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Propionic Acidemia

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Summary

Clinical characteristics

The spectrum of propionic acidemia (PA) ranges from neonatal onset to late-onset disease. Neonatal-onset PA, the most common form, is characterized by a healthy newborn with poor feeding and decreased arousal in the first few days of life, followed by progressive encephalopathy of unexplained origin. Without prompt diagnosis (often through newborn screening) and management, this is followed by progressive encephalopathy manifesting as lethargy, seizures, or coma that can result in death. It is frequently accompanied by metabolic acidosis with anion gap, lactic acidosis, ketonuria, hypoglycemia, hyperammonemia, and cytopenias.

Individuals with late-onset PA may remain asymptomatic and suffer a metabolic crisis under catabolic stress (e.g., illness, surgery, fasting) or may experience a more insidious onset with the development of multiorgan complications including vomiting, protein intolerance, failure to thrive, hypotonia, developmental delays or regression, movement disorders, or cardiomyopathy.

Isolated cardiomyopathy can be observed on rare occasions in the absence of clinical metabolic decompensation or neurocognitive deficits.

Manifestations of neonatal-onset and late-onset PA over time can include growth impairment, intellectual disability, seizures, basal ganglia lesions, pancreatitis, cardiomyopathy, and chronic kidney disease. Other rarely reported complications include optic atrophy, sensorineural hearing loss, and premature ovarian insufficiency.

Diagnosis/testing

PA is caused by deficiency of propionyl-coenzyme A carboxylase (PCC), the enzyme that catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. Newborns with PA tested by expanded newborn screening (NBS) have elevated C3 (propionylcarnitine). Testing of urine organic acids in persons who are symptomatic or those detected by NBS reveals elevated 3-hydroxypropionate and the presence of methylcitrate, tiglylglycine, propionylglycine, and lactic acid. Testing of plasma amino acids generally reveals elevated glycine.

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Confirmation of the diagnosis relies on detection of biallelic pathogenic variants in *PCCA* or *PCCB* by molecular genetic testing, or detection of deficient PCC enzymatic activity. In individuals with equivocal molecular genetic test results, a combination of enzymatic and molecular diagnostics may be necessary.

Management

Treatment of manifestations: The treatment of individuals with acutely decompensated PA is a medical emergency: treat precipitating factors such as infection, dehydration, vomiting; reverse catabolism by providing intravenous glucose and lipids; manage protein intake to reduce propiogenic precursors; remove toxic compounds using intravenous carnitine, and when necessary nitrogen scavenger medications and/or extracorporeal detoxification; transfer to a center with biochemical genetics expertise and the ability to support urgent hemodialysis, especially if hyperammonemia is present.

Prevention of primary manifestations: Individualized dietary management should be directed by an experienced physician and metabolic dietician to control the intake of propiogenic substrates and to guide increased caloric intake during illness to prevent catabolism, typically by using specialized medical food. Gastrostomy tube placement is an effective strategy to facilitate the administration of medications and nutrition during acute decompensations and to improve adherence in chronic management of PA. Medications may include L-carnitine supplementation to enhance excretion of propionic acid and oral metronidazole to reduce propionate production by gut bacteria. Orthotopic liver transplantation may be indicated in those with frequent metabolic decompensations, uncontrollable hyperammonemia, and/or poor growth.

Prevention of secondary complications: Consistent evaluation of the protein prescription, depending on age, sex, level of physical activity, severity of disorder, and presence of other factors such as intercurrent illness, surgery, and growth spurts to avoid insufficient or excessive protein intake is necessary. Excessive protein restriction or overreliance on medical foods can result in deficiency of essential amino acids and impaired growth, as well as catabolism-induced metabolic decompensation.

Surveillance: Monitor affected individuals with a catabolic stressor (fasting, fever, illness, injury, and surgery) closely to prevent and/or detect and manage metabolic decompensations early. Regularly assess: (1) growth, nutritional status, feeding ability, and psychomotor development; (2) vision and hearing; (3) cardiac function for signs of cardiomyopathy and prolonged QT interval; (4) metabolic status by monitoring routine chemistries, plasma ammonia, plasma amino acids, and plasma carnitine levels; (5) complete blood count; and (6) kidney function.

Agents/circumstances to avoid: Avoid prolonged fasting, catabolic stressors, and excessive protein intake. Lactated Ringer's solution is not recommended in individuals with organic acidemias. In individuals with QT abnormalities, avoid medications that can prolong the QT interval. Neuroleptic antiemetics (e.g., promethazine) can mask symptoms of progressive encephalopathy and are best avoided.

Evaluation of relatives at risk: Testing of at-risk sibs of an affected individual is warranted to allow for early diagnosis and treatment.

Genetic counseling

PA is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PCCA* or *PCCB* 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 *PCCA* or *PCCB* pathogenic variants have been identified in an affected family member, molecular genetic carrier testing of at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for propionic acidemia (PA) is primarily based on the quantification of propionylcarnitine (C3) and calculation of the C3/C2 ratio from the acylcarnitine profile on dried blood spots [Pajares et al 2021]. Other biochemical markers and ratios have been proposed as first-tier assessments to improve the accuracy of NBS, such as C17, C16:1-OH + C17, or C3/Met and C3/C16 ratios [Malvagia et al 2015, Martín-Rivada et al 2022].

Propionylcarnitine (C3) and/or C3/C2 ratio values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing (see Figure 1 and in Scenario 2, **Preliminary laboratory findings**). Some laboratories have implemented methylmalonate, 2-methylcitrate, total homocysteine, and 3-hydroxypropionic acid as a second-tier assessment to improve the positive predictive value of the NBS [Monostori et al 2017, Tangeraas et al 2020, Held et al 2022].

If the follow-up biochemical testing supports the diagnosis of PA, confirmatory testing is required (see Establishing the Diagnosis).

The following medical interventions need to begin immediately upon receipt of an abnormal NBS result while additional testing is being performed:

- Clinical evaluation of the newborn
- Education of the caregivers to avoid prolonged fasting and identify concerning symptoms, including poor feeding, hypothermia, difficulty breathing, vomiting, seizures, or lethargy
- Immediate intervention if concerning symptoms are present (see also Management):
  - Admission to the hospital
  - Obtain complete blood count (CBC), glucose, electrolytes, blood gas, ammonia, and urinary ketones
  - Infusion of IV glucose
  - Nutritional evaluation and consideration of dietary protein restriction
  - Carnitine supplementation

Scenario 2: Symptomatic Individual

A symptomatic individual who has either (1) typical findings associated with late-onset PA or (2) untreated infantile-onset PA resulting from NBS not performed, false negative NBS result, symptoms prior to receiving NBS result, or caregivers not adherent to the recommended treatment after a positive NBS result may have the following nonspecific clinical findings, preliminary laboratory findings, and family history.

Clinical findings

- Developmental delay
- Intellectual disability
- Failure to thrive
- Chronic gastrointestinal complaints
- Protein intolerance
- Acute psychosis
- Hypotonia
- Difficulty breathing
- Seizures

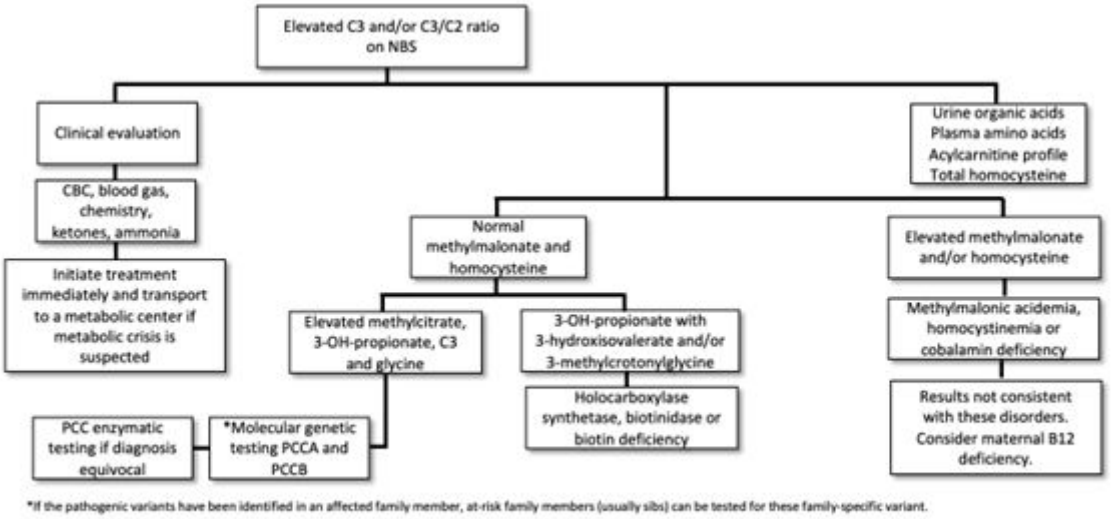

Figure 1. Immediate management and testing algorithm to be pursued simultaneously after abnormal newborn screening concerning for propionic acidemia

- Movement disorders such as dystonia and choreoathetosis
- Apparently isolated dilated or hypertrophic cardiomyopathy without a known history of metabolic decompensation or neurocognitive deficits

Preliminary laboratory findings. Biochemical findings consistent with PA include (see Figure 2):

- Plasma acylcarnitine profile. Elevated propionylcarnitine (C3)
- Urine organic acids
  - Elevated 3-hydroxypropionate
  - Elevated 2-methylcitrate
  - Presence of tiglylglycine and/or propionylglycine
- Plasma amino acids. Elevated glycine and/or low glutamine
- Pertinent negative findings. Individuals with propionic acidemia have normal methylmalonic acid and total plasma homocysteine levels.

