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Isolated Methylmalonic Acidemia

Synonym: Isolated Methylmalonic Aciduria

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Summary

Clinical characteristics

Isolated methylmalonic acidemia/aciduria, the topic of this *GeneReview*, is caused by complete or partial deficiency of the enzyme methylmalonyl-CoA mutase (mut^0 enzymatic subtype or mut^- enzymatic subtype, respectively), a defect in the transport or synthesis of its cofactor, adenosyl-cobalamin (*cblA*, *cblB*, or *cblD*-MMA), or deficiency of the enzyme methylmalonyl-CoA epimerase. Onset of the manifestations of isolated methylmalonic acidemia/aciduria ranges from the neonatal period to adulthood. All phenotypes are characterized by periods of relative health and intermittent metabolic decompensation, usually associated with intercurrent infections and stress.

- In the neonatal period the disease can present with lethargy, vomiting, hypotonia, hypothermia, respiratory distress, severe ketoacidosis, hyperammonemia, neutropenia, and thrombocytopenia and can result in death within the first four weeks of life.
- In the infantile/non-B_{12}-responsive phenotype, infants are normal at birth, but develop lethargy, vomiting, dehydration, failure to thrive, hepatomegaly, hypotonia, and encephalopathy within a few weeks to months of age.
- An intermediate B_{12}-responsive phenotype can occasionally be observed in neonates, but is usually observed in the first months or years of life; affected children exhibit anorexia, failure to thrive, hypotonia, and developmental delay, and sometimes have protein aversion and/or vomiting and lethargy after protein intake.
- Atypical and "benign"/adult methylmalonic acidemia phenotypes are associated with increased, albeit mild, urinary excretion of methylmalonate.

Major secondary complications of methylmalonic acidemia include: intellectual impairment (variable); tubulointerstitial nephritis with progressive renal failure; "metabolic stroke" (acute and chronic basal ganglia injury) causing a disabling movement disorder with choreoathetosis, dystonia, and para/quadriparesis; pancreatitis; growth failure; functional immune impairment; and optic nerve atrophy.

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Diagnosis/testing

Diagnosis of isolated methylmalonic acidemia relies on analysis of organic acids in plasma and/or urine by gas-liquid chromatography and mass spectrometry. Establishing the specific subtype of methylmalonic acidemia requires cellular biochemical studies (including ^{14}C propionate incorporation and B_{12} responsiveness, complementation analysis, and cobalamin distribution assays) and molecular genetic testing. The finding of biallelic pathogenic variants in one of the five genes (*MMUT*, *MMAA*, *MMAB*, *MCEE*, and *MMADHC*) associated with isolated methylmalonic acidemia – with confirmation of carrier status in the parents – can establish the diagnosis.

Management

Treatment of manifestations: Critically ill individuals are stabilized by restoring volume status and acid-base balance; reducing or eliminating protein intake; providing increased calories via high glucose-containing fluids and insulin to arrest catabolism; and monitoring serum electrolytes and ammonia, venous or arterial blood gases, and urine output. Management includes a high-calorie diet low in propiogenic amino acid precursors; hydroxocobalamin intramuscular injections; carnitine supplementation; antibiotics such as neomycin or metronidazole to reduce propionate production from gut flora; gastrostomy tube placement as needed; and aggressive treatment of infections. Other therapies used in a limited number of patients include *N*-carbamylglutamate for the treatment of acute hyperammonemic episodes; liver, kidney, or combined liver and kidney transplantation; and antioxidants for the treatment of optic nerve atrophy.

Prevention of primary manifestations: In some cases, newborn screening allows for presymptomatic detection of affected newborns and early treatment.

Agents/circumstances to avoid: Fasting and increased dietary protein.

Other: Medic Alert® bracelets and up-to-date, easily accessed, detailed emergency treatment protocols facilitate care.

Genetic counseling

Isolated methylmalonic acidemia is 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. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible using molecular genetic techniques if the pathogenic variants in the family are known. In some circumstances, prenatal diagnosis for pregnancies at increased risk is possible by enzyme analysis and metabolite measurements on cultured fetal cells (obtained by chorionic villus sampling or amniocentesis).

GeneReview Scope

Isolated Methylmalonic Acidemia/Aciduria: Included Phenotypes
• Complete or partial deficiency of the enzyme methylmalonyl-CoA mutase • Defect in transport or synthesis of the methylmalonyl-CoA mutase cofactor, adenosyl-cobalamin • Deficiency of the enzyme methylmalonyl-CoA epimerase

Diagnosis

For this review, the term "isolated methylmalonic acidemia" refers to a group of inborn errors of metabolism associated with elevated methylmalonic acid (MMA) concentration in the blood and urine that result from the failure to convert methylmalonyl-CoA into succinyl-CoA during propionyl-CoA metabolism in the

mitochondrial matrix, without hyperhomocysteinemia or homocystinuria, hypomethioninemia, or variations in other metabolites, such as malonic acid (Figure 1).

Isolated methylmalonic acidemia results from any ONE of the following:

- Complete (*mut*^{0} enzymatic subtype) deficiency or partial (*mut*$^-$ enzymatic subtype) deficiency of the enzyme methylmalonyl-CoA mutase encoded by *MMUT*
- Diminished synthesis of its cofactor 5'-deoxyadenosylcobalamin, associated with *cblA*, *cblB*, or *cblD*-MMA complementation groups caused by biallelic pathogenic variants in *MMAA, MMAB,* or *MMADHC*, respectively
- Deficient activity of methylmalonyl-CoA epimerase encoded by *MCEE*

Note that the following disorders are NOT included in the scope of this *GeneReview* (see Differential Diagnosis):

- Methylmalonic acidemia associated with succinyl-CoA ligase deficiency, caused by mutation of *SUCLA2* or *SUCLG1*, is discussed in *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria and *SUCLG1*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria, respectively.
- Methylmalonic acidemia associated with hyperhomocysteinemia or homocystinuria caused by defects in other steps of intracellular cobalamin metabolism is discussed in Disorders of Intracellular Cobalamin Metabolism.
- Rare defects, such as combined malonic and methylmalonic acidemia, methylmalonate semialdehyde dehydrogenase deficiency, transcobalamin receptor deficiency, and combined methylmalonic acidemia and homocysteinemia, *cblX* type, are discussed briefly under Differential Diagnosis.

Suggestive Findings

Because the presenting signs and symptoms of isolated methylmalonic acidemia are nonspecific, suggestive findings can include the following:

- In neonates: lethargy, vomiting, hypotonia, hypothermia, respiratory distress, severe ketoacidosis, hyperammonemia, neutropenia, and thrombocytopenia

  Note: In states with an expanded newborn screening program, isolated methylmalonic acidemia can be diagnosed in well-appearing newborns prior to an episode of acute decompensation.

- In older infants and children: failure to thrive, renal syndromes and hypotonia, intellectual disability or other acute (basal ganglia stroke) and chronic neurologic symptoms

In patients with partial *mut* enzymatic deficiency, *cblA*, or *cblB,* suggestive findings at various ages can include the following:

- An attenuated MMA phenotype [Lerner-Ellis et al 2004, Lerner-Ellis et al 2006, Hörster et al 2007]
- Isolated renal tubular acidosis or chronic renal failure [Dudley et al 1998, Coman et al 2006]
- Metabolic stroke of the basal ganglia [Korf et al 1986, Heidenreich et al 1988]
- Catastrophic/lethal ketoacidosis following an intercurrent illness [Ciani et al 2000]

Establishing the Diagnosis

An overview of the process of intracellular propionate and cobalamin metabolism is depicted in Figure 1. A flowchart for the work up of a person with elevated methylmalonic acid in urine and/or plasma is provided in Figure 2, a modified algorithm that includes the consideration of methylmalonyl-CoA epimerase deficiency, succinyl-CoA ligase deficiency, and other rare defects in the pathway, as well as the use of in vivo vitamin B_{12} responsiveness in the work up of an individual who is found to have methylmalonic acidemia at any age.

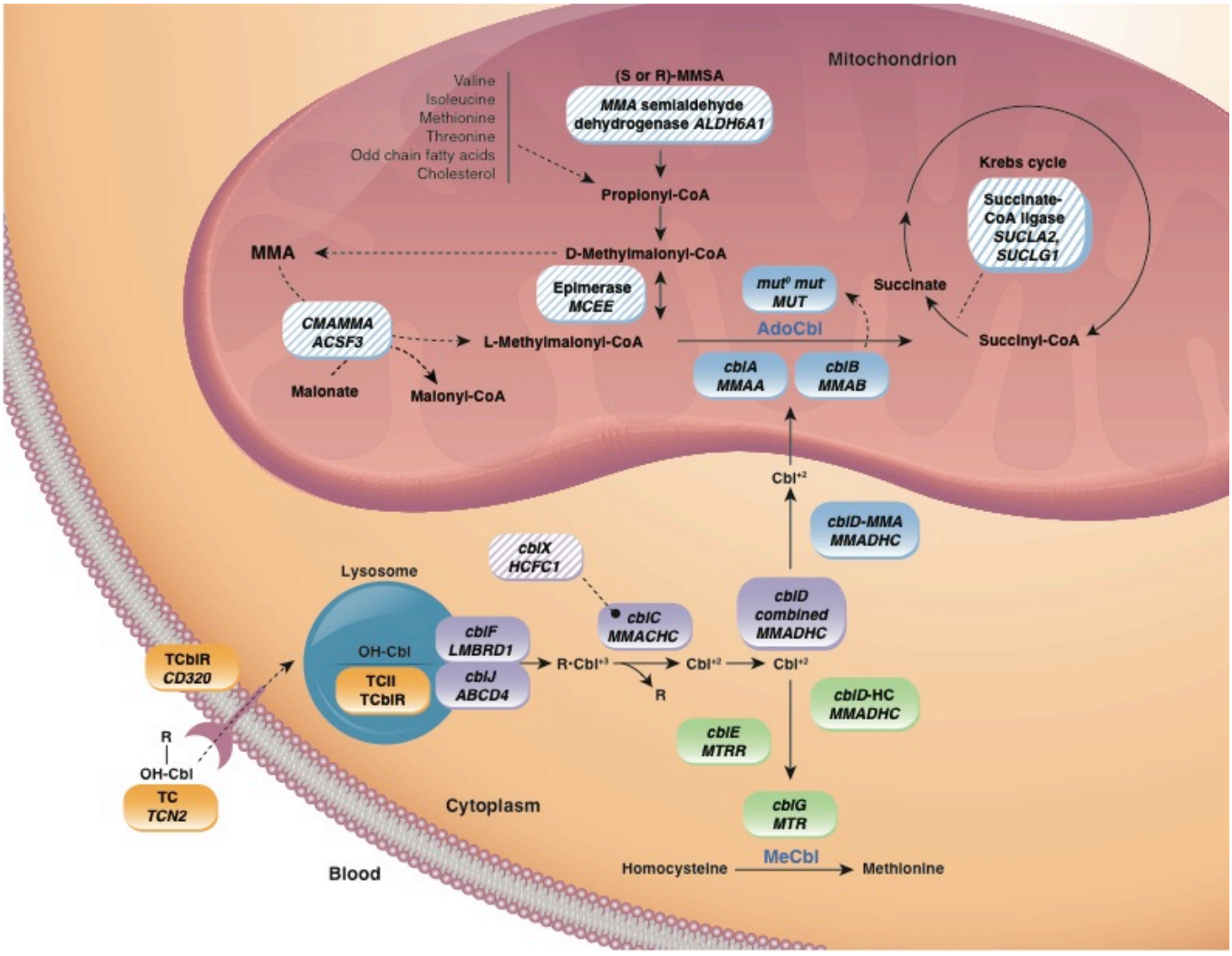


Figure 1. Major pathway of the conversion of propionyl-CoA into succinyl-CoA. The biotin-dependent enzyme propionyl-CoA carboxylase converts propionyl-CoA into D-methylmalonyl-CoA, which is then racemized into L-methylmalonyl-CoA and isomerized into succinyl-CoA, a Krebs cycle intermediate. The L-methylmalonyl-CoA mutase reaction requires adenosylcobalamin, an activated form of vitamin B_{12}. The pathway of cellular processing of cobalamin (OH-Cbl) in the formation of adenosyl- (AdoCbl) and methylcobalamin (MeCbl) is depicted. Adenosyl-cobalamin is the cofactor of the methylmalonyl-CoA mutase reaction; methylcobalamin is the cofactor of the methionine synthase reaction.

