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Isolated Methylmalonic Acidemia

Synonym: Isolated Methylmalonic Aciduria

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Summary

Clinical characteristics

For this *GeneReview*, 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 isomerize (convert) methylmalonyl-coenzyme A (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. Isolated MMA 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, 5-deoxy-adenosyl-cobalamin (*cblA*, *cblB*, or *cblD*-MMA), or deficiency of the enzyme methylmalonyl-CoA epimerase. Prior to the advent of newborn screening, common phenotypes included:

- Infantile/non-B_{12}-responsive form (mut^0 enzymatic subtype, *cblB*), the most common phenotype, associated with infantile-onset lethargy, tachypnea, hypothermia, vomiting, and dehydration on initiation of protein-containing feeds. Without appropriate treatment, the infantile/non-B_{12}-responsive phenotype could rapidly progress to coma due to hyperammonemic encephalopathy.
- Partially deficient or B_{12}-responsive phenotypes (mut^- enzymatic subtype, *cblA*, *cblB* [rare], *cblD*-MMA), in which symptoms occur in the first few months or years of life and are characterized by feeding problems, failure to thrive, hypotonia, and developmental delay marked by episodes of metabolic decompensation
- Methylmalonyl-CoA epimerase deficiency, in which findings range from complete absence of symptoms to severe metabolic acidosis. Affected individuals can also develop ataxia, dysarthria, hypotonia, mild spastic paraparesis, and seizures.

In those individuals diagnosed by newborn screening and treated from an early age, there appears to be decreased early mortality, less severe symptoms at diagnosis, favorable short-term neurodevelopmental outcome, and lower incidence of movement disorders and irreversible cerebral damage. However, secondary complications may still occur and can include intellectual disability, tubulointerstitial nephritis with progressive

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impairment of renal function, "metabolic stroke" (bilateral lacunar infarction of the basal ganglia during acute metabolic decompensation), pancreatitis, growth failure, functional immune impairment, bone marrow failure, optic nerve atrophy, arrhythmias and/or cardiomyopathy (dilated or hypertrophic), liver steatosis/fibrosis/cancer, and renal cancer.

Diagnosis/testing

The diagnosis of isolated MMA is established in a proband by identification of biallelic pathogenic variants in *MCEE*, *MMAA*, *MMAB*, *MMADHC*, or *MMUT* or (in some instances) by significantly reduced activity of one of the following enzymes: methylmalonyl-CoA mutase, methylmalonyl-CoA mutase enzyme cofactor 5'-deoxyadenosylcobalamin, or methylmalonyl-CoA epimerase. Because of its relatively high sensitivity, easier accessibility, and noninvasive nature, molecular genetic testing can obviate the need for enzymatic testing in most instances.

Management

Treatment of manifestations / Prevention of primary manifestations: When isolated MMA is suspected during the diagnostic evaluation due to elevated propionylcarnitine (C3) on a newborn blood spot, metabolic treatment should be initiated immediately, while the suspected diagnosis is being confirmed. Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach by experienced subspecialists from a specialized metabolic center. The main principles of treatment are to provide supplemental vitamin B_{12} to those who are known to be vitamin B_{12} responsive; restrict natural protein, particularly of propiogenic amino acid precursors, while maintaining a high-calorie diet; address feeding difficulties, recurrent vomiting, and growth failure; provide supplemental carnitine to those with carnitine deficiency; reduce propionate production from gut flora; and provide emergency treatment during episodes of acute decompensation with the goal of averting catabolism and minimizing central nervous system injury. In those with significant metabolic instability and/or renal failure, liver and/or renal transplantation may be considered.

Prevention of secondary complications: MedicAlert® bracelets and up-to-date, easily accessed, detailed emergency treatment and presurgical protocols to facilitate care.

Surveillance: Regular evaluations by a metabolic specialist and metabolic dietician; screening laboratory testing, including plasma amino acids, plasma and urine MMA levels, serum acylcarnitine profile and free and total carnitine levels, blood chemistries, and complete blood count at least every six months to one year, or more frequently in infants or in those who are unstable or require frequent changes in dietary management; measurement of renal function at least annually or as clinically indicated; assessment for liver disease at least annually or as clinically indicated; assessment of developmental progress and for signs of movement disorder at each visit; ophthalmology evaluation to monitor for optic atrophy at least annually or as clinically indicated; audiology evaluation at least annually in childhood and adolescence or as clinically indicated.

Agents/circumstances to avoid: Fasting, stress, increased dietary protein, supplementation with the individual propiogenic amino acids valine and isoleucine, nephrotoxic medications or agents, and agents that prolong QTc in the EKG.

Evaluation of relatives at risk: For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening, measure serum methylmalonic acid, urine organic acids, plasma acylcarnitine profile, plasma amino acids, and serum B_{12}; test for the familial isolated methylmalonic acidemia-causing pathogenic variants if biochemistry is abnormal.

Pregnancy management for an affected mother: Monitor for complications including acute decompensation or hyperammonemia, deterioration of renal function, and obstetric complications including preeclampsia and preterm delivery.

Pregnancy management for an unaffected mother with an affected fetus: 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; however, further study of this treatment is needed.

Genetic counseling

All forms of isolated MMA are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an isolated MMA-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the isolated MMA-causing pathogenic variants have been identified in an affected family member, molecular genetic carrier testing and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

Table. Isolated Methylmalonic Acidemia/Aciduria: Included Phenotypes

Enzymatic Subtype		Methylmalonic Acidemia Phenotype	Associated Gene
Complete deficiency of methylmalonyl-CoA mutase	*mut* ^{0}	Infantile/non-B_{12}-responsive	*MMUT*
Partial deficiency of methylmalonyl-CoA mutase	*mut* $^-$	Partially deficient or B_{12}-responsive	
Defect in the synthesis or transport of the methylmalonyl-CoA mutase cofactor, 5'-deoxyadenosyl-cobalamin	*cblA*	Partially deficient or B_{12}-responsive	*MMAA*
	cblB	Infantile/non-B_{12}-responsive or, rarely, partially deficient or B_{12}-responsive	*MMAB*
	cblD-MMA	Partially deficient or B_{12}-responsive	*MMADHC*
Deficient activity of methylmalonyl-CoA epimerase	*MCEE*	Methylmalonyl-CoA epimerase deficiency	*MCEE*

Diagnosis

For this *GeneReview*, 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 isomerize (convert) methylmalonyl-coenzyme A (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).

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

Newborn screening test. NBS for isolated methylmalonic acidemia is primarily based on quantification of the analyte propionylcarnitine (C3) on dried blood spots.

Elevated C3 values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing (see also the ACMG ACT Sheet).

- In the US, individual state NBS programs determine cutoffs based on analytic and other considerations, under the guidance of the CDC Newborn Screening Quality Assurance Program (NSQAP) and Association of Public Health Laboratories (APHL) [McHugh et al 2011, Held et al 2022].

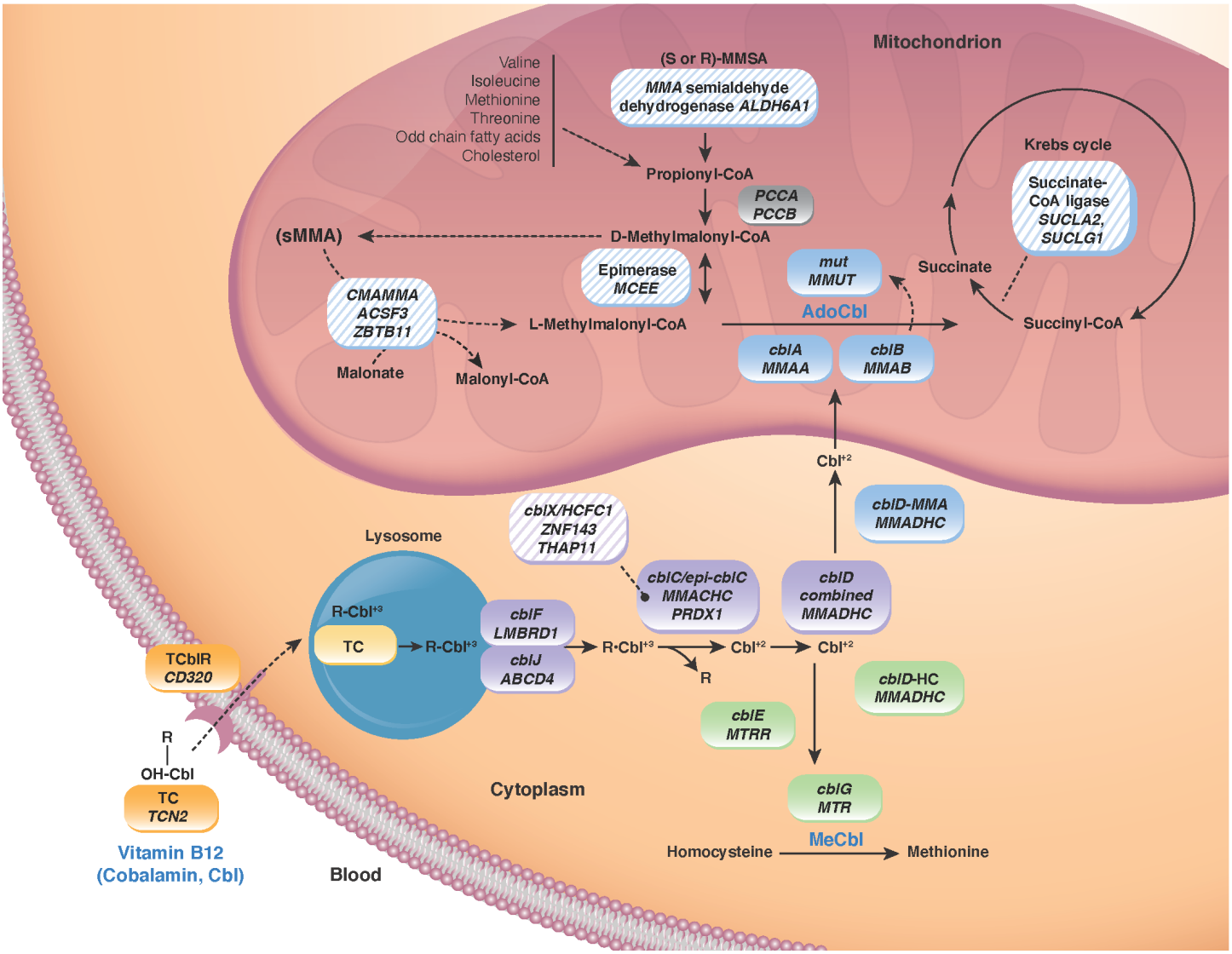

Figure 1. Major pathway of the conversion of propionyl-CoA into succinyl-CoA. The biotin-dependent enzyme propionyl-CoA carboxylase converts propionyl-CoA into D-methylmalonyl-CoA, which is then racemized into L-methylmalonyl-CoA and isomerized into succinyl-CoA, a Krebs cycle intermediate. The L-methylmalonyl-CoA mutase reaction requires 5'-deoxyadenosylcobalamin, an activated form of vitamin B_{12}. The pathway of cellular processing of cobalamin (reduction from Cbl^{+3} to Cbl^{+2}) and subsequently 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) methylmalonyl-CoA mutase or isolated AdoCbl deficiency and associated increase in serum methylmalonic acid [sMMA] (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 methylmalonic acidemia occurs: epimerase deficiency (*MCEE*) and succinate-CoA ligase deficiency (*SUCLA2/SUCLG1*), combined malonic and methylmalonic acidemia (*ACSF3, ZBTB11*), and methylmalonyl-semialdehyde dehydrogenase deficiency (*ALDH6A1*). The light purple striped box indicates *cblX* deficiency (*HCFC1*), the only X-linked disorder in this pathway and rare transcription factors (*ZNF143, THAP11*) or neighboring genes (*PRDX1*) associated with cblC deficiency or epi-cblC. See Disorders of Intracellular Cobalamin Metabolism.

MMA = methylmalonic acid; Cbl = cobalamin; Cbl^{+3} = oxidized cobalamin, Cbl^{+2} = reduced cobalamin; AdoCbl = 5'-deoxyadenosylcobalamin; MeCbl = methylcobalamin; TC = transcobalamin; TCblR = transcobalamin receptor.

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*-MMA)

MCEE

Isolated methylmalonic acidemia caused by mutation of *SUCLA2* and *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.

- Since propionylcarnitine is one of the analytes most frequently responsible for false positive results, ratios including C3/C2, C3/C0, C3/C16, C3/glycine, or C3/methionine 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 [Gavrilov et al 2020].
- Additional biomarkers such as C16:1OH (3-hydroxypalmitoleolyl-carnitine) or, more accurately, C17 (heptadecanoylcarnitine) have been suggested to improve the sensitivity of the first-tier newborn screening test [McHugh et al 2011, Malvagia et al 2015].
- Amino acid analysis of the dried blood spot will show normal methionine and elevated C3/methionine ratio.
- Precision newborn screening and avoidance of false positive results can be further improved with the utilization of the Collaborative Laboratory Integrated Reports software [Gavrilov et al 2020].

