U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Shchelochkov OA, Carrillo N, Venditti C. Propionic Acidemia. 2012 May 17 [Updated 2016 Oct 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Propionic Acidemia

Oleg A Shchelochkov, MD,[1] Nuria Carrillo, MD,[1] and Charles Venditti, MD, PhD[1]

Created: May 17, 2012; Updated: October 6, 2016.

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 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 occasion in the absence of clinical metabolic decompensation or neurocognitive deficits.

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

Diagnosis/testing

PA is caused by deficiency of propionyl-CoA carboxylase (PCC), the enzyme that catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. Newborns with PA tested by expanded newborn screening have elevated C3 (propionylcarnitine). Testing of urine organic acids in persons who are symptomatic or those detected by newborn screening reveals elevated 3-hydroxypropionate and the presence of methylcitrate, tiglylglycine, propionylglycine, and lactic acid. Testing of plasma amino acids reveals elevated glycine. Confirmation of the diagnosis relies on detection of biallelic pathogenic variants in *PCCA* or *PCCB* or of

Author Affiliation: 1 National Human Genome Research Institute National Institutes of Health Bethesda, Maryland; Email: oleg.shchelochkov@nih.gov; Email: carrilln@mail.nih.gov; Email: venditti@mail.nih.gov.

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 nitrogen scavenger medications, extracorporeal detoxification, and/or intravenous carnitine; 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. G-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 (OLT) may be indicated in those with frequent metabolic decompensations, uncontrollable hyperammonemia, and/or poor growth.

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

Surveillance: Monitor closely patients with a catabolic stressor (fasting, fever, illness, injury, and surgery) to prevent and/or detect and manage metabolic decompensations early. Regularly assess: (1) growth, nutritional status, feeding ability, psychomotor development; (2) vision and hearing (3) cardiac function for signs of cardiomyopathy; (4) metabolic status by monitoring urine organic acids and plasma amino acids; (5) complete blood count; (6) renal function.

Agents/circumstances to avoid: Prolonged fasting, catabolic stressors, and excessive protein intake. Lactated Ringer's solution is not recommended in patients with organic acidemias. In patients 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 a patient is warranted to allow for early diagnosis and treatment.

Genetic counseling

Propionic acidemia is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Propionic acidemia (PA) is caused by deficiency of the mitochondrial multimeric enzyme propionyl-CoA carboxylase that catalyzes the conversion of propionyl-CoA to D-methylmalonyl-CoA. The enzyme is composed of α- and β-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. In many countries, infants at risk for PA can be detected via newborn screening (NBS), although symptoms may be evident in the infant before NBS results are available. Clinical manifestations of PA are often nonspecific and age of onset is variable.

Suggestive Findings

Propionic acidemia (PA) **should be suspected** in individuals with any of the following presentations.

Neonatal-onset propionic acidemia (PA) is the most common clinical form of PA. In the first few days of life, infants present with:

- Lethargy
- Poor feeding
- Vomiting
- Hypotonia

Without treatment, this can progress to encephalopathy and cardiorespiratory failure.

Symptoms may be evident in the infant before NBS results are available.

Late-onset PA can present with a variety of concerns [Delgado et al 2007] including:

- Developmental delay
- Intellectual disability
- Failure to thrive
- Chronic gastrointestinal complaints
- Protein intolerance
- Acute psychosis
- Hypotonia
- Movement disorders such as dystonia and choreoathetosis

Acute decompensation can be precipitated by metabolic stressors including infection, injury, or surgery.

Cardiomyopathy can occur as an apparently isolated clinical phenomenon in previously healthy individuals without documented episodes of metabolic decompensation or neurocognitive deficits [Lee et al 2009, Laemmle et al 2014].

Testing

Newborn screening (NBS). Detection of PA in the neonatal period is possible using acylcarnitine analysis by tandem mass spectrometry (MS/MS) on dried blood spots.

- Acylcarnitine analysis reveals elevated propionylcarnitine (C3).
- Secondary markers including methionine, C3/C2, and C3/C16 ratios can be helpful to increase diagnostic accuracy [Couce et al 2011].

Biochemical analysis. Deficiency of propionyl-CoA carboxylase results in accumulation of propionic acid and propionyl-CoA related metabolites in plasma and urine, causing a wide range of laboratory test abnormalities (Figure 1).