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 cofactor deficiencies causing elevations in MMA and homocysteine (purple). Note: The light blue striped boxes indicate the enzymes (and the genes encoding them) that are deficient in different disorders in which isolated methylmalonic acidemia occurs: epimerase deficiency (*MCEE*) and succinate-CoA ligase deficiency (*SUCLA2/SUCLG1*), combined malonic and methylmalonic acidemia (*ACSF3*), and methylmalonyl-semialdehyde dehydrogenase deficiency (*ALDH6A1*). The light purple striped box indicates *cblX* deficiency (*HCFC1*), the only X-linked disorder in this pathway.

The genes (and the enzymatic subtypes) associated with isolated methylmalonic acidemia included in this *GeneReview* are:

MMUT (*mut*^{0}, *mut*$^-$)

MMAA (*cblA*)

MMAB (*cblB*)

MMADHC (*cblD* variant 2)

MCEE

Isolated methylmalonic acidemia caused by mutation of *SUCLA2* and *SUCLG1* is discussed in *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Mild Methylmalonic Aciduria and *SUCLG1*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria, respectively.

Step 1. In a proband with suspicious clinical findings and a positive urine organic acid screen for MMA, laboratory testing that can help to establish the diagnosis includes: glucose, electrolytes, ammonia, blood gas, lactate, CBC, and urine ketones, plasma MMA, tHcy, and B_{12} levels, plasma amino acids, and acylcarnitine profile. Relevant findings:

- High plasma and urine MMA with normal B_{12}, tHcy, and methionine levels
- Elevated propionylcarnitine (C3)
- High anion gap metabolic acidosis in arterial or venous blood gas testing and huge quantities of ketone bodies and lactate in the urine
- Hyperammonemia
- Hyperglycinemia
- Lactic acidosis
- CBC showing neutropenia, thrombocytopenia, anemia

Step 2. In newborns found to have elevation of propionylcarnitine (C3) by expanded newborn screening and in individuals at high genetic risk for the disorder (e.g., sibs of a proband), the first priority is to establish the presence of significantly elevated methylmalonic acid, which is best done by urine organic acid analysis (by GC/MS) and plasma acylcarnitine profile (by TMS). Note: At the same time, obtaining levels of plasma MMA, amino acids, plasma homocysteine, and serum vitamin B_{12} (in both the newborn and the mother) helps further differentiate the cause of methylmalonic acidemia should that be confirmed (see **Step 3**).

In addition to elevated methylmalonic acid, the following biochemical findings may also be seen:

- Presence of 3-hydroxypropionate, 2-methylcitrate, and tiglylglycine detected on GC/MS analysis of urine
- Elevated plasma concentration of glycine on plasma amino acid analysis
- Elevated plasma concentration of propionylcarnitine (C3) and variable elevations in C4-dicarboxylic or methylmalonic/succinylcarnitine (C4DC) measured by TMS

Step 3. Once elevation of methylmalonic acidemia and aciduria have been established, a normal plasma homocysteine and vitamin B_{12} level can help differentiate isolated MMA from other disorders (see Figure 2, left two columns). Note: Although plasma and/or urine methylmalonic acid concentration can be precisely quantitated (Table 1), this is generally not needed immediately for diagnostic purposes.

Table 1. Methylmalonic Acid Concentration in Phenotypes and Enzymatic Subtypes of Methylmalonic Acidemia

Methylmalonic Acidemia Phenotype/ Enzymatic Subtype [1]	Methylmalonic Acid Concentration	
	Urine [2]	Blood
Infantile/non-B_{12}-responsive [3] *mut*^{0}, *mut*$^-$, *cblB*	1,000-10,000 mmol/mol Cr	100-1,000 µmol/L
B_{12}-responsive [3] *cblA*, *cblD*-MMA *cblB*, *mut*$^-$ (rare)	Tens - hundreds mmol/mol Cr	5-100 µmol/L
"Benign"/adult methylmalonic acidemia [4]	10-100 mmol/mol Cr	100 µmol/L
MCEE deficiency [5]	50-1,500 mmol/mol Cr	7 µmol/L

Table 1. continued from previous page.

Methylmalonic Acidemia Phenotype/ Enzymatic Subtype [1]	Methylmalonic Acid Concentration	
	Urine [2]	Blood
Normal [6]	<4 mmol/mol Cr [7]	<0.27 µmol/L [7]

MCEE = methylmalonyl-CoA epimerase; ND = not determined

1. Biochemical parameters and clinical phenotype are not always concordant, partly because renal function can influence plasma MMA concentration [Kruszka et al 2013, Manoli et al 2013]. Patients in kidney failure show massive elevations in plasma MMA that can exceed 5,000 µmol/L.

2. In some centers, analysis of urine by ^{1}H-NMR spectroscopy can also be used to demonstrate increased methylmalonate concentration [Iles et al 1986].

3. Approximate numbers, representing the author's experience with >80 individuals with the B_{12}-responsive and non-B_{12}-responsive types

4. From Giorgio et al [1976] and converted into µmol/L for plasma concentration

5. Bikker et al [2006], Dobson et al [2006], Nagarajan et al [2005], Gradinger et al [2007]

6. From Gradinger et al [2007]

7. Normal values have not been exclusively derived from children or neonates. Some laboratories report urine 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.

Step 4. In vivo responsiveness to vitamin B_{12} should be determined in all affected individuals. No standard regimen has been documented. When stable, affected individuals can be given 1.0 mg of hydroxocobalamin (OH-Cbl) (see Note) intramuscularly or intravenously every day for one to two weeks followed by assessment of production of MMA and related metabolites (3-OH-propionic, 2-methylcitrate) by serial urine organic acid analyses and/or measurement of plasma concentrations of MMA, propionylcarnitine, and homocysteine. A significant (>50%) reduction in metabolite production and plasma concentration(s) is considered to indicate responsiveness [Fowler et al 2008, Kruszka et al 2013]. In vivo response was reported in all individuals with *cblA* and only rare individuals with *cblB* [Hörster et al 2007].

Note: Hydroxocobalamin (not cyanocobalamin) is the preferred preparation for treatment of methylmalonic acidemia; thus, if the in vivo response to intramuscular hydroxocobalamin is questionable or borderline, vitamin B_{12} administration should be continued and a skin biopsy should be obtained to isolate fibroblasts to assess B_{12} responsiveness by ^{14}C propionate incorporation in vitro.

Step 5. Molecular genetic testing (Table 2) can be used to establish the diagnosis of isolated MMA by identifying biallelic pathogenic variants in one of the five genes (*MMUT, MMAA*, *MMAB*, *MCEE*, and *MMADHC*) and confirming carrier status in the parents. In addition, the enzymatic subtype of isolated methylmalonic acidemia is mostly determined by molecular genetic testing due to the limited access to, cost of, and invasive nature of cellular biochemical testing.

Molecular testing approaches can include the following:

- **Tiered single-gene testing.** Because the phenotype of isolated methylmalonic acidemia can be identical regardless of the mutated gene, molecular genetic testing can be performed in the following order:
  1. *UT* and *MMAB* in vitamin B_{12}-non-responsive individuals
  2. *MMAA* in vitamin B_{12}-responsive individuals
  3. *MCEE* and *MMADHC* testing if results of testing of the first three genes (*MMUT,MMAB,* and *MMAA)* are unrevealing

  Note: For all genes, sequence analysis is performed first, followed by deletion/duplication analysis if only one pathogenic variant has been detected.

- **Use of a multigene panel** that includes these five genes and other genes in the metabolic pathway (see Differential Diagnosis). Note: 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.

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

Table 2. Molecular Genetic Testing Used in Isolated Methylmalonic Acidemia

Gene [1]	Proportion of Isolated MMA Attributed to Mutation of This Gene [2]	Proportion of Variants Detected by This Method	
		Sequence analysis [3]	Deletion/duplication analysis [4]
MMUT	60% (78% *mut*^{0} enzymatic subtype, 22% *mut*$^-$ enzymatic subtype)	96% [5, 6]	Unknown, none reported
MMAA	25%	97% [7]	Unknown, none reported
MMAB	12%	98% [8]	Unknown, none reported
MCEE	Unknown	4 probands/families [9]	Unknown, none reported
MMADHC	Unknown	6 probands/families [10]	Unknown, none reported