The following medical interventions need to begin immediately on receipt of an abnormal NBS result while additional testing is performed to determine whether this is a true positive NBS result and to establish the diagnosis of isolated MMA definitively (see Management):

- Prompt evaluation for prevention or treatment of possible hyperammonemia and metabolic ketoacidosis
- Daily intramuscular vitamin B_{12} administration (Hydroxocobalamin is preferred over cyanocobalamin, especially in individuals with cobalamin C deficiency.)
- Initiation of a low-protein diet
- Carnitine supplementation

Testing to consider after a positive NBS. A positive C3 screening result is followed by testing for methylmalonic acid, 2-methylcitrate, and total homocysteine in the dried blood spot to differentiate isolated MMA from propionic acidemia and defects resulting in combined methylmalonic acidemia and homocystinuria [Turgeon et al 2010, Weiss et al 2020, Pajares et al 2021].

Follow-up biochemical testing after an abnormal NBS typically demonstrates:

- Elevated plasma methylmalonic acid (MMA) level
- Elevated levels of urine MMA and the presence of 3-hydroxypropionate, 2-methylcitrate, and tiglylglycine on urine organic acids
- Elevated concentrations of glycine and possibly alanine with normal methionine on plasma amino acids
- Elevated plasma concentration of propionylcarnitine (C3) and variable elevations in C4-dicarboxylic or methylmalonic/succinylcarnitine (C4DC) on plasma acylcarnitine profile
- Elevated plasma ammonia, metabolic ketoacidosis, pancytopenia, lactic acidosis, hypoglycemia (in some cases)
- Normal serum B_{12} and plasma homocysteine

Note: (1) Although plasma and/or urine methylmalonic acid concentration can be precisely quantitated (see Table 1), this is generally not needed immediately for diagnostic purposes. (2) If MMA is confirmed, further

biochemical testing of plasma homocysteine and serum vitamin B_{12} (in both the newborn and the mother) helps further differentiate the cause of MMA (see Figure 2, left two columns).

If follow-up biochemical testing supports the likelihood of isolated methylmalonic acidemia, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

Scenario 2: Symptomatic Individual

A symptomatic individual may present with clinical findings associated with an attenuated MMA phenotype or untreated infantile-onset MMA (see **Note**). Onset of symptoms can range from the first days of life to adulthood [Kölker et al 2015a].

Note: Infantile-onset MMA may be untreated for any of the following reasons: NBS was not performed; NBS yielded a false negative result; caregivers were not adherent to recommended treatment following a positive NBS result.

Supportive – but nonspecific – clinical findings, brain MRI findings, and preliminary laboratory findings can include the following.

Clinical findings

In neonates:

- Lethargy
- Vomiting
- Hypotonia
- Hypothermia
- Respiratory distress
- Encephalopathy, coma
- Sepsis-like illness

In older infants and children:

- Failure to thrive / short stature
- Protein aversion
- Hypotonia
- Intellectual disability
- Acute and chronic neurologic symptoms including seizures and abnormal movements (choreoathetosis, dystonia, spasticity)
- Acute and chronic renal manifestations (dehydration, renal tubular acidosis, acute kidney injury)

Brain MRI findings include evidence of basal ganglia injury, specific to the globus pallidus [Baker et al 2015], typically in older infants and children.

Preliminary laboratory findings

Acutely:

- Severe ketoacidosis and lactic acidosis (may first present as a catastrophic/lethal ketoacidosis following an intercurrent illness)
- Hyperammonemia
- Anemia, neutropenia, and/or thrombocytopenia on complete blood count

In older untreated infants and children: isolated renal tubular acidosis or chronic renal failure

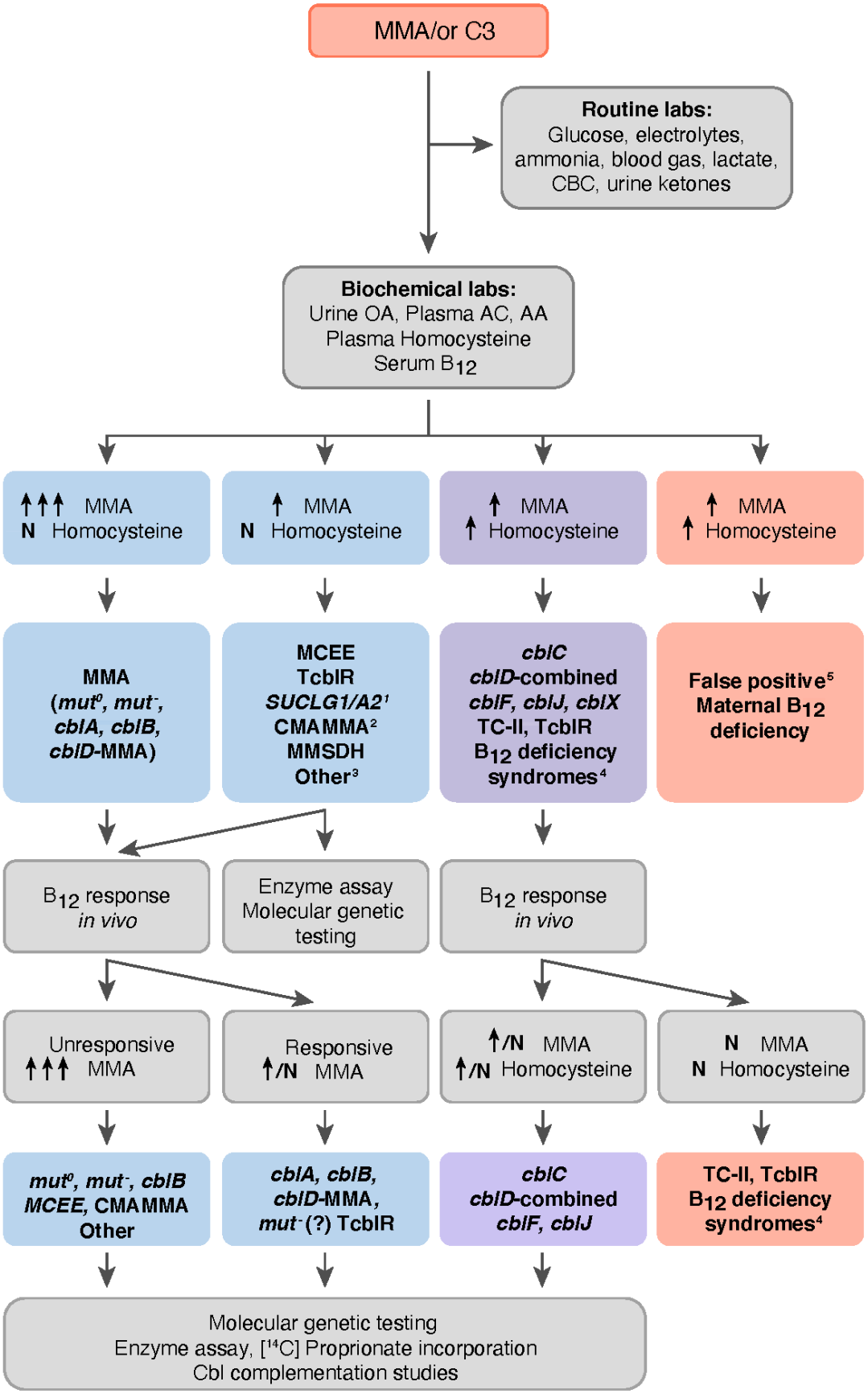

Figure 2. An algorithm of conditions to be considered in the differential diagnosis of elevated serum or urine methylmalonic acid

detected either during the follow up of an increased propionylcarnitine (C3) on newborn screening or following a positive urine organic acid screen in a symptomatic individual. The algorithm includes disorders that can present after the newborn period.

AC = acylcarnitine profile; CBC = complete blood count; Cbl = cobalamin; MMA = methylmalonic acid; Mut = mutase; OA = organic acids; PA = propionic acid; 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** propionylcarnitine (C3) in the plasma acylcarnitine profile and elevated methylmalonic and malonic acid in the plasma or urine. CMAMMA can be caused by biallelic pathogenic variants in *ACSF3* or *ZBTB11*.

3. Methylmalonyl-semialdehyde-dehydrogenase deficiency (MMASDH) 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. *cblF* and *cblJ* can have low serum B_{12} concentration due to abnormal gastrointestinal absorption.

5. In rare instances metabolites can be normal in affected individuals.

Establishing the Diagnosis

The diagnosis of isolated MMA **is established** in a proband by identification of biallelic pathogenic variants in one of the genes listed in Table 2 on molecular genetic testing or – in some instances – by significantly reduced activity of the enzymes listed below and in Table 1. Because of its relatively high sensitivity, easier accessibility, and noninvasive nature, molecular genetic testing can obviate the need for enzymatic testing, and is thus increasingly the preferred confirmatory test for isolated MMA.

Isolated MMA is caused by any ONE of the following:

- Complete (*mut*^{0} enzymatic subtype) or partial (*mut*$^-$) deficiency of the enzyme methylmalonyl-CoA mutase, encoded by *MMUT*
- Diminished synthesis of the methylmalonyl-CoA mutase enzyme 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-coenzyme A epimerase encoded by *MCEE*

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

Methylmalonic Acidemia Phenotype / Enzymatic Subtype [1]	Methylmalonic Acid Concentration	
	Urine	Blood
Infantile/non-B_{12}-responsive [2] / *mut*^{0}, *mut*$^-$, *cblB*	1,000-10,000 mmol/mol Cr	• 100-1,000 µmol/L (if eGFR >50 mL/min/1.73 m^2) • 1,000-10,000 µmol/L in those w/ advanced renal disease
B_{12}-responsive [2] / *cblA*, *cblD*-MMA, *cblB*, *mut*$^-$ (rare)	Tens - hundreds mmol/mol Cr	5-100 µmol/L
MCEE deficiency [3]	100-6,800 mmol/mol Cr	5-180 µmol/L

Table 1. continued from previous page.

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

Cr = creatinine; eGFR = estimated glomerular filtration rate; MCEE = methylmalonyl-coenzyme A epimerase
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. Approximate numbers, representing the author's experience with >150 individuals with the B_{12}-responsive and non-B_{12}-responsive types as well as data from Fowler et al [2008]
3. Bikker et al [2006], Dobson et al [2006], Gradinger et al [2007], Heuberger et al [2019]
4. 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.

Molecular genetic testing (see Table 2) can be used to establish the diagnosis of isolated MMA by identifying biallelic pathogenic variants in one of the genes listed in Table 2 and confirming carrier status in the parents.

Molecular Genetic Testing Approaches

Scenario 1: Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of isolated MMA, molecular genetic testing approaches include use of a **multigene panel**.

A methylmalonic acidemia multigene panel that includes the genes listed in Table 2 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Scenario 2: Symptomatic individual. For a symptomatic individual who has findings associated with attenuated isolated MMA OR untreated infantile-onset isolated MMA (see Suggestive Findings, Scenario 2, **Note**), a **methylmalonic acidemia multigene panel** should be pursued, as detailed above. When a molecular diagnosis is not reached by panel testing, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 2. Molecular Genetic Testing Used in Isolated Methylmalonic Acidemia

Gene [1, 2]	Proportion of Isolated MMA Attributed to Mutation of Gene [3]	Proportion of Pathogenic Variants [4] Detected by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
MCEE	Rare	25 probands/families [7]	Unknown, none reported [8]
MMAA	25%	97% [9]	Unknown, one large deletion reported [8, 10]
MMAB	12%	98% [11]	Unknown, none reported [8]
MMADHC	Rare	9 probands/families [12]	Unknown, none reported [8]
MMUT	60% (75%-78% mut^0 enzymatic subtype, 20%-22% mut^- enzymatic subtype)	96% [13, 14]	~1% [8]
Unknown [15]	Rare	NA	

NA = not applicable

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. Based on Worgan et al [2006], Hörster et al [2007], Hörster et al [2009], Forny et al [2016], Forny et al [2021], Hörster et al [2021]. Depending on the definition of B_{12} responsiveness these percentages vary in different reports and populations [Yu et al 2021].

4. See Molecular Genetics for information on allelic variants detected in this gene.

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Gradinger et al [2007], Heuberger et al [2019]

8. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

9. Lerner-Ellis et al [2004], Plessl et al [2017]

10. Nizon et al [2013]

11. Lerner-Ellis et al [2006], Forny et al [2016], Forny et al [2021]

12. Coelho et al [2008], Stucki et al [2012], Froese et al [2015], Wang et al [2018]

13. Worgan et al [2006], Forny et al [2016]

14. For individuals of Hispanic descent, targeted exon 2 analysis for the *MMUT* c.322C>T pathogenic variant may be considered (see Molecular Genetics).

15. Some individuals with isolated MMA remain undiagnosed despite extensive genome and RNA sequencing, suggesting that additional genetic causes of isolated or combined subtypes of MMA may be identified with future research [Abdrabo et al 2020].

