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Methylmalonic Acidemia

[*Methylmalonicaciduria , Methylmalonic Aciduria*]

Charles P Venditti, MD, PhD
Genetic Disease Research
National Human Genome Research Institute
National Institutes of Health
venditti@mail.nih.gov

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Summary

Disease characteristics. The phenotypic variants of methylmalonic acidemia share clinical presentations and periods of relative health and intermittent metabolic decompensations, usually associated with intercurrent infections and stress. The most common form of isolated methylmalonic acidemia, infantile/non-B_{12}-responsive phenotype, presents during infancy; infants are normal at birth, but develop lethargy, vomiting, dehydration, hepatomegaly, hypotonia, and encephalopathy. Laboratory findings show severe metabolic acidosis, ketosis and ketonuria, hyperammonemia, hyperglycinemia, thrombocytopenia, and neutropenia. The catastrophic neonatal presentation can result in death. An intermediate and also common form, the B_{12}-responsive phenotype, occurs in the first months or years of life; affected infants exhibit feeding problems, failure to thrive, hypotonia, and developmental delay, and sometimes have protein aversion and/or vomiting and lethargy after protein intake; they are also at risk for catastophic decompensation. A less common phenotype is seen in early childhood, when vomiting, dehydration, lethargy, or coma, often associated with respiratory distress, hepatomegaly, and seizures, occur and an episode of metabolic decompensation may follow. A "benign"/adult form of methylmalonic acidemia is associated with increased, albeit mild, urinary excretion of methylmalonate secondary to impaired activity of the enzyme methylmalonyl-CoA mutase; individuals seem stable but may have acute metabolic decompensation. Major secondary complications of methylmalonic acidemia include mental retardation, tubulointerstitial nephritis with progressive impairment of renal function, metabolic stroke and movement disorders, pancreatitis, growth failure, acrodermatitis-enteropathica-like lesions, and functional immune impairment.

Diagnosis/testing. Clinical diagnosis of methylmalonic acidemia relies upon specialized metabolic testing. Definitive diagnosis relies on analysis of organic acids in plasma and/or urine by gas-liquid chromatography and mass spectrometry; the concentration of methylmalonic acid is greatly increased in the plasma, urine, and CSF of affected individuals. Other non-specific findings on biochemical testing include 3-hydroxypropionate, methylcitrate, and tigylglycine detected in urine, huge quantities of ketone bodies and lactate detected in urine, increased concentration of glycine detected on plasma amino acid analysis, and elevated propionylcarnitine in the acylcarnitine ester profile. Establishing the specific phenotypic variant of methylmalonic acidemia requires studies on vitamin B_{12} responsiveness, C^{14} propionate tracer assays, complementation analysis, and cobalamin distribution assays. *MMAA*, *MMAB*, and *MUT* are the three genes known to be associated with isolated methylmalonic acidemia. Sequence analysis of *MUT*, *MMAA*, and *MMAB* is available clinically. The mutation detection rate in individuals known to have mutations in *MUT* through complementation studies is not yet known.

Management. An individual with methylmalonic acidemia who is critically ill must first be stabilized; the base deficit of the individual with metabolic acidosis is calculated and corrected using intravenous bicarbonate solutions containing glucose, and measurements of electrolytes, venous or arterial blood gases, urine output, and serum sodium concentrations are monitored. Insulin is infused if hyperglycemia develops. During times of illness, reducing or eliminating protein intake and increasing fluids and glucose ensure adequate calories and arrest lipolysis. Hospitalization is usually required if intercurrent infection is present. A gastrostomy tube is placed if anorexia and vomiting occur. Medic Alert™ bracelets and emergency treatment protocols outlining fluid and electrolyte therapy should be available for all affected individuals. Manifestations are prevented by dietary management (with a low-protein, high-calorie diet low in propiogenic amino acid precursors), hydroxycobalamin injections, carnitine supplementation, antibiotics such as neomycin or metronidizole to reduce propionate production from gut flora, and liver transplantation, which carries significant risks and indeterminate outcomes. Fasting and increased dietary protein should be avoided.

Genetic counseling. 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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Carrier testing using molecular genetic techniques is possible in families in which the mutations are known. Prenatal diagnosis for methylmalonic acidemia is possible by biochemical analysis. Prenatal diagnosis for families with *MUT*, *MMAB*, or *MMAA* mutations is clinically available using molecular genetic testing after the mutation in the proband has been identified.

Diagnosis

Clinical Diagnosis

The phenotype of isolated methylmalonic acidemia is nonspecific and can be shared by several related conditions. Definitive diagnosis relies upon specialized biochemical testing.

Testing

For this review, the term "isolated methylmalonic acidemia" refers to a group of inborn errors of metabolism associated with elevated methylmalonic acid (MMA) levels in the blood and urine without hyperhomocysteinemia or homocystinuria, resulting from the failure to convert L-methylmalonyl-CoA into succinyl-CoA during propionyl-CoA metabolism in the mitochondrial matrix (Figure 1).

Isolated methylmalonic acidemia results from either (1) deficient activity of the enzyme methylmalonyl-CoA mutase encoded by the *MUT* gene or (2) diminished synthesis of its cofactor adenosylcobalamin. In addition to mutations in the methylmalonyl-CoA mutase gene, mutations in the *MMAA* and *MMAB* genes as well as mutations in the gene(s) underlying the cblH and cblD variant 2 complementation groups can cause isolated methylmalonic acidemia.

Specialized metabolic testing is required to diagnose methylmalonic acidemia. See Testing for laboratories offering testing.