Biochemical findings in propionic acidemia include:

- Plasma acylcarnitine profile: elevated propionylcarnitine (C3)
- Urine organic acids:
  - Elevated 3-hydroxypropionate
  - Presence of:
    - Methylcitrate
    - Tiglylglycine
    - Propionylglycine
    - Lactic acid
- Plasma amino acids: elevated glycine

Common laboratory abnormalities during acute decompensation include:

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

Establishing the Diagnosis

In a proband who has the clinical, laboratory, and biochemical findings reviewed above and in Figure 2, the diagnosis of PA **is established** using the following strategies.

I. Identification of biallelic pathogenic variants in *PCCA* or *PCCB* on molecular genetic testing (see Table 1). Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Serial single-gene testing** can be considered if (1) mutation of a particular gene accounts for a large proportion of the condition **or** (2) factors such as clinical findings, laboratory findings, and ancestry indicate that mutation of a particular gene is most likely.

  For PA, neither gene is more common and there are no characteristic findings to distinguish between *PCCA*- and *PCCB*-associated PA.

  In instances where this testing approach is the only one available, sequence analysis of either *PCCA* or *PCCB* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

- **A multigene panel** that includes *PCCA* and *PCCB* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified

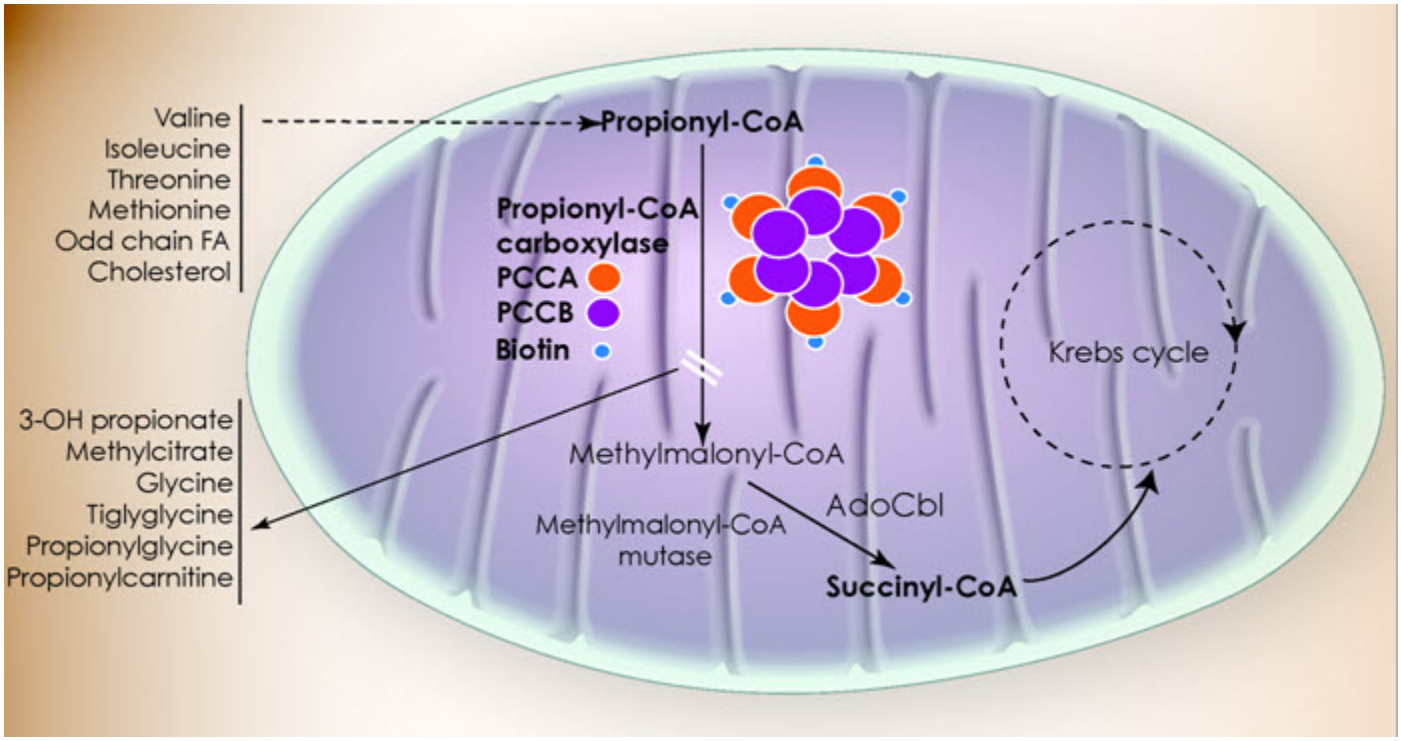

Figure 1. Metabolic pathway. Propionyl-CoA carboxylase (PCC) catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA, which enters the Krebs cycle via succinyl-CoA. Sources of propionate include: valine, isoleucine, threonine, methionine, odd-chain fatty acids, and cholesterol. Deficiency of PCC 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 α-subunits (orange) and six β-subunits (purple). Biotin (blue), bicarbonate, and ATP have binding sites in the α-subunit. The β-subunits form a central core.

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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *PCCA* and *PCCB*) fails to confirm a diagnosis in an individual with features of propionic acidemia. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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] Detected by Method [3]	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