Note: Because elevations of PA metabolites individually are not entirely specific to PA, follow-up molecular or enzymatic testing is required to establish or rule out the diagnosis of PA (see Establishing the Diagnosis).

Common laboratory abnormalities during acute decompensation include:

- High-anion gap metabolic acidosis
- Lactic acidosis
- Hyperammonemia
- Elevated plasma and urinary ketones
- Low-to-normal blood glucose
- Neutropenia, anemia, and/or thrombocytopenia

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not exclude the diagnosis of propionic acidemia.

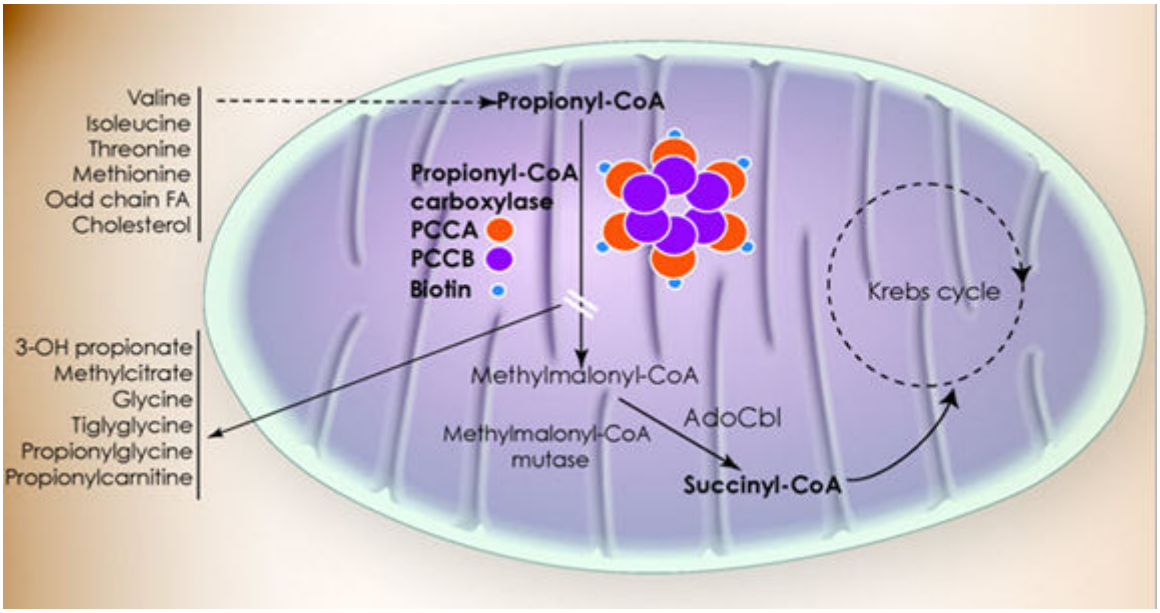

Figure 2. Metabolic pathway. Propionyl-coenzyme A carboxylase (PCC) catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA, which enters the Krebs cycle via succinyl-CoA. Sources of propionate include: valine, isoleucine, threonine, methionine, odd-chain fatty acids, and cholesterol. Deficiency of PCC results in propionic acidemia (PA) and accumulation of 3-OH propionate, methylcitrate, and glycine, among other metabolites. PCC, located inside the mitochondrion, is a heterododecamer (α6β6) comprising six alpha subunits (orange) and six beta subunits (purple). Biotin (blue), bicarbonate, and ATP have binding sites in the alpha subunit. The beta subunits form a central core.

Establishing the Diagnosis

The diagnosis of propionic acidemia **is established** in a proband with biallelic pathogenic (or likely pathogenic) variants in either *PCCA* or *PCCB* identified by molecular genetic testing (Table 1) or significantly reduced activity of propionyl-coenzyme A carboxylase (PCC) in lymphocytes or cultured skin fibroblasts. Given the high sensitivity of molecular genetic testing and characteristic findings on biochemical tests, enzymatic testing is rarely used.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *PCCA* or *PCCB* variant of uncertain significance does not establish or rule out the diagnosis.

Scenario 1: Abnormal NBS result. When NBS results and other laboratory findings suggest the diagnosis of propionic acidemia, molecular genetic testing approaches include use of a **multigene panel**.

A multigene panel that includes *PCCA*, *PCCB*, and sometimes 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: A symptomatic individual. When the diagnosis of PA has not been considered (because an individual has atypical findings associated with late-onset PA or untreated infantile-onset PA resulting from NBS not performed, symptoms prior to NBS result, or false negative NBS result), **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 1. Molecular Genetic Testing Used in Propionic Acidemia

Gene [1]	Proportion of PA Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Identified by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
PCCA	50% [5]	78% [6]	20.5% [6, 7]
PCCB	50% [5]	97% [6]	3% [6, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single exon deletions or duplications.
5. Gupta et al [2016] reported a total of 73 *PCCA* and 73 *PCCB* pathogenic variants causing PA.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]. Desviat et al [2009] reported that only 1.5% of individuals with *PCCA*-related PA could not be characterized molecularly when analyzed using both sequencing and copy number analysis [Desviat et al 2009]. See also Rivera-Barahona et al [2018], Shchelochkov et al [2019], and Liu et al [2022].
7. Exon deletions account for to ~20% of *PCCA* disease-causing alleles [Zayed 2015, Stenson et al 2020, Wang et al 2020, Maryami et al 2023].
8. Fewer than 10 *PCCB* large-deletion alleles have been reported [Stenson et al 2020].

Enzyme analysis. In individuals with inconclusive genetic testing results, enzymatic activity measurements can help to establish the diagnosis [Forny et al 2021]. The assay uses lymphocytes or cultured skin fibroblasts to determine enzyme activity of PCC.

Clinical Characteristics

Clinical Description

Propionic acidemia (PA) presents with a wide spectrum of symptoms and age of onset. The onset of symptoms in PA varies depending on several factors, including residual enzymatic activity, intake of propiogenic precursors, and the occurrence of catabolic stressors.

Neonatal-Onset PA

A common presentation of PA in the neonatal period is characterized by a healthy newborn with poor feeding and decreased arousal in the first few days of life, followed by progressive encephalopathy of unexplained origin. Most individuals eventually diagnosed with PA become symptomatic in the first weeks of life, with 50%-60%

exhibiting clinical signs at the time of the newborn screen (NBS) report. Without prompt diagnosis and management, neonates can develop progressive encephalopathy manifesting as lethargy, seizures, or coma that can result in death (see Table 2).