Responsiveness to Vitamin B_{12}

In vivo responsiveness to vitamin B_{12} should be determined in all affected individuals, following the proposed protocol by Fowler et al [2008], according to the E-IMD guidelines [Baumgartner et al 2014, Forny et al 2021].

- When stable, affected individuals can be given 1.0 mg of hydroxocobalamin (OH-Cbl) (see **Note**) intramuscularly every day for three to five days or longer, 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. At least three samples on different days should be obtained at baseline and over the course of the following one to two weeks and mean pre- and post-concentrations compared. Protein and energy intake should be specified.
- A significant (>50%) reduction in plasma or urine mean methylmalonic acid concentration(s) is considered indicative of responsiveness [Fowler et al 2008].

- In vivo response was reported in all individuals with *cblA* and only rare individuals with *cblB*, who have the C terminal pathogenic variants c.700C>T (p.Gln234Ter) or c.656_659del (p.Tyr219SerfsTer4) in *MMAB* [Hörster et al 2007, Forny et al 2021, Hörster et al 2021].

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

Enzymatic Testing

Cellular biochemical testing on skin fibroblasts was historically the gold standard for determining the MMA subtype and B_{12} responsiveness in vitro, although molecular genetic testing is now more widely used as the first diagnostic step. Enzymatic testing is useful when molecular genetic testing fails to provide a firm diagnosis to guide management. While the in vitro cellular assay can provide some insight into responsiveness to exogenous administration of cobalamin, it is not always predictive of the in vivo response.

See Therapies Under Investigation for information about a surrogate biomarker of disease severity that is currently being evaluated.

Clinical Characteristics

Clinical Description

The phenotypes of isolated methylmalonic acidemia (MMA) described below that are associated with the enzymatic subtypes *mut*^{0}, *mut*$^-$, *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. Table 3 reviews the phenotypes, causative genes, enzymatic subtypes, and clinical correlations that will be discussed further in this section.

Table 3. Phenotype Correlations by Gene and Enzymatic Subtype of Isolated Methylmalonic Acidemia

Methylmalonic Acidemia Phenotype	Gene	Enzymatic Subtype	Clinical Correlation
Infantile / non-B_{12}-responsive [1]	*MMUT*	*mut* ^{0}	• Most common & severe form, typically presenting in infancy • Higher rate of mortality & neurologic & other multisystem complications than in those w/*mut*$^-$ & *cblA* subtypes • Renal disease may manifest in childhood in ~43%-60%, w/ median age of onset 6-11 yrs. [2]
	MMUT	*mut* $^-$	• Onset may occur later, in 1st few mos or yrs of life. • Symptoms often incl feeding problems, failure to thrive, hypotonia, & DD. • Catastrophic decompensation can occur when diagnosis is delayed, incl injury in basal ganglia → movement disorder. • Some persons have isolated renal tubular acidosis or chronic renal failure as primary finding.

Table 3. continued from previous page.

Methylmalonic Acidemia Phenotype	Gene	Enzymatic Subtype	Clinical Correlation
	MMAB	*cblB*	• Most affected persons have phenotype that resembles *mut*^{0}, although certain pathogenic variants may be assoc w/milder phenotype. • Higher rate of mortality & neurologic & other multisystem complications than in those w/*mut*$^-$ & *cblA* sybtypes • Chronic renal failure occurs in ~66% & is less frequent than in those w/*cblA* subtype.
B_{12}-responsive [3]	*MMAA*	*cblA*	If diagnosed early & consistently treated w/injectable B_{12} [4]: • Milder disease course • Normal life expectancy • Slower decline in renal function w/≈9%-12% developing chronic renal failure [5] • Better neurocognitive outcomes than in *mut*^{0}/*mut*$^-$ & *cblB* subtypes If not adherent to diet & injectable B_{12} therapy: at risk for significant neurologic & multiorgan complications [6]
	MMADHC [7]	*cblD*-MMA	Metabolic acidosis, respiratory distress, hyperammonemia, & neurologic symptoms
	MMAB	*cblB*	• Only rarely is this subtype responsive to injectable B_{12} therapy. • May present w/isolated renal tubular acidosis or chronic renal failure
	MMUT	*mut* $^-$	See **Infantile/non-B_{12}-responsive**; this phenotype is rarely B_{12}-responsive.
MCEE deficiency	*MCEE*	*MCEE*	• In general, milder features ranging from no symptoms to severe metabolic acidosis. • Not responsive to injectable B_{12} therapy • A rare cause of persistent moderate MMA

DD = developmental delay; MCEE = methylmalonyl-coenzyme A epimerase
1. The most common phenotype, which typically presents during infancy
2. Cosson et al [2009], Kruszka et al [2013], Dao et al [2021]
3. Sometimes referred to as partial deficiency
4. Hörster et al [2021], Manoli et al [2021]
5. Hörster et al [2021], Marelli et al [2022]
6. Including optic nerve atrophy, basal ganglia injury, and multiorgan failure [Valayannopoulos et al 2009]
7. See also Genetically Related Disorders for other phenotypes associated with mutation of this gene.

Effect of Newborn Screening

Decreased early mortality, less severe symptoms at diagnosis, favorable short-term neurodevelopmental outcome, and lower incidence of movement disorders and irreversible cerebral damage were recorded in affected individuals identified through expanded NBS, though a number of infants with the *mut*^{0} enzymatic subtype present clinically before the NBS results become available [Leonard et al 2003, Dionisi-Vici et al 2006, Heringer et al 2016]. Limited observations in sibs with the *cblA* enzymatic subtype suggest that the IQs of the individuals treated from the newborn period were significantly higher than those of their older affected sibs who were diagnosed after the onset of symptoms [Hörster et al 2007].

Common Phenotypes and Associated Features

As described prior to newborn screening (NBS) availability, the common phenotypes and associated features of isolated MMA included the following.

Infantile/non-B_{12}-responsive phenotype (*mut*^{0} enzymatic subtype, *cblB*). The catastrophic neonatal presentation of isolated MMA 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.

- The most common phenotype of isolated MMA presents during infancy. Infants are normal at birth but develop lethargy, tachypnea, hypothermia, vomiting, and dehydration on initiation of protein-containing feeds.
- This can rapidly progress to coma due to hyperammonemic encephalopathy, if untreated.
- 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 [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.

Partially deficient or B_{12}-responsive phenotypes (*mut*$^-$, *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, infants are at risk for a catastrophic decompensation (like that in neonates) [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 (see Treatment of Manifestations) is not instituted and the symptoms are misdiagnosed (as, e.g., diabetic ketoacidosis) [Ciani et al 2000].
- Before the availability of NBS, or in cases that are false negative on NBS due to borderline C3 elevations, infants with the *cblA* or *mut*$^-$ subtypes would present with a devastating injury in the basal ganglia in the context of acute metabolic crisis / encephalopathy (more specifically lacunar infarcts in the globus pallidus) resulting in a debilitating movement disorder [Korf et al 1986, Heidenreich et al 1988].
- Individuals with partial enzymatic deficiency (*mut*$^-$), *cblA*, or *cblB* can also present with isolated renal tubular acidosis or chronic renal failure [Dudley et al 1998, Coman et al 2006].

Methylmalonyl-coenzyme A epimerase (MCEE) deficiency. Findings in infants/children with biallelic pathogenic variants in *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, Heuberger et al 2019].

- Screening of a large cohort of individuals with undefined MMA identified ten individuals with MCEE deficiency with symptoms including metabolic ketoacidosis, hypoglycemia, seizures, developmental delay, and spasticity. Cardiomyopathy was reported in a single individual, with a similarly affected sib with biochemical but no clinical findings [Heuberger et al 2019].
- Individuals with MCEE deficiency were not responsive to B_{12} supplementation in vitro or in vivo and urine MMA concentrations ranged between 100 and 600 mmol/mol creatinine (normal: 0.3-1.1 mmol/mol) [Heuberger et al 2019].
- A 78-year-old individual with Parkinson disease, dementia, and stroke was found to have *MCEE* biallelic pathogenic variants c.139C>T (p.Arg47Ter) and c.419del (p.Lys140ArgfsTer6), associated with

methylmalonic acidemia and increased plasma C3; he was not responsive to high-dose hydroxocobalamin [Andréasson et al 2019].

Secondary Complications

Secondary complications can be observed in any enzymatic subtype but may be dependent on the specific subtype and degree of metabolic control and adherence (see Table 3). Despite increased knowledge about isolated MMA and possibly earlier symptomatic diagnosis, isolated MMA continues to be associated with substantial morbidity and mortality [de Baulny et al 2005, Dionisi-Vici et al 2006, Kölker et al 2015b, Tuncel et al 2018] that correlates with the underlying defect [Hörster et al 2007, Hörster et al 2021]. Individuals with the *mut*^{0} and *cblB* subtypes have a higher rate of mortality and neurologic and other multisystem complications than those with the *mut*$^{-}$ and *cblA* subtypes. Multiorgan complications associated with secondary mitochondrial dysfunction accumulate with age and were shown to be associated with a higher total protein intake and imbalanced special metabolic food prescription [Manoli et al 2016b, Molema et al 2018, Haijes et al 2019a, Molema et al 2021a].

Therefore, primary and secondary biomarkers are important for monitoring affected individuals and supporting efficacy in therapeutic clinical trials [Longo et al 2022] (see Therapies Under Investigation and Molecular Genetics). As an example, plasma fibroblast growth factor 21 (FGF21) was shown to correlate with disease severity and long-term complications in different cohorts of affected individuals [Manoli et al 2018, Molema et al 2018, Manoli et al 2021].

The major secondary complications include the following.

Intellectual disability. Intellectual disability may or may not be present even in those with severe disease.

- In one study about 50% of individuals with *mut*^{0} subtype, 85% with *mut*$^{-}$, 48% with *cblA*, and 70% with *cblB* had an IQ above 90 [Hörster et al 2007].
- In a natural history study, the mean FSIQ of all individuals with isolated MMA (n=37) was 85.0 ± 20.68, which is in the low-average range (80≤IQ≤89) [O'Shea et al 2012].
    - Individuals with *cblA* (n=7), *cblB* (n=6), and *mut* diagnosed prenatally or by NBS (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.

Tubulointerstitial nephritis with progressive impairment of renal function. All individuals with isolated MMA, even those who are mildly affected or who have received a liver allograft [Noone et al 2019], are at risk of developing renal insufficiency [Cosson et al 2009, Kruszka et al 2013, Manoli et al 2013, Morath et al 2013, Dao et al 2021, Hörster et al 2021], which can progress to end-stage renal disease requiring kidney transplantation (see Table 3).

- Cystatin-C levels and age-appropriate equations to calculate estimated glomerular filtration rate (GFR) – or preferably, measurement of GFR by iohexol clearance or other methods – should be used for clinical monitoring, due to the fact that creatinine is a late marker of renal dysfunction in individuals with low muscle mass, as is seen in isolated MMA (see Surveillance). This will allow for earlier referral to nephrology services and initiation of renoprotective measures – including, importantly, blood pressure control.
- 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 [Dao et al 2021].

- Secondary mitochondrial dysfunction rather than direct nephrotoxicity of methylmalonic acid is hypothesized as the cause for renal disease [Atkuri et al 2009, Mc Guire et al 2009, Manoli et al 2013, Zsengellér et al 2014].
- Comorbidities of renal disease including anemia, acidosis, hyperuricemia, secondary hyperparathyroidism, osteopenia/osteoporosis, hypertension, and short stature should be monitored regularly by a multidisciplinary care team (see Surveillance).

Neurologic findings. Some individuals develop a "metabolic stroke" or bilateral lacunar infarction of the basal ganglia during acute metabolic decompensation, which can produce an incapacitating movement disorder.

- **Individuals who have not undergone solid organ transplant**
  - The reported incidence in different cohorts is 17%-30% [Baumgarter & Viardot 1995, Hörster et al 2007]. Distinct segments of the globus pallidus (globus pallidus externa) and sometimes the substantia nigra in the cerebral peduncles are affected, suggesting a non-uniform, cell-specific susceptibility as the underlying mechanism of injury [Baker et al 2015].
  - Delayed myelination, incomplete opercularization, subcortical white matter changes, cortical atrophy, and brain stem and cerebellar changes have also been described [Hörster et al 2007, Harting et al 2008, Radmanesh et al 2008].
- **Individuals who have undergone liver and/or kidney transplantation**
  - After transplant, individuals can still develop acute lesions of the basal ganglia without overt metabolic decompensation, suggesting that the enzyme deficiency in the brain remains unchanged and trapping of toxic metabolites in the central nervous system compartment can lead to injury despite other systemic benefits of the transplantation. It is therefore important to continue dietary restrictions and metabolic care [Chakrapani et al 2002, Kaplan et al 2006, Vernon et al 2014].
  - Neurotoxicity from anti-rejection medications, especially calcineurin inhibitors (e.g., tacrolimus), has been observed in individuals with MMA who have undergone solid organ transplantation. These include tremors, seizures, and posterior reversible encephalopathy syndrome [Molema et al 2020]. This is important to consider because symptoms can improve with dose reduction/discontinuation of calcineurin inhibitors.