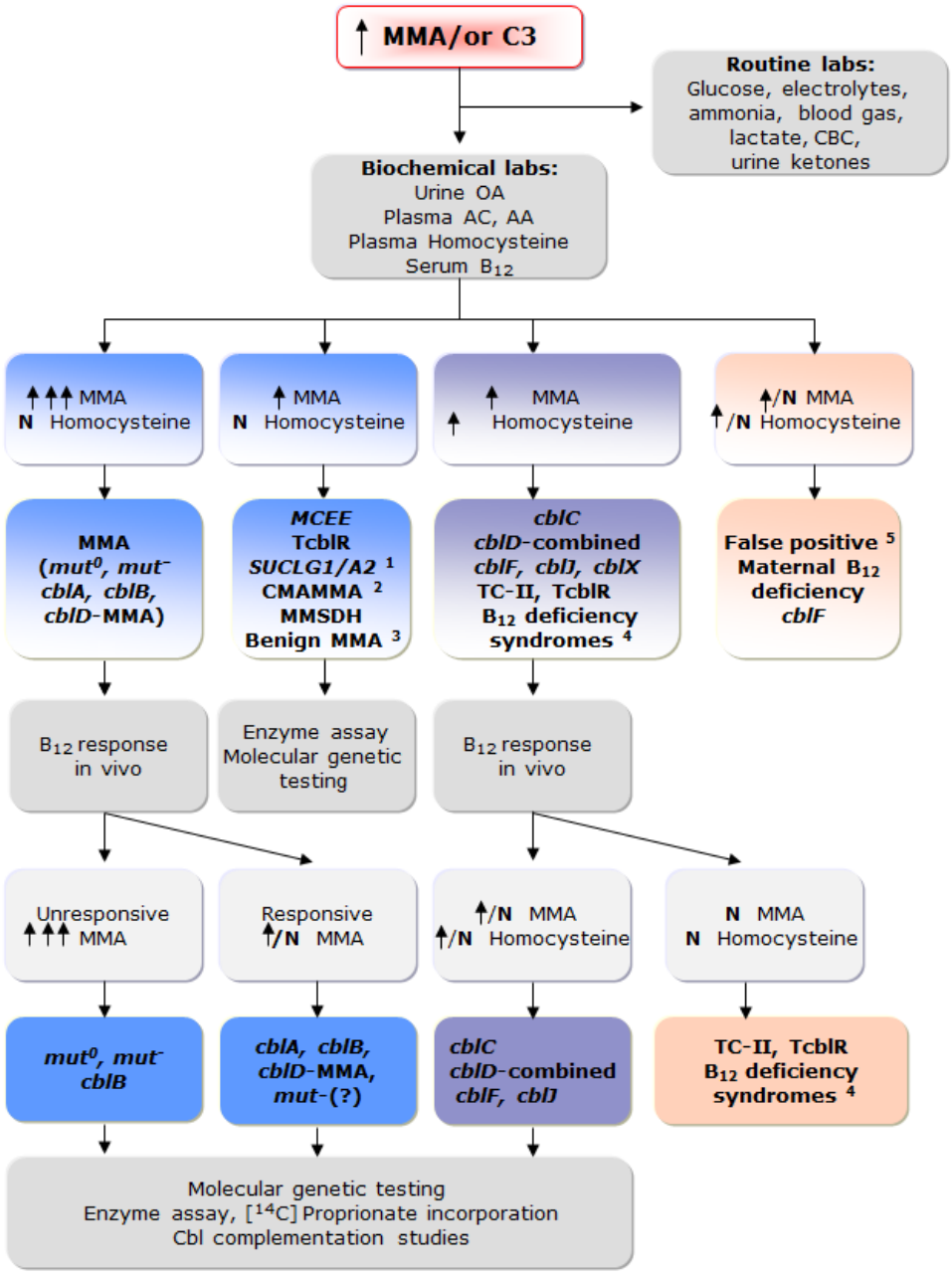
1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. Based on Worgan et al [2006] and Hörster et al [2007]
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
5. Worgan et al [2006]
6. For individuals of Hispanic descent, targeted exon 2 analysis for the *MMUT* c.322C>T pathogenic variant may be considered.
7. Lerner-Ellis et al [2004]
8. Lerner-Ellis et al [2006]
9. Gradinger et al [2007]
10. Stucki et al [2012]

Step 6. Cellular biochemical testing on skin fibroblasts is the gold standard for determining the MMA subtype and B_{12} responsiveness in vitro and is useful when the above testing methods fail to provide a firm diagnosis to guide management. For details of biochemical testing, click here (pdf).

Newborn Screening

In the past decade, the implementation of tandem mass spectrometry (MS/MS) in newborn screening (NBS) by many states in the US and countries worldwide has identified newborns with methylmalonic acidemia through detection of elevated concentration of blood propionylcarnitine (C3), a metabolite increased in the blood of individuals with methylmalonic acidemia and the related disorder, propionic acidemia [Chace et al 2001, Therrell et al 2014].

Note: Since propionylcarnitine is one of the analytes most frequently responsible for false positive results, ratios including C3/C2, C3/C0, C3/C16, and new biomarkers such as C16:1OH are recommended in combination with high blood concentration of C3 as decision criteria for "positive" testing in newborn screening acylcarnitine analysis by MS/MS for methylmalonic acidemia and propionic acidemia [Lindner et al 2008].



MMA = methylmalonic acid; C3 = propionylcarnitine; OA = organic acids; AC = acylcarnitine; AA = amino acids; CBC = complete blood count; *mut* = mutase; *cbl* = cobalamin; TC-II = transcobalamin II

Footnotes:

1. Succinate ligase deficiency (caused by biallelic pathogenic variants in *SUCLA2* or *SUCLG1*) presents with lactic acidosis; excess 2-methylcitric, 3-hydroxyproprionic acid, and 3-hydroxyisovaleric acid in the urine; and excess C3-propionylcarnitine and C4-dicarboxylic carnitine (C4DC) in the blood and/or urine.
2. CMAMMA presents with normal C3 in the plasma acylcarnitine profile and elevated methylmalonic and malonic acid in the plasma or urine.
3. Methylmalonyl-semialdehyde-dehydrogenase deficiency (MMASDH), "benign MMA," and other ill-defined syndromes should be considered (see **Differential Diagnosis**).
4. B_{12} deficiency syndromes include intrinsic factor deficiency, Imerslund-Gräsbeck syndrome, and others.
5. In rare instances metabolites can be normal in affected individuals.

Figure 2. An algorithm of conditions to be considered in the differential diagnosis of elevated serum or urine methylmalonic acid detected either during the follow up of an increased propionylcarnitine (C3) on newborn screening or a positive urine organic acid screen in a symptomatic individual. The algorithm includes disorders that can present after the newborn period.

Second-tier testing of 3-hydroxypropionic, methylmalonic, and/or 2-methylcitric acids could be used to reduce the costs and anxiety associated with false positive results [Matern et al 2007, la Marca et al 2008].

- If C3 and C5OH are increased, the diagnosis of holocarboxylase deficiency and/or biotinidase deficiency needs to be considered.
- Elevated C4-dicarboxylic acylcarnitine (C4DC) is a marker for both methylmalonylcarnitine and succinylcarnitine, and can indicate methylmalonic aciduria associated with succinyl-CoA ligase deficiency [Fowler et al 2008, Morava et al 2009].

Recommended action (ACT) sheet and confirmatory algorithm describing the basic necessary steps involved in follow up of an infant who has screened positive are available; see American College of Medical Genetics (ACMG) Newborn Screening ACT Sheet and National Academy of Clinical Biochemistry Guidelines (pdf) [Dietzen et al 2009].

Clinical Characteristics

Clinical Description

The phenotypes of isolated methylmalonic acidemia described below that are associated with the *mut*^{0} enzymatic subtype, *mut*$^-$ enzymatic subtype, *cblA*, *cblB*, and *cblD*-MMA share clinical presentations and a natural history characterized by periods of relative health and intermittent metabolic decompensation, usually associated with intercurrent infections and stress [Zwickler et al 2012]. Each such decompensation can be life-threatening. Of note, the natural history of isolated methylmalonic acidemia requires further study, particularly with respect to medical complications including renal disease, the effect of solid organ transplantation, and molecular pathology.

Infantile/non-B_{12}-responsive phenotype (*mut*^{0} enzymatic subtype, *cblB*). The most common phenotype of isolated methylmalonic acidemia presents during infancy. Infants are normal at birth but rapidly develop lethargy, vomiting, and dehydration on initiation of protein-containing feeds. At presentation, they exhibit hepatomegaly, hypotonia, and in many, hyperammonemic encephalopathy. Laboratory findings typically show a severe, high anion-gap metabolic acidosis, ketosis and ketonuria (highly abnormal in neonates and strongly suggestive of an organic aciduria), hyperammonemia, and hyperglycinemia [Matsui et al 1983, Kölker et al 2015a]. Dialysis may be needed especially if hyperammonemia is significant and persistent.

Thrombocytopenia and neutropenia, suggestive of neonatal sepsis, can be seen.

The catastrophic neonatal presentation of isolated methylmalonic acidemia can result in death, despite aggressive intervention. Infants with the B_{12}-responsive *mut*$^-$ enzymatic subtype or *cblA* can also present with an acute neonatal crisis.

Partially deficient or B_{12}-responsive phenotypes (*mut*$^-$ enzymatic subtype, *cblA*, *cblB* [rare], *cblD*-MMA). This intermediate phenotype of isolated methylmalonic acidemia can occur in the first few months or years of life. Affected infants can exhibit feeding problems (typically anorexia and vomiting), failure to thrive, hypotonia, and developmental delay. Some have protein aversion and/or clinical symptoms of vomiting and lethargy after protein intake.

Until the diagnosis is established and treatment initiated these infants are at risk for a catastrophic decompensation (like that in neonates) [Shapira et al 1991, Lerner-Ellis et al 2004, Lerner-Ellis et al 2006, Hörster et al 2007].

During such an episode of metabolic decompensation, the child may die despite intensive intervention if prompt treatment specific for MMA is not instituted and the symptoms are misdiagnosed as, for example, diabetic ketoacidosis [Ciani et al 2000].

Before the onset of newborn screening, infants with the subtypes *cblA* or *mut*$^{-}$ would present with a devastating injury in the basal ganglia (more specifically lacunar infarcts in the globus pallidus) resulting in a debilitating movement disorder [Korf et al 1986, Heidenreich et al 1988].

Patients with partial *mut* enzymatic deficiency, *cblA*, or *cblB* can also present with isolated renal tubular acidosis or chronic renal failure [Dudley et al 1998, Coman et al 2006].

Methylmalonyl-CoA epimerase deficiency. Pathogenic variants in *MCEE* are a very rare cause of persistent moderate methylmalonic aciduria. Findings in infants/children with mutation of *MCEE* have ranged from complete absence of symptoms to severe metabolic acidosis with increased MMA and 2-methylcitrate and ketones in the urine at initial presentation [Dobson et al 2006, Gradinger et al 2007]. Symptoms include ataxia, dysarthria, hypotonia, mild spastic paraparesis, and seizures; however, many affected persons were from consanguineous unions — including the first identified individual, who also had a DOPA-responsive dystonia resulting from homozygous pathogenic variants of *SPR*, the gene encoding sepiapterin reductase [Bikker et al 2006].

Secondary complications. Despite increased knowledge about isolated methylmalonic acidemia and possibly earlier symptomatic diagnosis, isolated methylmalonic acidemia continues to be associated with substantial morbidity and mortality [de Baulny et al 2005, Dionisi-Vici et al 2006, Kölker et al 2015b] that correlates with the underlying defect [Hörster et al 2007]. Individuals with the *mut*^{0} enzymatic subtype and the *cblB* subtype have a higher rate of mortality and neurologic complications than those with the *mut*$^{-}$ enzymatic subtype and *cblA*.

The major secondary complications include:

- **Intellectual disability.** Intellectual disability may or may not be present even in those with severe disease. In a retrospective, survey-based review, about 50% of individuals with the *mut*^{0} enzymatic subtype and 25% of those with the *cblA*/*cblB* enzymatic subtype had an IQ below 80 and significant neurologic impairment [Baumgarter & Viardot 1995].

  In another study about 50% of individuals with *mut*^{0}, 85% with *mut*$^{-}$, 48% with *cblA*, and 70% with *cblB* had an IQ above 90 [Hörster et al 2007].

  In a recent natural history study, the mean FSIQ of all individuals with isolated methylmalonic acidemia (n = 37) was 85.0 ± 20.68, which is in the low average range (80 ≤ IQ ≤89). Individuals with *cblA* (n = 7), *cblB* (n = 6), and *mut* diagnosed prenatally or by newborn screening (n = 3) had mean FSIQs in the average range (90 ≤ IQ ≤109). The age of disease onset, the presence of severe hyperammonemia at diagnosis, and a history of seizures were associated with more severe impairments [O'Shea et al 2012].

- **Tubulointerstitial nephritis with progressive impairment of renal function.** All individuals with isolated methylmalonic acidemia, even those who are mildly affected or who have received a liver allograft [Nyhan et al 2002], are at risk of developing renal insufficiency [Walter et al 1989, Kruszka et al 2013]. End-stage renal disease (ESRD) was common in individuals with the *mut*^{0} enzymatic subtype (61%) and the *cblB* (66%) enzymatic subtype, and occurred less frequently in those with the *cblA* (21%) enzymatic subtype [Hörster et al 2007].

