maintenance. Doses for children and infants are available in the Harriet Lane Handbook [Tschudy & Arcara 2012] and other common reference texts.

Dietary management. Individuals may be able to tolerate a normal diet.

- Low-protein diets and medical foods designed for isolated methylmalonic acidemia are **not** recommended [Huemer et al 2017] as they can result in hypomethioninemia, which can be detrimental [Ribes et al 1990, Rossi et al 2001, De Bie et al 2009].
  - The use of low-protein diets correlated with lower height-for-age z-scores [Manoli et al 2016], and intake of medical foods (methionine-free formulas) was associated with decreased head circumference in two cohorts of individuals with *cblC* [Manoli et al 2016, Ahrens-Nicklas et al 2017].
  - Medical foods designed for isolated methylmalonic acidemia do not contain methionine and also have an increased amount of leucine, which may compete with methionine for uptake to the brain and potentially exacerbate cerebral methionine deficiency.
- Gastrostomy tube placement may be required in the presence of feeding difficulties and failure to thrive.

Other Therapeutic Considerations

The following have not been fully validated:

- **Methionine supplementation.** Hypomethioninemia is usually responsive to appropriate treatment with OHCbl, betaine, and optimal dietary management. The need for exogenous methionine supplementation may be minimized by these strategies, as the efficacy of this therapy is uncertain [Smith et al 2006].
- **Pyridoxine.** Vitamin B_6 is a cofactor for cystathionine beta-synthase and therefore has been proposed as a means of maximizing the removal of homocysteine. Persons with disorders of intracellular cobalamin metabolism generally do not respond to pyridoxine unless they have a dietary deficiency.
- **Levocarnitine.** Indicated for low plasma carnitine levels. Most individuals take 50-200 mg/kg/day to aid in the removal of excess propionyl-CoA groups.
- **Metanx.** A supplement that contains L-methylfolate (active form of folate), methylcobalamin, and pyridoxal-5'-phosphate (active form of vitamin B_6) is prescribed as a treatment for neuropathy. It may be used in individuals with cobalamin disorders (in particular teens and adults with clinical indication for

neuropathy) and also considered in all individuals with cobalamin disorders to replace individual folate and B_6 supplements.
- **Aspirin.** Antiplatelet doses of aspirin may be given to individuals with isolated homocystinuria to decrease the risk for thrombosis [Brunel-Guitton et al 2010].

Treatment of infantile spasms, seizures, congenital heart malformations, and hydrocephalus is done in a routine manner.

Prenatal Therapy

Prenatal therapy of an affected fetus by administration of intramuscular OHCbl to the mother may improve neurocognitive outcome; however, the ophthalmologic manifestations are often still present [Patton et al 2000, Huemer et al 2005, Brooks et al 2016, Trefz et al 2016].

- The dose and frequency of OHCbl administration to pregnant mothers has not been established.
- Favorable outcomes of prenatal treatment have been reported by using dosages between 1 and 10 mg per day, 2-3 times a week, starting as early as 15 weeks' gestational age [Huemer et al 2005, Trefz et al 2016].

Prevention of Primary Manifestations

Early institution of injectable hydroxocobalamin improves survival and may reduce but not completely prevent primary manifestations.

To prevent metabolic decompensations, affected individuals should be advised to avoid situations that result in catabolism, such as prolonged fasting and dehydration, and always remain on a weight-appropriate dose of hydroxocobalamin. Of note, during an intercurrent illness individuals may be treated with glucose-containing IV fluid.

Flu prevention (i.e., immunization) should be a routine part of health maintenance.

Surveillance

The following evaluations are performed at different intervals depending on age and disease severity:

- During the first year of life, infants may need to be evaluated once or twice a month by a metabolic specialist.
- Toddlers and school-age children should be evaluated at least twice a year to adjust medication dosing (hydroxocobalamin, betaine) during growth and to evaluate nutritional status.
- Teens and adults may be seen on a yearly basis.