Pancreatitis. Acute pancreatitis is a well-recognized complication of isolated MMA, with a reported incidence of 10%-27% in different cohorts [Marquard et al 2011, Forny et al 2018, Hwang et al 2021]. It can occur acutely or chronically. Several affected individuals have recurrent pancreatitis episodes. Pancreatitis may be underrecognized because it can manifest nonspecifically with vomiting and abdominal pain. It is therefore recommended that acutely ill individuals with MMA undergo testing for lipase and amylase (see Management).

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 more than three standard deviations below the mean for both length and weight [Manoli et al 2016b].

- Rarely, affected individuals have documented growth hormone (GH) deficiency, for which GH therapy has been used.
- GH therapy has also been used for its anabolic effects or as part of the management of chronic kidney disease [Al-Owain et al 2004, Kao et al 2009, Baumgartner et al 2014].
- Response to GH therapy may vary; careful monitoring of the diet and metabolic parameters is necessary (see Management).

Functional immune impairment results in an increased susceptibility to severe infections, particularly by fungal and gram-negative organisms. Defects in both humoral and cellular immunity have been documented [Alizadeh Najjarbashi et al 2015, Harrington et al 2016, Altun et al 2022].

Bone marrow failure. During episodes of metabolic decompensation affected individuals can exhibit pancytopenia, with bone marrow hypoplasia and/or dysplasia that most frequently reverts to normal with supportive care [Bakshi et al 2018]. Anemia due to chronic disease or iron deficiency or secondary to progressive renal failure is common. Essential amino acid deficiencies can be a contributing factor in some individuals [Kölker et al 2015b].

Optic nerve atrophy. Late-onset optic atrophy associated with acute or subacute visual loss, resembling the presentation of the mitochondrial disorder Leber hereditary optic neuropathy (LHON), has been reported in 7%-11% of individuals with isolated MMA [Williams et al 2009, Pinar-Sueiro et al 2010, Traber et al 2011, Martinez Alvarez et al 2016] and up to 52% in a cohort of affected Middle Eastern individuals [Al-Owain et al 2019]. Response to antioxidant therapies (idebenone, coenzyme Q_{10}, and vitamin E) has been variable.

Cardiac complications

- **Arrhythmias or cardiomyopathy** (dilated or hypertrophic) have been reported in 10%-20% of individuals with isolated MMA, primarily *mut*^{0} or *mut-* (and *cblB* subtypes, as well as in the B_{12}-responsive *cblA* subtype) [Prada et al 2011, Chao et al 2012, Hörster et al 2021].
- **Arterial hypertension** associated with chronic kidney disease is common and necessitates monitoring and early intervention for renoprotection [Kölker et al 2015b, Park et al 2020].
- Additional cardiometabolic risk factors, including obesity, insulin resistance, and hyperlipidemia, need to be monitored regularly to optimize cardiovascular health [Gancheva et al 2020].

Liver steatosis, fibrosis, and cancer. Progressive liver toxicity associated with elevated transaminases (including GGT) and mild elevations of alpha-fetoprotein (AFP) has been observed in a number of individuals with isolated MMA. Liver ultrasound can show hepatomegaly and/or hyperechoic liver texture. Liver biopsies in three individuals showed steatosis, fibrosis, and (rarely) cirrhosis as early as age eight years [Imbard et al 2018].

- Liver neoplasms have been reported in five individuals, all severely affected (4 with *mut*^{0} subtype and 1 with *cblB*) [Cosson et al 2008, Chan et al 2015, Forny et al 2019]:
  - Three children had hepatoblastoma (diagnosed at 4 months, 19 months, and 11 years of age).
  - Two adults had hepatocellular carcinoma (diagnosed at age 22 years and 31 years).
- Periodic screening (typically at least annually or as clinically indicated) including liver transaminases, serum AFP level, and liver ultrasound is recommended in individuals with severe MMA subtypes (see Surveillance).

Renal cancer. A single case of a pediatric renal cell carcinoma has been reported in a female age six years with complete *MMUT* deficiency (*mut*^{0}), complicated by renal tubular acidosis, Stage 4 chronic renal disease, and hypercalcemia with increasing parathyroid hormone-related protein. Inactivating somatic variants in *TSC2* were identified in the tumor tissue [Potter et al 2017].

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]. Five-year survival improved from 33% in the 1970s to more than 80% in the 1990s.

- Overall mortality was about 50% for those with the *mut*^{0} enzymatic subtype (median age of death: 2 years) and for the *cblB* enzymatic subtype (median age of death: 2.9 years) compared to 40% for the *mut*$^-$ enzymatic subtype (median age of death: 4.5 years) and only about 5% for the *cblA* enzymatic subtype (1 death at age 14 days) [Hörster et al 2007].
- More recent reports from the European Registry and Network for Intoxication Type Metabolic Diseases notes a 6% mortality for *mut* MMA (combined *mut*$^-$ and *mut*^{0} populations) and a 100% survival for those with the B_{12}-responsive *cblA* subtype of MMA [Hörster et al 2021].

- Improvements likely reflect changes in diagnosis and NBS, improved treatment guidelines for acute crises/hyperammonemia, optimized nutrition with gastrostomy tube feeding, access to intensive care, hemodialysis and N-carbamylglutamate for the management of hyperammonemia, as well as earlier referral and better morbidity and mortality associated with solid organ transplantation.

Genotype-Phenotype Correlations

Precise genotype-phenotype correlations are difficult to determine since most affected individuals are compound heterozygotes and many pathogenic variants are not recurrent in the population.

MMAB

- **c.556C>T (p.Arg186Trp).** This is the most common pathogenic variant, present in 29%-33% of alleles from European and North American cohorts [Lerner-Ellis et al 2006, Forny et al 2022].

  Individuals homozygous for this pathogenic variant typically present in the neonatal period and are not responsive to hydroxocobalamin treatment.

- **c.700C>T (p.Gln234Ter).** Individuals with at least one c.700C>T (p.Gln234Ter) pathogenic variant generally have more variable, often later age of presentation/diagnosis (range: 2 days – 6.5 years) and some affected individuals demonstrate a biochemical response to hydroxocobalamin therapy [Forny et al 2022]. This variant is located in the last exon and may avoid nonsense-mediated decay, resulting in a partially functional protein.

MMADHC. Truncating pathogenic variants in the N-terminal region (exons 3, 4) cause isolated methylmalonic aciduria due to a defect in adenosylcobalamin synthesis; pathogenic variants elsewhere in this gene cause the other two biochemical phenotypes (see Genetically Related Disorders).

MMUT. 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 [Acquaviva et al 2005].

- Persons with two truncating pathogenic variants usually have the *mut*^{0} enzymatic subtype.
- Most of the pathogenic variants identified in the N-terminal domain have been associated with *mut*^{0} enzymatic subtype of methylmalonic acidemia [Acquaviva et al 2005, Forny et al 2016]
- The *mut*$^{-}$ enzymatic subtype is known to be associated mostly, but not exclusively, with pathogenic variants in the adenosylcobalamin-binding C-terminal domain of the MMUT protein.
- The *mut*$^{-}$ enzymatic subtype pathogenic variant usually plays a dominant role when in compound heterozygous state with a *mut*^{0} enzymatic subtype pathogenic variant, given a OH-Cbl response in the in vitro assay [Lempp et al 2007, Forny et al 2016].
- A linker domain spanning residues 482-585 separates the N-terminal, or substrate (methylmalonyl-CoA) binding domain from the C-terminal cobalamin-binding domain. This linker region is less conserved and has a lower frequency of pathogenic variants [Forny et al 2016].

Table 4. *MMUT* Pathogenic Missense Variants and Their Typical Enzymatic Subtype

Mut Enzymatic Subtype (when Homozygous)	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
mut^{0}	c.19C>T	p.Gln7Ter	NM_000255.4 NP_000246.2
mut^{0}	c.52C>T	p.Gln18Ter	
mut^{0}	c.91C>T	p.Arg31Ter	
mut^{0}	c.278G>A	p.Arg93His	

Table 4. 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} [1]	c.322C>T [2]	p.Arg108Cys	
mut^{0}	c.397G>A [3]	p.Gly133Arg	
mut^{0}	c.410C>T [4]	p.Ala137Val	
mut^{0}	c.415G>A [3]	p.Asp139Asn	
mut^{0}	c.521T>C	p.Phe174Ser	
mut^{0}	c.572C>A [5]	p.Ala191Glu	
mut^{0}	c.607G>A	p.Gly203Arg	
mut^{0}	c.643G>A [5]	p.Gly215Ser	
mut^{0}	c.655A>T [2, 3, 5]	p.Asn219Tyr	
mut^{0}	c.935G>T	p.Gly312Val	
mut^{0}	c.982C>T [3]	p.Leu328Phe	
mut^{0}	c.1105C>T	p.Arg369Cys	
mut^{0}	c.1106G>A [2, 3, 5, 6]	p.Arg369His	
mut^{0}	c.1280G>A	p.Gly427Asp	
mut^{0}	c.1553T>C	p.Leu518Pro	
mut^{0}	c.1843C>A [3]	p.Pro615Thr	
mut^{0}	c.1867G>A	p.Gly623Arg	
mut^{-}	c.299A>G [4, 6]	p.Tyr100Cys	
mut^{-}	c.566A>T [3, 7]	p.Asn189Ile	
mut^{-}	c.828G>C [3]	p.Glu276Asp	
mut^{-}	c.947A>G [2]	p.Tyr316Cys	
mut^{-}	c.970G>A [2]	p.Ala324Thr	
mut^{-}	c.1097A>G [4]	p.Asn366Ser	
mut^{-}	c.1160C>T [8]	p.Thr387Ile	
mut^{-}	c.1276G>A [2, 3]	p.Gly426Arg	
mut^{-}	c.1277G>A [3]	p.Gly426Glu	
mut^{-}	c.1663G>A [9]	p.Ala555Thr	
mut^{-}	c.1846C>T [2, 6]	p.Arg616Cys	
mut^{-}	c.1898T>G [10, 10]	p.Val633Gly	
mut^{-}	c.1924G>C [6]	p.Gly642Arg	
mut^{-}	c.2020C>T [8]	p.Leu674Phe	
mut^{-}	c.2054T>G [2, 10]	p.Leu685Arg	
mut^{-}	c.2080C>T [4, 6]	p.Arg694Trp	
mut^{-}	c.2099T>A [3, 5]	p.Met700Lys	

Table 4. continued from previous page.

Mut Enzymatic Subtype (when Homozygous)	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
mut^{-} [11]	c.2150G>T [2, 3, 6]	p.Gly717Val	
mut^{-}	c.2206C>T [3]	p.Leu736Phe	

Data in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
mut^{0} = *mut*^{0} enzymatic subtype
mut^{-} = *mut*$^{-}$ enzymatic subtype
NA = not applicable
1. Observed in individuals of Mexican/Hispanic descent.
2. Worgan et al [2006]
3. Forny et al [2014], Forny et al [2016]
4. Lempp et al [2007]
5. Acquaviva et al [2005]
6. Manoli et al [2021]
7. Chu et al [2016]
8. Dündar et al [2012]
9. Liang et al [2021], observed in individuals of Chinese descent
10. Adjalla et al [1998]
11. Observed in individuals of African descent

Prevalence

Several studies have estimated the birth prevalence of isolated methylmalonic acidemia. Urine screening for isolated methylmalonic acidemia in Quebec identified "symptomatic methylmalonic aciduria" in approximately 1:80,000 newborns screened [Sniderman et al 1999].

The aggregate incidence from different newborn screening (NBS) programs in the US is reported as 1:159,614 [Therrell et al 2014, Chapman et al 2018]. A meta-analysis [Almási et al 2019] confirmed that the detection rate of MMA and isolated MMA in North America, Europe and Asia-Pacific regions was <1:100,000, while rates in the Middle East, North Africa, and Japan were higher [Shigematsu et al 2002].

Genetically Related (Allelic) Disorders

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

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. The reason for the different phenotypes has been explained by reinitiation of translation at the Met62 or Met116 sites in the protein product of *MMADHC*, resulting in a truncated protein product that is sufficient for methylcobalamin synthesis [Jusufi et al 2014].

Differential Diagnosis

Other genetic causes of elevated methylmalonic acidemia/aciduria are listed in Table 5. Biochemical findings typically allow differentiation of these disorders from isolated methylmalonic acidemia (MMA).

It is important to note that individuals with *cblF* or *cblJ* enzymatic subtypes can have decreased serum vitamin B_{12} levels (the finding of decreased serum vitamin B_{12} levels suggests a role for the lysosome in intestinal uptake of ingested cobalamin).

With the exception of *cblX* deficiency due to variants in *HCFC1*, which is inherited in an X-linked manner, the disorders summarized in Table 5 are inherited in an autosomal recessive manner.