PCCA	50%	78%	18% [6]

Table 1. continued from previous page.

Gene [1]	Proportion of PA Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method [3]	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
PCCB	50%	97%	3% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Kraus et al [2012] reported no identifiable pathogenic variants in 7% (4/54) and one identifiable variant in 4% (2/54) of individuals with propionic acidemia. Some of the variants may have escaped detection by existing sequencing methods, but could have been detected by copy number analysis [Kraus et al 2012]. 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].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. 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.
6. Exon deletions account for to ~20% of *PCCA* disease-causing alleles [Yang et al 2004, Kaya et al 2008, Desviat et al 2009, Aradhya et al 2012].
7. Three *PCCB* large-deletion alleles have been described [Desviat et al 2006, Kraus et al 2012, Chiu et al 2014].

II. An alternative approach involves the assay of propionyl-CoA carboxylase (PCC) enzyme activity in lymphocytes or cultured skin fibroblasts followed by molecular diagnosis [Baumgartner et al 2014]. In individuals with equivocal molecular genetic test results, a combination of enzymatic and molecular diagnostics may be necessary.

Clinical Characteristics

Clinical Description

Propionic acidemia 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. See Table 3a (pdf) and Table 3b (pdf) for a summary of major clinical findings in propionic acidemia (PA) and the reported frequency of symptoms.

Perinatal course. Reported maternal prenatal course, gestational age, and birth length, weight, and head circumference are similar to what is reported for unaffected infants [Kölker et al 2015a]. Increased frequency of miscarriages of affected fetuses is possible [Ottolenghi et al 2010].

Neonatal onset PA. A typical 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. Without prompt diagnosis and management, neonates can develop progressive encephalopathy manifesting as lethargy, seizures, or coma that can result in death (see Table 2). 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 report [Surtees et al 1992, Dionisi-Vici et al 2006, Grünert et al 2012].