Table 2. Propionic Acidemia: Findings During Initial Metabolic Crisis

Symptoms	Prevalence [1, 2]
Feeding difficulties	42%-87%
Poor weight gain and growth	58%-71%
Vomiting	45%-61%
Hypotonia	47%-69%
Somnolence	35%-70%
Coma	12%-26%
Seizures	12%-60%
Tachypnea	29%-48%
Hypothermia	20%
Hyperammonemia [3]	41%-97%
Metabolic acidosis	55%-73%
Hypoglycemia	19%-20%
Anemia	8%-57%
Leukopenia	25%-52%
Thrombocytopenia	8%-23%

1. The differences in the reported prevalence of findings may reflect variable sizes of the cohorts, age of the last evaluation, length of follow up, differences in therapeutic approaches, availability, turnaround time and sensitivity of NBS, screening method (NBS vs selective metabolic screen), overlap of affected individuals in the reported cohorts, and ascertainment and recall bias.
2. Prevalences derived from Grünert et al [2012], Kölker et al [2015a], McCrory et al [2017], Liu et al [2022], and Unsal et al [2022].
3. The mean plasma ammonia levels in people with neonatal-onset PA was reported to vary between 207 and 697 µmol/L [Grünert et al 2012, Kölker et al 2015a]. Reported plasma ammonia levels fall between 86 and 3,377 µmol/L [Kölker et al 2015a]. In contrast to urea cycle disorders, hyperammonemia in PA is usually accompanied by low or normal level of glutamine.

Following initial clinical and biochemical stabilization, individuals with neonatal-onset PA may experience metabolic decompensations and can develop a range of symptoms affecting different organ systems.

Metabolic decompensations. Individuals affected by PA can develop episodic metabolic decompensations, especially in the first years of life. Metabolic acidosis, hyperammonemia, pancreatitis, metabolic strokes, cardiomyopathy, bone marrow suppression, seizures, and encephalopathy can accompany acutely deranged metabolism.

- These episodes can be life-threatening and are often precipitated by illnesses, infections, surgery, or any physiologic stress that can trigger a catabolic state.
- Infectious complications (e.g., sepsis or bacterial meningitis) often accompany metabolic crises and are the major contributors to mortality.
- The long-term cognitive outcome of individuals with PA is negatively correlated with the number of metabolic decompensations [Grünert et al 2012] or the residual enzyme activity [Shchelochkov et al 2021].

Growth. Linear growth delay and deceleration of the head circumference may become evident with age and can be seen in both earlier- and later-onset groups [Kölker et al 2015b, Saleemani et al 2021]. Poor growth may be

exacerbated by malnutrition secondary to feeding difficulties, recurrent emesis, excessive protein restriction, and potentially iatrogenic amino acid imbalances [Manoli et al 2016].

Neurologic manifestations include developmental delay, developmental regression, intellectual disability, seizures, hypotonia, spasticity, and movement disorders [Nizon et al 2013, Shchelochkov et al 2024].

- **Seizures** were reported in 13%-53% and EEG abnormalities in 40%-63% of individuals with PA [Karimzadeh et al 2014, AlGhamdi et al 2018]. Reported types of seizures include infantile spasms, tonic-clonic, tonic, myoclonic, atonic, absence, and focal. Seizures were one of the presenting features of the initial metabolic episode in 12%-26% of affected individuals [Kölker et al 2015b].
- **Basal ganglia and brain MRI findings.** Individuals with PA are at high risk for basal ganglia lesions, especially during episodes of acute encephalopathy or metabolic instability [Nizon et al 2013, Karimzadeh et al 2014].
  - Basal ganglia changes seen in 7%-56% of individuals may be preceded by an acute "stroke-like" episode and manifest as altered mental status, dystonia, choreoathetosis, or hemiplegia.
  - The frequency of movement disorders in individuals with PA appears to be independent of the age of symptom onset [Kölker et al 2015a, Kölker et al 2015b].
  - A unique pattern of cortical and subcortical diffusion restriction can be seen on brain MRI in some affected individuals [Pfeifer et al 2018].
  - Other brain MRI findings can include delayed myelination, white matter changes, cerebral atrophy, cerebellar atrophy, and cerebellar hemorrhage.
  - Clinically unstable individuals appear to be at higher risk of developing brain abnormalities. In a study of 17 individuals with PA who had clinical seizures, all had abnormal MRI findings and a history of more than ten metabolic decompensations [Haberlandt et al 2009].
  - Magnetic resonance spectroscopy (MRS) can reveal decreased myoinositol and N-acetylaspartate and abnormal Glx (glutamine, glutamate, and gamma-aminobutyric acid) peaks in the basal ganglia.
- **Intellectual disability.** Developmental delays and neurologic dysfunction can be documented even in individuals without known episodes of hyperammonemia or ketoacidosis [Schreiber et al 2012]. The prevalence of intellectual disability varies between 32% and 76% depending on the reported cohort [Pena & Burton 2012, Shchelochkov et al 2024].
- **Psychiatric manifestations.** Autism spectrum disorder is seen in 21%-39% of individuals with PA [Cotrina et al 2019, Shchelochkov et al 2024]. The prevalence of other comorbidities such as attention-deficit/hyperactivity disorder, anxiety, and acute psychosis is incompletely characterized [Nizon et al 2013, Vernon et al 2014].

Cardiomyopathy has been recognized as a common complication of PA. Both dilated and hypertrophic cardiomyopathy have been observed. The reported prevalence varies between 7% and 39% in PA cohorts [Romano et al 2010, Kovacevic et al 2020].

- Early clinical manifestations of cardiomyopathy include increased fatigue, tachypnea, hepatomegaly, hypotension, tachycardia, or bradycardia.
- The median age of onset of cardiomyopathy ranges from 7 to 14.4 years [Romano et al 2010, Kovacevic et al 2020].
- The age of PA diagnosis and frequency of metabolic decompensation do not correlate with presence/absence of cardiomyopathy in individuals with PA [Romano et al 2010].
- Rarely, cardiomyopathy can occur as an apparently isolated clinical phenomenon in previously healthy individuals without documented episodes of metabolic decompensation or neurocognitive deficits [Laemmle et al 2014, Riemersma et al 2017, Grotto et al 2018, Son et al 2021].
- Cardiomyopathy can progress to cardiac failure and may be associated with sudden death.

Cardiac rhythm abnormalities. A prolonged QT interval is often detected in individuals with PA [Kölker et al 2015b]. This can be associated with syncope, arrhythmia, and cardiac arrest [Della Rossa et al 2022].

Gastrointestinal manifestations

- Pancreatitis (reported in 3%-18% of individuals with PA) may be recurrent and present with anorexia, recurrent nausea, and abdominal pain. In some individuals, recurrent pancreatitis can lead to insulin-dependent diabetes [Hwang et al 2021] and/or evolve into exocrine pancreatic insufficiency presenting with diarrhea, fatty stools, constipation, and unexplained weight loss.
- Poor feeding and lack of appetite are common, affecting up to 76% of affected individuals.
- Emesis and diarrhea are commonly reported in individuals with PA, and are a recurrent problem in approximately 6% [Kölker et al 2015b].
- Liver manifestations include hepatomegaly, hypoalbuminemia, and abnormal liver function tests (ALT, AST, GGT, INR, and bilirubin) [Silva et al 2024]. The mechanisms of hepatic dysfunction are poorly understood. Prothrombin time and partial thromboplastin time outside of episodes of acute metabolic decompensation tend to remain in the reference range [Imbard et al 2018, Silva et al 2024].

Renal abnormalities. Chronic kidney disease is observed in half of individuals with PA and can lead to kidney failure and the need for kidney transplantation [Shchelochkov et al 2019].

Hematologic abnormalities. Although anemia, leukopenia, and thrombocytopenia are common, pancytopenia is seen less frequently, in 6%-15% of individuals [Kölker et al 2015b].

Immune system. Early retrospective data suggested a high frequency of recurrent infections, seen in 60%-80% of affected individuals. Factors predisposing to infectious complications are likely diverse and may include bone marrow suppression, immune dysfunction instigated by propionic acid metabolites, indwelling catheters (e.g., central lines), frequent hospitalizations, and potential nutritional deficiencies caused by dietary modification.

Hypogammaglobulinemia, B-cell lymphopenia, neutropenia, decreased CD4 and CD8 counts, decreased naïve T cells, and abnormal CD4/CD8 ratio have been described [Altun et al 2022]. Hypogammaglobulinemia, reported in as many as 15% of affected individuals, has required treatment with immunoglobulin in some cases [Pena & Burton 2012].

Ophthalmologic manifestations. Eye findings include dyschromatopsia, optic nerve atrophy, scotomas, and abnormal electroretinogram and visual evoked potentials. In addition, optic tract and cortical abnormalities have been occasionally noted [Noval et al 2013, Arias et al 2014].

Optic neuropathy occurs in 11%-25% of affected individuals [Pena & Burton 2012, Martinez Alvarez et al 2016]. The onset of optic neuropathy can be acute or insidious; further deterioration can occur during metabolic decompensations triggered by infections or surgery [Martinez Alvarez et al 2016]. The mean age of diagnosis is approximately 13 years (range: 2-24 years) [Arias et al 2014, Martinez Alvarez et al 2016].