Table 5. Genetic Disorders with Methylmalonic Acidemia/Aciduria in the Differential Diagnosis of Isolated Methylmalonic Acidemia

Gene	Disorder	Biochemical Features	Clinical Features
ABCD4	*cblJ* deficiency (See Disorders of Intracellular Cobalamin Metabolism.)	Combined methylmalonic acidemia & hyperhomocysteinemia / homocystinuria; can present w/low serum B_{12} levels	5 persons reported: 3 presented neonatally w/ poor growth, feeding problems, hypotonia, respiratory distress, bone marrow suppression, & congenital heart defect. 2 presented in early childhood w/ hyperpigmentation & premature graying, & transient ischemic attack (in 1 of 2 children).
ACSF3	Combined malonic & methylmalonic aciduria (OMIM 614265)	High MA & MMA levels in urine or plasma, w/MMA excretion typically higher than MA excretion (MMA/MA >5). Because C3 (propionylcarnitine) is not ↑, affected infants are not detected by NBS based on a dried blood spot acylcarnitine analysis. [1]	Broad phenotypic spectrum ranging from completely asymptomatic to adults w/ neurologic syndromes (seizures, memory problems, psychiatric disease, ±cognitive decline) to children w/a wide range of manifestations (e.g., coma, ketoacidosis, hypoglycemia, FTT, ↑ transaminases, microcephaly, dystonia, axial hypotonia, &/or DD). No biochemical or clinical response to B_{12} therapy. A largely benign clinical course was reported in an unselected cohort (children-young adult) ascertained through urine NBS in Quebec. [1]
ALDH6A1	Methylmalonate semialdehyde dehydrogenase deficiency (OMIM 614105)	Extremely variable biochemical phenotypes: may be assoc w/3-hydroxyisobutyric, 3-OH propionic aciduria, 3-aminoisobutyric, & β-alanine, &/or transient methylmalonic acidemia/ aciduria [2]	Extremely variable clinical phenotypes incl severe ID, dysmorphic features; assoc w/ significant brain myelination defects [2]
AMN *CUBN*	Imerslund-Grasbeck syndrome (OMIM PS261100)	Low serum B_{12}, combined methylmalonic acidemia & hyperhomocysteinemia / homocystinuria, proteinuria in ~50% of affected persons	Megaloblastic anemia, pallor, FTT, recurrent infections, mild proteinuria.
CD320	Transcobalamin receptor defect (TcblR) (OMIM 613646)	Identified on NBS w/an ↑ C3 & ↑ C3/C2 ratio, ↑ plasma & urine MMA, ± ↑ homocysteine & normal or mildly ↑ serum vitamin B_{12} levels [3]	Largely asymptomatic. Normal biochemistry w/parenteral hydroxocobalamin or oral B_{12} supplementation. Bilateral central retinal artery occlusion assoc w/ hyperhomocysteinemia reported in 1 person. Most reported persons are homozygous for NM_016579.3:c.262_264del (p.Glu88del). [3, 4]
HCFC1 *THAP11* *ZNF143*	*cblX* & cblX-like deficiency (See Disorders of Intracellular Cobalamin Metabolism.)	Combined methylmalonic acidemia & hyperhomocysteinemia	IUGR, congenital malformations, severe DD w/significant ID, early-onset intractable seizures; microcephaly, brain malformations, & dysmorphic features in some persons

Table 5. continued from previous page.

Gene	Disorder	Biochemical Features	Clinical Features
LMBRD1	*cblF* deficiency (See Disorders of Intracellular Cobalamin Metabolism.)	Combined methylmalonic acidemia & hyperhomocysteinemia / homocystinuria; presents w/low serum B_{12} levels.	Often presents in infancy w/IUGR, poor postnatal growth, feeding difficulties, & DD; may also have stomatitis ± glossitis & congenital heart malformations
MMACHC *PRDX1*	*cblC* deficiency (See Disorders of Intracellular Cobalamin Metabolism.)	↑ plasma concentrations of homocysteine & methylmalonic acid, w/↓ levels of methionine	Frequently assoc w/DD, ID, progressive pigmentary retinopathy, "bull's eye" maculopathy, seizures; highly variable age of onset
MLYCD	Malonyl-CoA decarboxylase deficiency (OMIM 248360)	Combined methylmalonic & malonic aciduria w/significantly ↑ malonic vs methylmalonic acid levels; ↑ C3DC in acylcarnitine profile; ketotic dicarboxylic aciduria; hypoglycemia [5]	Hypoglycemia, metabolic acidosis, ketosis, cognitive impairment, seizures, microcephaly. Cardiomyopathy (left ventricular non-compaction, dilated or hypertrophic) is the leading cause of morbidity & mortality. [5]
SUCLA2	*SUCLA2*-related mtDNA depletion syndrome, encephalomyopathic form w/ methylmalonic aciduria (succinyl-CoA ligase deficiency)	Methylmalonic aciduria ranges from 10 to 200 mmol/mol creatinine & is accompanied by ↑ plasma concentrations of lactate, methylcitrate, 3-hydroxyproprionic & 3-hydroxyisovaleric acid, proprionylcarnitine, & C4-dicarboxylic carnitine (C4DC). [6]	Hypotonia, muscle atrophy (presenting at age ~3-6 mos), hyperkinesia, seizures, severe hearing impairment, & growth failure. Leigh syndrome-like disorder, cortical & basal ganglia atrophy, & dystonia. ~30% of affected persons succumb during childhood.
SUCLG1	*SUCLG1*-related mtDNA depletion syndrome, encephalomyopathic form w/ methylmalonic aciduria (succinyl-CoA ligase deficiency)	Methylmalonic aciduria ranges from 10 to 200 mmol/mol creatinine & is accompanied by ↑ plasma concentrations of lactate, methylcitrate, 3-hydroxyproprionic & 3-hydroxyisovaleric acid, proprionylcarnitine, & C4-dicarboxylic carnitine (C4DC) [6]	Hypotonia, muscle atrophy, feeding difficulties, & lactic acidosis. Affected infants commonly manifest DD/cognitive impairment, growth restriction/FTT, hepatopathy, hearing impairment, dystonia, & hypertonia. Life span is shortened (median survival: 20 mos).
TCN2	Transcobalamin II deficiency (OMIM 275350)	Combined methylmalonic acidemia & hyperhomocysteinemia. Mostly normal serum B_{12}, but ↓ unsaturated B_{12} binding capacity & ↓TCII detected by immunoassay. [7]	Pallor, FTT, diarrhea, pancytopenia (can be misdiagnosed as leukemia), recurrent infections, megaloblastic anemia, immunodeficiency, neurologic abnormalities if delayed or inadequate treatment winjectable B_{12}. [7]

Table 5. continued from previous page.

Gene	Disorder	Biochemical Features	Clinical Features
ZBTB11	*ZBTB11*-related intellectual developmental disorder (OMIM 618383)	Biochemical phenotype similar to ACSF3 deficiency w/high MA & MMA levels in urine or plasma, w/MMA excretion typically higher than MA excretion (MMA/MA >5). Because C3 (propionylcarnitine) is not ↑, affected infants are not detected by NBS based on a dried blood spot acylcarnitine analysis.	DD, ID, FTT, microcephaly, cataracts, brain abnormalities; some persons can have isolated ID & no biochemical phenotype. [8]

cbl = cobalamin; DD = developmental delay; FTT = failure to thrive; ID = intellectual disability; IUGR = intrauterine growth restriction; MA = malonic acid; MMA = methylmalonic acid; mtDNA = mitochondrial DNA; NBS = newborn screening

1. Alfares et al [2011], Sloan et al [2011], Levtova et al [2019]

2. Chambliss et al [2000], Sass et al [2012], Marcadier et al [2013], Dobrowolski et al [2020]

3. Quadros et al [2010], Hannah-Shmouni et al [2018], Pangilinan et al [2022], Pappas et al [2022]

4. Polymorphisms in *CD320* have been associated with increased risk for neural tube defects in an Irish cohort [Pangilinan et al 2010].

5. FitzPatrick et al [1999], Froese et al [2013], Chapel-Crespo et al [2019]

6. Elpeleg et al [2005], Carrozzo et al [2007], Ostergaard et al [2007], Morava et al [2009]

7. Schiff et al [2010], Trakadis et al [2014]

8. Strømme et al [1995], Fattahi et al [2018], Sumathipala et al [2022]

"Benign" MMA, "atypical"MMA, and MMA of unknown cause. Newborn screening (NBS) performed on urine rather than dried blood spots (a test method utilized in the province of Quebec and in the early years of the Massachusetts NBS program) identified infants with mild-to-moderate urinary methylmalonic acid excretion. Follow up of such infants revealed resolution in more than 50% of children, as well as an apparently benign, persistent, low-moderate methylmalonic acidemia in some [Giorgio et al 1976, Coulombe et al 1981, Ledley et al 1984, Sniderman et al 1999]. Relatively benign MMA with distal renal tubular acidosis (one sibship [Dudley et al 1998]) and isolated methylmalonic aciduria with normal plasma concentrations have also been reported [Sewell et al 1996, Martens et al 2002].

These older reports were published before the identification of *ACSF3* pathogenic variants as a cause of CMAMMA (*c*ombined *m*alonic *a*nd *m*ethyl*m*alonic *a*cidemia; OMIM 614265). Given the high minor allele frequency of known *ACSF3* pathogenic variants (MAF ~ 0.005, with a predicted incidence of 1:37,000) and benign clinical phenotypes in some individuals [Levtova et al 2019], it is likely thaT many of these individuals harbor pathogenic variants in *ACSF3*. In a large cohort of individuals with MMA of unknown cause, 6% of individuals were found to have pathogenic variants in *ACSF3, SUCLG1,* or *TCN2* [Pupavac et al 2016].

"Atypical" MMA has also been reported in an individual with mitochondrial depletion syndrome/complex IV deficiency and combined propionic and methylmalonic acidemia [Yano et al 2003]. The phenotype has similarities to the phenotypes in individuals with SUCLA2 or SUCLG1 deficiency.

Despite extensive genome and RNA sequencing, the genetic cause of isolated MMA and low propionate incorporation remains unknown in many individuals [Abdrabo et al 2020].

Vitamin B_{12} deficiency. Individuals with vitamin B_{12} deficiency can have elevated MMA and homocysteine and develop significant hematologic, neurologic, and psychiatric manifestations of B_{12} deficiency. Serum methylmalonic acid and plasma total homocysteine are more sensitive markers than B_{12} concentrations for detecting B_{12} deficiency [Stabler 2013].

Maternal B_{12} deficiency can produce an MMA syndrome in an infant that ranges from severe encephalopathy to elevated serum concentration of propionylcarnitine (C3) detected by NBS [Chace et al 2001, Campbell et al 2005, Hinton et al 2010, Scolamiero et al 2014]. This metabolic abnormality can also 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 bypass surgery [Grange & Finlay 1994, Celiker & Chawla 2009, González et al 2016]. 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.

It is important to screen pregnant mothers by testing maternal serum B_{12}, as well as serum methylmalonic acid and plasma total homocysteine, especially in all infants with positive NBS for elevated propionylcarnitine (C3) [Hinton et al 2010, Held et al 2022]. The addition of second-tier strategies of measuring methylmalonic/3-OH-propionic/methylcitric and homocysteine in dried blood spots can greatly improve detection of acquired vitamin B_{12} deficiency during NBS and allow treatment to prevent serious neurologic manifestations that can result from prolonged B_{12} deficiency in both infant and mother [Gramer et al 2020, Pajares et al 2021].

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 MMA [Chang et al 2000].

Management

Consensus guidelines on the diagnosis, management, and follow-up for individuals with methylmalonic acidemia were published in 2014 [Baumgartner et al 2014] (full text) and revised in 2021 [Forny et al 2021] (full text). Several additional expert reviews and publications detail management in acute crises and chronic monitoring, treatment of hyperammonemia, dietary practices, and other aspects of clinical care: Ktena et al [2015b], Fraser & Venditti [2016], Manoli et al [2016b], Valayannopoulos et al [2016], Aldubayan et al [2017], Evans et al [2017], Molema et al [2019], Pinto et al [2020], and Molema et al [2021b], among others.

When isolated MMA is suspected during the diagnostic evaluation due to elevated propionylcarnitine (C3) on a newborn blood spot, metabolic treatment should be initiated immediately, while the suspected diagnosis is being confirmed.

Once confirmed, development and evaluation of treatment plans, training and education of affected individuals and their families, and careful monitoring of dietary treatment (to avoid malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with isolated MMA, the evaluations summarized Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis of Isolated Methylmalonic Acidemia

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases is strongly recommended. • Consider short hospitalization at a center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises). • Review diet/food records w/metabolic dietitian. • Provide patient/family w/sick-day diet instructions & emergency treatment letter detailing mgmt plan & specialist contact information (see Table 12).

Table 6. continued from previous page.