  Secondary mitochondrial dysfunction rather than direct nephrotoxicity of methylmalonic acid is hypothesized. Cell-specific mitochondrial pathology primarily in the proximal tubules, associated with cytochrome *c* oxidase deficiency and increased markers of oxidative stress in the urine and plasma, have been shown in human and mouse studies [Atkuri et al 2009, Mc Guire et al 2009, Manoli et al 2013, Zsengellér et al 2014].

An acute renal syndrome, seen in the setting of metabolic decompensation, may also exist [Stokke et al 1967] and requires further clinical delineation. Moreover, renal tubular dysfunction presenting as a decrease in urine concentrating ability and acidification, hyporeninemic hypoaldosteronism, tubular acidosis type 4, and hyperkalemia have been reported in a number of affected individuals, and are supported by murine studies [Walter et al 1989, D'Angio et al 1991, Pela et al 2006, Manoli et al 2013].

- **Neurologic findings.** Some individuals develop a "metabolic stroke" or infarction of the basal ganglia (characteristically the globus pallidus externa) during acute metabolic decompensation, which can produce an incapacitating movement disorder [Korf et al 1986, Heidenreich et al 1988]. The reported incidence in different cohorts is 17%-30% [Baumgarter & Viardot 1995, Hörster et al 2007]. Distinct segments of the globus pallidus (and sometimes the substrantia nigra in the cerebral peduncles) are affected, suggesting a non-uniform, cell-specific sensitivity to the mechanism of infarct [Baker et al 2015].

  Delayed myelination, incomplete opercularization, subcortical white matter changes, and brain stem and cerebellar changes have been described [Harting et al 2008, Radmanesh et al 2008].

  Of note, individuals who have undergone liver and/or kidney transplantation can develop acute lesions without overt metabolic decompensation, suggesting that the enzyme deficiency in the brain remains unchanged and trapping of toxic metabolites in the CNS compartment can lead to injury despite other systemic benefits of the transplantation [Chakrapani et al 2002, Kaplan et al 2006, Vernon et al 2014].

- **Pancreatitis.** The incidence of pancreatitis in isolated methylmalonic acidemia is unknown, but it is a well-recognized complication [Kahler et al 1994]. It can occur acutely or chronically. Pancreatitis may be under-recognized because it can manifest nonspecifically with vomiting and abdominal pain.

- **Growth failure.** Growth failure is frequent and multifactorial. It is the result of severe chronic illness and perhaps relative protein malnutrition that is complicated further by chronic renal failure. Many infants are less than three standard deviations below normal for both length and weight.

  Some children have documented growth hormone (GH) deficiency, but response to GH therapy may vary (see Management).

- **Functional immune impairment.** This results in an increased susceptibility to severe infections, particularly by fungal and gram-negative organisms [Oberholzer et al 1967, Wong et al 1992].

- **Bone marrow failure.** During episodes of metabolic decompensation patients can exhibit pancytopenia, with bone marrow hypoplasia and/or dysplasia that most frequently revert to normal with supportive care.

- **Optic nerve atrophy.** Late-onset optic atrophy associated with acute visual loss, resembling the presentation of the mitochondrial disorder Leber hereditary optic neuropathy (LHON), has been reported in isolated methylmalonic acidemia [Wasserstein et al 1999, Williams et al 2009, Pinar-Sueiro et al 2010, Traber et al 2011], as well as in propionic acidemia [Williams et al 2009, Martinez Alvarez et al 2016].

- **Hepatoblastoma**. Isolated instances of hepatoblastoma have been reported in the native or donor liver in individuals with *mut* MMA; however, the overall incidence of cancer in these patients is unknown [Cosson et al 2008, Chan et al 2015]

Survival in isolated methylmalonic acidemia has improved over time [Matsui et al 1983, van der Meer et al 1994, Baumgarter & Viardot 1995, Nicolaides et al 1998, Kölker et al 2015a].

In those with the *mut*^{0} enzymatic subtype, survival at age one year has improved from 65% in the 1970s to more than 90% in the 1990s; five-year survival has improved from 33% in the 1970s to more than 80% in the 1990s.

In one series, the median age of death of those with the *mut*^{0} enzymatic subtype was compared over time: 100% died at a median age of 1.6 years in the 1970s, 50% died at a median age of 7.6 years in the 1980s, and 20% died

at a median age of 2.2 years in the 1990s. Overall mortality was about 50% for those with the *mut*^{0} enzymatic subtype (median age of death 2 years) as compared to 50% for the *cblB* enzymatic subtype (median age of death 2.9 years), 40% for the *mut*$^-$ enzymatic subtype (median age of death 4.5 years), and about 5% for the *cblA* enzymatic subtype (1 death at 14 days) [Hörster et al 2007].

The effect of early organ transplantation on overall survival has not been systematically studied.

Effect of newborn screening. The limited number of infants detected by newborn screening (NBS) and the short duration of their follow up do not allow conclusions regarding the effect of NBS on the long-term outcome of methylmalonic acidemia [Leonard et al 2003, Dionisi-Vici et al 2006]. Moreover, it must be emphasized that a significant number of infants with the *mut*^{0} enzymatic subtype may present clinically before the NBS results become available. Limited observations in sibs with the *cblA* enzymatic subtype suggest that the IQs of the individuals treated from the newborn period were significantly better than those of their older affected sibs who were diagnosed after the onset of symptoms [Hörster et al 2007].

Of note, before the availability of newborn screening individuals with *cblA* and some with *cblB* often manifested in early childhood with encephalopathy and globus pallidus injury, which in theory could have been avoided if they had been detected by NBS and treated before symptoms appeared.

Genotype-Phenotype Correlations

Precise genotype-phenotype correlations are difficult to determine since most affected individuals are compound heterozygotes.

Homozygosity for the p.Asn219Tyr *MMUT* pathogenic variant is frequently associated with severe mutase deficiency (i.e., the *mut*^{0} enzymatic subtype) [Acquaviva et al 2001]. p.Arg108Cys, which is also associated with a *mut*^{0} enzymatic subtype, is more common in individuals of Hispanic descent [Worgan et al 2006].

Homozygosity for the p.Gly717Val *MMUT* pathogenic variant, which is associated with the *mut*$^-$ enzymatic subtype [Worgan et al 2006], is more common in individuals of African descent.

The clinical phenotype depends on a number of factors that cannot be accurately predicted by the genotype, including whole-body enzyme activity, in vivo responsiveness to cobalamin, environmental factors, and perhaps the efficiency and activation of alternative propionyl-CoA disposal pathways. It is possible that better understanding of clinical correlations in isolated methylmalonic acidemia could be achieved by estimating the amount of whole-body residual metabolic capacity based on stable isotope studies [Leonard 1997].

Prevalence

Several studies have estimated the birth prevalence of isolated methylmalonic acidemia [Sniderman et al 1999]. Urine screening for isolated methylmalonic acidemia in Quebec identified "symptomatic methylmalonic aciduria" in approximately 1:80,000 newborns screened [Sniderman et al 1999], which approximates the observation of Chace et al [2001] of ten cases of isolated methylmalonic acidemia identified in a sample of 908,543 newborns screened by mass spectrometry in the US.

In Japan, the birth prevalence may be as high as 1:50,000 [Shigematsu et al 2002].

It appears that the prevalence of isolated methylmalonic acidemia may therefore fall between 1:50,000 and 1:100,000; confirmation, however, would require larger studies.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *MMUT*, *MMAA*, *MMAB*, or *MCEE*.

One individual with *mut*^{0} MMA and insulin-dependent diabetes mellitus caused by paternal isodisomy of chromosome 6 has been reported [Abramowicz et al 1994].

MMADHC biallelic pathogenic variants are also associated with *cblD*-combined (methylmalonic acidemia/aciduria and hyperhomocysteinemia/homocystinuria) and *cblD*-homocystinuria (hyperhomocysteinemia/homocystinuria), which are discussed in Disorders of Intracellular Cobalamin Metabolism.

Differential Diagnosis

Atypical methylmalonic acidemia is associated with increased, usually mild urinary excretion of methylmalonate. Rare defects, such as succinate-CoA ligase deficiency, combined malonic and methylmalonic aciduria, *cblX* deficiency, transcobalamin receptor defect, and methylmalonate semialdehyde dehydrogenase deficiency can cause methylmalonic acidemia/aciduria, although most patients will have additional biochemical findings.

The only known X-linked disorder related to the intracellular cobalamin metabolic pathway is *cblX* deficiency, caused by mutation of *HCFC1* and associated with combined methylmalonic acidemia and hyperhomocysteinemia, severe intellectual disability, complex seizures, and other neurologic findings. *cblX* deficiency is a recently described disorder with unknown spectrum, but likely to include X-linked developmental delay either without biochemical abnormalities or with isolated elevations of methylmalonic acid.

"Benign" methylmalonic acidemia. Newborn screening in the province of Quebec identified infants with mild-to-moderate urinary methylmalonic acid excretion. Follow up revealed resolution in more than 50% of children, as well as an apparently benign, persistent, low-moderate methylmalonic acidemia in some [Ledley et al 1984, Sniderman et al 1999]. Additional individuals with a relatively benign type of methylmalonic acidemia have been reported [Coulombe et al 1981, Martens et al 2002]. Caution is necessary in follow up of these individuals as some can belong to a mild *mut*$^{-}$ enzymatic subtype and carry a significant risk for acute metabolic crisis [Shapira et al 1991].

The long-term outcome and clinical phenotype of these individuals awaits further description. Of note, a subgroup had a combined biochemical phenotype of malonic and methylmalonic acidemia and therefore likely represents combined malonic and methylmalonic (CMAMMA) caused by ACSF3 deficiency.

Combined malonic and methylmalonic aciduria (CMAMMA) caused by ACSF3 deficiency. Patients with CMAMMA show high malonic acid (MA) and methylmalonic acid (MMA) levels in their urine or plasma, with MMA excretion typically being higher than MA excretion (MMA/MA >5). Because C3 (propionylcarnitine) is not elevated, infants with CMAMMA are not detected by newborn screening based on a dried blood spot acylcarnitine analysis.

The phenotypic spectrum is broad, ranging from completely asymptomatic individuals to adults with neurologic syndromes (seizures, memory problems, psychiatric disease, and/or cognitive decline) or children with a wide range of manifestations, such as coma, ketoacidosis, hypoglycemia, failure to thrive, elevated transaminases, microcephaly, dystonia, axial hypotonia, and/or developmental delay. The full natural history of this disorder remains to be elucidated.

Mutation of *ACSF3* (encoding a methylmalonyl- and malonyl-CoA synthetase that produces the first substrate, malonyl-CoA, for intra-mitochondrial fatty acid synthesis) is causative [Alfares et al 2011, Sloan et al 2011].

Methylmalonate semialdehyde dehydrogenase deficiency (MMSDH). In the last enzymatic steps in the valine degradation pathway, 3-hydroxyisobutyrate dehydrogenase converts 3-hydroxyisobutyrate to (S)-methylmalonic semialdehyde (MMSA), and methylmalonate semialdehyde dehydrogenase (MMSDH) converts (S)-methylmalonic semialdehyde to propionyl-CoA). Of note, the same enzyme catalyzes the oxidative

decarboxylation of the (R)-methylmalonic semialdehyde enantiomer generated from thymine metabolism to propionyl-CoA.