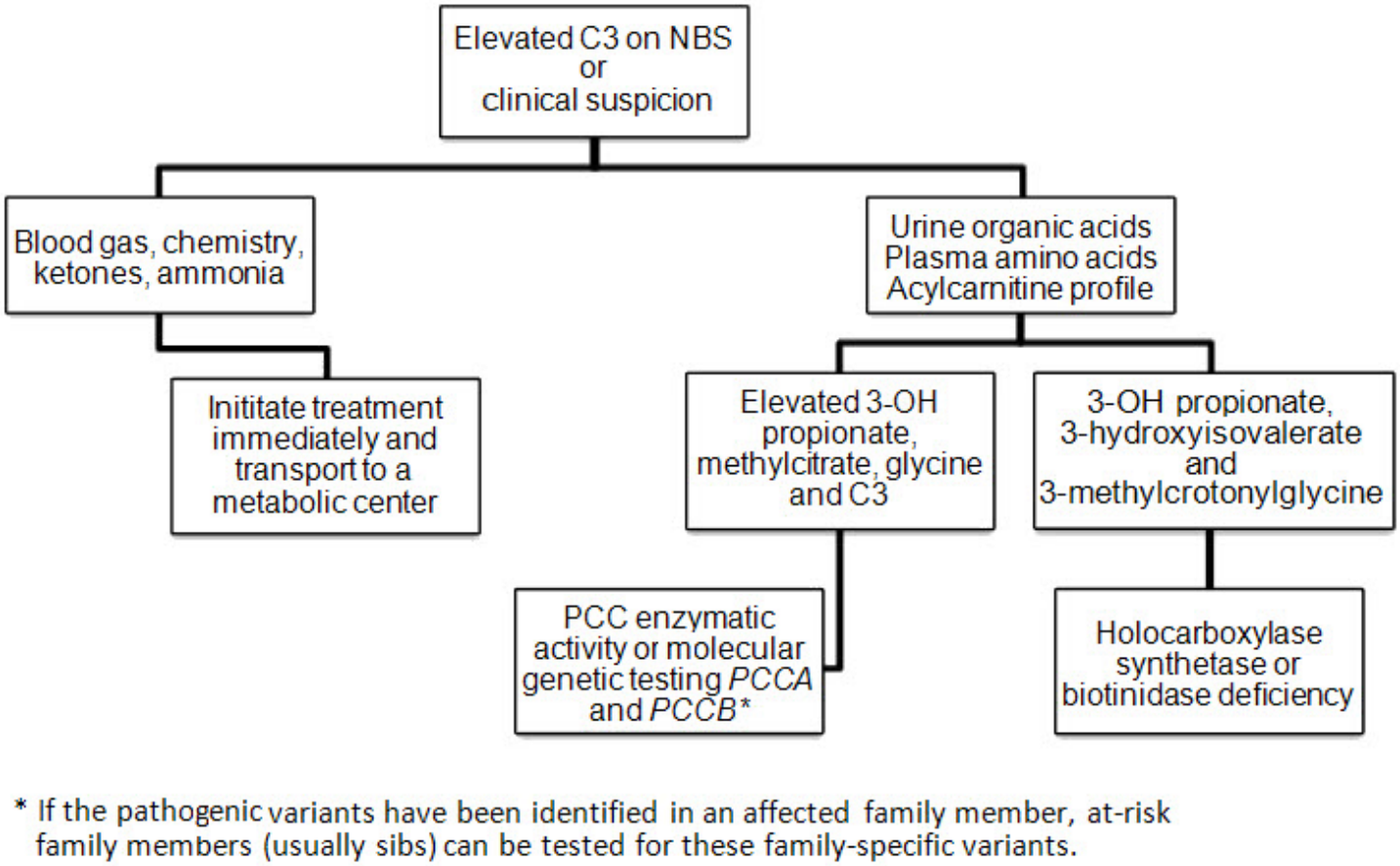

Figure 2. Immediate management and testing algorithm to be pursued simultaneously after the clinical or laboratory suspicion of PA

Table 2. Features of Neonatal-Onset Propionic Acidemia

Clinical Features	Laboratory Findings
• Poor feeding • Vomiting • Irritability • Lethargy • Progressive encephalopathy • Seizures • Coma • Respiratory failure	• High anion-gap metabolic acidosis • Ketonuria • Hyperammonemia (>90%) • Hypoglycemia • ↑ 3-OH propionic acid & methylcitric acid • Hyperglycinemia • ↑ propionylcarnitine • Anemia • Leukopenia • Thrombocytopenia

See Table 3a (pdf) for a summary of the prevalence of major clinical findings during metabolic crisis in propionic acidemia.

Following initial clinical and biochemical stabilization, individuals with neonatal-onset PA may develop a range of symptoms affecting different organ systems. See following and Table 3b (pdf).

Late-onset PA. Residual activity of propionyl-CoA carboxylase may delay the onset of symptoms beyond the neonatal period.

Individuals with late-onset PA may remain asymptomatic and suffer a metabolic crisis under catabolic stress (e.g., illness, surgery, fasting) or experience a more insidious onset with the development of multiorgan complications as summarized in Table 4. See also Table 3b.