Evaluation	Comment
Assessment of vitamin B_{12} responsiveness	• Generally, 1.0-mg injections (preferably of OHCbl) daily for 3-5 days • Obtain >1 baseline & follow-up measures over 10 days to assess for a ↓ in serum & urine methylmalonic acid (>50% ↓ is considered a positive B_{12} response).
Consider screening laboratory testing, which may incl: • Serum vitamin B_{12} concentration (in newborns; see above for vitamin B_{12} responsiveness.) • Serum chemistry panel incl renal function, liver enzymes [2] • CBC w/differential, iron status, folate • Arterial or venous blood gas • Plasma ammonium & lactic acid concentration • Urinalysis & urine ketone measurement • Quantitative plasma amino acids • Urine organic acids [3] • Serum methylmalonic acid & (if available) methylcitrate levels • Measurement of free & total carnitine levels • Pancreatic enzymes (amylase, lipase) • Serum albumin, total protein, & prealbumin to assess for nutritional status	The choice of screening labs depends on the patient's current age & clinical status.
Cardiac eval, which may incl: • Blood pressure measurement • EKG • Echocardiogram • Consult w/cardiologist	To assess for hypertension, abnormal QT interval, or other cardiac issues
Measure growth parameters (weight, length/height, head circumference).	To assess for failure to thrive, poor growth, &/or short stature
Baseline bone age & bone density (DXA)	• Assess for evidence of growth failure, need for gastrostomy tube to meet caloric needs, growth hormone treatment. • Prevent & treat osteopenia due to low-protein diet, renal osteodystrophy, delayed puberty.
Developmental assessment	Consider referral to developmental pediatrician after newborn period.
Consultation w/neurologist	• To assess for signs & symptoms of mvmt disorder, seizures, neuropathy • Brain imaging (MRI, MRS) in case of abnormal neurologic exam findings
Ophthalmology eval	To assess for optic nerve atrophy, which typically develops in older persons
Audiology eval	To assess for hearing loss [4]
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parental / affected person's coping skills & resources

Table 6. continued from previous page.

Evaluation	Comment
Genetic counseling by genetics professionals [5]	To inform affected persons & families re nature, MOI, & implications of isolated MMA in order to facilitate medical & personal decision making

CBC = complete blood count; OHCbl = hydroxocobalamin (as opposed to cyanocobalamin); MOI = mode of inheritance
1. After a new diagnosis of isolated methylmalonic acidemia in a child, the closest hospital and local pediatrician should also be informed. The family needs to have an updated emergency treatment letter and plan.
2. Na^+, K^+, CI^-, glucose, urea, creatinine, bicarbonate, AST, ALT, alkaline phosphatase, bilirubin [T/U], lipid panel, and cystatin-C.
3. By gas chromatography and mass spectrometry (GC-MS)
4. Hearing loss may occur in those who have experienced episodes of metabolic decompensation. The risk of hearing loss likely increases with age and can be seen along with optic nerve atrophy.
5. Medical/biochemical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

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. See Baumgartner et al [2014] (full text) and Forny et al [2021] (full text).

Table 7. Routine Daily Treatment in Individuals with Isolated Methylmalonic Acidemia

Principle/Manifestation	Treatment	Considerations/Other
Vitamin B_{12} supplementation in those known to be vitamin B_{12} responsive (See Table 6 .)	1 mg hydroxocobalamin administered by intramuscular injections, 1-3x/wk to daily, depending on metabolic response	Treatment w/cyanocobalamin is **contraindicated** in persons w/cobalamin C deficiency.
Restriction of natural protein, particularly of propiogenic amino acid precursors [1], while maintaining a high-calorie diet [2]	• Safe levels of natural protein per age group should be the aim (see 2007 FAO/WHO/UNU report). • The individual protein amount prescribed depends on growth parameters, metabolic stability, & stage of renal failure. • A propiogenic amino acid-deficient formula [3, 4] & a protein-free formula [5] (medical foods) are often used to provide addl calories • Use medical foods in moderation, w/relative intake of natural protein to propiogenic amino-acid-deficient formula not exceeding a ratio of 1:1	• Natural protein must be carefully titrated to allow for normal growth. [6] • As infants grow, total protein load is slowly ↓, based on growth, plasma amino acid concentrations, & plasma & urine methylmalonic acid concentrations. • Adjustment of dietary whole (complete)-protein intake (based on lab findings) is required lifelong (see Surveillance). • Isolated valine & isoleucine deficiencies may be caused in part by overuse of propiogenic amino-acid deficient formula; individual amino acid supplementation should be avoided (see Agents/ Circumstances to Avoid). • A ratio of complete protein to medical formula of 60%/40% to 70%/30% of total protein prescription is usually not assoc w/ deficiency of valine or isoleucine [Authors, personal observation]. • Attn to protein:energy ratio is important; when available, accurate assessment of resting energy expenditure can guide dietary & caloric prescriptions & avoid overfeeding. [7] • Plasma amino acids should be drawn ~4 hrs after food intake. • Continue protein restriction & dietary monitoring after liver transplantation to avoid extrahepatic disease complications.

Table 7. continued from previous page.

Principle/Manifestation	Treatment	Considerations/Other
Addressing feeding difficulties, recurrent vomiting, growth failure	Fundoplication, gastrostomy, or jejunostomy	Adequate provision of dietary information & education to parents, affected persons, & caregivers
Secondary carnitine deficiency	• Oral dosage of 50-100 mg/kg/day, up to ~300 mg/kg/day, of L-carnitine divided into 3-4 doses is common. • Dose is adjusted on an individual basis to maintain plasma free carnitine concentration w/in normal age-appropriate reference range.	Lifelong carnitine supplementation is generally recommended. [8]
Reduction in propionate production from gut flora	Metronidazole at a dose of 10-15 mg/kg/day typically given 1 wk to 10 days every 1-3 mos	• Rotating antibiotic regimens may be considered in some persons. • Responsiveness to antibiotic should be determined by a ↓ in serum methylmalonic acid concentration compared to patient's baseline value, or a ↓ in whole-body output of methylmalonic acid on antibiotic therapy by a timed urine collection compared to patient's baseline value. • Chronic cyclic antibiotic therapy is not innocuous; it introduces the risk of repopulation w/resistant flora & has been assoc w/peripheral neuropathy. [9]

1. Propiogenic amino acid precursors include isoleucine, valine, methionine and threonine
2. These dietary guidelines **do not apply** for patients with *CblC* deficiency, a separate disorder in the pathway [Manoli et al 2016a, Manoli et al 2016b].
3. For example, Propimex®-1/2, XMTVI-1/2, or OA-1/2
4. 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, especially if propiogenic amino-acid deficient formula is prescribed in excess of complete protein sources [Manoli et al 2016a, Manoli et al 2016b, Molema et al 2019, Pinto et al 2020, Molema et al 2021a].
5. For example, Pro-Phree® or Duocal®
6. In patients with low protein tolerance, severe restriction of propiogenic amino acid precursors (isoleucine, valine, methionine, and threonine) can produce a nutritional deficiency state.
7. Hauser et al [2011], Evans et al [2017]
8. 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.
9. 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 [Diodato et al 2018, Forny et al 2021].

Table 8. Treatment of Secondary Complications in Individuals with Isolated Methylmalonic Acidemia

Manifestation	Treatment	Consideration/Other
Developmental delay / Intellectual disability	• Supportive developmental therapies (may incl PT, OT, speech & cognitive therapies) • Coordination of individualized educational plan in school	Specialists in physiatry, PT, & OT & developmental pediatrician can help address the complex challenges faced by patients & families, maximize functionality, & improve quality of life. [1]

Table 8. continued from previous page.

Manifestation	Treatment	Consideration/Other
Tubulointerstitial nephritis	Standard therapy per nephrologist incl mgmt of chronic acidosis (bicitra or sodium bicarbonate), hypertension, anemia, hyperuricemia, & renal osteodystrophy/ osteopenia	• See Table 13 for recommended surveillance of renal function. • Avoid nephrotoxic medications (see Agents/ Circumstances to Avoid).
End-stage renal disease	Standard therapy, which may incl renal replacement therapy such as dialysis	Renal transplantation should be considered ideally before the need for hemodialysis, as those w/MMA are at risk for exacerbation of complications (e.g., hospitalizations, optic nerve disease)
Anemia / Bone marrow suppression [2]	Iron supplementation & erythropoietin may be considered; per nephrologiat	This is a typical complication of chronic renal failure & may resolve after renal transplantation.
Pancreatitis	Standard therapy incl bowel rest, analgesia, institution of IVF hydration & calories, & careful enteral alimentation w/low-fat preparations	Providing TPN w/intralipids can exacerbate pancreatitis.
Liver disease	Liver transplantation may be considered.	See also Prevention of Primary Manifestations.
Optic nerve atrophy	No specific treatment is available.	Community vision services
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Growth hormone deficiency	Growth hormone therapy	Dose & diet must be carefully adjusted. [3]
Movement disorders / Dystonia	Standard therapy per neurologist	Antispasmodic medications (trihexyphenidil, baclofen pump) or deep brain stimulation have been used in persons w/severe basal ganglia strokes.
Spasticity	Orthopedics / physical medicine & rehab / PT/OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.

IVF = intravenous fluids; OT = occupational therapy; PT = physical therapy; TPN = total parenteral nutrition
1. Ktena et al [2015b]
2. Inoue et al [1981], Guerra-Moreno et al [2003], MacFarland & Hartung [2015]
3. Documented growth hormone deficiency is a rare cause of growth failure [Bain et al 1995, Al-Owain et al 2004]

Table 9. Emergency Outpatient Treatment in Individuals with Isolated Methylmalonic Acidemia

Manifestation	Treatment	Consideration/Other
Vomiting, mildly increased catabolism [1]	• Carbohydrate supplementation orally or via tube feed [2] • Reduce natural protein intake [3] • Increase carnitine supplementation [4]	• Trial of outpatient treatment at home for up to 12 hours • Initiation of sick-day dietary plan • Reassessment (~every 2 hours) for clinical changes [5]
Fever	Administration of antipyretics (acetaminophen) if temperature rises >38.5°C	• Limit ibuprofen/NSAID use for renoprotection. • Avoid excessive acetaminophen use for risk of liver toxicity.

Table 9. continued from previous page.

Manifestation	Treatment	Consideration/Other
Occasional vomiting	Antiemetics [6]	Avoid repeat doses of ondansetron as it can prolong the QTc interval on EKG.

1. Fever <38.5°C (101°F); enteral or gastrostomy tube feeding is tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability)
2. Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide nutritional arrangements in the outpatient setting, with some centers recommending frequent provision of carbohydrate-rich, protein-free beverages every two hours, with frequent reassessment.
3. Some centers advocate additional steps such as reducing natural protein intake to zero or to 50% of the normal prescribed regimen for short periods (<24 hours) in the outpatient setting during intercurrent illness. Protein restriction more than 24-48 hours could lead to catabolism and should be avoided.
4. Temporarily increasing L-carnitine doses (e.g., to 200 mg/kg/day in infants) may be considered.
5. Alterations in mentation/alertness, fever, and enteral feeding tolerance, with any new or evolving clinical features should be discussed with the designated center of expertise for inherited metabolic diseases.
6. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

Acute manifestations (e.g., lethargy, encephalopathy, seizures, or progressive coma), often occurring in the setting of intercurrent illness and/or inadequate caloric intake, should be managed symptomatically and with generous caloric support in a hospital setting, with aggressive treatment and supportive care. Immediate consultation with a metabolic/biochemical geneticist is essential. Individuals with MMA can deteriorate rapidly and consultations with neurology, nephrology, and ICU teams are often required during crises (see Table 10).

Table 10. Acute Inpatient Treatment in Individuals with Methylmalonic Acidemia

Manifestation	Treatment [1]	Consideration/Other
↑ catabolism (due to fever, perioperative/peri-interventional fasting periods, repeated vomiting/diarrhea)	• Administration of high-energy IV fluids (D10/0.45 or 0.9 saline) at 1.5x maintenance rate to achieve age-appropriate glucose infusion rate (GIR), &, if needed insulin [2, 3] • Lipid emulsion is often necessary to provide sufficient calories at a dose of 1- 2 g/kg/day. • Address electrolytes & pH imbalances w/bicarbonate bolus, expect need for potassium replacement, as needed. [4] • ↓ or omit total protein for ≤24-48 hours. [5] • L-carnitine IV supplementation at 50-100 mg/kg/day either BID or QID	• Blood glucose, electrolyte concentrations (particularly sodium, potassium & bicarbonate concentrations), blood gases (w/monitoring of the anion gap), complete blood count & differential, serum lactate, urine ketones & urine output should be followed serially. • Central or peripheral TPN, which typically contains glucose & amino acids, & in some instances lipids, may be required. Thiamine may be added, esp in the presence of lactic acidosis. • Lipid infusions must be used w/caution due to risk of pancreatitis. • Dietary protein should be reintroduced enterally as soon as is feasible given the clinical scenario & may need to be further augmented w/TPN. • Nasograstric or orogastric feeding should be strongly considered so that enteral feedings can be reintroduced w/o delay.

Table 10. continued from previous page.