Organic acid analysis. Definitive diagnosis relies on analysis of organic acids in plasma and/or urine by gas-liquid chromatography with confirmation of peaks by mass spectrometry (GC/MS). The concentration of methylmalonic acid is massively increased in the plasma, urine, and cerebrospinal fluid (CSF) in severely affected individuals. Whole-body MMA excretion is typically elevated 1000-fold. Approximate concentrations of MMA in various body fluids are listed in Table 1.

Table 1. Methylmalonic Acid Concentration in Subtypes of Methylmalonic Acidemia

Phenotypic variant [1]	Methylmalonic Acid Concentration		
	Urine [2]	Blood	CSF
Infantile/non-B_{12} responsive [3]	1000-10,000 mmol/mol/Cr	100-1000 µM	Usually higher than blood
B_{12} responsive [3]	Tens - hundreds mmol/mol/Cr	5-100 µM	ND
"Benign" /adult methylmalonic acidemia [4]	10-100 mmol/mol/Cr	100 µM	ND
Normal [5]	<4 mmol/mol/Cr	<0.27 µM	0.59 µM

ND = not determined

1. Concordance between biochemical parameters and clinical phenotype does not always exist, partly because renal function can influence plasma MMA concentration.

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

3. Approximate numbers, representing the author's experience with >20 individuals with the B_{12}-responsive and non-B_{12}-responsive types

4. From Giorgio et al (1984) and converted into µM for plasma values

5. Standard values have not been exclusively derived from pediatric patients 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.

Nonspecific findings on biochemical testing include the following:

- 3-hydroxypropionate, methylcitrate, and tigylglycine detected in GC/MS analysis of urine
- Huge quantities of ketone bodies and lactate detected in the urine in the decompensated state
- Increased concentration of glycine detected on plasma amino acid analysis
- Elevated propionylcarnitine in the acylcarnitine ester profile, analyzed by tandem mass spectrometry

Establishing the specific phenotypic variant of methylmalonic acidemia requires the following studies:

Vitamin B_{12} responsiveness. In vivo responsiveness to vitamin B_{12} should be determined in all affected individuals. There is no standard regimen. When stable, affected individuals can be given one mg of hydroxycobalamin (OH-Cbl) intramuscularly or intravenously every day for five days followed by assessment of production of MMA and related metabolites by serial urine organic acid analyses and /or measurements of plasma concentrations of MMA and methylcitrate. A significant reduction in metabolite production and plasma concentration(s) indicates a response.

Note: Hydroxycobalamin (not the cyano form) is the preferred preparation for treatment of methylmalonic acidemia.

C^{14} propionate tracer assay. The in vitro assay of propionate conversion indirectly assays the activity of the enzyme methylmalonyl-CoA mutase by assessing the incorporation of the ^{14}C radiolabel in the precursor, propionate, into protein following its intramitochondrial activation to propionyl-CoA and subsequent emersion to the TCA in cultured skin fibroblasts. The technique involves incubating cells from the affected individual with C^{14}-labeled propionic acid which is converted as indicated in Figure 1 into succinyl-CoA, then through the Krebs cycle into amino acids, and then into protein. A block (mutation) at any of the steps can result in reduced incorporation of C^{14} into protein; hence, this assay is not specific for methylmalonyl-CoA mutase deficiency.

The following variants in methylmalonyl-CoA mutase are recognized:

- *mut* ^{0}, in which enzymatic activity is non-detectable
- *mut* $^{-}$, in which residual enzymatic activity is present

Note: In addition, this in vitro assay can be used to provide insight into responsiveness to exogenous administration of cobalamin, particularly if in vivo studies are questionable or borderline; however, it should be noted that the in vitro results do not always predict cofactor responsiveness.

Complementation analysis. This assay assigns a genetic group or class to the enzymatic block (i.e., *mut* ^{0}, *cblA, cblB, cblH, cblD, cblC, and cblF*) using heterokaryon rescue or enzymatic cross-correction [Gravel et al 1975]. The cell line from the affected individual is mixed with a panel of established cell lines of known status (e.g., *mut* ^{0}, *cblA*). Assignment of the enzymatic block to a particular complementation group is especially important if the abnormality is not in the L-methylmalonyl-CoA mutase gene (see Differential Diagnosis). For more details about complementation analysis, click here.

Cobalamin distribution. This assay reveals the intracellular amounts and relative proportions of CN-Cbl, OH-Cbl, Adenosyl-Cbl (AdoCbl), and Methyl-Cbl (MeCbl).

An overview of the steps of intracellular cobalamin metabolism are depicted in Figure 2.

Newborn screening. In the past several years, the implementation of tandem mass spectrometry in newborn screening by many states in the US and countries worldwide has identified newborns with methylmalonic acidemia through detection of elevated propionylcarnitine, a metabolite increased in the blood of individuals with methylmalonic acidemia and the related disorder, propionic acidemia [Chace et al 2001]. The effect of early diagnosis afforded by newborn screening is under investigation.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. *MMAA*, *MMAB*, and *MUT* are the three genes known to be associated with isolated methylmalonic acidemia.

Clinical uses

- Carrier detection
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Clinical testing

- **Sequence analysis.** Sequence analysis of *MUT*, *MMAA*, and *MMAB* is available clinically. The mutation detection rate in individuals known to have mutations in *MUT* through complementation studies is not yet known.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Methylmalonic Acidemia

Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method	Test Availability
Sequence analysis	Sequence alterations in *MUT*	Unknown	Clinical Testing
	Sequence alterations in *MMAA*		Clinical Testing
	Sequence alterations in *MMAB*		Clinical Testing

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

A skin biopsy to construct a primary fibroblast cell line should be obtained as soon as the affected individual is stable, or in the event of poor suspected outcome, prior to death. Studies on the cell line are needed for definitive diagnosis through the C^{14} propionate tracer assay to prove there is a block in the pathway, and then complementation analysis follows to assign a class to the lesion.