Table 4. Features of Late-Onset Propionic Acidemia

Clinical Features	Laboratory Findings
• Encephalopathy, coma, &/or seizures precipitated by catabolic stressors (e.g., intercurrent illness, surgery) • Vomiting, protein intolerance, failure to thrive, hypotonia, developmental regression, mvmt disorders • Isolated cardiomyopathy [1]	• ± metabolic acidosis or hyperammonemia • ↑ 3-OH propionic acid & methylcitric acid • Hyperglycinemia • MRI abnormalities incl basal ganglia lesions [2]

1. Lee et al [2009]
2. Broomfield et al [2010]

Metabolic decompensations. Children with PA can develop episodic metabolic decompensations, especially in the first years of life. Acidosis, hyperammonemia, pancreatitis, metabolic stroke, 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 stress augmenting catabolism. Infectious complications (e.g., sepsis or bacterial meningitis) often accompany metabolic crises and are the major contributors to mortality [Rousson & Guibaud 1984, North et al 1995]. The long-term cognitive outcome of individuals with PA is negatively correlated to the number of metabolic decompensations [Grünert et al 2012].

Growth. Linear growth delay and deceleration of the head circumference may become evident with age and can be seen in both earlier- and late-onset groups [Kölker et al 2015b]. Failure to thrive 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 [Grünert et al 2012, Pena & Burton 2012, Nizon et al 2013]. Developmental delays and neurologic dysfunction can be seen even in individuals without documented episodes of hyperammonemia or ketoacidosis [North et al 1995, Nyhan et al 1999, Schreiber et al 2012]. The prevalence of intellectual disability can vary between approximately 35% and 76% depending on the reported cohort [de Baulny et al 2005, Dionisi-Vici et al 2006, Touati et al 2006, Grünert et al 2012, Pena & Burton 2012].

- **Seizures** were reported in 13%-53% and EEG abnormalities in 40%-63% of Individuals with PA. Reported forms of seizures included infantile spasms, tonic-clonic, tonic, myoclonic, atonic, absence, and focal [Haberlandt et al 2009, Schreiber et al 2012, Karimzadeh et al 2014, Kölker et al 2015b]. Seizures were one of the presenting features of the initial metabolic episode in 12%-26% of cases [Grünert et al 2012, Kölker et al 2015a].
- **Basal ganglia changes.** Individuals with PA are predisposed to basal ganglia lesions, especially during episodes of acute encephalopathy or metabolic instability [Broomfield et al 2010]. 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 [de Baulny et al 2005, Scholl-Bürgi et al 2009, Grünert et al 2012, Pena & Burton 2012, Nizon et al 2013, Karimzadeh et al 2014]. The frequency of movement disorders in PA appears to be independent of the age of symptom onset [Kölker et al 2015a].
- **Psychiatric manifestations.** The prevalence of other comorbidities such as attention deficit disorder, autism spectrum disorder, anxiety, and acute psychosis is incompletely characterized [de Baulny et al 2005, Pena & Burton 2012, Nizon et al 2013, Vernon et al 2014]. Acute psychosis can be a presenting feature of PA in older individuals, especially in those not evaluated by newborn screen, thus warranting a

high index of suspicion for this uncommon cause of psychosis in the general population [Shuaib et al 2012, Nizon et al 2013, Dejean de la Bâtie et al 2014].

- **Brain MRI findings** include delayed myelination, white matter changes, basal ganglia abnormalities, cerebellar hemorrhage, and cerebral atrophy [Schreiber et al 2012]. Clinically unstable individuals appear to be at higher risk of developing brain abnormalities. In a study of 17 PA individuals with 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, N-acetylaspartate and elevated Glx (glutamine, glutamate, and gamma-aminobutyric acid) peaks in basal ganglia [Bergman et al 1996].

Cardiomyopathy has been recognized as a common complication of PA. Both dilated and hypertrophic cardiomyopathy have been reported [Romano et al 2010]. In the period between 2000 and 2015, its reported prevalence varied between 7% and 24% in various PA cohorts [Dionisi-Vici et al 2006, Romano et al 2010, Grünert et al 2012].

- Early clinical manifestations of cardiomyopathy include tachypnea, hepatomegaly, hypotension, tachycardia, or bradycardia.
- The mean age of onset of cardiomyopathy was seven years in a study by Romano et al [2010].
- The age of PA diagnosis, frequency of metabolic decompensation, and residual enzymatic activity 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 [Lee et al 2009, Laemmle et al 2014].
- Cardiomyopathy can progress to cardiac failure and may be associated with sudden death [Dionisi-Vici et al 2006].