A small number of patients with pathogenic variants in *ALDH6A1*, which encodes the MMSDH enzyme, have had extremely variable biochemical phenotypes: some have displayed 3-hydroxyisobutyric aciduria [Chambliss et al 2000, Sass et al 2012], while others have also displayed transient methylmalonic acidemia/aciduria [Marcadier et al 2013]. They have also had extremely variable clinical phenotypes, including severe intellectual impairment associated with significant brain myelination defects.

Transcobalamin receptor defect (TCblR/CD320). The index case and four additional affected individuals were asymptomatic newborns identified on NBS with an elevated C3 and elevated C3/C2 ratio. They also had increased plasma and urine MMA and normal serum vitamin B_{12} levels; two of the four were stated to have elevated homocysteine.

In the index case, biochemical abnormalities normalized with a single hydroxocobalamin injection and remained normal for nine months [Quadros et al 2010]. Fibroblasts showed decreased uptake of transcobalamin.

A *CD320* pathogenic variant was also identified in a boy age seven weeks with retinal artery occlusions born to consanguineous parents [Karth et al 2012]. All reported affected individuals are homozygous for NM_016579.3:c.262_264del (p.Glu88del). Polymorphisms in the TCblR have been associated with increased risk for neural tube defects in an Irish cohort [Pangilinan et al 2010].

Combined methylmalonic acidemia and hyperhomocysteinemia/homocystinuria. Disorders that interfere with the intracellular metabolism of cobalamin can cause a perturbation in the synthesis of adenosylcobalamin and/or methylcobalamin. However, these conditions are usually accompanied by clinically significant hyperhomocysteinemia. The following are included in this group of disorders:

- Cobalamin C deficiency (*cblC*) is perhaps the most common inborn error of intracellular cobalamin metabolism. Individuals with this disorder almost always have increased plasma concentrations of homocysteine and methylmalonic acid, with low levels of methionine, and historically a highly variable age of onset. Affected individuals frequently have developmental delay and develop a pigmentary retinopathy and a "bull's eye" maculopathy. *cblC* is caused by biallelic pathogenic variants in *MMACHC* which encodes a protein involved in the processing and trafficking of intracellular cobalamin. The pathogenic variant c.271dupA;p.Arg91LysfsTer14 accounts for approximately 40% of alleles [Lerner-Ellis et al 2006].
- Deficiencies of complementation groups *cblD*, *cblF*, and *cblJ* are extremely rare autosomal recessive disorders.
    - ***cblD* deficiency** is biochemically heterogeneous [Suormala et al 2004]. Coelho et al [2008] determined that mutation of *MMADHC* (previously known as *C2ORF25)* is responsible for *cblD* and identified genotype/phenotype correlations. *MMADHC* has multiple translation initiation codons (ATG), and encodes distant polypeptides. The location and nature of the pathogenic variant therefore determines whether a patient will display methylmalonic aciduria, homocystinuria, or both metabolic abnormalities:
        - The *cblD*-methylmalonic aciduria subtype (*cblD*-MMA) (previously known as *cblD*-variant 2) is caused by pathogenic nonsense and frame-shifting variants in exons 3 and 4;
        - The *cblD*-homocystinuria subtype (previously known as *cblD* variant 1) is caused by pathogenic missense variants in exons 6-8;
        - A *cblD*-combined subtype (*cblD*) that features elevations of both MMA and homocysteine is caused by frame-shifting pathogenic variants in exon 5, exon 8, and intron 7.

Note: Individuals with complementation *cblD*-homocystinuria [Coelho et al 2008], *cblE* (methionine synthase reductase), and *cblG* (methionine synthase) abnormalities do not have methylmalonic acidemia, but rather isolated homocystinuria/hyperhomocysteinemia caused by impaired methyl-cobalamin synthesis.

- ***cblF* deficiency** is caused by mutation of *LMBRD1*, which encodes a putative lysosomal cobalamin exporter [Rutsch et al 2009], affecting the synthesis of the cofactors for the enzyme methylmalonyl-CoA mutase (encoded by *MMUT*) and the enzyme methyltetrahydrofolate: homocysteine methyltransferase, also known as methionine synthase (MS) (encoded by *MTR*).
- ***cblJ* deficiency** caused by mutation of *ABCD4*, an ATP-binding cassette (ABC) transporter that affects the lysosomal release of Cbl into the cytoplasm similar to cblF and presents with hypotonia, lethargy, poor feeding, bone marrow suppression, macrocytic anemia, and congenital heart disease in some patients [Coelho et al 2012].

  It is important to note that several individuals with *cblF or cblJ* can have decreased serum vitamin B_{12} levels, suggesting a role for the lysosome in intestinal uptake of ingested cobalamin.
- ***cblX* deficiency** is caused by mutation of the X-linked gene *HCFC1*, a transcriptional co-regulator affecting the expression of *MMACHC*. All described affected males to date had MMAemia and MMAuria, and most, when studied, displayed combined hyperhomocystinuria and methylmalonic acidemia. The clinical phenotype features intractable epilepsy and profound neurocognitive impairment without the specific bull's-eye maculopathy of *cblC* deficiency [Yu et al 2013]; however, the phenotype needs further characterization.

Vitamin B_{12} deficiency. Individuals with vitamin B_{12} deficiency can have methylmalonic acidemia and homocystinuria.

Maternal B_{12} deficiency can produce a methylmalonic acidemia syndrome in an infant that ranges from severe encephalopathy to elevated serum concentration of propionylcarnitine (C3) detected by newborn screening [Chace et al 2001]. This metabolic abnormality can occur in a breastfed infant of a vegan mother, in an infant born to a mother with subclinical pernicious anemia [Marble et al 2008], and in infants born to mothers who have had gastric surgery [Grange & Finlay 1994, Celiker & Chawla 2009]. The mother does not necessarily have a very low serum concentration of vitamin B_{12}. Intramuscular vitamin B_{12} replacement therapy to normalize vitamin B_{12} serum concentration reverses the metabolic abnormality.

Mitochondrial encephalomyopathy with elevated methylmalonic acid. Mild methylmalonic aciduria has been described in succinate-ligase alpha subunit (caused by biallelic *SUCLG1* pathogenic variants) and succinate-ligase ADP-forming beta subunit (caused by biallelic *SUCLA2* pathogenic variants) associated with mitochondrial DNA depletion presenting with severe lactic acidosis and encephalomyopathy.

Succinyl-CoA ligase (SUCL) catalyzes the reversible conversion of succinyl-CoA and ADP or GDP to succinate and ATP or GTP, and comprises an α subunit encoded by *SUCLG1* and a β subunit encoded by either *SUCLA2* or *SUCLG2*.

Biallelic pathogenic variants in *SUCLG1* result in a severe phenotype, associated with lactic acidosis and early death in the first week of life. (See *SUCLG1*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria.)

Biallelic *SUCLA2* pathogenic variants are associated with hypotonia, muscle atrophy presenting around ages three to six months (with mtDNA depletion, complex I, III, and IV deficiency in the muscle), hyperkinesia, seizures, severe hearing impairment, and growth failure. Patients develop a Leigh syndrome-like disorder, cortical and basal ganglia atrophy, and dystonia. Some affected individuals die in infancy; others have survived

into their 20s. (See *SUCLA2*-Related mtDNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria.)

Methylmalonic aciduria ranges from 10 to 200 mmol/mol creatinine in these individuals and is accompanied by raised plasma concentrations of lactate, methylcitrate, 3-hydroxyproprionic and 3-hydroxyisovaleric acid, proprionylcarnitine, and C4-dicarboxylic carnitine (C4DC) [Elpeleg et al 2005, Carrozzo et al 2007, Ostergaard et al 2007, Morava et al 2009].

Reye-like syndrome. A Reye-like syndrome of hepatomegaly and obtundation in the face of a mild intercurrent infection can be seen as an unrecognized presentation of a number of inborn errors of metabolism, including isolated methylmalonic acidemia [Chang et al 2000].

Other entities that can display methylmalonic acidemia despite normal methylmalonyl-CoA mutase enzyme activity include the following:

- "Atypical" methylmalonic acidemia with progressive neurodegenerative disease, microcephaly, and cataracts (2 sibs) [Strømme et al 1995] or with a mitochondrial depletion syndrome/complex IV deficiency and combined propionic and methylmalonic acidemia (1 person) [Yano et al 2003]. These cases have similarities with the phenotype caused by mutation of *SUCLA2*.
- Benign methylmalonic acidemia with distal renal tubular acidosis (one sibship) [Dudley et al 1998]
- Malonyl-CoA decarboxylase deficiency, usually associated with combined methylmalonic and malonic aciduria, with significantly higher malonic versus methylmalonic acid levels [Brown et al 1984]
- Isolated methylmalonic aciduria and normal plasma concentrations of methylmalonic acidemia (2 families) [Sewell et al 1996, Martens et al 2002]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with isolated methylmalonic acidemia, the following evaluations are recommended:

- A serum chemistry panel (Na^+, K^+, CI^-, glucose, urea, creatinine, bicarbonate, AST, ALT, alkaline phosphatase, bilirubin [T/U], triglycerides, and cholesterol); complete blood count with differential; arterial or venous blood gas; plasma ammonium and lactic acid concentration; formal urinalysis and ketone measurement; quantitative plasma amino acids; and urine organic acid analysis by gas chromatography and mass spectrometry (GC-MS)
- If possible, measurement of plasma concentrations of methylmalonic acid, methylcitrate, free and total carnitine, and an acylcarnitine profile to document propionylcarnitine (C3 species) concentration
- Measurement of serum vitamin B_{12} concentration to determine if a nutritional deficiency is present in the patient and possibly the mother (in newborns)
- Biochemical genetics consultation

Treatment of Manifestations

No consensus exists among various metabolic centers regarding treatment of acute and chronic complications of methylmalonic acidemia. Recent guidelines developed by professionals across 12 European countries and the US based on rigorous literature evaluation and expert group meetings outline the current management recommendations and areas for further research [Baumgartner et al 2014].

Stabilization of critically ill individuals

- Volume replacement with isotonic solutions

- All IV solutions should contain glucose, preferably D_{10} or $D_{12.5}$. If hyperglycemia develops, an insulin infusion may be needed.
- The total base deficit should be followed serially with repeat electrolyte and venous or arterial blood gas measurements and corrected by hydration and bicarbonate replacement, as needed [Baumgartner et al 2014]. Adequate kcals must be delivered. Central or peripheral total parenteral nutrition (TPN), which typically contains glucose and amino acids, and in some instances, lipids, may be required. Total protein administration is usually completely withdrawn for no more than 24-48 hours and reinstated gradually depending on the patient's acid-base balance and remaining test values, including ammonia, lactic acid, and plasma amino acids among others.
- Lipid infusions must be used with caution for the risk of pancreatitis.
- Carnitine may be administered intravenously at 50-100 mg/kg/d bid-qid.
- Urine output and serum sodium and potassium concentration need to be monitored.
- Dietary protein should be reintroduced enterally as soon as is feasible given the clinical scenario and may need to be further augmented with TPN. Nasograstric or orogastric feeding should be strongly considered so that enteral feedings can be reintroduced without delay.
- N-carbamylglutamate (NCG, Carbaglu®) may be considered in the event of hyperammonemia. NCG allosterically activates CPS1 (carbamyl phosphate synthetase 1), the first step of the urea cycle. It has been effective in normalizing the blood ammonia concentration in patients with a deficiency of NAGS (N-acetylglutamate synthase) and can also benefit some patients with propionic and possibly methylmalonic acidemia [Tuchman et al 2008, Ah Mew et al 2010].
- Hemodialysis or hemofiltration may be required in the event of treatment failure (uncontrollable acidosis and/or hyperammonemia).