If the in vivo response to intramuscular OH-Cbl is questionable or borderline, vitamin B_{12} administration should be continued until the results of the in vitro studies are available.

Genetically Related Disorders

No other phenotypes are known to be associated with mutations in the *MMAA, MMAB,* and *MUT* genes.

Clinical Description

Natural History

The phenotypic variants of isolated methylmalonic acidemia described below that are associated with the genetic variants (*mut* ^{0}, *mut* $^-$, *cblA, cblB, cblH, cblD variant 2*) share clinical presentations and a natural history of periods of relative health and intermittent metabolic decompensations, usually associated with intercurrent infections and stress.

Infantile/ non-B_{12}-responsive phenotype. The most common phenotype of isolated methylmalonic acidemia presents during infancy [Matsui et al 1983, van der Meer et al 1994, Baumgarter & Viardot 1995]. Infants are normal at birth, but rapidly develop lethargy, vomiting, and dehydration. Upon presentation, they exhibit hepatomegaly, hypotonia, and encephalopathy. Laboratory findings typically show a severe metabolic acidosis, ketosis and ketonuria, hyperammonemia, and hyperglycinemia [Matsui et al 1983]. Dialysis may be needed in the acute setting, especially at the time of diagnosis if hyperammonemia is significant and persistent. Thrombocytopenia and neutropenia, suggestive of neonatal sepsis, can be seen. The catastrophic neonatal presentation of methylmalonic acidemia can result in death, despite aggressive intervention.

B_{12}-responsive phenotype. An intermediate phenotype that occurs in the first few months or years of life is also common. 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. These infants

are at risk for a catastophic decompensation, as can occur in the neonate, until the diagnosis is established.

Less common is a phenotype characterized by early childhood presentation. Typically there is no clinical evidence of disease before the first episode of vomiting, dehydration, lethargy, or coma that is often associated with respiratory distress, hepatomegaly, and seizures. As with the phenotypes in other metabolic diseases, an intermittent episode may mimic sepsis or Reye syndrome. During an episode of metabolic decompensation, the child may die despite intensive intervention if prompt treatment is not instituted. Establishing the diagnosis may be delayed, especially if a co-existing medical condition confounds the clinical picture [Ciani et al 2000].

"Benign"/adult form of methylmalonic acidemia. A "benign" form of methylmalonic acidemia is associated with increased, albeit mild, urinary excretion of methylmalonate secondary to impaired activity of the enzyme methylmalonyl-CoA mutase [Giorgio et al 1976]. Affected individuals have been viewed as stable but may be prone to acute metabolic decompensation [Shapira et al 1991].

Secondary complications. Despite increased knowledge about isolated methylmalonic acidemia and possibly earlier symptomatic diagnosis, methylmalonic acidemia continues to be associated with substantial morbidity [Baumgarter & Viardot 1995]. The major secondary complications:

- **Mental retardation.** Mental retardation is not always present even in those who have severe disease. Mental retardation is likely related to the decompensated state, and may depend on the magnitude and duration of hyperammonemia. In a retrospective, survey-based review, about 50% of individuals with the *mut* ^{0} phenotypic variant and 25% of those with the *cblA/cblB* phenotypic variant had an IQ below 80 and significant neurological impairment [Baumgarter & Viardot 1995].
- **Tubulointerstitial nephritis with progressive impairment of renal function.** It appears that many individuals develop renal impairment and eventually end stage renal disease (ESRD) [Baumgarter & Viardot 1995]. All individuals with isolated methylmalonic acidemia, even those who are mildly affected or who have received a liver allograft, are at risk of developing renal insufficiency [Nyhan et al 2002]; direct nephrotoxicity of methylmalonic acid is hypothesized. The renal insufficiency seen in isolated methylmalonic acidemia usually occurs in the chronic state in older children [Walter et al 1989] and can occur in individuals with mild disease [Van Calcar et al 1998]. An acute renal syndrome, seen in the setting of metabolic decompensation, may also exist [Stokke et al 1967] and requires further clinical delineation.
- **Metabolic stroke and movement disorders.** Some individuals develop a metabolic stroke or infarction of the basal ganglia, which can produce an incapacitating movement disorder [Korf et al 1986, Heidenreich et al 1988]. Of the survivors in one series, 20% had choreoathetosis and lesions in the basal ganglia [Baumgarter & Viardot 1995].
- **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. Because pancreatitis can manifest non-specifically, with vomiting and abdominal pain, it may be under-recognized.
- **Growth failure.** Growth failure may be caused by both chronic illness and relative protein malnutrition. Many infants are less than three standard deviations below normal for both length and weight. If a neonatal crisis is severe and accompanied by prolonged hyperammonemia, microcephaly can also be prominent. Some children have documented growth hormone (GH) deficiency, but may not have an optimal

response to GH therapy unless titration to the replacement dose is carefully adjusted [Bain et al 1995]. The indications for GH replacement therapy and the response to GH replacement in treated individuals require further investigation.

- **Acrodermatitis-enteropathica-like lesions.** [De Raeve et al 1994].
- **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].