Manifestation	Treatment [1]	Consideration/Other
Hyperammonemia	• N-carbamylglutamate (NCG, Carbaglu®) [4, 6] • Administer IV sodium benzoate [4, 7]; if hyperammonemia persists consider sodium phenylbutyrate/acetate. • Hemodialysis or hemofiltration in consultation w/nephrologist may be required in the event of treatment failure (uncontrollable acidosis &/or hyperammonemia).	• A STAT plasma ammonia level should be obtained in the ED or on admission. • NCG activates the first step in the urea cycle (CPS1 enzyme) & is effective in lowering ammonia concentration during acute crises in patients w/MMA. Chronic or periodic use has been attempted in cases w/frequent decompensations, but has not obtained regulatory approval. [6] • Use of phenylacetate may accentuate low glutamine levels by generating phenylacetylglutamine & deplete 2-ketoglutarate in the TCA cycle.
New or evolving neurologic symptoms (↓ consciousness, seizures, dystonic/ choreoathetotic movements of face/extremities, changes in visual acuity)	• Initiate the treatment listed above for ↑ catabolism. • Neurologic consultation • Brain MRI	Symptoms of mvmt disorder can evolve gradually & periodic neurologic exam during crises is important for early initiation of PT to preserve function.
Bone marrow failure [8]	Granulocyte-colony stimulating factor may be considered.	Supportive care of the metabolic disease typically results in resolution of this finding.

BID = twice a day; ED = emergency department; PT = physical therapy; QID = four times a day; TPN = total parenteral nutrition
1. Inpatient emergency treatment should:
(1) take place at the closest medical facility,
(2) be started without delay, and
(3) be supervised by physicians and specialist dieticians at the responsible metabolic center, who should be contacted without delay.
2. Intravenous glucose solutions should preferably consist of D_{10} or $D_{12.5}$ (10 - 12.5% dextrose).
3. Use of insulin if hyperglycemia emerges; intravenous insulin given at a starting dose of 0.01-0.02 IU/kg/hour in the event of persistent hyperglycemia (>150-180 mg/dL in plasma, or glucosuria)
4. Consult published guidelines, Baumgartner et al [2014], Fraser & Venditti [2016], and Forny et al [2021]. Emergency laboratory studies can include amylase/lipase, plasma amino acid levels (to guide TPN prescription), plasma free and total carnitine levels (to guide carnitine supplementation), and serum MMA level.
5. Total protein can be gradually reintroduced depending on the patient's acid-base balance and remaining laboratory values, including ammonia, lactic acid, and plasma amino acids, among others.
6. The dose of N-carbamylglutamate (NCG) is 100 mg/kg bolus, followed by 25-62 mg/kg every 6 hours PO (orally). NCG is an N-acetylglutamate analog that allosterically activates CPS1 (carbamyl phosphate synthetase 1), the first step of the urea cycle [Tuchman et al 2008, Ah Mew et al 2010, Valayannopoulos et al 2016, Alfadhel et al 2021, Kiykim et al 2021].
7. The dose of sodium benzoate is 250 mg/kg as a bolus given over 90-120 min, followed by 250 mg/kg/day for maintenance, administered in 10% dextrose IV (intravenously). The same dose regimen is used for sodium phenylbutyrate (PBA). The maximum dose of sodium benzoate or sodium PBA is 5.5 g/m^2 or 12 g/d.
8. May include both bone marrow hypoplasia and/or dysplasia

Transition from pediatric to adult-centered multidisciplinary care settings. As MMA is a lifelong disorder with varying implications according to age, smooth transition of care from the pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties. Standardized procedures for transitional care do not exist for isolated MMA due to the absence of multidisciplinary outpatient departments.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with isolated methylmalonic acidemia together with pediatric or adult metabolic experts, dietitians, psychologists, and social workers.

- As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized and there is limited availability of clinics for adults with IEMs, continuous supervision by a center with expertise in metabolic diseases with sufficient resources is essential.

Prevention of Primary Manifestations

See also Table 7, which outlines dietary therapies that can help to prevent a metabolic crisis.

Large case series of affected individuals undergoing elective liver or combined liver/kidney transplantation (as opposed to isolated kidney transplantation) have detailed the indications, peri-operative complications, surgical and anesthesia approaches, anti-rejection regimens, and long-term outcomes in people with MMA undergoing these procedures. Inclusion of enzymatic and genotype information in case series of transplanted individuals allows for 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 is increasingly offered to younger affected individuals with significant metabolic instability, often in infancy, as a measure to prevent neurologic damage from recurrent metabolic crises associated with hyperammonemia. Referral to centers with experience in managing people with organic acidemias and continued monitoring and dietary therapy are essential for all MMA transplant recipients.

Table 11. Prevention of Primary Manifestations in Individuals with Isolated Methylmalonic Acidemia

Principle	Prevention	Considerations/Other
Protection against metabolic instability [1]	Liver transplantation [2]	• The underlying biochemical parameters & frequency of metabolic decompensation improve significantly in persons undergoing liver transplantation despite persistent metabolic abnormalities. • Liver transplantation is not curative. Patients remain at risk for long-term complications incl renal disease, basal ganglia injury & neurologic complications, & optic nerve atrophy. [3] High CSF concentrations of methylmalonic acid have been reported, especially when protein intake is liberalized. • Neurotoxicity due to calcineurin inhibitors has been described in transplanted patients. [4]

Table 11. continued from previous page.

Principle	Prevention	Considerations/Other
	Kidney transplantation [5]	• More mildly affected persons w/*mut*- or *cblA* MMA subtypes who have primarily renal failure may undergo isolated renal transplantation. • Elective kidney transplantation, before the onset of renal disease, cannot stabilize persons w/*mut*^{0} MMA and is not recommended. Double liver kidney transplant offers a higher amount of enzyme activity and allows for better control of kidney rejection. [6]

1. Most of the metabolic conversion of propionate occurs in the liver, so liver transplantation has the potential to provide enough enzymatic activity to avert severe metabolic crises for the most significantly affected individuals (MMA *mut*^{0} subtype) and is performed electively in younger people to avoid recurrent hospitalizations.
2. More than 100 individuals with MMA have undergone living-donor [Kasahara et al 2006, Morioka et al 2007, Kasahara et al 2014, Sakamoto et al 2016, Jang et al 2021] or cadaveric, orthotopic, or partial liver transplantation, or combined liver-kidney transplantation [van 't Hoff et al 1998, van't Hoff et al 1999, Kayler et al 2002, Nyhan et al 2002, Hsui et al 2003, McGuire et al 2011, Niemi et al 2015, Sloan et al 2015, Spada et al 2015, Critelli et al 2018, Jiang & Sun 2019, Chu et al 2019, Pillai et al 2019, Brassier et al 2020, Yap et al 2020, Molema et al 2021b]. Living-related donor transplants from heterozygote (carrier) parents may be associated with higher incidence of steatosis in the graft liver [Irie et al 2020].
3. Liver transplantation is associated with complications related to surgery (hepatic artery thrombosis, bile duct stenosis, perforation), graft rejection, and lifelong immunosuppressive therapy [Chakrapani et al 2002, Nyhan et al 2002, Kaplan et al 2006, Cosson et al 2008, McGuire et al 2011, Vernon et al 2014].
4. Neurotoxicity from calcineurin inhibitors, including posterior reversible encephalopathy syndrome (PRES), has been reported [Molema et al 2021b].
5. A smaller number (~20) of individuals with MMA (mostly with milder *mut*- or *cblA* subtypes) have received isolated renal allografts [Van Calcar et al 1998, Coman et al 2006, Cosson et al 2008, Clothier et al 2011, Lubrano et al 2013].
6. Brassier et al [2013], Brassier et al [2020]. 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.

Antioxidants. One individual with isolated MMA who was documented to be glutathione deficient after a severe metabolic crisis responded to ascorbate therapy [Treacy et al 1996]. Several studies document increased oxidative stress, glutathione depletion, and specific respiratory chain complex deficiencies in persons with the *mut*^{0} enzymatic subtype of MMA [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 individuals.

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]. Thiamine can help with severe lactic acidosis by overcoming pyruvate dehydrogenase inhibition during the treatment of acute metabolic crises (see Table 10). Whether chronic administration of CoQ10, vitamin E, or N-acetylcysteine could prevent long-term complications requires further study [Haijes et al 2019b].

Base replacement. Individuals with MMUT methylmalonic academia (subtype *mut*^{0} or *mut*$^-$) have renal tubular dysfunction and low-grade chronic acidosis that can accelerate the progression of their chronic kidney disease. Sodium bicarbonate or citrate (Bicitra®) replacement aiming for a serum bicarbonate concentration of 22-24 µmol/L, is recommended per standard guidelines for management of chronic kidney disease in children [KDOQI Work Group 2009, Brown et al 2020]. Bicitra has the additional benefit of offering citrate for TCA cycle anaplerosis and was studied in propionic acidemia [Longo et al 2017]. Polycitra contains potassium, which should be monitored closely due to the risk of developing hyperkalemia in individuals with kidney disease.

Prevention of Secondary Complications

One of the most important components of management (as it relates to prevention of secondary complications) is education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors (see also Tables 9 and 10). Adherence to a low-protein diet and frequent monitoring by the primary metabolic clinic (see Table 13), as well as continued care by other specialists (nephrologist, neurologist, gastroenterologist, cardiologist, and others), is necessary throughout life.

Table 12. Prevention of Secondary Manifestations in Individuals with Isolated Methylmalonic Acidemia

Manifestation/ Situation	Prevention	Considerations/Other
Acute encephalopathic crisis	• Intense & ongoing education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute encephalopathic crises • Treatment protocols & provision of emergency letters or cards to incl guidance for care in the event of illness while on holiday/vacation • MediAlert® bracelets/pendants, or car seat stickers • Adequate supplies of specialized dietary products (protein-free or propiogenic amino acid deficient formulas); medication required for maintenance & emergency treatment (vitamin B_{12}, carnitine, antipyretics, base replacement, in some cases Carbaglu®,& other medications, as well as gastrostomy or tube feeding supplies) should always be maintained at home.	• Written protocols for maintenance & emergency treatment should be provided to parents & primary care providers/ pediatricians, & to teachers & school staff. [1, 2] • Emergency letters/cards should be provided summarizing key information & principles of emergency treatment for MMA & containing contact info for the primary treating metabolic center. • For any planned travel or vacations, consider contacting a center of expertise near the destination prior to travel dates.
Surgery or procedure (incl dental) [3]	• Notify designated metabolic center in advance of the procedure to discuss perioperative management w/ surgeons & anesthesiologists. [4] • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional management).	Consider placing a "flag" in the affected person's medical record so that all care providers are aware of the diagnosis & the need to solicit opinions & guidance from designated metabolic specialists in the setting of certain procedures.

1. Essential information including written treatment protocols should be in place in anticipation of possible future need for inpatient emergency treatment.
2. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5°C; (2) vomiting/ diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms occur.
3. Special considerations regarding choices of anesthetic agents in this patient population may apply [Ktena et al 2015a, Ruzkova et al 2015].
4. Perioperative/perianesthetic management precautions may include visitations at specialist anesthetic clinics for affected persons deemed to be at high risk for perioperative complications.

Surveillance

During the first year of life, infants may need to be evaluated as frequently as every week and continued at intervals determined by the frequency of metabolic crises/admissions, growth patterns, and dietary needs. Attention to transition periods (e.g., after the first two years, in adolescence) with other stressors in the family are necessary for modification of dietary prescription.

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the following are recommended. See Table 13.

Table 13. Recommended Surveillance for Individuals with Isolated Methylmalonic Acidemia

Manifestation	Evaluation	Frequency/Comment
Poor growth	Measurement of growth & head circumference	At each visit
Metabolic abnormalities	Screening lab testing, incl: • Plasma amino acids [1] • Plasma & urine MMA levels • Serum acylcarnitine profile & free & total carnitine levels • Blood chemistries [2] • CBC	At least every 6-12 mos; more frequently in infants or in those who are unstable or require frequent changes in mgmt
Renal insufficiency [3]	• Measurement of creatinine, cystatin-C, & (if available) GFR (e.g., iohexol plasma decay) [4, 5, 6] • Renal imaging • Bone mineral density (DXA) [7] • Early referral to nephrologist is critical for consideration of renoprotective measures. • Monitoring of renal comorbidities by multidisciplinary team	At least annually, or as clinically indicated
Liver disease	• Liver ultrasound • Measurement of liver transaminases & alpha-fetoprotein [8]	Annually, or as clinically indicated [9]
Delayed acquisition of developmental milestones	Monitor developmental milestones. [10]	At each visit
	Neuropsychological testing using age-appropriate standardized assessment batteries, development of an individualized education plan.	As clinically indicated
	Standardized quality-of-life assessment tools for affected persons & parents/caregivers	As needed
Movement disorder	Assessment for clinical symptoms & signs of mvmt disorders, severity, & responses to treatment, PT, & pharmacologic interventions	At each visit
Optic nerve atrophy	Ophthalmology eval [11]	At least annually, or as clinically indicated

Table 13. continued from previous page.