A letter given to the family to present to emergency department physicians that specifies the recommended acute management protocol should be standard of care.

Medic Alert® bracelets and emergency treatment protocols outlining fluid and electrolyte therapy should be available for all affected individuals.

Other

Aside from episodes of critical illness, patients with intercurrent illness such as viral infection or those undergoing surgery for various reasons should have aggressive fluid, metabolic, and nutritional management.

Specialists in physiatry, physical therapy, and occupational therapy can help address the complex challenges faced by patients and families, maximize functionality, and improve quality of life [Ktena et al 2015b].

Special considerations regarding choices of anesthetic agents in this patient population may apply [Ktena et al 2015a, Ruzkova et al 2015].

Most individuals require "sick day" management regimens, which typically consist of reducing or eliminating protein intake and increasing fluids and glucose to ensure delivery of adequate calories and to arrest lipolysis. Immediate hospitalization is usually required if signs suggest intercurrent infection.

Although all of the treatments discussed above may be needed in fragile individuals, they still may not prevent death, the severe sequelae of metabolic decompensation (e.g., metabolic stroke of the basal ganglia), or renal disease. The correlation and identification of treatment patterns and outcomes is needed to develop more effective management protocols for individuals with isolated methylmalonic acidemia.

Many affected individuals require gastrostomy/gastrojejunostomy tube feeding because of anorexia and vomiting to ensure caloric and fluid intake and improve growth.

Bone marrow failure during episodes of metabolic decompensation on rare occasion requires granulocyte-colony stimulating factor (GCSF).

Anemia is an expected complication of chronic renal failure and is treated with erythropoietin and eventually renal transplantation [Inoue et al 1981, Guerra-Moreno et al 2003, MacFarland & Hartung 2015].

Some children have had documented growth hormone (GH) deficiency; however, because response to GH therapy may vary, diet and GH replacement dose need to be carefully adjusted [Bain et al 1995, Al-Owain et al 2004]. The indications for GH replacement therapy and the response to GH replacement in treated individuals require further investigation.

Prevention of Primary Manifestations

Dietary Management

Nutrition. After stabilization, nutritional management is critical. This typically includes instituting a low-protein, high-calorie diet. When available, accurate assessment of resting energy expenditure can guide dietary and caloric prescriptions and eliminate overfeeding [Hauser et al 2011].

Natural protein needs to be carefully titrated to allow for normal growth, while avoiding an excessive propiogenic amino acid load (isoleucine, valine, methionine, and threonine) into the pathway. Adjustment of dietary whole (complete)-protein intake, based on clinical and laboratory findings, is needed throughout life for these patients.

The FAO/WHO/UNU report [2007] recommended that safe levels per age group should be the aim for natural protein intake [Baumgartner et al 2014]; however, the individual protein amount prescribed will depend on growth parameters, metabolic stability, stage of renal failure, and other factors. A propiogenic amino acid-deficient formula (e.g., Propimex®-1/2,› XMTVI-1/2, OA-1/2) and protein-free formula (e.g., Pro-Phree®, Duocal®) are given to some individuals to provide extra fluid and calories. As the infant grows, the total protein load is slowly reduced, based on growth, plasma amino acid concentrations, and plasma and urine methylmalonic acid concentrations.

Of note, in patients with low protein tolerance, severe restriction of propiogenic amino acid precursors (isoleucine, valine, methionine, and threonine) can produce a nutritional deficiency state. Furthermore, an iatrogenic essential amino acid deficiency can be induced by the relatively high leucine intake through the MMA formulas that can negatively affect long-term growth and possibly other outcomes [Manoli et al 2016b]. Medical foods should be used in moderation with the relative intake of natural protein to propiogenic amino-acid deficient formula not exceeding a ratio of 1:1. Isolated valine or isoleucine supplementation should be avoided.

These dietary guidelines do not apply for patients with *CblC* deficiency, a separate disorder in the pathway [Manoli et al 2016a].

Hydroxocobalamin injections. 1.0-mg injections every day to every other day are usually required in individuals who are vitamin B_{12} responsive. The regimen of B_{12} injections needs to be individually adjusted according to the patient's age and, possibly, weight.

Carnitine can be given at a dose of 50-100 mg/kg/day, up to approximately 300 mg/kg/day. As a dietary supplement, carnitine may replace the free carnitine pool and enhance the conjugation and excretion of propionylcarnitine. The contribution of propionylcarnitine excretion to the total propionate load is, however, small. The relief of intracellular CoA accretion may be the mechanism by which carnitine supplementation benefits some individuals.

Antibiotics. A variety of antibiotic regimens to reduce the production of propionate from gut flora can be used:

- Oral neomycin, 250 mg by mouth 4x/day, was the original regimen reported by Snyderman et al [1972].
- Metronidazole at 10-15 mg/kg/day has also been reported.

The intervals at which affected individuals are treated may vary, but a typical course is one week to ten days of treatment per one to three months.

Although oral antibiotics reduce the propionate load that derives from gut flora in affected individuals, chronic antibiotic therapy is not innocuous; it introduces the risk of repopulation of the individual with resistant flora. This could pose a serious infectious threat and could be especially dangerous to individuals with isolated methylmalonic acidemia, since most deaths are related to metabolic decompensation, often precipitated by infection.

Response to antibiotic administration should be determined in treated persons by demonstrating either a decrease in whole body output of methylmalonic acid on antibiotic therapy by a timed urine collection or a decrease in the plasma methylmalonic acid concentration compared to the baseline value for that individual.

Rotating antibiotic regimens may be considered in some persons.

Antioxidants. One individual with isolated methylmalonic acidemia who was documented to be glutathione deficient after a severe metabolic crisis responded to ascorbate therapy [Treacy et al 1996]. Several recent studies document increased oxidative stress, glutathione depletion, and specific respiratory chain complex deficiencies in persons with the *mut*^{0} enzymatic subtype with methylmalonic acidemia [Schwab et al 2006, Atkuri et al 2009, Chandler et al 2009, de Keyzer et al 2009, Manoli et al 2013], suggesting a potential benefit of treatment with antioxidants or other mitochondria-targeted therapies in these patients.

A regimen of coenzyme Q_{10} and vitamin E has been shown to prevent progression of acute optic nerve involvement in a patient with MMA [Pinar-Sueiro et al 2010] and was shown to attenuate the progression of kidney disease in a mouse model of MMA [Manoli et al 2013].

Organ Transplantation

The number of individuals who have undergone liver and/or kidney transplantation, the detailed effects on the underlying metabolic disorder, and the overall outcome in those undergoing this procedure have yet to be determined [Sloan et al 2015]. Inclusion of enzymatic and genotype information in case series of transplanted patients will allow better comparisons of the outcomes and genotype-phenotype associations that could inform decisions about the indication and timing of transplantation in individual cases.

Liver transplantation. Because most of the metabolic conversion of propionate occurs in the liver, replacing the liver could contribute enough enzyme activity to avert metabolic decompensation. Liver transplantation has been shown to largely protect against metabolic instability but is not curative, and individuals with isolated MMA remain at risk for long-term complications of MMA including renal disease, basal ganglia injury, and neurologic complications [Chakrapani et al 2002, Nyhan et al 2002, Kaplan et al 2006, Vernon et al 2014]. To date, more than 35 individuals with isolated methylmalonic acidemia have undergone living donor or cadaveric, orthotopic, or partial liver transplantation or combined liver-kidney transplantation (>20 patients) [van't Hoff et al 1998, van't Hoff, McKiernan et al 1999, Kayler et al 2002, Nyhan et al 2002, Hsui et al 2003, Kasahara et al 2006, Morioka et al 2007, McGuire et al 2011, Niemi et al 2015].

- The underlying biochemical parameters and the frequency of metabolic decompensation improved significantly in individuals undergoing liver transplantation despite persistent metabolic abnormalities [Nyhan et al 2002, Kaplan et al 2006, Niemi et al 2015], probably as a result of increased extrahepatorenal methylmalonic acid production primarily from the skeletal muscle [Chandler et al 2007].

- Following liver transplantation, some individuals continued to have progressive renal failure as well as high CSF concentrations of methylmalonic acid [Nyhan et al 2002, Kaplan et al 2006].
    - Neurologic complications post-transplant, including globus pallidus injuries [Chakrapani et al 2002, Cosson et al 2008, McGuire et al 2011] suggest that adequate protein restriction and supportive care should be continued after the transplantation.

      Earlier transplantation particularly for individuals with *mut*^{0} (who are very fragile) is gaining support as surgery techniques and outcomes improve [Niemi et al 2015, Spada et al 2015]. The choice of the kind and timing of the indicated transplant procedure remains challenging for families and treating physicians [Sloan et al 2015]. In the long term, the details regarding development of renal disease, optic nerve atrophy, and neurologic complications will be most important.

Kidney transplantation. Some individuals have received only renal allografts [Van Calcar et al 1998, Lubrano et al 2001, Coman et al 2006, Cosson et al 2008, Clothier et al 2011].

One of the first reports on isolated renal transplantation in *mut*^{0} methylmalonic acidemia was claimed to provide enough enzyme activity to normalize methylmalonic acid excretion and allow for increased dietary protein tolerance; however, it was later determined that that patient had *cblA* deficiency and responded to vitamin B_{12}. Thus, this individual, who has a much milder case, is not representative of the outcomes of isolated renal transplantation in individuals with severe MMA subtypes (*mut*^{0} or *cblB*) [Lubrano et al 2001, Lubrano et al 2007, Lubrano et al 2013].

Elective kidney transplantation, even before the onset of renal disease, has been advocated as a form of "cell therapy" to help stabilize individuals with *mut*^{0} MMA [Brassier et al 2013]. However, one patient died after developing hepatoblastoma, neurologic deterioration accompanied by CSF lactic acidosis, and multiorgan failure; a second patient developed progressive neurologic symptoms; and two others developed metabolic decompensations post transplant. Long-term follow up is necessary to determine if this is a safe alternative to liver transplantation or liver-kidney transplantation, especially in persons with severe *mut*^{0} MMA.

Prevention of Secondary Complications

Frequent monitoring of plasma amino acids is necessary to avoid deficiencies of essential amino acids (particularly isoleucine, valine, and methionine) as a result of excessive protein restriction and the development of acrodermatitis-enteropathica-like cutaneous lesions in methylmalonic aciduria, as in other organic acidurias (glutaric aciduria-I) and amino acid disorders (maple syrup urine disease) [De Raeve et al 1994].

Low plasma amino acids can reflect low natural protein intake, imbalanced intake of branched chain amino acid from use of metabolic formulas, or effects of chronic acidosis on branched chain amino acid metabolism [Manoli et al 2016b].

Surveillance

During the first year of life, infants may need to be evaluated as frequently as every week. No guidelines regarding the recommended type or frequency of laboratory testing have been published.