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]. In those with the *mut* ^{0} phenotypic variant, survival at one year of age was 65% in the 1970s, but over 90% in the 1990s; five-year survival has improved from 33% in the 1970s to over 80% in the 1990s [Baumgarter & Viardot 1995]. The median age of death for children with isolated methylmalonic acidemia was two years, with a range of five days to 15 years; 40% of individuals with the *mut* ^{0} phenotyic variant died. The overall mortality in the group was 36% and all deaths occurred during or following an acute metabolic crisis [Baumgarter & Viardot 1995]. Nevertheless, despite the trend toward earlier diagnosis, the mortality rate remains high [Baumgarter & Viardot 1995, Nicolaides et al 1998]. In the largest single center experience reported to date, the median survival of the early-onset (presentation at less than one month), non-B_{12}-responsive group was 6.4 years [Nicolaides et al 1998].

The effect of newborn screening on the outcome in isolated methylmalonic acidemia has not been determined and prospective outcomes for the living patient cohort(s) are unknown. The natural history of methylmalonic acidemia requires further study, particularly with respect to medical complications including renal disease, the effect of solid organ transplantation, and molecular pathology.

Genotype-Phenotype Correlations

Individuals with infantile/non-B_{12}-responsive methylmalonic acidemia more typically harbor cobalamin non-responsive blocks, *mut* ^{0}. Precise genotype-phenotype correlations are difficult to ascertain because most individuals are compound heterozygotes. Certain mutations are associated with severe mutase deficiency (i.e., the *mut* ^{0} phenotype) in the homozygous state [Acquaviva et al 2005].

Because the observed phenotype depends on whole body enzyme activity, in vivo responsiveness to cobalamin, environmental factors, and perhaps the efficiency and activation of alternative propionyl-CoA disposal pathways in affected individuals, a more appropriate consideration of clinical correlations in methylmalonic acidemia might be with the amount of whole body residual metabolic capacity.

Prevalence

Several studies have estimated the birth prevalence of methylmalonic acidemia [Coulombe et al 1981, Lemieux et al 1988, Sniderman et al 1999]. Urine screening for 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) in a sample of nearly one million newborns screened by mass spectrometry in the US in which ten cases of isolated methylmalonic acidemia were identified in 908,543 newborns screened.

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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

"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 over 50% of children, as well as an apparently benign, persistent, low-moderate hypermethylmalonic acidemia in some [Sniderman et al 1999]. Additional individuals with a relatively benign type of methylmalonic acidemia have been reported [Martens et al 2002]. The long-term outcome and clinical phenotype of these individuals awaits further description. Some of these individuals had a combined biochemical genetic phenotype of malonic and methylmalonic acidemia and therefore may not have a defect in methylmalonyl-CoA mutase activity or cobalamin metabolism [Sniderman et al 1999].

Combined methylmalonic acidemia and homocystinuria Disorders that interfere with the intake, uptake, absorption, intestinal transport, delivery, and early metabolism of cobalamin can cause a perturbation in the synthesis of adenosylcobalamin and methylcobalamin. However, these conditions are usually accompanied by clinically significant hyperhomocysteinemia. Included in this group of disorders:

- Cobalamin C deficiency, *cblC,* perhaps the most common inborn error of intracellular cobalamin metabolism. These individuals almost always have increased homocystine.
- Complementation groups *cblD* and *cblF,* extremely rare disorders. The *cblD* group appears to be heterogeneous [Suormala et al 2004].

Note: Individuals with complementation cblD variant 1 [Suormala et al 2004], cblE (methionine synthase reductase), and cblG (methionine synthase) abnormalities do not have methylmalonic acidemia but homocystinuria caused by impaired methyl-cobalamin synthesis.

Vitamin B_{12} deficiency. Individuals with vitamin B_{12} deficiency can have increased methylmalonic acidemia and homocystinuria. Maternal B_{12} deficiency can produce a methylmalonic acidemia syndrome in an infant that ranges from severe encephalopathy [Higginbottom et al 1978] to elevated propionylcarnitine detected by newborn screening [Chace et al 2001]. IM replacement therapy to normalize vitamin B_{12} serum concentation reverses the metabolic abnormality. This can occur in a breast-fed infant of a vegan mother and in an infant born to a mother with subclinical pernicious anemia. The mother does not necessarily have a very low serum concentration of vitamin B_{12}.

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 methylmalonic acidemia [Chang et al 2000].

Other entities often described in one individual or one family that can display methylmalonic acidemia despite normal methylmalonyl-CoA mutase enzyme activity:

- Benign methylmalonic acidemia with distal renal tubular acidosis (one sibship) [Dudley et al 1998]
- Malonyl-CoA decarboxylase deficiency, usually associated with significant methylmalonic acid elevations and malonic acid increase relative to methylmalonic acidemia [Brown et al 1984]
- Elevated methylmalonic acid and malonic acid with methylmalonic acid predominating [Gregg et al 1998]

- Isolated methylmalonic acidemia, possibly caused by methylmalonic semialdehyde dehydrogenase deficiency [Roe et al 1998]
- Isolated methylmalonic aciduria and normal plasma concentrations of methylmalonic acidemia (one family) [Martens et al 2002].
- Cobalamin-unresponsive methylmalonic acidemia and progressive neurodegenerative disease with microcephaly and cataracts (two siblings) [Stromme et al 1995, Mayatepek et al 1996]
- A mitochondrial deletion syndrome with a combined-propionic and methylmalonic acidemia syndrome (one person) [Yano et al 2003]

Management

Evaluations at Initial Diagnosis

A serum chemistry panel (Na^+, K^+, CI^-, glucose, urea, creatinine, AST, ALT, alkaline phosphatase, bilirubin [T/U], triglycerides, and cholesterol); complete blood count with differential, arterial, or venous blood gas; plasma ammonium concentration; formal urinalysis; quantitative plasma amino acids; and urine organic acid analysis by mass spectrometry. If possible, measurement of plasma concentrations of methylmalonic acid, methylcitrate, free and total carnitine, and an acylcarnitine profile to document propionylcarnitine (C3 species) concentration should be obtained.