Hearing loss. Sensorineural hearing loss was reported in 1% and 13% in two large cohorts of individuals with PA [Grünert et al 2012, Kölker et al 2015b].

Musculoskeletal system. Severe osteopenia and osteoporosis have been described in adults with PA [Grünert et al 2012].

Dermatologic manifestations resembling acrodermatitis enteropathica are frequently associated with deficiency of essential amino acids, particularly isoleucine, which can be inadvertently overrestricted in the diet of persons with PA [Domínguez-Cruz et al 2011].

Other rare complications. Isolated case reports describe clinical findings that could be causally associated with propionic acidemia but require further characterization: muscle lipidosis [de Baulny et al 2005]; myopathy

[Martinez Alvarez et al 2016]; premature ovarian insufficiency [Lam et al 2011]; oligomenorrhea [Martín-Hernández et al 2009]; hypothyroidism [Vernon et al 2014, Martinez Alvarez et al 2016]; and parathyroid hormone resistance resolving after hemodialysis [Griffin et al 1996].

Late-Onset PA

Relatively high residual activity of propionyl-CoA carboxylase may delay the onset of symptoms beyond the neonatal period.

Individuals with late-onset PA may remain asymptomatic during infancy [Cappuccio et al 2017, Scott Schwoerer et al 2018, Wang et al 2018, Ehrenberg et al 2022] until they present later in life with cardiomyopathy [Laemmle et al 2014, Riemersma et al 2017, Grotto et al 2018, Scott Schwoerer et al 2018, Son et al 2021, Ehrenberg et al 2022], arrhythmia [Scott Schwoerer et al 2018], pancreatitis [Choe et al 2019], metabolic crisis [Scott Schwoerer et al 2018, Henning & Glasser 2023], or basal ganglia injury with or without associated hyperammonemia [Xiu-yun et al 2021, Ji et al 2022, Jiang et al 2022, Li et al 2022]. Some individuals have experienced acute severe symptoms precipitated by a catabolic stress event such as illness [Scott Schwoerer et al 2018, Henning & Glasser 2023], surgery, alcohol ingestion [Xiu-yun et al 2021], high-protein diet [Ji et al 2022], or vomiting/fasting [Li et al 2022]. Others have experienced a more insidious onset of disease with the development of multiorgan complications. Acute psychosis can be a presenting feature of PA in older individuals, especially in those not evaluated by NBS, thus warranting a high index of suspicion for this uncommon cause of psychosis in the older general population [Dejean de la Bâtie et al 2014]. Reported features of late-onset PA are summarized in Table 3.

Table 3. Features of Late-Onset Propionic Acidemia

Clinical Features	Laboratory Findings
• Encephalopathy, coma, weakness, gait abnormalities, &/or seizures precipitated by catabolic stressors (e.g., intercurrent illness, surgery) • Vomiting, protein intolerance, failure to thrive, hypotonia, developmental regression, movement disorders • Cardiomyopathy [1] • Long QT syndrome [2] • Psychiatric symptoms [3] • Pancreatitis [4]	• ± metabolic acidosis or hyperammonemia • Missed [5] on NBS or mild C3 elevation [5, 6] • Normal [6] or elevated [7] 3-OH-propionic acid & 2-methylcitric acid • Hyperglycinemia • MRI abnormalities incl basal ganglia lesions [8]

1. Lee et al [2009], Laemmle et al [2014], Riemersma et al [2017], Grotto et al [2018],Scott Schwoerer et al [2018], Son et al [2021], Ehrenberg et al [2022]
2. Liu et al [2022]
3. Li et al [2022]
4. Choe et al [2019]
5. Scott Schwoerer et al [2018], Ehrenberg et al [2022]
6. Cappuccio et al [2017]
7. Choe et al [2019], Son et al [2021]
8. Broomfield et al [2010], Xiu-yun et al [2021], Ji et al [2022], Jiang et al [2022], Li et al [2022]

Life Span

PA is associated with a high risk of mortality. However, reported mortality rates appear to be on the decline: 41%-90% in the 1980-1990s, 17%-72% in the 2000s, and 7%-18% in the 2010s [Rousson & Guibaud 1984, Surtees et al 1992, van der Meer et al 1996, Pérez-Cerdá et al 2000, Sass et al 2004, de Baulny et al 2005, Dionisi-Vici et al 2006, Touati et al 2006, Grünert et al 2012, Najafi et al 2016]. Observed decline in reported mortality likely reflects the length of follow up, introduction of NBS, expansion of the PA phenotype, proactive medical management, and elective liver transplantation.

Genotype-Phenotype Correlations

Although there is no evidence that identification of the underlying pathogenic variants in *PCCA* or *PCCB* can guide management or prognosis of PA, as no genotype-phenotype correlation is known [Pena et al 2012, Forny et al 2021], certain pathogenic variants in *PCCA* or *PCCB* may be associated with neonatal-onset or late-onset propionic acidemia [Liu et all 2022].

- Some homozygous missense pathogenic variants, in which partial enzymatic activity is retained, have been associated with a less severe phenotype.
  - The homozygous *PCCB* c.1606A>G (p.Asn536Asp) pathogenic variant in Amish and Mennonite populations is associated with high residual propionyl-coenzyme A carboxylase (PCC) activity. Individuals homozygous for this variant can be missed by NBS and present with metabolic crisis and cardiomyopathy after the newborn period [Scott Schwoerer et al 2018, Hannah et al 2019, Ehrenberg et al 2022].
  - The homozygous pathogenic variant *PCCB* c.1304T>C (p.Tyr435Cys) has been detected in apparently asymptomatic or mildly affected children identified through NBS in Japan [Tajima et al 2021].
- However, some *PCCB* missense pathogenic variants (p.Gly112Asp, p.Arg512Cys, and p.Leu519Pro) that affect heterododecamer formation can result in undetectable PCC enzyme activity and a severe phenotype.
- The homozygous *PCCA* pathogenic variant c.425G>A (p.Gly142Asp) in the Saudi Arabian population is associated with a severe phenotype with neonatal onset [Al-Hamed et al 2019].

Nomenclature

Propionic acidemia and propionyl-coenzyme A carboxylase deficiency are the two most common terms used to describe this condition. Ketotic hyperglycinemia was used in the 1960s before defects in PCC were determined to be the underlying cause of PA. The term propionic aciduria is used infrequently.

Prevalence

PA is an ultrarare metabolic disorder, and its prevalence varies by population. While PA is included in routine NBS in the United States, many countries still rely on clinical presentation for diagnosis, and therefore, the worldwide incidence of PA remains unknown. However, PA is more frequent in certain ancestral groups due to the founder effect of specific pathogenic variants.

- In the US, the birth incidence of PA is estimated to be ~0.14-0.77 in 100,000 (1 in 129,792 to 1 in 733,000) [Chapman et al 2018, Adhikari et al 2020].
- The incidence in other parts of the world is generally higher [Almási et al 2019]:
  - 0.32-2.20 in 100,000 in Europe
  - 0.05-5.05 in 100,000 in the Asia-Pacific
  - 3.6-8.14 in 100,000 in the Middle East and North Africa

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PCCA* or *PCCB*.