Clinical evaluation should assess the following:

- Growth including weight, linear growth, and head circumference
- Nutritional status
- Feeding ability
- Developmental and neurocognitive progress, as age-appropriate

Laboratory evaluation should include the following:

- Metabolic studies including urine organic acids, serum methylmalonic acid analysis, plasma amino acids (methionine), plasma tHcy concentration
- CBC to monitor for cytopenias
- Nutritional studies, if indicated: electrolytes, albumin, prealbumin, plasma amino acids, vitamin levels (including thiamine and 25-hydroxyvitamin D), essential fatty acids, and trace minerals

Routine evaluations should include the following:

- Ophthalmologic evaluation for retinal and optic nerve changes in those with *cblC* and *cblG* and if visual symptoms are present. Recommendations for the ophthalmologic follow up of individuals with *cblC* and related disorders have been published [Weisfeld-Adams et al 2015].
- Neurologic evaluations for early signs of developmental delays, behavioral disturbances, seizures, and myelopathy
- Brain MRI and/or EEG as clinically indicated
- Echocardiogram

Agents/Circumstances to Avoid

Potentially exacerbating circumstances:

- Prolonged fasting (longer than overnight without dextrose-containing intravenous fluids)
- Dietary protein intake below the recommended dietary allowance (RDA) for age
- Dietary protein intake greater than that prescribed by a metabolic specialist especially in individuals with *cblC*, *cblD*-combined, *cblF*, or *cblJ*
- Medical foods. Medical foods given to infants with isolated methylmalonic acidemia do not contain methionine and should be avoided as the decreased methionine intake may worsen hypomethioninemia and long-term use may contribute to poor head and linear growth [Manoli et al 2016, Ahrens-Nicklas et al 2017], among other complications.
- Nitrous oxide, an anesthetic that is potentially toxic as it depletes the body stores of vitamin B_{12} and inhibits methionine synthase activity [Kondo et al 1981, Abels et al 1990, Drummond & Matthews 1994, Baum 2007]

Evaluation of Relatives at Risk

If the pathogenic variant(s) in the family are known, at-risk sibs may be tested prenatally to allow initiation of treatment in utero or as soon as possible after birth.

If the newborn sib of an affected individual has not undergone prenatal testing, molecular genetic testing can be performed in the first week of life if the pathogenic variant(s) in the family are known. If the pathogneic variant(s) are not known, evaluation of urine organic acids and plasma amino acids, measurement of total plasma homocysteine, serum methylmalonic acid analysis, and acylcarnitine profile analysis can be used for the purpose of early diagnosis and treatment.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

A good pregnancy outcome was reported in two women with *cblC* [Brunel-Guitton et al 2010, Liu et al 2015]. In addition, an unaffected infant was born to an asymptomatic woman with *cblC* who was diagnosed following her child's positive NBS for low carnitine [Lin et al 2009].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Disorders of intracellular cobalamin metabolism caused by pathogenic variants in *ABCD4*, *LMBRD1*, *MMACHC*, *MMADHC*, *MTR*, *MTRR*, *THAP11*, or *ZNF143* are inherited in an autosomal recessive manner.

The disorder of intracellular cobalamin metabolism caused by pathogenic variants in *HCFC1* is inherited in an X-linked manner.

A single report of a deceased child with a paternally inherited *LMBRD1* pathogenic variant and a maternally inherited *MTR* pathogenic variant suggests that digenic inheritance may also be possible [Farwell Gonzalez et al 2015].

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with a disorder of intracellular cobalamin metabolism are obligate heterozygotes (carriers) for an *ABCD4*, *LMBRD1*, *MMACHC*, *MMADHC*, *MTR*, *MTRR*, *THAP11*, or *ZNF143* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ABCD4*, *LMBRD1*, *MMACHC*, *MMADHC*, *MTR*, *MTRR*, *THAP11*, or *ZNF143* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *ABCD4*, *LMBRD1*, *MMACHC*, *MMADHC*, *MTR*, *MTRR*, *THAP11*, or *ZNF143* pathogenic variants in the family.

Biochemical testing is not reliable for carrier detection.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizyous for the *HCFC1* variant, and he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives

and if the *HCFC1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo HCFC1* pathogenic variant, in which case the mother is not a heterozygote (carrier). Because very few families with *HCFC1* pathogenic variants have been described, the frequency of *de novo* pathogenic variants is not known.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother.

- If the mother of the proband has an *HCFC1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit the pathogenic variant will be heterozygous and will usually not be affected (no affected females have been described to date).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *HCFC1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of maternal germline mosaicism.

Offspring of a proband. Affected males transmit the *HCFC1* variant to:

- All of their daughters, who will be carriers (heterozygotes) and will usually not be affected; and
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the *HCFC1* pathogenic variant, and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes for the pathogenic variant (carrier females) or of being affected (males).

Heterozygote Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *HCFC1* pathogenic variant in the family. Note: Females who are heterozygous (carriers) for this X-linked disorder will usually not be affected.