Measurement of serum vitamin B_{12} concentration should be done to determine if a nutritional deficiency is present.

Treatment of Manifestations

During the initial evaluation, the affected individual must first be stabilized if critically ill.

The base deficit is the primary concern in acutely ill persons with metabolic acidosis; the total base deficit should be calculated and corrected aggressively using intravenous bicarbonate solutions. All IV solutions should contain glucose, preferably D10 or D12.5%. The total base deficit should be followed serially with repeat electrolyte measurements and measurement of venous or arterial blood gases. Urine output and serum sodium concentrations need to be monitored. If hyperglycemia develops, an insulin infusion may be needed. Adequate kcals must be delivered to ill individuals to maximize the efficacy of other interventions.

During times of illness, aggressive fluid, metabolic, and nutritional management is necessary. 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 there are any signs of intercurrent infection.

Most affected individuals require gastrostomy tube placement because of anorexia and vomiting.

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

Prevention of Primary Manifestations

Dietary management. After stabilization, nutritional management is critical. This typically includes instituting a low-protein, high-calorie diet. Propiogenic amino acid precursors, such as isoleucine and valine, may be severely restricted in some individuals, which can produce a

nutritional deficiency state and requires vigilant monitoring of plasma amino acid concentrations. When stable, a typical neonate may be placed on a diet that provides 1.5 g/kg/d of whole protein plus a branched-chain-deficient formula such as Propimex™. A protein-free formula, such as Prophree™ or 80056, is given to some individuals to provide extra fluid and calories. As the infant grows, the total protein load is slowly reduced, based on growth, amino acid concentrations, and plasma and urine methylmalonic acid levels.

Hydroxycobalamin injections, 1 mg every day to every other day are usually required in responsive individuals. However, some individuals with variant disease can be managed with one mg IM every three to six weeks or with daily oral cobamine.

Carnitine can be given at a dose of 50-100 mg/kg/day and perhaps doses at up to 300 mg/kg/day. As a dietary supplement, carnitine may increase intracellular CoA pools and enhance the 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 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 *po qid*, was the original regimen reported by Synderman et al (1972). Metronidizole at 10-15 mg/kg/day has also been used with success [Bain et al 1988]. The intervals at which affected individuals are treated may vary, but typically feature one week to ten days of treatment per month. Although oral antibiotics reduce the propionate load that derives from gut flora in affected individuals [Bain et al 1988], 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 might be especially dangerous to individuals with methylmalonic acidemia, since most deaths are related to metabolic decompensation, often precipitated by infection. Proof of therapy should be determined in treated persons by demonstrating 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 vs the baseline value for that individual. Rotating antibiotic regimens may be required in some persons.

Glutathione deficieincy. One individual with methylmalonic acidemia, documented to be glutathione deficient after a severe metabolic crisis, responded to ascorbate therapy [Treacy et al 1996].

Organ transplantation. Preliminary data suggest that liver transplantation can increase metabolic homeostasis and protect against metabolic decompensation, but carries significant pre- and post-procedural risks and is not curative. It remains to be determined how many individuals have received organ transplantation, the detailed effects on the underlying metabolic disorder, and what the overall outcome may be in the transplanted patient cohort.

Because most of the metabolic conversion of propionate occurs in the liver, replacing the liver might contribute enough enzyme activity to avert metabolic decompensation. To date, few individuals with methylmalonic acidemia have undergone liver transplantation or combined liver-kidney transplantation [van 't Hoff et al 1998, Kayler et al 2002, Nyhan et al 2002, Hsui et al 2003]. The underlying biochemical parameters improved in all individuals undergoing liver transplantation despite persistent metabolic abnormalities. Following transplantation, some individuals continued to have high CSF concentrations of methylmalonic acid. One had a metabolic infarction of the brain, supporting the hypothesis that methylmalonic acid is produced de novo in the CNS [Oberholzer et al 1967, Chakrapani et al 2002].

Some individuals have received only renal allografts [Van Calcar et al 1998, Lubrano et al 2001]; the transplanted kidney in one person provided enough enzyme activity to normalize

methylmalonic acid excretion and allow for increased dietary protein tolerance [Lubrano et al 2001].

Surveillance

During the first year of life, infants may need to be evaluated once or twice a month. No guidelines recommend how often certain laboratory tests should be performed.

Agents/Circumstances to Avoid

Fasting stress and increased dietary protein should be avoided. During acute illness, adequate calories are very important to arrest/prevent decompensation.

Testing of Relatives at Risk

It is appropriate to evaluate the concentration of methylmalonic acid and related metabolites in urine and/or plasma of the siblings of a proband in order to institute treatment as soon as possible in those who are found to be affected.

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

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 methylmalonic acidemia.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Methylmalonic acidemia 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 mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with methylmalonic acidemia are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing using molecular genetic techniques is possible in families in which the *MUT*, *MMAA*, or *MMAB* mutation are known.