The following should be monitored on a regular six-month to one-year basis or more frequently if the patient is unstable and requires frequent changes in management:

- Plasma amino acids
- Plasma and urine MMA levels
- Serum acylcarnitines and free and total carnitine levels
- Chemistry: Na+, K+, CI–, glucose, urea, creatinine, bicarbonate, AST, ALT, alkaline phosphatase, bilirubin (T/U), triglycerides, and cholesterol

- Liver, kidney, and bone health
- Bone marrow indices

Monitoring of kidney function periodically with creatinine, cystatin-C, and, if available, studies of glomerular filtration rate (GFR) (e.g., iohexol plasma decay), in addition to imaging of the kidneys, will allow for early referral to nephrology and appropriate timing of renal transplantation when needed [van't Hoff et al 1999, Kruszka et al 2013]. Combined equations based on creatinine and cystatin-C are expected to reflect more accurately the kidney function in this patient population [Schwartz et al 2009].

Regular ophthalmology and audiology evaluations to screen for optic nerve thinning/pallor and hearing loss [Authors, unpublished observations] are recommended.

Agents/Circumstances to Avoid

The following should be avoided:

- Fasting. During acute illness, intake of adequate calories is necessary to arrest/prevent decompensation.
- Stress
- Increased dietary protein
- Supplementation with the individual propiogenic amino acids valine and isoleucine, as they directly increase the toxic metabolite load in patients with disordered propionate oxidation [Nyhan et al 1973, Hauser et al 2011, Manoli et al 2016b]

Evaluation of Relatives at Risk

Depending on the genotype and phenotype of the proband, evaluation of sibs at risk should be performed using biochemical testing with treatment instituted as soon as possible if a sib is affected. Molecular genetic testing (if the pathogenic variants in the family are known) or cellular enzymology typically can further confirm the results of biochemical studies. Prenatal diagnosis of at-risk sibs may allow for prompt treatment of affected newborns at the time of delivery.

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

Pregnancy Management

Oral and intramuscular vitamin B_{12} has been administered to women pregnant with a fetus with vitamin B_{12}-responsive MMA, resulting in decreased maternal MMA urine output [Ampola et al 1975, van der Meer et al 1990]. Despite these observations, maternal vitamin B_{12} supplementation for isolated MMA needs further study.

Despite high maternal MMA levels, fetal growth and development were normal for all reported pregnancies of women with MMA [Wasserstein et al 1999, Deodato et al 2002].

Complications observed in pregnancies of women with MMA can include acute decompensation or hyperammonemia, deterioration of renal function, and obstetric complications including preeclampsia, preterm delivery, and cesarean section [Raval et al 2015].

Therapies Under Investigation

Carefully designed clinical studies are required to evaluate the efficacy of antioxidant regimens in patients with MMA.

Gene therapy. Preliminary studies in human-derived hepatocytes and animal models of methylmalonic acidemia suggest a potential benefit of gene therapy [Chandler & Venditti 2008, Carrillo-Carrasco et al 2010, Chandler & Venditti 2010, Chandler & Venditti 2012, Sénac et al 2012]. The effect of that therapeutic approach

in patients and especially on the long-term complications of methylmalonic acidemia remains to be elucidated in appropriate clinical studies.

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Isolated methylmalonic acidemia (complete or partial deficiency of the enzyme methylmalonyl-CoA mutase; defect in transport or synthesis of the methylmalonyl-CoA mutase cofactor, adenosyl-cobalamin; and deficiency of the enzyme methylmalonyl-CoA epimerase) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC* pathogenic variant.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each full 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.

Offspring of a proband. The offspring of an individual with isolated methylmalonic acidemia are obligate heterozygotes (carriers) for a pathogenic variant in *MMUT*, *MMAA*, *MMAB, MCEE*, or *MMADHC*.

Other family members. Each full sib of the proband's parents is at a 50% risk of being a carrier for a pathogenic variant in *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC*.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC* pathogenic variants in the family.

Methods other than molecular genetic testing are not reliable for carrier testing.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing 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 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Prenatal testing for pregnancies at 25% risk for isolated methylmalonic acidemia is possible by:

- **Molecular genetic testing** if the *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC* pathogenic variants have been identified in an affected family member.

  Note: Due to the limited availability and longer turnaround time for cellular biochemical assays, the preferred method for prenatal diagnosis is molecular genetic testing.

- The use of fetal cell-free DNA in maternal plasma [Gu et al 2014].

- **Biochemical testing.** Historically both amniotic fluid measurements and cellular biochemical assays were used:

  - Amniotic fluid analysis of methylmalonic acid. The absolute positive predictive and negative predictive values of metabolite analysis only have yet to be determined. Elevation of metabolites below the range of affected fetuses can indicate a heterozygous status and should therefore be followed by confirmatory testing in cell studies.

  - Incorporation of ^{14}C propionate and complementation assay of cultured fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Studies on chorionic villus cells can be false negative and should be followed up by studies on cultured amniocytes [Morel et al 2005]. Confirmation of the diagnosis by the same assay in an affected family member must be obtained before prenatal testing can be performed.

    Note: For pregnant women not interested in pursuing prenatal diagnosis by amniocentesis or CVS, a urine organic acid test may be helpful since women carrying an affected fetus have been shown to excrete MMA in their urine [Ampola et al 1975, van der Meer et al 1990].

Preimplantation genetic diagnosis (PGD) may be an option for families in which the *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC* pathogenic variants have been identified.

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.

- **My46 Trait Profile**

  Methylmalonic acidemia

- **National Library of Medicine Genetics Home Reference**

  Methylmalonic acidemia

- **Save Babies Through Screening Foundation, Inc.**
  P. O. Box 42197
  Cincinnati OH 45242
  Phone: 888-454-3383
  Email: email@savebabies.org
  www.savebabies.org
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Fax: 866-539-4060 (toll-free)
  Email: kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml

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. Isolated Methylmalonic Acidemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MCEE	2p13.3	Methylmalonyl-CoA epimerase, mitochondrial	ZJU-CGGM Database (MCEE)	MCEE	MCEE
MMAA	4q31.21	Methylmalonic aciduria type A protein, mitochondrial	ZJU-CGGM Database (MMAA)	MMAA	MMAA
MMAB	12q24.11	Corrinoid adenosyltransferase	MMAB @ LOVD ZJU-CGGM Database (MMAB)	MMAB	MMAB
MMADHC	2q23.2	Methylmalonic aciduria and homocystinuria type D protein, mitochondrial	MMADHC @ LOVD ZJU-CGGM Database (MMADHC)	MMADHC	MMADHC
MMUT	6p12.3	Methylmalonyl-CoA mutase, mitochondrial	ZJU-CGGM Database (MUT)	MMUT	MMUT

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 Isolated Methylmalonic Acidemia (View All in OMIM)

251000	METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-CoA MUTASE DEFICIENCY
251100	METHYLMALONIC ACIDURIA, cblA TYPE
251110	METHYLMALONIC ACIDURIA, cblB TYPE

Table B. continued from previous page.

251120	METHYLMALONYL-CoA EPIMERASE DEFICIENCY
277410	METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE; MAHCD
607481	MMAA GENE; MMAA
607568	MMAB GENE; MMAB
608419	METHYLMALONYL-CoA EPIMERASE; MCEE
609058	METHYLMALONYL-CoA MUTASE; MUT
611935	MMADHC GENE; MMADHC

MMAA

Gene structure. *MMAA* comprises seven exons; the first is non-coding [Dobson et al 2002b]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 20 pathogenic variants have been described, including missense, nonsense, and splicing variants, deletions, and insertions [Dobson et al 2002a, Lerner-Ellis et al 2004, Yang et al 2004, Merinero et al 2008].

Table 3. *MMAA* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.64C>T	p.Arg22Ter	NM_172250.1 NP_758454.1
c.161G>A	p.Trp54Ter	
c.266T>C	p.Leu89Pro	
c.283C>T	p.Gln95Ter	
c.358C>T	p.Gln120Ter	
c.397C>T	p.Gln133Ter	
c.433C>T [1]	p.Arg145Ter [1]	
c.503delC [2]	p.Thr168MetfsTer9 [2]	
c.562G>C	p.Gly188Arg	
c.650T>A	p.Leu217Ter	
c.653G>A	p.Gly218Glu	
c.733+1G>A	--	
c.988C>T	p.Arg330Ter	
c.1076G>A	p.Arg359Gln	
c.592_595delACTG	p.Thr198SerfsTer6	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. The most common pathogenic variant identified; accounts for 43% of mutated alleles identified in one large study [Lerner-Ellis et al 2004]. This variant resides on a common haplotype and has also been seen in Spanish individuals [Martínez et al 2005].
2. In Japan, a common pathogenic deletion, c.503delC, has been observed [Yang et al 2004].

Normal gene product. The gene is predicted to encode a protein of 418 amino acids. The predicted gene product possesses a mitochondrial leader sequence and appears to belong to the ArgK protein subfamily of G3E GTPases [Leipe et al 2002]. While this protein was originally proposed to function in cobalamin entry into the mitochondria [Dobson et al 2002a], it was recently characterized as a metallochaperone GTPase that acts to protect the methylmalonyl-CoA mutase enzyme from oxidative inactivation during catalytic cycles and to facilitate cofactor (adenosylcobalamin) binding [Korotkova & Lidstrom 2004, Hubbard et al 2007].

Abnormal gene product. The precise biochemical function of the *MMAA* gene product is unknown but suspected to be similar to homologs in bacteria. Missense pathogenic variants appear to fall in evolutionarily conserved residues or consensus splice sites. Environmental, dietary, and (possibly) epigenetic modifiers may operate to define the phenotype in this condition, especially since individuals with homozygous pathogenic variants can exhibit disparate phenotypes [Lerner-Ellis et al 2004].

MMAB

Gene structure. *MMAB* comprises nine exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Several missense, nonsense/frameshift, and splice site pathogenic variants have been identified [Dobson et al 2002a, Yang et al 2004, Martínez et al 2005, Lerner-Ellis et al 2006]. More than half occurred in exon 7 [Lerner-Ellis et al 2006]:

Two individuals of African American descent with a late presentation (ages 3 and 8 years) both had three *MMAB* pathogenic variants: c.403G>A, c.571C>T, and c.656A>G [Lerner-Ellis et al 2006].

Table 4. *MMAB* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.287T>C	p.Ile96Thr	NM_052845.3 NP_443077.1
c.291-1G>A	--	
c.403G>A	p.Ala135Thr	
c.556C>T [1]	p.Arg186Trp [1]	
c.568C>T	p.Arg190Cys	
c.569G>A	p.Arg190His	
c.571C>T	p.Arg191Trp	
c.572G>A	p.Arg191Gln	
c.656A>G	p.Tyr219Cys	
c.197-1G>T	--	
c.700C>T	p.Gln234Ter	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. The most common pathogenic variant in a large series [Lerner-Ellis et al 2006], accounting for 33% of all alleles and seen exclusively among affected individuals of European descent, was associated with early onset of symptoms (age <1 year).

Normal gene product. The gene encodes the 250-amino-acid ATP-dependent mitochondrial protein cob(I)alamin adenosyltransferase, an enzyme that transfers the adenosyl group from ATP to Co[+1] balamin

[Leal et al 2003] to form adenosylcobalamin and shuttles this cofactor to the MUT enzyme. The crystal structure of a bacterial homologue has been determined [Saridakis et al 2004].