Biochemical testing is not reliable for carrier testing.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the pathogenic variant(s) have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Biochemical testing. If the pathogenic variant(s) have not been identified in an affected family member, prenatal testing for pregnancies at risk for a disorder of intracellular cobalamin metabolism may be possible using these methods:

- Complementation analysis of cultured amniocytes [Morel et al 2005, Watkins & Rosenblatt 2014]
- Measurement of MMA and tHcy concentrations in amniotic fluid using mass spectrometric techniques [Morel et al 2005, Watkins & Rosenblatt 2014].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **HCU Network America**
  623 Creek Lane
  Flourtown PA 19031
  Phone: 630-360-2087
  Email: hcunetworkamerica@gmail.com
  www.hcunetworkamerica.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Email: info@oaanews.org
  oaanews.org
- **European Network and Registry for Homocystinurias and Methylation Defects (E-HOD)**
  www.e-hod.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Disorders of Intracellular Cobalamin Metabolism: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCD4	14q24.3	Lysosomal cobalamin transporter ABCD4		ABCD4	ABCD4
HCFC1	Xq28	Host cell factor 1	HCFC1 @ LOVD	HCFC1	HCFC1

Table A. continued from previous page.

LMBRD1	6q13	Lysosomal cobalamin transport escort protein LMBD1	LMBRD1 database ZJU-CGGM Database (LMBRD1)	LMBRD1	LMBRD1
MMACHC	1p34.1	Cyanocobalamin reductase / alkylcobalamin dealkylase	MMACHC database ZJU-CGGM Database (MMACHC)	MMACHC	MMACHC
MMADHC	2q23.2	Cobalamin trafficking protein CblD	ZJU-CGGM Database (MMADHC) MMADHC @ LOVD	MMADHC	MMADHC
MTR	1q43	Methionine synthase	MTR @ LOVD ZJU-CGGM Database (MTR)	MTR	MTR
MTRR	5p15.31	Methionine synthase reductase	MTRR @ LOVD ZJU-CGGM Database (MTRR)	MTRR	MTRR
THAP11	16q22.1	THAP domain-containing protein 11		THAP11	THAP11
ZNF143	11p15.4	Zinc finger protein 143		ZNF143	ZNF143

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Disorders of Intracellular Cobalamin Metabolism (View All in OMIM)

156570	5-@METHYLTETRAHYDROFOLATE-HOMOCYSTEINE S-METHYLTRANSFERASE; MTR
236270	HOMOCYSTINURIA-MEGALOBLASTIC ANEMIA, cblE TYPE; HMAE
250940	HOMOCYSTINURIA-MEGALOBLASTIC ANEMIA, cblG TYPE; HMAG
277380	METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblF TYPE; MAHCF
277400	METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblC TYPE; MAHCC
277410	METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE; MAHCD
300019	HOST CELL FACTOR C1; HCFC1
309541	METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblX TYPE; MAHCX
602568	METHIONINE SYNTHASE REDUCTASE; MTRR
603214	ATP-BINDING CASSETTE, SUBFAMILY D, MEMBER 4; ABCD4
603433	ZINC FINGER PROTEIN 143; ZNF143
609119	THAP DOMAIN-CONTAINING PROTEIN 11; THAP11
609831	METABOLISM OF COBALAMIN ASSOCIATED C; MMACHC
611935	METABOLISM OF COBALAMIN ASSOCIATED D; MMADHC
612625	LMBR1 DOMAIN-CONTAINING PROTEIN 1: LMBRD1

See Figure1. For detailed summaries of gene and protein information for the genes discussed in this section, see Table A, **Gene**.

ABCD4

Gene structure. The longest transcript variant of *ABCD4* is 3,157 bp with 19 exons (NM_005050.3) [Holzinger et al 1998]. Alternative splicing results in multiple transcript variants.

Pathogenic variants. Missense, frameshift, and splicing variants have been reported [Coelho et al 2012, Kim et al 2012].

Normal gene product. The ABCD4 protein contains 606 amino acids (NP_005041.1) and has a mass of 73 kd [Shani et al 1997]. It is an ATP-binding cassette (ABC) transporter that colocalizes with lysosomal proteins LAMP1 and LMBRD1 (*cblF*). It is thought that its ATPase activity may be involved in the intracellular processing of cobalamin [Coelho et al 2012].

Abnormal gene product. Pathogenic variants are expected to affect the lysosomal transport of cobalamin into the cytoplasm [Coelho et al 2012].

HCFC1

Gene structure. *HCFC1* is a gene of about 24 kb; it comprises 26 exons.