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 [Baumgartner et al 2007, Jameson & Walter 2008, Pena & Burton 2012].

Gastrointestinal manifestations

- Pancreatitis (reported in 3%-18% of individuals) may be recurrent and may present with anorexia, recurrent nausea, and abdominal pain [Dionisi-Vici et al 2006, Grünert et al 2012, Pena & Burton 2012]. In some individuals recurrent pancreatitis can lead to insulin-dependent diabetes.
- Poor feeding and lack of appetite are common, affecting up to 76% of affected individuals [Touati et al 2006].
- Emesis and diarrhea are commonly reported in individuals with PA, becoming a recurrent problem in approximately 6% [Kölker et al 2015b].
- Liver issues include hepatomegaly, hypoalbuminemia, and abnormal liver function tests (ALT, AST, GGT, INR, and bilirubin) [Karimzadeh et al 2014, Kölker et al 2015b]. The etiology of hepatic dysfunction has not been determined with certainty but may include the inherent metabolic derangement as well as cardiac dysfunction in individuals with cardiomyopathy.

Renal abnormalities have been infrequently documented and are likely underreported. Examples have included impaired renal function [Lehnert et al 1994], chronic renal insufficiency leading to renal transplant at age 42 years [Lam et al 2011], and progressive kidney disease in the third decade of life [Vernon et al 2014].

Hematologic abnormalities. Although anemia, leukopenia, and thrombocytopenia are common, pancytopenia is seen less frequently, in 6%-15% of individuals [Grünert et al 2012, Pena & Burton 2012, Karimzadeh et al 2014, Kölker et al 2015b]. Myelodysplastic changes in the bone marrow are uncommon [Stork et al 1986, Sipahi et al 2004].

Immune system. Early retrospective data suggested high frequency of recurrent infections seen in 60%-80% of affected individuals [Lehnert et al 1994, Al Essa et al 1998]. Factors predisposing to infectious complications were likely diverse and included 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. Although staphylococcal scalded skin syndrome and *Candida* skin infections were reported in the earlier literature [Lehnert et al 1994, Al Essa et al 1998], more recent natural history studies suggest that such complications are uncommon [Baumgartner et al 2014, Kölker et al 2015b].

Hypogammaglobulinemia, B-cell lymphopenia, decreased CD4 and CD8 counts, and abnormal CD4/CD8 ratio have been described [Müller et al 1980, Griffin et al 1996, Al Essa et al 1998, Pena & Burton 2012]. Hypogammaglobulinemia, reported in as many as 15% of affected individuals, has required treatment with immunoglobulin in some cases [Müller et al 1980, Raby et al 1994, Pena & Burton 2012].

Ophthalmologic manifestations. Eye findings include dyschromatopsia, optic atrophy, scotomas, abnormal electroretinogram, visual evoked potentials, and optical coherent tomography. 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% [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 [Noval et al 2013, 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 over-restricted 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]; parathyroid hormone resistance resolving after hemodialysis [Griffin et al 1996].

Life span. PA confers a high risk of mortality. Reported mortality rates appear to be on the decline: 41%-90% in the 1980-90s, 17%-72% in 2000s, and 7%-12% in early 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]. Observed decline in reported mortality likely reflects the length of follow up, introduction of newborn screening, expansion of the PA phenotype, proactive medical management, and elective liver transplantation.

Long-term adult outcomes. Systematic studies of adult individuals with PA are lacking. Early reports suggest that adults with PA can experience significant osteopenia, osteoporosis, renal failure, and premature ovarian failure [Martín-Hernández et al 2009, Lam et al 2011, Vernon et al 2014].

Atypical presentation. Apparently asymptomatic individuals with PA (9%-17% in different cohorts) represent a heterogeneous group consisting of otherwise healthy infants identified after newborn screening, sibs ascertained through evaluation prompted by diagnosis of the proband, and individuals with a diagnosis of PA with incomplete clinical characterization [Grünert et al 2012, Kölker et al 2015a].

Genotype-Phenotype Correlations

Although precise genotype-phenotype correlations do not exist, some general comments related to molecular genetics are relevant.