Differential Diagnosis

Genetic Disorders

Table 4. Genes of Interest in the Differential Diagnosis of Propionic Acidemia

Biochemical Finding	Gene(s)	Disorder	MOI	Comment
↑ C3 (propionylcarnitine) on NBS	*MMUT*	Methylmalonyl-CoA mutase deficiency (See Isolated Methylmalonic Acidemia.)	AR	↑ C3 on NBS can be caused by methylmalonic acidemias resulting from methylmalonyl-CoA mutase deficiency & disorders of intracellular cobalamin metabolism or cobalamin transport.
	CD320 *ABCD4* *HCFC1* *LMBRD1* *MMACHC/PRDX1* *MMADHC* *MTR* *MTRR* *THAP11* *ZNF143*	Intracellular cobalamin metabolism	AR (XL) [1]	
	TCN2	Transcobalamin II deficiency (OMIM 275350)	AR	
↑ 3-hydroxypropionate ± 2-methylcitrate on urine organic acid assay	*ALDH6A1*	Methylmalonic semialdehyde dehydrogenase deficiency (OMIM 614105)	AR	May result in accumulation of 3-hydroxyisobutyric, 3-hydroxypropionic, 3-aminoisobutyric, & methylmalonic acids [2]
	BTD	Biotinidase deficiency	AR	Multiple carboxylase deficiency (biotinidase & holocarboxylase synthetase deficiencies) shows ↑ of lactic acid, 3-hydroxyvaleric acid, & 3-methylcrotonylglycine caused by defective activity of pyruvate carboxylase, propionyl-CoA carboxylase, & 3-methylcrotonyl-CoA carboxylase.
	HLCS	Holocarboxylase synthetase deficiency (OMIM 253270)	AR	
	MCEE *MMAA* *MMAB* *MMADHC* *MMUT*	Isolated methylmalonic acidemia	AR	Assoc w/ ↑ 2-methylcitric acid, ↑ 3-hydroxypropionate acid, & ↑ methylmalonic acid. Cobalamin C, D, & F metabolism defects result in abnormal homocysteine metabolism. Total plasma homocysteine can help in diagnostic workup of persons ascertained w/↑ propionylcarnitine.
	CA5A	Carbonic anhydrase VA deficiency	AR	Urine organic acid assay can reveal ↑ 3-hydroxypropionate, propionylglycine, & 2-methylcitrate as well as 3-methylcrotonylglycine, 3-hydroxybutyrate, alpha-ketoglutarate, & 3-hydroxyisovalerate. Plasma acylcarnitine profile in carbonic anhydrase VA deficiency is usually normal.
	>1,000 genes	Primary mitochondrial disorders	AD AR Mat XL	May be included in differential diagnosis when persons present w/hyperammonemia, metabolic acidosis, ketonuria, & hypoglycemia [3]

Table 4. continued from previous page.

Biochemical Finding	Gene(s)	Disorder	MOI	Comment
Hyperglycinemia	*AMT* *GLDC* (*GCSH*) [4]	Nonketotic hyperglycinemia	AR	Hyperglycinemia can be seen in a wide range of clinical conditions incl nonketotic hyperglycinemia, ketotic hyperglycinemia, & transient glycine encephalopathy.
Hyperammonemia	*ARG1* *ASL* *ASS1* *CPS1* *NAGS* *OTC* *SLC25A13* *SLC25A15*	Urea cycle disorders	AR XL [5]	Hyperammonemia in neonatal PA can prompt consideration of other disorders affecting ammonia metabolism (e.g., urea cycle disorders, organic acidemias, pyruvate carboxylase deficiency, & carbonic anhydrase VA deficiency). Usually, glutamine levels in hyperammonemic persons w/PA are normal or low. [6]
	PC	Pyruvate carboxylase deficiency	AR	
	CA5A	Carbonic anhydrase VA deficiency	AR	
↑ anion-gap metabolic acidosis	>65 genes [7]	Organic acidemias	AR (XL)	

AD = autosomal dominant; AR = autosomal recessive; CoA = coenzyme A; Mat = maternal; MOI = mode of inheritance; NBS = newborn screening; NL = normal; PA = propionic acidemia; XL = X-linked

1. Most disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner. *HCFC1*-related intracellular cobalamin metabolism is inherited in an X-linked manner.

2. Dobrowolski et al [2020]

3. Baumgartner et al [2014]

4. Biallelic pathogenic variants in *GCSH* have been proposed as a cause of nonketotic hyperglycinemia in two individuals; however, this remains unconfirmed (see Nonketotic Hyperglycinemia).

5. Ornithine transcarbamylase deficiency is inherited in an X-linked manner. The rest of the urea cycle disorders are inherited in an autosomal recessive manner.

6. Summar & Mew [2018]

7. Ramsay et al [2018]

Acquired Disorders and Other Considerations

Maternal B_{12} deficiency can be associated with elevated C3 (propionylcarnitine) on newborn screening. Additional testing in the mother and newborn usually reveals elevated total plasma homocysteine along with increased methylmalonic acid with or without 2-methylcitrate on urine organic acids. Maternal risk factors for cobalamin deficiency are malabsorption or vegan diet. In maternal vitamin B_{12} deficiency, the infant's vitamin B_{12} levels can be in the normal range [Gramer & Hoffmann 2020].

Bacterial overgrowth (including *Propionibacterium or Lactobacterium*) or short gut syndrome [Kumps et al 2002] can be associated with elevated 3-hydroxypropionate.

Valproate treatment can be associated with hyperglycinemia [Ahmad et al 2021].

Conditions included in the commonly used mnemonic **MUDPILES: *m*ethanol, *u*remia (chronic kidney failure), *d*iabetic ketoacidosis, *p*ropylene glycol, *i*nfection, *i*ron, *i*soniazid, *l*actic acidosis, *e*thylene glycol, *s*alicylates** can be associated with increased anion-gap metabolic acidosis.

Poisoning and child abuse. In at least one individual with organic acidemia, propionic acid was misidentified as ethylene glycol [Hoffman 1991]. In another case, ethylene glycol poisoning presented with hyperglycinemia and glycolic acid in urine [Woolf et al 1992].

Management

Several proposed acute and chronic clinical management guidelines for individuals with propionic acidemia (PA) have been published and revised [Baumgartner et al 2014, Forny et al 2021].

When PA is suspected (i.e., an abnormal newborn screening [NBS] result or suggestive symptoms), metabolic treatment should be initiated immediately.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PA, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Propionic Acidemia: Recommended Evaluations Following Initial Diagnosis

Evaluation	Comment
Consultation w/metabolic physician, biochemical geneticist, & specialist metabolic dietitian [1]	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended). • Consider short hospitalization at a center w/expertise for inherited metabolic conditions to provide caregivers with detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises).
Laboratory studies in symptomatic persons	• Blood gas w/base balance • Electrolytes w/anion gap, calcium, & phosphorus • Glucose • Plasma ammonia level • Urine ketones • Plasma amino acids • Urine organic acids • Acylcarnitine profile • Total & free carnitine levels • Complete blood count [2] • Amylase & lipase [3]
Laboratory studies in asymptomatic or stabilized persons	• Assessment of nutritional status (calcium, phosphorus, albumin, plasma amino acids, vitamin levels [incl thiamine & 25-hydroxyvitamin D]) • Iron panel • Kidney function (e.g., cystatin C, parathyroid hormone, erythropoietin) • CBC to assess for cytopenias
Measurement of growth parameters	Assessment for growth failure & microcephaly
Neurologic eval	• Consider brain MRI if the neurologic eval is abnormal. • Consider EEG if seizures are a concern.
EKG & echocardiogram [4]	Assessment for cardiomyopathy, prolonged QTc interval, & arrhythmia
Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk or significant feeding difficulties.
Immunology & hematology eval	• Consider in persons w/cytopenias or suspicion for immunodeficiency. • To assess for hypogammaglobulinemia, B-cell lymphopenia, & ↓ CD4 & CD8 counts • Complete adherence to regional immunization schedules & influenza vaccination is indicated. [5]
Dilated eye exam	Assessment for optic atrophy & other vision abnormalities
Audiology eval	Assessment for sensorineural hearing loss

Table 5. continued from previous page.

Evaluation	Comment
Developmental assessment	• Consultation w/PT, OT, & speech therapist • Consider referral to developmental pediatrician.
Osteopenia eval	• Consider in persons w/history of fractures or nutritional concerns. • DXA scan might aid in eval in persons age ≥3 yrs.
Consultation w/psychologist &/or social worker	Assessment of parental & affected person's coping skills & resources
Genetic counseling by genetics professionals [6]	To obtain a pedigree & inform affected persons & families re nature, MOI, & implications of PA

CBC = complete blood count; DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance; OT = occupational therapist; PA = propionic acidemia; PT = physical therapist

1. After a new diagnosis of PA in a child, the closest hospital and local pediatrician should also be informed.

2. To evaluate for cytopenias. Consider initiating an evaluation for sepsis if the CBC and clinical signs are suggestive of an infection.

3. To evaluate for pancreatitis

4. Consider ambulatory EKG monitoring.

5. Baumgartner et al [2014], Forny et al [2021]

5. Medical geneticist, certified genetic counselor, and certified advanced genetic nurse

Treatment of Manifestations

The mainstay nutritional intervention is modification of diet to control the intake of propiogenic substrates (isoleucine, valine, methionine, and threonine), while ensuring normal protein synthesis and preventing protein catabolism, amino acid deficiencies, and growth restriction.