Pathogenic variants. Five missense variants were identified in 14 individuals with *cblX*: c.202C>G, c.217G>A, c.218C>T, c.343G>A, and c.344C>T [Yu et al 2013]. These variants were located in the first two Kelch domains, which are conserved ~50-amino-acid sequences that interact to form a β-propeller structure and are involved in protein-protein interactions. An additional variant, c.307T>C, was reported in another family [Gérard et al 2015].

Other *HCFC1* variants have been reported in individuals with intellectual disability with or without congenital malformations, in the absence of known biochemical abnormalities (although biochemical testing has not always been performed) [Huang et al 2012, Jolly et al 2015, Koufaris et al 2016].

Variants listed in Table 5 are only those *HCFC1* variants reported to cause a cobalamin disorder phenotype.

Table 5. *HCFC1* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.202C>G	p.Gln68Glu	NM_005334.2 NP_005325.2
c.217G>A	p.Ala73Thr	
c.218C>T	p.Ala73Val	
c.307T>C	p.Tyr103His	
c.343G>A	p.Ala115Thr	
c.344C>T	p.Ala115Val	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *HCFC1* encodes host cell factor C-1 (aka HCF-1), a transcriptional coregulator. The protein is 2,035 amino acids long and is known to interact with transcription factors including those encoded by *THAP11* and *ZNF143*. The HCFC1 complex has been reported to regulate hundreds of genes [Dejosez et al 2010].

Abnormal gene product. Fibroblasts from individuals with p.Ala73Val and p.Ala115Val showed decreased *MMACHC* RNA and protein expression, suggesting the failure of mutated HCFC1 protein to regulate *MMACHC* expression – potentially the result of disrupted protein-protein interactions via the Kelch domains.

LMBRD1

Gene structure. *LMBRD1* is a gene of 121 kb; it comprises 16 exons [Rutsch et al 2009].

Pathogenic variants. Rutsch et al [2009] studied 12 unrelated individuals with *cblF* confirmed by complementation analysis. A common variant, c.1056delG, was seen in 18/24 independent alleles; this variant causes a frameshift yielding a premature stop codon in exon 11 [Rutsch et al 2009]. Altogether five different DNA variants accounted for 22 of 24 observed pathogenic variants. Eight additional variants have been reported including small deletions, splice site variants, and a large (6-kb) deletion, the latter described by Miousse et al [2011].

Table 6. *LMBRD1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1056delG	p.Asn353IlefsTer18	NM_018368.3 NP_060838.3

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The probable lysosomal cobalamin transporter LMBR1 domain-containing one protein (LMBD1) is 540 amino acids and has a predicted molecular weight of 61.3 kd (the longest isoform). The predicted protein structure includes nine transmembrane regions and multiple potential glycosylation sites. The protein has been shown by immunocytofluorescence to colocalize with the lysosomal marker LAMP1. The protein is predicted to be a lysosomal membrane transporter [Rutsch et al 2009] and interacts in a complex with ABCD4 (*cblJ*) [Fettelschoss et al 2017].

Abnormal gene product. Pathogenic variants cause the defective release of cobalamin from lysosomes.

MMACHC

Gene structure. *MMACHC* is 11 kb and comprises four exons [Lerner-Ellis et al 2006].

Pathogenic variants. More than 90 variants have been identified in persons with *cblC*. Table 7 includes variants common in certain populations, such as c.609G>A, which is common in individuals of Chinese ancestry. The most common variant, present in an estimated 30%-50% of alleles, is c.271dupA, historically associated with infantile-onset disease.

Table 7. *MMACHC* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change [1]	Predicted Protein Change	Reference Sequences
c.271dupA [2]	p.Arg91LysfsTer140	NM_015506.2 NP_056321.2
c.331C>T [3]	p.Arg111Ter	
c.347T>C	p.Leu116Pro	
c.394C>T [4]	p.Arg132Ter	
c.440G>C	p.Gly147Ala	
c.482G>A [5]	p.Arg161Gln	
c.609G>A [6]	p.Trp203Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.
2. Accounts for approximately 30%-50% of disease alleles in individuals of European ancestry [Lerner-Ellis et al 2006, Lerner-Ellis et al 2009, Fischer et al 2014]
3. Common in people of Cajun and French Canadian ancestry [Lerner-Ellis et al 2009]
4. Common in people of Indian and Middle Eastern ancestry [Lerner-Ellis et al 2009]; associated with a late-onset phenotype
5. Associated with milder disease, and may be more common in individuals of Hispanic descent [Almannai et al 2017]
6. Common in people of Chinese ancestry [Liu et al 2010]

Recently, three individuals who are double heterozygous for pathogenic variants in *MMACHC* and *PRDX1* have been identified. *PRDX1* is a neighboring gene on chromosome 1 transcribed from the reverse strand. Variants identified in *PRDX1* located at the intron 5 splice acceptor site caused skipping of exon 6, transcription of antisense *MMACHC*, and hypermethylation of the *MMACHC* promoter/exon 1, resulting in no gene expression from that allele [Guéant et al 2018].