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

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for methylmalonic acidemia caused by *MUT*, *MMAA*, or *MMAB* mutations is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Biochemical testing. Prenatal testing for pregnancies at 25% risk is possible by:

- Enzyme analysis of cultured fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at

approximately 10-12 weeks' gestation. Biochemical confirmation of the diagnosis in an affected family member must be obtained before prenatal testing can be performed.

- Amniotic fluid analysis of metabolites. The absolute positive predictive and negative predictive values of metabolite analysis only have yet to be determined.

Note: The most prudent recommendation is to perform both metabolite analysis AND enzymatic assays of cultured CVS or amniocytes.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Methylmalonic Acidemia

Gene Symbol	Chromosomal Locus	Protein Name
MMAA	4q31.1-q31.2	Methylmalonic aciduria type A protein
MMAB	12q24	Cob(I)alamin adenosyltransferase
MUT	6p21	Methylmalonyl-CoA Mutase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Methylmalonic Acidemia

251000	METHYLMALONICACIDURIA DUE TO METHYLMALONIC CoA MUTASE DEFICIENCY
251100	METHYLMALONICACIDURIA, VITAMIN B12-RESPONSIVE, DUE TO DEFECT IN SYNTHESIS OF ADENOSYLCOBALAMIN--cbl A
251110	METHYLMALONICACIDURIA, VITAMIN B12-RESPONSIVE, DUE TO DEFECT IN SYNTHESIS OF ADENOSYLCOBALAMIN--cbl B
251120	METHYLMALONICACIDURIA III
277400	VITAMIN B12 METABOLIC DEFECT WITH METHYLMALONICACIDEMIA AND HOMOCYSTINURIA
607481	MMAA GENE; MMAA
607568	MMAB GENE; MMAB

Table C. Genomic Databases for Methylmalonic Acidemia

Gene Symbol	Entrez Gene	HGMD
MMAA	166785 (MIM No. 607481)	
MMAB	326625 (MIM No. 607568)	
MUT	4594 (MIM No. 251000)	MUT

For a description of the genomic databases listed, click here.

MMAA

Normal allelic variants: The *MMAA* gene contains seven exons [Dobson et al 2002a].

Pathologic allelic variants: More than 20 mutations have been described, including missense mutations, deletions, insertions, and splicing mutations. [Dobson et al 2002a, Lerner-Ellis et al 2004, Yang et al 2004]. One common mutation, R145X, accounts for 43% of mutant alleles identified in one large study [Lerner-Ellis et al 2004]. This mutation resides on a common haplotype and has also been seen in Spanish individuals [Martinez et al 2005]. In Japan, a common deletion, 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 family. While this gene was orginally proposed to function in cobalamin entry into the mitochonria [Dobson et al 2002a], a more likely role may be to protect the methylmalonyl-CoA mutase enzyme from inactivation during catalytic cycles [Korotkova & Lidstrom 2004].

Abnormal gene product: The biochemical function of the gene product is unknown. Missense mutations 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 homozygous for identical mutations can exhibit disparate phenotypes [Lerner-Ellis et al 2004].

MMAB

Normal allelic variants: The *MMAB* or *ATR* gene contains nine exons [Dobson et al 2002b]. Two allelic variants have been described: R19Q and M239K. The M239K protein has kinetic parameters that are physiologically appropriate [Leal et al 2004].

Pathologic allelic variants: Several missense mutations and a splice-site mutation have been identified in a small number of cell lines [Dobson et al 2002b, Yang et al 2004, Martinez et al 2005].

Normal gene product: The gene encodes an enzyme that transfers the adenosyl group from ATP to Co[+1] balamin [Leal et al 2003]. The crystal structure of a bacterial homologue has been determined [Saridakis et al 2004].

Abnormal gene product: The reported missense mutations fall into residues that are evolutionarily conserved [Dobson et al 2002b]. One mutation destroys a splice site [Dobson et al 2002b, Martinez et al 2005]. Several mutant alleles have been biochemically characterized [Saridakis et al 2004].

MUT

Normal allelic variants: The *MUT* gene contains 13 exons. A number of normal alleles at this locus exist, including the H532R and V671I changes [Ledley & Rosenblatt 1997].

Pathologic allelic variants: More than 150 mutations have been described [Acquaviva et al 2005, Jung et al 2005, Martinez et al 2005, Worgan et al 2006]. Nonsense mutations, missense mutations, splice-site mutations, deletions, and insertions have all been described. Several alleles have been repeatedly identified in diverse populations.

- G717V has been noted in African-Americans [Adjalla et al 1998].
- E117X is seen in Japan [Ogasawara et al 1994].
- The missense mutation N219Y was identified in five unrelated families of French and Turkish descent as well as in other populations [Acquaviva et al 2001, Acquaviva et al 2005].

- R108C has been noted in Hispanic individuals with *mut* class methylmalonic acidemia [Niles et al 2004].
- R369C has been seen in diverse populations [Jung et al 2005].
- A splice-site mutation IVS8+3A↓G recurs in the Arab-Moslem population [Berger et al 2001].
- One exonic deletion has been documented [Acquaviva et al 2005].
- One instance of uniparental paternal isodisomy for 6p24 caused a syndrome of methylmalonic acidemia and transient neonatal diabetes mellitus by reduction to homozygosity [Abramowicz et al 1994].

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

Normal gene product: Methylmalonyl-CoA mutase enzyme is a nuclear-encoded, mitochondrially-localized enzyme that exists as a homodimer. The protein contains 750 amino acids and has a 32-amino-acid N-terminal mitochondrial leader sequence that is removed by the mitochondrial importation and processing machinery. The protein contains a mole of adenosylcobalamin per mole of subunit and performs a 1, 2 rearrangment reaction, isomerizing L-methylmalonyl-CoA into succinyl-CoA [Fenton et al 2001].