Abnormal gene product. The reported pathogenic missense variants fall into residues that are evolutionarily conserved [Dobson et al 2002b]. One pathogenic variant destroys a splice site [Dobson et al 2002b, Martínez et al 2005]. Several pathogenic variants have been biochemically characterized [Saridakis et al 2004].

MMUT

Gene structure. *MMUT* comprises 13 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 190 pathogenic variants have been described, including 103 (54%) missense; 27 (14%) nonsense; 18 (9%) splicing; 42 (22%) small insertions/deletions; and one large deletion of exon 12. The pathogenic variants are distributed throughout the entire coding sequence except for exon 1, which is untranslated [Crane et al 1992, Crane & Ledley 1994, Ogasawara et al 1994, Ledley & Rosenblatt 1997, Adjalla et al 1998, Fuchshuber et al 2000, Acquaviva et al 2001, Acquaviva et al 2005, Jung et al 2005, Martínez et al 2005, Worgan et al 2006, Gradinger et al 2007, Lempp et al 2007, Sakamoto et al 2007, Merinero et al 2008].

For a list of pathogenic variants that have been repeatedly identified in diverse populations, click here (pdf).

While some individuals are homozygous for a given pathogenic variant, most are compound heterozygotes. The phenomenon of interallelic complementation makes prediction of genotype/phenotype/enzyme activity difficult because some individuals who have two pathogenic variants can have a *mut*$^{-}$ enzymatic subtype in the compound state but a *mut*^{0} enzymatic subtype in the homozygous state [Janata et al 1997, Ledley & Rosenblatt 1997, Acquaviva et al 2005].

Persons with two truncating pathogenic variants usually have the *mut*^{0} enzymatic subtype.

Nonsense pathogenic variants have been described in the following codons: 7, 18, 23, 31, 54, 84, 117, 121, 135, 152, 156, 161, 224, 228, 284, 342, 403, 413, 414, 426, 429, 451, 467, 474, 494, 511, 544, 581, 589, 688, and 727.

Only a few of the frequently reported pathogenic variants are seen in homozygous form; p.Arg108Cys, p.Asn219Tyr, and p.Arg369His cause a *mut*^{0} enzymatic subtype when homozygous [Acquaviva et al 2001, Worgan et al 2006], while p.Gly717Val and p.Arg694Trp are associated with a *mut*$^{-}$ enzymatic subtype when homozygous [Worgan et al 2006].

One case of chromosome 6 paternal isodisomy resulting in *mut*^{0} MMA and insulin-dependent diabetes mellitus has been reported [Abramowicz et al 1994].

The *mut*$^{-}$ enzymatic subtype is known to be associated mostly, but not exclusively, with pathogenic variants in the cobalamin binding domain of the *mut* protein. The *mut*$^{-}$ enzymatic subtype pathogenic variant plays usually a dominant role when in compound heterozygote state with a *mut*^{0} enzymatic subtype pathogenic variant, given a OH-Cbl response in the in vitro assay [Lempp et al 2007].

Table 5. *MMUT* Pathogenic Missense Variants Discussed in This *GeneReview*

Mut Enzymatic Subtype (when Homozygous)	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
mut^{0}	c.19C>T	p.Gln7Ter	NM_000255.1 NP_000246.1
mut^{0}	c.52C>T	p.Gln18Ter	
mut^{0}	c.91C>T	p.Arg31Ter	
mut^{0}	c.278G>A	p.Arg93His	

Table 5. continued from previous page.

Mut Enzymatic Subtype (when Homozygous)	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
mut^0	c.284C>G	p.Pro95Arg	
mut^0	c.313T>C	p.Trp105Arg	
mut^0	c.322C>T [1]	p.Arg108Cys	
mut^0	c.521T>C	p.Phe174Ser	
mut^0	c.572C>A	p.Ala191Glu	
mut^0	c.607G>A	p.Gly203Arg	
mut^0	c.643G>A	p.Gly215Ser	
mut^0	c.655A>T	p.Asn219Tyr	
mut^0	c.935G>T	p.Gly312Val	
mut^0	c.1105C>T	p.Arg369Cys	
mut^0	c.1106G>A	p.Arg369His	
mut^0	c.1280G>A	p.Gly427Asp	
mut^0	c.1867G>A	p.Gly623Arg	
mut$^-$	c.299A>G	p.Tyr100Cys	
mut$^-$	c.691T>A	p.Tyr231Asn	
mut$^-$	c.1097A>G	p.Asn366Ser	
mut^0	c.1553T>C	p.Leu518Pro	
mut^0	c.1867G>A	p.Gly623Arg	
mut$^-$ [2]	c.2054T>G	p.Leu685Arg	
mut$^-$	c.2080C>T	p.Arg694Trp	
mut$^-$	c.2099T>A	p.Met700Lys	
mut$^-$	c.2150G>T	p.Gly717Val	
mut^0	c.2179C>T	p.Arg727Ter	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
mut^0 = *mut*^{0} enzymatic subtype
mut$^-$ = *mut*$^-$ enzymatic subtype
NA = not applicable
1. Observed in individuals of Hispanic descent.
2. Worgan et al [2006]

Normal gene product. Methylmalonyl-CoA mutase enzyme, a nuclear-encoded enzyme localized in the mitochondria, exists as a homodimer. The protein comprises 750 amino acids and has an N-terminal mitochondrial leader sequence (residues 1-32) that is removed by the mitochondrial importation and processing machinery. The mitochondrial leader signal is followed by the N-terminal extended segment (residues 33-87), which is involved in subunit interaction. The N-terminal barrel is the substrate-binding domain (residues 88-422) and is attached to the C-terminal adenosylcobalamin-binding domain (residues 578-750) by a long linker region (423-577). The protein contains a mole of adenosylcobalamin per mole of subunit and performs a

1, 2 rearrangement reaction, isomerizing L-methylmalonyl-CoA into succinyl-CoA [Fenton et al 2001]. The crystal structure of the human enzyme has been solved [Froese et al 2013].

Abnormal gene product. Only selected pathogenic variants have been studied enzymatically. The methylmalonyl-CoA mutase protein has several functional domains; pathogenic variants have been described in each.

A mitochondrial leader sequence lies at the amino terminus. Three nonsense pathogenic variants fall into this domain: p.Gln7Ter [Acquaviva et al 2005] and p.Gln18Ter and p.Arg31Ter [Worgan et al 2006]. One report noted that a truncated protein, likely translated from an internal AUG, arose from the p.Gln18Ter variant. This mutated protein is "mis-targeted" and not functional.

The putative dimerization domain of the enzyme subunits is adjacent to, but distinct from, the mitochondrial leader sequence.

The coenzyme-A binding pocket spans the middle of the second exon to the end of the sixth exon. Pathogenic variants that reside in this location, between amino acids 86 and 423, may destroy substrate binding and are predicted to impede catalysis by a variety of mechanisms. Some, such as p.Arg93His, can participate in interallelic complementation. The mechanism underlying this phenomenon is unclear [Worgan et al 2006].

A linker domain spanning residues 424-577 separates the C-terminal cobalamin-binding domain. Most of the pathogenic variants identified in this domain are splice site or nonsense changes and have been associated with *mut*^{0} enzymatic subtype of methylmalonic acidemia [Acquaviva et al 2005], while the only pathogenic missense variant (c.1553T>C) located in the middle of this segment affects a highly conserved amino acid [Worgan et al 2006].

Most of the mut^{-} enzymatic subtype pathogenic variants reside in the cobalamin binding domain, which is located between amino acids 578 and 750. Some pathogenic variants in this region can display purely K_m effects, as could be expected for a cofactor binding pathogenic variant, while others affect the K_m and V_{max} [Janata et al 1997]. This region also contains residues that can participate in interallelic complementation [Ledley & Rosenblatt 1997].

Detailed functional characterization is available for a small number of missense variants shown to cause (a) reduced protein level due to misfolding, (b) increased thermolability, (c) impaired enzyme activity, and (d) reduced cofactor response in substrate turnover [Forny et al 2014].

MCEE

Gene structure. *MCEE* comprises four exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. After the initial identification of two individuals with methylmalonic aciduria who were homozygous for the p.Arg47Ter pathogenic variant [Bikker et al 2006, Dobson et al 2006], an additional four of 229 individuals with elevated MMA of unknown etiology were reported to have a pathogenic variant in *MCEE* [Gradinger et al 2007]. Two persons with decreased [^{14}C]propionate incorporation were homozygous for the pathogenic nonsense variant c.139C>T in exon 2. Among 199 persons with normal [^{14}C]propionate incorporation, one was homozygous for the novel pathogenic missense variant c.178A>C in exon 2, and two were heterozygous for the novel pathogenic missense variant c.427C>T in exon 3.

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

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.139C>T	p.Arg47Ter	NM_032601.3 NP_115990.3
c.178A>C	p.Lys60Gln	
c.427C>T	p.Arg143Cys	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *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. *MCEE* encodes the 176-amino-acid enzyme methylmalonyl-CoA epimerase, which converts D-methylmalonyl-CoA to L-methylmalonyl-CoA.

Abnormal gene product. The pathogenic variants described to date are either missense or nonsense and are predicted to decrease or eliminate function.

MMADHC

Gene structure. *MMADHC* (formerly *C2orf25*) comprises eight exons and spans 18 kb [Coelho et al 2008]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in the C-terminal region (exons 3, 4, or 5) that cause a cblD variant 2 only phenotype (isolated methylmalonic aciduria) are listed in Table 7.

Pathogenic missense variants in the N-terminal region (exons 6 and 8) cause cblD variant 1 only phenotype (isolated homocystinuria), while truncating pathogenic variants in exons 5 and 8 and intron 7 cause the classic cblD phenotype (combined homocystinuria and methylmalonic aciduria) [Coelho et al 2008, Miousse et al 2009].

Table 7. Isolated MMA-Associated *MMADHC* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.57_64delCTCTTTAG	p.Ser20Ter (Cys19fsTer20)	NM_015702.2 NP_056517.1
c.60_61insAT (60insAT)	p.Leu21IlefsTer2 (Leu20fsTer21)	
c.133dupG	p.Arg45GlyfsTer15	
c.160C>T	p.Arg54Ter	
c.228dupG	p.Asn77GlufsTer5	
c.307_324dup	p.Leu103_Ser108dup	
c.455dupC	p.Cys153MetfsTer10 (Thr152fsTer162)	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *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 *MMADHC* product is predicted to have 296 amino acids with a calculated molecular mass of 32.8 kd. It shows homology to the putative ATPase component of a bacterial ABC transporter. There is an N-terminal mitochondrial leader sequence and a predicted B_{12} binding sequence [Coelho et al 2008] and MMADHC has been localized to both the cytoplasm and mitochondria in vitro [Mah et al 2013].

Abnormal gene product. The *cblD*-MMA mutated alleles (c.57_64delCTCTTTAG, c.60_61insAT, c.133dupG, c.160C>T, and c.228dupG) were expressed in an immortalized cell line from a patient with the *cblD*-combined phenotype and were able to rescue MeCbl synthesis [Stucki et al 2012]. This work showed that additional reinitiation codons at Met62 and Met116 result in shorter functional *cblD* proteins that lack the putative mitochondrial leader sequence but allow for normal methylcobalamin synthesis [Coelho et al 2008, Stucki et al 2012]. Each patient with *cblD*-MMA reported to date appears to have at least one pathogenic variant causing premature stop towards the N terminus of the enzyme.

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Chapter Notes

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