Table 6. Propionic Acidemia: Routine Daily Treatment

Principle/Manifestation	Treatment	Considerations/Other
↓ of propiogenic load while maintaining safe protein & energy intake	• Dietary restriction of propiogenic amino acids (isoleucine, valine, methionine, & threonine) by using specialized medical foods [1] • Specific dietary protein prescription might vary based on multiple factors incl disease severity & growth rate. [2] • Additional calories can be provided using protein-free formulas.	• Dietary mgmt needs to be directed by experienced physician & metabolic dietician. • Recommended protein intake is age- & sex-dependent. [3] • The ratio of natural source protein to medical foods varies depending on clinical status, laboratory parameters, & growth trajectory. [2] • Screening laboratory studies to guide nutritional intervention are listed in Table 10.
↓ of propionic acid production in intestinal gut flora	Oral metronidazole therapy may be considered.	• 1 regimen uses a 1-week-on, 3-weeks off approach. [4] • Possible benefits may need to be balanced against known side effects (constipation, diarrhea, optic neuropathy, & pancreatitis). [5]
Secondary carnitine deficiency	• Oral levocarnintine, 100 mg/kg/day [6, 7] • Dose is adjusted on individual basis to maintain plasma free L-carnitine concentration w/in reference range.	Lifelong carnitine supplementation is recommended.

Table 6. continued from previous page.

Principle/Manifestation	Treatment	Considerations/Other
Impaired ureagenesis	Carglumic acid can be considered in persons w/recurrent acute hyperammonemia. [8]	
Addressing ↑ energy/caloric demands	Gastrostomy or jejunostomy to address feeding issues	Adequate provision of info & education to parents, affected persons, & caregivers
Biotin trial	Given favorable profile of biotin, short therapeutic trial may be considered.	• There is no consensus re use of biotin supplementation or optimal dose in treatment of PA. • There is no evidence that a biotin-responsive form of PA exists. [9]
Dystonic movement disorders	Standard therapeutic options may incl use of benzodiazepines, baclofen, trihexyphenidyl, &/or botulinum toxin type A	Referral to neurologist for ongoing mgmt
Optic nerve atrophy	Coenzyme Q_{10} & vitamin E administration could help improve visual symptoms in some persons; [10] however, there is no established standard of care.	Referral to ophthalmologist for ongoing mgmt
Hearing loss	Treatment per audiologist	
Chronic kidney disease	Referral to nephrologist for ongoing mgmt	• Advanced kidney disease may require dialysis &/or kidney transplant. • Avoidance of nephrotoxic drugs
Cardiomyopathy	Treatment per cardiologist	• Liver transplant (LT) has been proposed as therapeutic measure in persons w/heart failure, w/improvement of LVEF reported in some persons. [11] • However, recurrence of cardiomyopathy after LT has also been reported. [12] • Successful cases of combined heart & liver transplantation & isolated heart transplantation have been reported. [13]
Prolonged QTc	Treatment per cardiologist	Special caution has to be taken w/medications that can prolong QT interval such as antipsychotics or ondansetron.
Arrhythmia		Placement of automated implantable defibrillator has been reported. [14]
Cytopenias	Treatment per hematologist	
Global developmental delay	• Consider speech therapy, PT, &/or OT as needed. • Rehab therapy	
Psychotic episodes	Thorough eval to rule out hyperammonemia, metabolic acidosis, & CNS abnormalities	• Care must be taken when using antipsychotic medications, as they can mask clinical signs of encephalopathy or cause adverse effects in persons w/PA. • Special caution should be exercised w/ antipsychotic medications that have QT interval prolongation potential.

Table 6. continued from previous page.

Principle/Manifestation	Treatment	Considerations/Other
Persistent dermatitis or eczema	Nutritional eval that may result in dietary changes or supplemental vitamins &/or minerals	Evaluate for iatrogenic dietary deficiencies of essential amino acids, essential fatty acids, vitamins, & minerals.

CNS = central nervous system; LVEF = left ventricular ejection fraction; OT = occupational therapy; PA = propionic acidemia; PT = physical therapy

1. For protein restriction, the authors suggest adherence to the recommended age- and sex-specific safe levels of protein and energy intake [Joint WHO/FAO/UNU Expert Consultation 2007] (full text [pdf]). Restriction of the essential amino acids should be done under control of growth and laboratory parameters.

2. Jurecki et al [2019]

3. See Baumgartner et al [2014], Table 11 and Forny et al [2021].

4. Chapman et al [2012], Sutton et al [2012]

5. Anwyll et al [2020]

6. The optimal dose of levocarnitine has not been established.

7. When calculating the daily dose of levocarnitine, one needs to consider the presence of this pharmaceutic compound in medical foods and the maximum daily dose in older affected individuals.

8. Alfadhel et al [2021], Yap et al [2024]

9. Forny et al [2021]

10. Pinar-Sueiro et al [2010]

11. Romano et al [2010], Critelli et al [2018]

12. Berry et al [2020], Hejazi et al [2023]

13. Genuardi et al [2019], Seguchi et al [2022], Lotan et al [2023]

14. Peregud-Pogorzelska et al [2019], Della Rossa et al [2022]

Home management of metabolic status. The detection and management of metabolic decompensations at home are a critical part of the chronic management of PA. Affected individuals and care providers should notify their medical team about new symptoms and discuss the appropriateness of home management. Strategies to achieve home management should be tailored to each affected individual and family.

Table 7. Propionic Acidemia: Home Management of Mild Metabolic Status

Manifestation	Treatment	Consideration/Other
Mildly ↑ catabolism [1]	• Carbohydrate supplementation orally or via tube feed [2] • Reduce natural protein intake[3] • Increasing carnitine supplementation[4]	• Trial of outpatient treatment at home for up to 12 hrs • Reassessment (every ~2 hrs) for clinical changes [5] • At-home detection & monitoring of urine ketones may be considered.
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperature rises >38.5 °C [6]	

Table 7. continued from previous page.

Manifestation	Treatment	Consideration/Other
Occasional vomiting	Antiemetics [7]	

1. Fever; enteral or gastrostomy tube feeding is tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability, hypotonia, dystonia)
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.
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 discussed with the designated center of expertise for inherited metabolic diseases
6. More aggressive fever management might be indicated in individuals with history of arrythmias and/or prolonged QT interval.
7. 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 (see Agents/Circumstances to Avoid).

Acute metabolic decompensation. Birth, infections, trauma, surgery, postpartum recovery, or other forms of stress and hormonal changes can result in a catabolic response that leads, among other things, to protein breakdown with release of propiogenic amino acids that cannot be adequately broken down in PA. The goal of acute management is to reverse this process through promotion of anabolism and removal of toxic intermediates. Treatment of individuals with acutely decompensated PA is a medical emergency and requires transfer to a center with biochemical genetics expertise and the ability to support urgent hemodialysis, especially if hyperammonemia is present.

Table 8. Propionic Acidemia: Acute Inpatient Treatment [1]

Manifestation	Treatment	Consideration/Other
Identification of precipitating factors	Treatment, as indicated, based on precipitating factor	May incl eval & treatment of infections, fever, dehydration, pain, vomiting, or other sources of physical stress
↑ catabolism (due to fever, perioperative/peri-interventional fasting periods, repeated vomiting/diarrhea)	• Address electrolytes & pH imbalances w/IV fluid mgmt. • Administration of high-energy fluids &, if hyperglycemia develops, insulin [2, 3] • IV intralipids • ↓ or omit natural protein for <24 hours [4, 5, 6] • L-carnitine supplementation (100 mg/kg/day IV divided in 3 doses) [7, 8]	• The volume, glucose content, & electrolyte composition of IV fluids is determined by age, target glucose infusion rates, cardiovascular status, kidney condition, & coadministration of other medications. • Blood glucose, electrolyte concentrations, blood gases, plasma amino acids, plasma carnitine levels, urine pH, & ketone screening may all be of use in guiding mgmt. • Ongoing assessment of hemodynamic status & for new neurologic signs is critical. • Inadequate or delayed start of emergency treatment is a risk factor for basal ganglia injury, dystonia, & consequent long-term disability.

Table 8. continued from previous page.