Abnormal gene product: Only selected mutations have been studied enzymatically. The methylmalonyl-CoA mutase protein has several functional domains and mutations have been described in each. A mitochondrial leader sequence lies at the amino terminus. Two nonsense mutations that fall into this domain have been described: Q7X [Acquaviva et al 2005] and Q18X [Ledley et al 1990]. One report noted that a truncated protein, likely translated from an internal AUG, arose from the Q18X mutant allele [Ledley et al 1990]. This mutant protein is "mis-targeted" and not functional. Adjacent to, but distinct from, the mitochondrial leader sequence is the putative dimerization domain of the enzyme subunits. The coenzyme-A binding pocket spans the middle of the second exon to the end of the sixth exon. Mutations 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 R93H, can participate in interallelic complementation [Raff et al 1991]. A linker domain spanning residues 424-577 separates the C-terminal cobalamin-binding domain. While no mutations have been described to date in the amino acid encoding exons of this domain, splice-site changes in the introns in this region have been associated with *mut* ^{0} class methylmalonic acidemia [Acquaviva et al 2005]. Most of the *mut* $^{-}$ mutations reside in the cobalamin binding domain, which is located between amino acids 578 and 750 [Crane & Ledley 1994]. Some mutations in this region can display purely K_m effects, as might be expected for a cofactor binding mutations, while others affect the K_m and V_{max} [Janata et al 1997]. This region also contains residues that can participate in interallelic complementation [Raff et al 1991, Crane & Ledley 1994, Ledley & Rosenblatt 1997].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Methylmalonic acidemia

Organic Acidemia Association
13210 - 35th Avenue North
Plymouth, MN 55441
Phone: 763-559-1797
Fax: 763-694-0017
Email: oaanews@aol.com
www.oaanews.org

Save Babies Through Screening Foundation, Inc
4 Manor View Circle
Malvern, PA 19355-1622
Phone: 888-454-3383
Fax: 610-647-5757
Email: email@savebabies.org
www.savebabies.org/index.htm

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Dr Venditti is a pediatrician and biochemical geneticist. He is the director of the Organic Acid Disorder Research Unit at the National Human Genome Research Institute and an attending physician at the National Institutes of Health Clinical Center.

Revision History

- 18 January 2007 (cd) Revision: testing for mutations in *MMAA* and *MMAB* clinically available
- 16 August 2005 (me) Review posted to live Web site
- 11 May 2004 (cpv) Original submission