Normal gene product. The methylmalonic aciduria and homocystinuria type C (MMACHC) protein has 282 amino acids and a predicted molecular weight of 31.7 kd. The MMACHC protein has been crystallized and in vitro studies have shown that MMACHC removes the upper B-axial ligand of cobalamin derivatives (e.g., CN, OH, Ado, Me) through dealkylation or decyanation using glutathione; it is also thought to be involved in intracellular trafficking of cobalamins [Koutmos et al 2011]. MMACHC resides in a complex with MMADHC and other proteins in the pathway [Gherasim et al 2013, Bassila et al 2017].

Abnormal gene product. Defects in MMACHC disrupt its ability to process newly internalized cobalamins in the cytosol [Hannibal et al 2009].

MMADHC

Gene structure. *MMADHC*, previously known as *C2orf25*, is 18 kb and comprises eight exons (NM_015702.2) [Coelho et al 2008].

Pathogenic variants. There are no clearly identified common disease-causing variants; 13 variants have been reported to date. Pathogenic variants in *MMADHC* can result in three different phenotypes – *cblD*-MMA (AdoCbl deficiency), *cblD*-Hcy (MeCbl deficiency), and *cblD*-combined (AdoCbl and MeCbl deficiency). The pathogenic variants described to date are either missense or truncating (nonsense, splice, or frameshift) variants.

- Truncating variants in exons 3 and 4, encoding the N-terminus of the protein, cause AdoCbl deficiency (*cblD*-MMA) [Coelho et al 2008, Plesa et al 2011, Stucki et al 2012].

- Missense variants in exons 6 and 8, encoding the C-terminus, cause MeCbl deficiency (*cblD*-Hcy) [Coelho et al 2008, Stucki et al 2012].
- Truncating variants in exons 5, 7, and 8 and intron 7 cause combined AdoCbl and MeCbl deficiency [Coelho et al 2008, Stucki et al 2012].

Normal gene product. The *MMADHC* product is predicted to have 296 amino acids with a calculated molecular mass of 32.8 kd (NP_056517.1) [Stucki et al 2012]. There is an N-terminal mitochondrial leader sequence [Coelho et al 2008]. The C-terminus is thought to guide vitamin B_{12} to methionine synthase [Plesa et al 2011]. In vitro studies suggest that MMADHC does not directly bind cobalamin but may act as a chaperone given that it binds to MMACHC [Deme et al 2012, Gherasim et al 2013]. The crystal structure showed that MMADHC is a modified nitroreductase fold with structural similarity to MMACHC [Froese et al 2015, Yamada et al 2015].

Abnormal gene product. The type and location of pathogenic variants within the protein is thought to determine whether the synthesis of AdoCbl, MeCbl, or both is affected. Variants in the region encoding the mitochondrial targeting sequence (amino acid position 1-61) affect AdoCbl synthesis.

MTR

Gene structure. *MTR* is 105.24 kb and comprises 33 exons [Brody et al 1999].

Pathogenic variants. About 40 pathogenic variants have been identified. The most common disease-causing allele in persons with *cblG* is a missense variant, c.3518C>T, accounting for 40% of alleles [Watkins et al 2002].

A subset of severe pathogenic variants (including frameshifting deletions and nonsense variants) [Watkins et al 2002] and a variant resulting in a cryptic splice site are thought to result in premature translation termination and mRNA instability [Wilson et al 1998, Watkins et al 2002].

Leclerc et al [1996] identified two pathogenic variants specifically near the cobalamin-binding domain.

Table 8. *MTR* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.3518C>T	p.Pro1173Leu	NM_000254.2 NP_000245.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The MTR enzyme has 1,265 amino acids and weighs 140.5 kd. There are at least three functional domains:

- The 38-kd C-terminal domain binds AdoMet.
- A domain comprising amino acids 650 to 896 includes the binding domain for the required cofactor methylcobalamin.
- The 70-kd N-terminal domain binds homocysteine and methyltetrahydrofolate.