Manifestation	Treatment	Consideration/Other
Hyperammonemia	• Sodium benzoate has been used in mgmt of acute hyperammonemia in persons w/PA. [9] • Oral carglumic acid (150 mg/kg/day in persons <15 kg & 3.3 gm/m^2 in persons >15 kg) can aid in detoxification of ammonia during neonatal & acute decompensations. • Extracorporeal detoxification can be considered (see **Metabolic acidosis** in this table).	Cautious use of sodium phenylacetate & sodium phenylbutyrate in treatment of hyperammonemia in persons w/PA is advised, since they can accentuate frequently observed low plasma glutamine. [10, 11]
Metabolic acidosis	• Correction of metabolic acidosis using IV fluids • Extracorporeal detoxification may be required for persistent acidosis & hyperammonemia (plasma ammonia level >250-300 µmol/L) not responding to fluid & drug treatment.	• Judicious use of IV sodium bicarbonate to improve acid-base balance under control of fluid status & electrolyte balance • Methods of extracorporeal detoxification incl continuous venovenous hemofiltration, extracorporeal membrane oxygenation, or hemodialysis.
Pancreatitis	Treatment per gastroenterologist	
Respiratory failure	Ventilatory support, incl intubation, in an ICU setting	
Arrythmia/Cardiomyopathy	Treatment per cardiologist	See Prevention of Primary Manifestations.
Cytopenias	Packed red blood cell or platelet transfusions may be considered.	Cytopenias typically improve w/metabolic control.
Seizures	Anti-seizure medication per neurologist	The use of valproic acid in organic acidemias is not recommended; however, several authors have described its use in persons w/PA. [12]

ICU = intensive care unit; IV = intravenous; PA = propionic acidemia

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 D10 ½ normal saline typically between 100% and 150% of the maintenance requirements is a common starting fluid. Dextrose solutions exceeding the concentration of 12.5% require a central line placement. The target glucose infusion rates vary by age [Baumgartner et al 2014].

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. Protein intake can be gradually advanced as tolerated; careful introduction of non-propiogenic amino acids from medical foods might be needed to achieve a positive nitrogen balance [Jurecki et al 2019].

5. If transition to enteral feedings within 48 hours is not possible, total parenteral nutrition is required.

6. Parenteral amino acid solutions are prescribed based on the recommended daily intake of age-appropriate energy and protein needs and adjusted using daily and weekly growth data and plasma amino acid concentrations.

7. L-carnitine (with options to increase the dose) can be given intravenously, which enhances bioavailability.

8. Carnitine supplementation may enhance the detoxification of propionic acid by conjugating into propionylcarnitine, which is excreted by the kidneys. Alternatively, it may relieve intracellular coenzyme A accretion.

9. Forny et al [2021]

10. Al-Hassnan et al [2003], Filipowicz et al [2006]

11. For a discussion regarding the use of sodium benzoate vs sodium phenylacetate and sodium phenylbutyrate in PA, see Baumgartner et al [2014] and Forny et al [2021].

12. Haberlandt et al [2009], Schreiber et al [2012]

Transitional care from pediatric to adult-centered multidisciplinary care settings. As 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.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with PA together with pediatric metabolic experts, dietitians, psychologists, and social workers.
- As the long-term course of metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise in metabolic diseases is essential.

Prevention of Primary Manifestations

Prevention and proactive management of metabolic crises (see Tables 6, 7, and 8) is important to maximize favorable clinical outcomes of PA.

Orthotopic liver transplantation (OLT) may be indicated in those individuals who, despite adequate medical treatment, continue to experience frequent metabolic decompensations [Yap et al 2020]. Elective liver transplant has been used as a preventive measure for severe phenotypes [Zhou et al 2021]. However, OLT in individuals with PA is not curative. It does not completely protect against metabolic strokes, hyperammonemia, progressive renal dysfunction, or metabolic decompensations [Romano et al 2010, Charbit-Henrion et al 2015, Yap et al 2020, Sivananthan et al 2021].

The indication of liver transplantation for dilated cardiomyopathy with severe heart dysfunction is less clear, with reports showing a short-term improvement or stabilization of heart function [Romano et al 2010, Critelli et al 2018]. However, development of cardiomyopathy after liver transplantation [Yap et al 2020, Zhou et al 2021] and the reoccurrence of cardiomyopathy have been reported by others [Berry et al 2020, Hejazi et al 2023]. Continuous hemofiltration, extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices have been used while waiting for OLT.

The current evidence with short- or medium-term follow up has not demonstrated superiority of unrelated donors compared to heterozygous related donors for liver transplant [Zeng et al 2022].

Close monitoring of metabolic and nutritional status around the perioperative period by a highly specialized team is recommended. Disease-specific metabolites such as 3-hydroxypropionate can be elevated during the anhepatic phase [Quintero et al 2018].

Metabolic decompensation during liver transplantation poses a higher mortality risk [Ryu et al 2013].

Benefits of OLT include decrease in the frequency of metabolic decompensations and potential stabilization of the neurodevelopmental decline [Zhou et al 2021], as well as improved quality of life, increased life expectancy, and lifetime cost savings [Li et al 2015].

Complications of liver transplantation were summarized in a meta-analysis with the following pooled estimated rates [Zhou et al 2021]:

- Patient survival of 0.95 (95% CI: 0.80-1)
- Allograft survival of 0.91 (95% CI: 0.72-1)
- Rejection of 0.20 (95% CI: 0.05-0.39)
- Hepatic artery thrombosis of 0.08 (95% CI: 0.00-0.21)
- Biliary complications of 0.03 (95% CI: 0.00-0.15)
- Cytomegalovirus / Epstein-Barr virus infection of 0.14 (95% CI: 0.00-0.37)

Lifelong post-transplant management is recommended, as well as continuation of L-carnitine supplementation after liver transplantation. The authors recommend continued protein restriction after transplant using the WHO/FAO/UNU recommendations for energy and protein intake [Joint WHO/FAO/UNU Expert Consultation 2007]. However, the current data is insufficient to determine the best approach [Jurecki et al 2019].

Other transplantation. Successful kidney transplantation has been reported in an adult with kidney failure [Lam et al 2011]. Heart transplantation was reported in an adolescent with secondary cardiomyopathy [Seguchi et al 2022].

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 offered expediently during intercurrent illnesses or other catabolic stressors (see also Tables 6 and 7).

Table 9. Propionic Acidemia: Prevention of Secondary Manifestations

Manifestation/Situation	Intervention	Considerations/Other
Acute metabolic crisis	• Education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute metabolic crises • Treatment protocols & provision of emergency letters or cards to incl guidance for care in event of illness while traveling • MedicAlert® bracelets/pendants or car seat stickers • Adequate supplies of specialized dietary products (carbohydrate-only formulas or other caloric sources), specialized amino acid formula, & medication required for maintenance & emergency treatment (carnitine, antipyretics) should always be maintained at home & during travel.	• Written protocols for maintenance & emergency treatment should be provided to parents & primary care providers / pediatricians, & to teachers & school staff. [1] • Emergency letters/cards should be provided summarizing key info & principles of emergency treatment for PA & containing contact info for primary treating metabolic center. • For any planned travel or vacations, consider contacting a center of expertise near destination prior to travel dates.
Surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/ surgeons & anesthesiologists. [2] • Emergency surgeries & elective procedures require input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional mgmt).	Consider placing a "flag" in affected person's medical record such that all care providers are aware of diagnosis & need to solicit opinions & guidance from designated metabolic specialists in the setting of certain procedures.
Acrodermatitis enteropathica, hair loss, & cutaneous *Candida* infections	• Reassessment of dietary therapy to identify essential amino acid deficiencies or other vitamin or mineral deficiencies • Rule out iatrogenic overrestriction of essential amino acid intake.	

1. Essential information including written treatment protocols should be provided *before* inpatient emergency treatment might be necessary.
2. Perioperative/perianesthetic management precautions may include visitations at specialist anesthetic clinics for affected individuals deemed to be at high risk for perioperative complications (see www.orphananesthesia.eu [pdf]).

Surveillance

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations summarized in Table 10 are recommended.