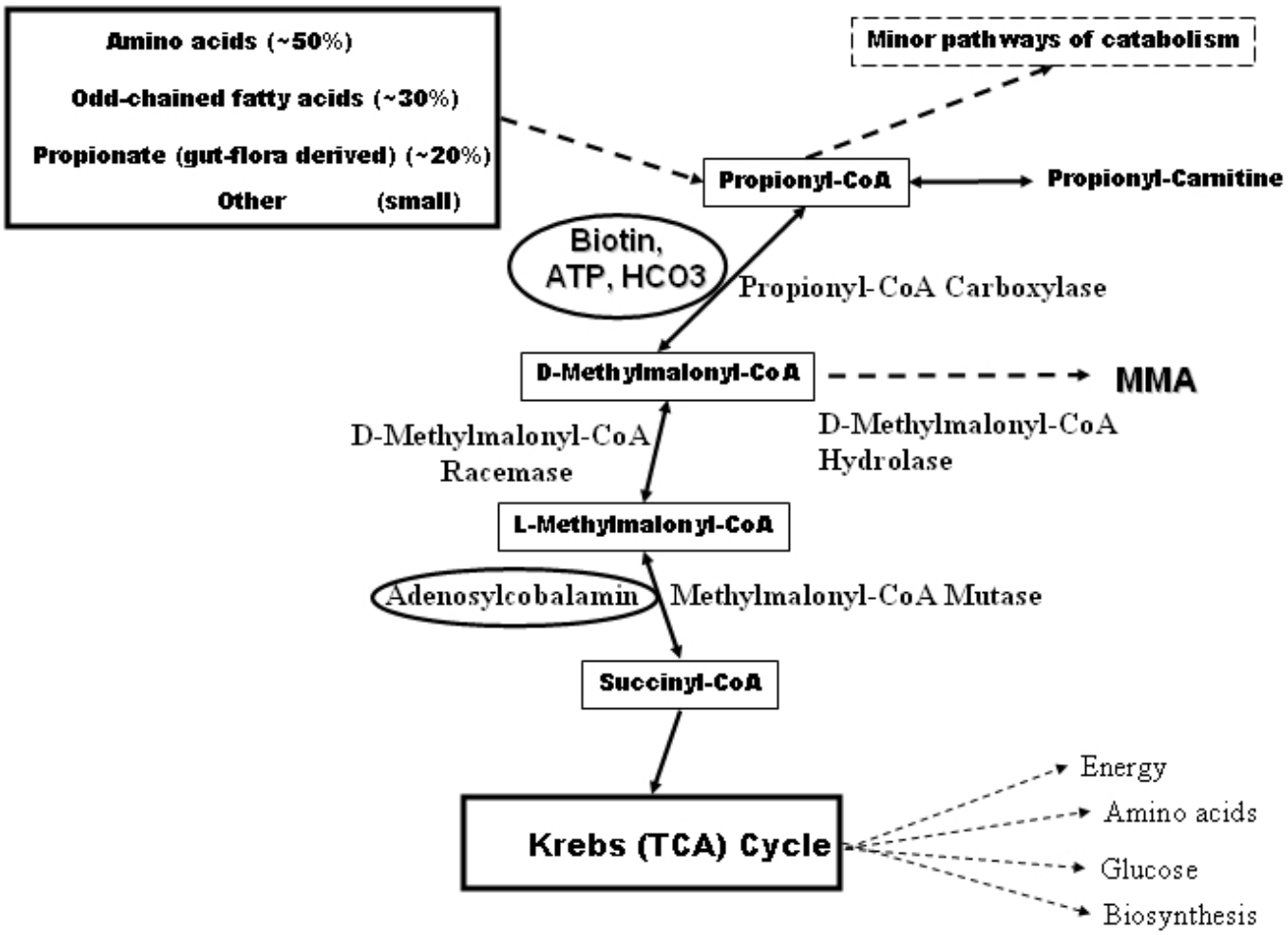

Figure 1. Major pathway of the conversion of propionyl-CoA into succinyl-CoA. The precursors are indicated with their approximated contribution to whole body propionate metabolism in the fasting state [Thompson et al 1990]. The biotin-dependent enzyme propionyl-CoA carboxylase converts propionyl-CoA 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}.

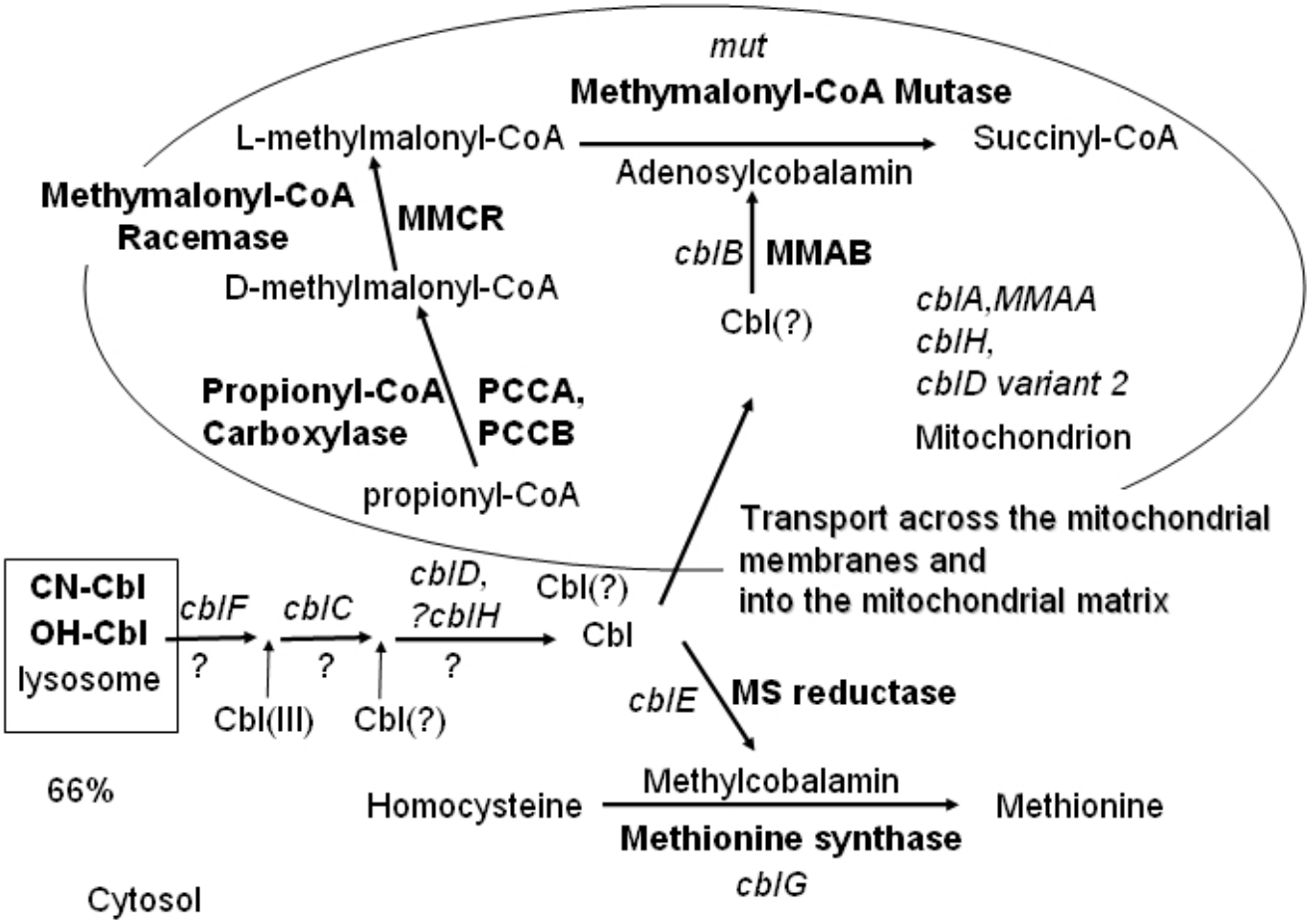

Figure 2. Pathway of cellular processing of cobalamin (OH-cbl). The class and genes associated with isolated methylmalonic acidemia are:
cblH, ? unknown gene [Watkins et al 2000]
cblA (MMAA)
cblB (MMAB)
cblD variant 2 [Suormala et al 2004] ? unknown gene
mut (MCM)