The latter two activities may be on separate domains within this region [Goulding et al 1997].

Abnormal gene product. Pathogenic variants are expected to decrease enzymatic activity.

MTRR

Gene structure. The longest transcript variant of *MTRR* (NM_002454.2) comprises 15 exons and encodes the shorter protein isoform of 698 amino acids (NP_002445.2). In comparison, the transcript variant NM_024010.2 uses an alternate splice site in the 5' region and initiates translation at an alternate start codon. The encoded protein isoform NP_076915.2 has 725 amino acids with a longer N-terminus.

Pathogenic variants. More than 25 variants in *MTRR* have been reported.

- The most common disease-causing variant, accounting for 25% of alleles, is a deep intronic variant in intron 6 (c.903+469T>C) that activates a splice enhancer site in a pseudoexon resulting in its inclusion [Zavadáková et al 2002, Zavadáková et al 2005, Homolova et al 2010].
- The c.1361C>T variant is common in persons of Iberian ancestry. Reports suggest a milder phenotype with no neurologic involvement [Zavadáková et al 2005].

Other variants have been described [Leclerc et al 1999, Zavadáková et al 2002]. Most reported variants have been nonconservative missense variants.

Table 9. *MTRR* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.903+469T>C (903_904ins140)	--	NM_002454.2 NP_002445.2
c.1361C>T	p.Ser545Leu	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. The MTRR protein isoform NP_002445.2 has 698 amino acids. MTRR shares homology with human cytochrome P450 reductase [Leclerc et al 1999]. MTRR has some chaperone-like activity with regard to MTR [Yamada et al 2006]. The longer N-terminus isoform NP_076915.2 was initially predicted to have a mitochondrial leader sequence [Leclerc et al 1999], but in vitro experiments suggest that the protein is primarily cytosolic [Froese et al 2008].

Abnormal gene product. Pathogenic variants are expected to decrease enzymatic activity.

THAP11

Gene structure. The *THAP11* transcript NM_020457.2 is ~2 kb and contains a single exon.

Pathogenic variants. A single variant, NM_020457.2:c.240C>G (p.Phe80Leu), was identified in the homozygous state in a single individual with a *cblX*-like clinical and biochemical phenotype [Quintana et al 2017].

Table 10. *THAP11* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.240C>G	p.Phe80Leu	NM_020457.2 NP_065190.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org).See Quick Reference for an explanation of nomenclature.

Normal gene product. The transcript (NM_020457) encodes a 314-amino-acid protein (NP_065190.2). THAP11 (THAP containing protein 11) is a transcription factor located in a complex with HCFC1, ZNF143, and other proteins that regulate the expression of hundreds of genes including *MMACHC*.

Abnormal gene product. The variant reported may interfere with DNA binding or disrupt the interactions with HCFC1, ZNF143, and other proteins in the complex, resulting in decreased expression of *MMACHC* and other genes.

ZNF143

Gene structure. The gene is 67 kb and is composed of 16 exons.

Pathogenic variants. The two variants shown in Table 11 have been reported in a single case [Pupavac et al 2016].

Table 11. *ZNF143* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	ReferenceSequences
c.851T>G	p.Leu284Ter	NM_003442.5 NP_003433.3
c.1019C>T	p.Thr340Ile	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org).See Quick Reference for an explanation of nomenclature.

Normal gene product. The longest transcript is 2.9 kb (NM_003442) encoding a protein of 638 amino acids. ZNF143 is a transcription factor located in a complex with HCFC1, THAP11, and other proteins that regulate the expression of hundreds of genes.

Abnormal gene product. The variants reported may interfere with DNA binding or disrupt the interactions with HCFC1, ZNF143, and other proteins in the complex, resulting in decreased expression of *MMACHC* and other genes.

Chapter Notes

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Revision History

- 16 December 2021 (js) Revision: Figure 2 corrected
- 6 September 2018 (ha) Comprehensive update posted live
- 21 November 2013 (me) Comprehensive update posted live
- 11 August 2009 (cd) Revision: targeted mutation analysis for c.271dupA mutation in cblC and prenatal diagnosis for cblD and variants available clinically.
- 2 June 2009 (cd) Revision: sequence analysis available clinically for *MMADHC* mutations causing cblD, cblD variant 1, and cblD variant 2
- 25 February 2008 (me) Review posted live
- 22 December 2006 (cpv) Original submission

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