Table 10. Propionic Acidemia: Recommended Surveillance

System/Concern	Evaluation	Frequency/Comment
Growth	• Measurement of weight, length, & head circumference • Eval of nutritional status & safety of oral intake [1]	At each visit
Metabolic control [2]	• Plasma ammonia • Quantitative plasma acylcarnitine profile • Electrolytes & venous blood gas • Urinary ketones, plasma lactic acid, & 2-methylcitric acid [3]	As clinically indicated
Nutritional eval	• Plasma amino acids (esp isoleucine, leucine, valine, threonine, & methionine) collected 2 hrs after last typical meal • Plasma free & total carnitine	
Nutritional deficiencies	• Mineral panel (calcium, phosphorus) • Hemoglobin &/or CBC [4] • Vitamin D • Iron studies • Essential fatty acids • Trace minerals (selenium & zinc)	
Kidney function	• Plasma creatinine • Serum cystatin C may be more sensitive than plasma creatinine to identify chronic kidney disease.	At least annually
Delayed acquisition of developmental milestones	Monitor developmental milestones	At each visit
	• Neuropsychological testing using age-appropriate standardized assessment batteries • Standardized quality-of-life assessment tools for affected persons & parents/caregivers	As needed
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	At each visit
Pancreatitis	Amylase & lipase	As clinically indicated
Cardiovascular	Monitor for clinical signs of heart disease (e.g., tachycardia, tachypnea, syncope, shortness of breathy, exercise intolerance, chest pain, hepatomegaly)	At each visit
	Echocardiogram, EKG, & 24-hr Holter or other ambulatory monitor [5]	Annually or as clinically indicated
Integumentary	Eval of skin, hair, gastrostomy tube, & central line insertion sites	At each visit
Eyes	Ophthalmology eval, incl dilated eye exam [6]	Annually or as clinically indicated
Hearing	Audiology eval	
Musculoskeletal	DXA scan	Periodically starting in adolescence

Table 10. continued from previous page.

System/Concern	Evaluation	Frequency/Comment
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

CBC = complete blood count; DXA = dual-energy x-ray absorptiometry
1. This should also include interval assessment for the need for a gastrostomy tube in those who do not already have one.
2. The following evaluations are performed at different intervals depending on factors such as age, disease severity, and presence of catabolic stressors; evaluation frequency can range from every three months to annually.
3. To monitor and adjust nutritional management
4. To monitor for cytopenias
5. To screen for cardiomyopathy and arrythmia
6. To assess for optic nerve and retinal changes

Agents/Circumstances to Avoid

Avoid prolonged fasting, catabolic stressors, and excessive protein intake.

Lactated Ringer's solution is not recommended in individuals with organic acidemias.

In individuals with QT interval abnormalities, avoid medications that can prolong the QT interval.

Ondansetron, an antiemetic drug used to control nausea, has been associated with QT interval prolongation on EKG [Tay et al 2014] and therefore should be used cautiously in individuals with PA who have cardiomyopathy and QT interval abnormalities.

Nephrotoxic medications (e.g., aminoglycosides) should be avoided.

Neuroleptic antiemetics (e.g., promethazine) can mask symptoms of progressive encephalopathy and are best avoided.

Evaluation of Relatives at Risk

Testing of at-risk sibs is warranted to allow for early diagnosis and treatment. If prenatal testing has not been performed on at-risk sibs, measure urine organic acids, plasma amino acids, and acylcarnitine profile immediately in the newborn period in parallel with newborn screening.

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

Pregnancy Management

Although successful pregnancy outcomes have been reported in individuals with PA [Van Calcar et al 1992, Langendonk et al 2012], pregnancy can pose a significant management challenge. Hyperemesis gravidarum may require the use of an antiemetic, but the risk of QT interval prolongation and the effect on the central nervous system need to be considered [Baumgartner et al 2014]. Baseline evaluation and monitoring of cardiomyopathy before, during, and after pregnancy is recommended. Reference ranges for total and free plasma carnitine differ during pregnancy [Schoderbeck et al 1995]. Close nutritional follow up and fetal growth monitoring is necessary, as energy and protein requirements change throughout pregnancy. Close postpartum clinical and biochemical follow up and delayed discharge from the hospital are recommended. In the postpartum period, increased caloric and protein needs during lactation should be taken into consideration.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

Propionic acidemia (PA) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *PCCA* or *PCCB* 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 a *PCCA* or *PCCB* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PCCA* or *PCCB* 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) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has PA or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *PCCA* or *PCCB*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PCCA* or *PCCB* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *PCCA* or *PCCB* pathogenic variants in the family.

Biochemical testing. Quantitative plasma amino acids, urine organic acids, acylcarnitine profile, and fibroblast enzymatic analyses are **not** reliable for detection of heterozygotes.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk sibs 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.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with PA, particularly if both partners are of the same ancestry. Founder variants have been identified in several populations (see Table 11).

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

Once the *PCCA* or *PCCB* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

If biallelic *PCCA* or *PCCB* pathogenic variants have **not** been identified in an affected family member, biochemical prenatal testing may be considered. Metabolite analysis of amniotic fluid for prenatal diagnosis of PA has been reported [Dai et al 2020].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Propionic Acidemia Foundation**
  Phone: 877-720-2192
  Email: paf@pafoundation.com
  pafoundation.com
- **MedlinePlus**
  Propionic acidemia
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Email: info@oaanews.org
  oaanews.org
- **European 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. Propionic Acidemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PCCA	13q32.3	Propionyl-CoA carboxylase alpha chain, mitochondrial	PCCA database	PCCA	PCCA
PCCB	3q22.3	Propionyl-CoA carboxylase beta chain, mitochondrial	PCCB database	PCCB	PCCB

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 Propionic Acidemia (View All in OMIM)

232000	PROPIONYL-CoA CARBOXYLASE, ALPHA SUBUNIT; PCCA
232050	PROPIONYL-CoA CARBOXYLASE, BETA SUBUNIT; PCCB
606054	PROPIONIC ACIDEMIA

Molecular Pathogenesis

Propionic acidemia (PA) is caused by deficiency of the mitochondrial multimeric enzyme propionyl-coenzyme A carboxylase (PCC), a biotin-dependent carboxylase located in the mitochondrial inner space that catalyzes the conversion of propionyl-CoA to D-methylmalonyl-CoA. The enzyme is composed of alpha and beta subunits encoded by their respective genes, *PCCA* and *PCCB*. Deficient activity of propionyl-CoA carboxylase results in accumulation of propionic acid and propionyl-CoA-related metabolites, which can be detected biochemically.

PCC is a heterododecamer (α6β6) composed of six alpha subunits encoded by *PCCA* and six beta subunits encoded by *PCCB* [Huang et al 2010]. The beta subunits form a central core, and each of the alpha subunits attaches to a beta subunit (see Figure 2).

PCC catalyzes the conversion of propionyl-CoA to D-methylmalonyl-CoA, which eventually enters the Krebs cycle as succinyl-CoA. Propionyl-CoA is common to the pathway for degradation of some amino acids (isoleucine, valine, threonine, and methionine), odd-chain fatty acids, and a side chain of cholesterol. Gut bacteria (e.g., *Propionibacterium sp.*) are also an important source of propionate metabolized through PCC.

The deficiency of PCC enzymatic activity profoundly deranges metabolism at several levels. Possible explanations include:

- The toxic effects of free organic acids and ammonia;
- The accumulation of propionyl-CoA, which in turn can inhibit other enzyme systems including oxidative phosphorylation [de Keyzer et al 2009], resulting in decreased energy production;
- Decreased production of Krebs cycle intermediates.

Mechanism of disease causation. Loss of function

Table 11. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene	Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
PCCA	NM_000282.3 NP_000273.2 NC_000013.10	c.425G>A	p.Gly142Asp	Founder pathogenic variant in Saudi Arabia; severe neonatal phenotype [Al-Hamed et al 2019]
PCCB	NM_000532.4 NP_000523.2 NC_000003.11	c.335G>A	p.Gly112Asp	Severe phenotype due to pathogenic variant affecting heterododecamer formation [Muro et al 2001, Tummolo et al 2018]
		c.1304T>C	p.Tyr435Cys	Detected in apparently asymptomatic or mildly affected newborns through NBS in Japan [Yorifuji et al 2002, Tajima et al 2021]
		c.1534C>T	p.Arg512Cys	Severe phenotype due to pathogenic variant affecting heterododecamer formation [Muro et al 2001, Chiu et al 2014, Stanescu et al 2020]
		c.1538_1540dup (1540insCCC)	p.Ala513_Arg514insPro (513insP)	Common pathogenic variant among Inuits in Greenland; carrier frequency in that community of ~5% [Ravn et al 2000]
		c.1556T>C	p.Leu519Pro	Severe phenotype due to pathogenic variant affecting heterododecamer formation [Muro et al 2001]
		c.1606A>G	p.Asn536Asp	Less severe when homozygous; seen in some Amish & Mennonite communities; may present w/late-onset phenotype such as cardiomyopathy [Scott Schwoerer et al 2018, Wenger et al 2020, Ehrenberg et al 2022]

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

For a list of variants reported as pathogenic for PA, see ClinVar Miner.

Chapter Notes

Author Notes

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