Manifestation	Evaluation	Frequency/Comment
Hearing loss [12]	Audiology eval	At least annually in childhood & adolescence, or as clinically indicated

CBC = complete blood count; GFR = glomerular filtration rate; PT = physical therapy
1. 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].
2. Including Na+, K+, CI–, glucose, urea, creatinine, bicarbonate, AST, ALT, alkaline phosphatase, bilirubin (T/U), triglycerides, and cholesterol
3. Comorbidities of renal disease may include anemia, acidosis, hyperuricemia, secondary hyperparathyroidism, osteopenia/osteoporosis, hypertension, and short stature. In addition to cystatin-C, biochemical markers of bone health (Ca, P, alkaline phosphatase, parathyroid hormone, 1.25 dihydroxy-vit D (D3), and uric acid should be assessed periodically.
4. Combined equations based on creatinine and cystatin-C and measured GFR by iohexol clearance or other methods are expected to reflect more accurately the kidney function in people with MMA [Dao et al 2021]. Age-appropriate formulas to estimate GFR are available for both pediatric patients and adult patients.
5. To allow for early referral to nephrologist and appropriate timing of renal transplantation when needed [van't Hoff et al 1999, Kruszka et al 2013].
6. Nephrotoxic medication should be avoided (see Agents/Circumstances to Avoid).
7. DXA scan is typically done in older individuals, starting in adolescence, unless there is evidence for renal disease earlier.
8. Imbard et al [2018]
9. Particularly in individuals with severe MMA subtypes
10. Enrollment in early intervention programs for physical, occupational, and speech therapy is recommended.
11. To assess for optic nerve thinning/pallor
12. Hearing loss can occur in isolated MMA and may be a result of episodes of metabolic decompensation.

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]
- Nephrotoxic medications or agents (e.g. ibuprofen)
- Agents that prolong QTc in the EKG

Evaluation of Relatives at Risk

Evaluation of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of isolated methylmalonic acidemia.

For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening, measure serum methylmalonic acid, urine organic acids, plasma acylcarnitine profile, plasma amino acids, and serum B_{12}; and test for the familial isolated methylmalonic acidemia-causing pathogenic variants if biochemistry is abnormal.

Prenatal diagnosis of at-risk sibs may allow for prompt treatment of affected newborns at the time of delivery or prenatal administration of vitamin B_{12} in responsive subtypes, especially cblA.

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

Pregnancy Management

Affected mother

- In pregnancies of affected women with MMA, complications observed included acute decompensation or hyperammonemia, deterioration of renal function, and obstetric complications including preeclampsia, preterm delivery, and cæsarean section [Raval et al 2015].
- Despite high maternal MMA levels, fetal growth and development have been reported to be normal, suggesting negligible teratogenic effects to the fetus from exposure to high methylmalonic acid levels in utero, though long-term follow up with age-appropriate neurocognitive testing is limited [Wasserstein et al 1999, Deodato et al 2002].
- Pregnancies in transplant recipients are rare and further studies on the health of the offspring are needed [Marcellino et al 2021].

Unaffected mother with an affected fetus. 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]. These observations notwithstanding, maternal vitamin B_{12} supplementation for isolated MMA needs further study.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

13-C-propionate breath test. A stable isotope 13-C-propionate breath test has been developed as a surrogate biomarker of disease severity and was shown to correlate with in vitro 14-C-propionate incorporation, isolated MMA subtype, and several disease-related manifestations (rate of progression of chronic renal disease, growth parameters, and cognitive outcomes). Moreover, it showed a response to B_{12} supplementation or solid organ transplantation [Manoli et al 2021]. It can be used in specialized centers to help prognosticate disease severity and select affected individuals with very low oxidation rates for referral to transplantation or clinical trials testing novel genomic therapies.

Increased understanding of the underlying pathophysiology and the generation of disease-specific animal or cellular models has allowed the development of several novel therapies for isolated MMA [Chandler & Venditti 2019, Luciani et al 2020, Dimitrov et al 2021, Head et al 2022]. The effect of each of these therapeutic approaches on the long-term clinical outcomes of MMA remains to be elucidated.

- Liver-targeted genomic therapies including systemic canonic recombinant adeno-associated virus (rAAV) gene therapy [Chandler & Venditti 2008, Carrillo-Carrasco et al 2010, Chandler & Venditti 2010, Chandler & Venditti 2012, Sénac et al 2012, Chandler et al 2021], systemic mRNA replacement [An et al 2017], and genome editing into the albumin locus [Chandler et al 2021] have shown significant promise in animal models and are reaching Phase I/II clinical trials as promising alternatives to liver transplantation.
- Studies using primary hepatocytes from individuals with methylmalonic and propionic acidemia have found that administration of the small molecule 2,2-dimethylbutanoic acid (HST5040) leads to a dose dependent reduction in levels of methylmalonyl-CoA and other serum metabolites. This small molecule is being tested in clinical trials [Armstrong et al 2021].
- Investigational therapies intended to increase CoA levels by allosterically modulating pantothenate kinases, key enzymes in the CoA biosynthesis pathway, have been shown to increase free CoA and alleviate mitochondrial dysfunction in mouse models of propionic academia (PA) [Subramanian et al 2021] and are being tested in clinical trials for MMA and PA.
- Carefully designed clinical studies are required to evaluate the efficacy of antioxidant regimens in people with MMA.

Review the following for more information on current clinical trials on isolated MMA:

clinicaltrials.gov/ct2/show/NCT04581785

clinicaltrials.gov/ct2/show/NCT04732429

clinicaltrials.gov/ct2/show/NCT04899310

clinicaltrials.gov/ct2/show/NCT04836494

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

Genetic Counseling

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

Mode of Inheritance

All forms of isolated methylmalonic acidemia (MMA) – including complete or partial deficiency of the enzyme methylmalonyl-CoA mutase; defect in transport or synthesis of the methylmalonyl-CoA mutase cofactor, 5'deoxyadenosyl-cobalamin; and deficiency of the enzyme methylmalonyl-CoA epimerase – are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an isolated MMA-causing pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband. Uniparental isodisomy has been reported (*MMUT* [id(6)pat] and *MMAA* [segmental upd(4)mat] [Abramowicz et al 1994, Chen et al 2020].)
- Heterozygotes (carriers) of a pathogenic variant in an isolated MMA-related gene (i.e., *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC*) have normal metabolite concentrations.

Sibs of a proband

- If both parents are known to be heterozygous for an isolated MMA-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) of a pathogenic variant in an isolated MMA-causing gene (i.e., *MMUT*, *MMAA*, *MMAB*, *MCEE*, or *MMADHC*) have normal metabolite concentrations.

Offspring of a proband. Unless an affected individual's reproductive partner also has isolated MMA or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in an isolated MMA-related gene.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an isolated MMA-causing pathogenic variant.

Carrier Detection

- Carrier testing for at-risk relatives requires prior identification of the isolated MMA-causing pathogenic variants in the family.
- *MMUT* is included in the recommended gene list for carrier screening (Tier II) and may be included on expanded carrier screening panels [Gregg et al 2021].

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

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the isolated MMA-causing pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical testing. Both amniotic fluid measurements for methylmalonic acid and cellular biochemical assays (^{14}C propionate incorporation and complementation assays) on cultured fetal cells obtained by amniocentesis or chorionic villus sampling have been used for prenatal testing [Morel et al 2005]. However, due to the limited availability and longer turnaround time for cellular biochemical assays, the preferred method for prenatal diagnosis is molecular genetic testing.

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.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  MMA

- **MedlinePlus**
  Methylmalonic acidemia
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Email: info@oaanews.org
  oaanews.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  e-imd.org/event/european-registry-and-network-intoxication-type-metabolic-diseases

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	ZJU-CGGM Database (MMAB) MMAB @ LOVD	MMAB	MMAB
MMADHC	2q23.2	Cobalamin trafficking protein CblD	ZJU-CGGM Database (MMADHC) MMADHC @ LOVD	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; MAMM
251100	METHYLMALONIC ACIDURIA, cblA TYPE; MACA
251110	METHYLMALONIC ACIDURIA, cblB TYPE; MACB
251120	METHYLMALONYL-CoA EPIMERASE DEFICIENCY
607481	METABOLISM OF COBALAMIN ASSOCIATED A; MMAA
607568	METABOLISM OF COBALAMIN ASSOCIATED B; MMAB
608419	METHYLMALONYL-CoA EPIMERASE; MCEE
609058	METHYLMALONYL-CoA MUTASE; MMUT

Table B. continued from previous page.

611935	METABOLISM OF COBALAMIN ASSOCIATED D; MMADHC
620953	METHYLMALONIC ACIDURIA, cblD TYPE; MACD

Molecular Pathogenesis

Isolated MMA results from the failure to isomerize (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). Several different enzyme deficiencies affecting these metabolic steps can cause isolated MMA (Figure 2), including the methylmalonyl-CoA mutase itself and those providing the adenosylcobalamin as a cofactor. *MMAA* encodes a GTPase critical for the mitochondrial assembly of adenosylcobalamin (AdoCbl) to the methylmalonyl-CoA enzyme [Froese et al 2010]. *MMAB* encodes an ATP:cob(I)alamin adenosyltransferase (ATR) that transfers 5′-deoxyadenosyl from ATP to Cbl forming AdoCbl and delivers it to the methylmalonyl-CoA enzyme. *MMUT* encodes methylmalonyl-CoA mutase, a mitochondrial enzyme that catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA, which requires AdoCbl as coenzyme. *MMADHC* encodes a protein necessary in the early metabolic pathway of AdoCbl formation.

Aberrant post-translational modifications (methylmalonylation) have inhibitory effects on critical enzymes in the urea cycle and glycine cleavage pathways, causing the secondary disease manifestations such as hyperammonemia and hyperglycinemia in MMA [Head et al 2022].

Plasma fibroblast growth factor 21 (FGF21) has been characterized as a marker of hepatic mitochondrial dysfunction in MMA murine models and was shown to correlate with disease severity and long-term complications in different patient cohorts [Manoli et al 2018, Molema et al 2018, Manoli et al 2021].

Mechanism of disease causation. Loss of function

Table 14. Isolated Methylmalonic Acidemia: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
MCEE	A deep intronic variant (c.379-644A>G) that may not be detected by routine NGS panels or WES (depending on coverage) has been reported.
MMUT	Intronic variants that may not be detected by routine NGS panels or WES (depending on coverage) have been reported.

NGS = next generation sequencing; WES = whole-exome sequencing
1. Genes from Table 2 in alphabetic order

Notable variants by gene. See Table 4 for a list of specific pathogenic *MMUT* variants, that when in a homozygous state, lead to a specific predicted enzymatic phenotype. Further notable pathogenic variants by gene are listed in Table 15.

Table 15. Isolated Methylmalonic Acidemia: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
MCEE	NM_032601.4 NP_115990.3	c.139C>T	p.Arg47Ter	Common pathogenic variant, observed in homozygous state in >50% of reported persons [Heuberger et al 2019]
	NM_032601.4	c.379-644A>G	--	Deep intronic variant that creates new splice site [Waters et al 2016]
	NM_032601.4 NP_115990.3	c.419del	p.Lys140ArgfsTer6	Reported in an adult w/↑ serum MMA, neurodegeneration initially attributed to Parkinson disease, dementia, & stroke [Andréasson et al 2019]
MMAA	NM_172250.3 NP_758454.1	c.433C>T	p.Arg145Ter	Common pathogenic variant, accounting for 43% of mutated alleles [Lerner-Ellis et al 2004]
		c.503del	p.(Thr168MetfsTer10)	This variant resides on a common haplotype & has also been seen in Spanish persons [Martínez et al 2005]
MMAB	NM_052845.4 NP_443077.1	c.556C>T	p.Arg186Trp	Most common pathogenic variant, accounts for 33% of all alleles; seen exclusively in persons of European descent; assoc w/early onset of symptoms (age <1 yr) whether in heterozygous or homozygous state [Lerner-Ellis et al 2006]
		c.700C>T	p.Gln234Ter	Cobalamin-responsive variant assoc w/late-onset disease & an attenuated phenotype [Forny et al 2021]
		c.656_659del	p.Tyr219SerfsTer4	In vivo response to vitamin B_{12} reported in heterozygotes [Hörster et al 2007, Hörster et al 2021, Forny et al 2022]
MMUT [2]	NM_000255.4 NP_000246.2	c.322C>T	p.Arg108Cys	Observed in persons of Hispanic descent [Worgan et al 2006]
		c.2150G>T	p.Gly717Val	More common in persons of African descent [Worgan et al 2006]
		c.655A>T	p.Asn219Tyr	Observed more frequently in persons of European descent [Forny et al 2016]
		c.1106G>A	p.Arg369His	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Genes from Table 2 in alphabetic order

2. See also Table 4 for a list of variants and their predicted enzymatic activities when homozygous.

Chapter Notes

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- 18 January 2007 (cd) Revision: testing for mutations in *MMAA* and *MMAB* clinically available
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