- Null variants (*PCCA*: p.Arg313Ter, p.Ser562Ter; *PCCB*: p.Gly406fs, p.Gly94Ter, and out-of-frame small deletions/insertions, genomic abnormalities) result in loss-of-function alleles and are associated with a more severe form of PA [Desviat et al 2004, Desviat et al 2009].
- Homozygous missense pathogenic variants, in which partial enzymatic activity is retained (*PCCA*: p.Ala138Thr, p.Ile164Thr, p.Arg288Gly; *PCCB*: p.Asn536Asp) have been associated with a less severe phenotype.
- Some missense pathogenic variants (*PCCB* p.Gly112Asp, p.Arg512Cys, and p.Leu519Pro) which affect heterododecamer formation can result in undetectable PCC enzyme activity and severe phenotype [Muro et al 2001].

A homozygous *PCCB* variant in Amish and Mennonite populations, p.Asn536Asp, is associated with high residual PCC activity. It confers a lower risk of developing metabolic crisis, but can lead to late-onset cardiomyopathy.

A homozygous *PCCB* variant, p.Tyr435Cys, has been detected in apparently asymptomatic or mildly affected children identified through newborn screening in Japan [Yorifuji et al 2002].

Nomenclature

Propionic acidemia and propionyl-CoA carboxylase deficiency are the two most common terms used to describe the condition. Ketotic hyperglycinemia was used in the 1960s before defects in propionyl-CoA carboxylase were determined to be the underlying cause of PA [Hsia et al 1969]. The term propionic aciduria is used infrequently.

Prevalence

Worldwide, the incidence of PA varies widely. The estimated live-birth incidence of PA is 1:105,000-1:130,000 in the US [Chace et al 2001, Couce et al 2011], 1:166,000 in Italy [Dionisi-Vici et al 2002] and 1:250,000 in Germany [Schulze et al 2003].

The incidence appears to be higher in the Middle East. In the United Arab Emirates, the birth incidence of PA is ~1:20,000-1:45,000 [Al-Shamsi et al 2014]. In Saudi Arabia the birth incidence is 1:28,000 [Rashed 2001], and can be higher in some Saudi tribes: 1:2000-1:5000 [Zayed 2015].

In Japan, the live birth incidence of severe propionic acidemia is 1:465,000, but increases to 1:17,400 when combined with an apparently asymptomatic form of PA identified through newborn screening [Yorifuji et al 2002].

The highest reported birth incidence is found among the Greenlandic Inuits: 1:1000 [Ravn et al 2000].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Elevated C3 (propionylcarnitine) on newborn screening can be caused by methylmalonic acidemias resulting from methylmalonyl-CoA mutase deficiency, disorders of intracellular cobalamin metabolism, and maternal B_{12} deficiency.

The presence of elevated **3-hydroxypropionic with or without methylcitric acid on** the urine organic acid assay should prompt additional diagnostic considerations:

- Multiple carboxylase deficiency (biotinidase and holocarboxylase synthetase deficiencies), which also shows elevation of lactic acid, 3-hydroxyvaleric acid and 3-methylcrotonylglycine caused by defective activity of pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase
- Methylmalonic acidemias, which have elevations of 2-methylcitric acid and 3-hydroxypropionic acid, and additionally show elevations of methylmalonic acid. Cobalamin C, D, and F metabolism defects result in abnormal homocysteine metabolism. Total plasma homocysteine can help in the diagnostic workup of individuals ascertained with elevated propionylcarnitine.
- Maternal B_{12} deficiency identified through elevated propionylcarnitine on the newborn screen can also present with elevated urinary methylmalonic acid and total plasma homocysteine in infant. In maternal vitamin B_{12} deficiency, infant vitamin B_{12} levels can be in the normal range [Sarafoglou et al 2011].
- Urine organic acid assay in individuals with carbonic anhydrase VA deficiency can reveal elevated 3-hydroxypropionic acid, propionylglycine, and methylcitric acid as well as 3-methylcrotonylglycine, 3-hydroxybutyric, alpha-ketoglutaric, and 3-hydroxyisovaleric acids. Plasma acylcarnitine profile in individuals with carbonic anhydrase VA deficiency is usually normal.
- Methylmalonic semialdehyde dehydrogenase deficiency may result in accumulation of 3-hydroxyisobutyric, 3-hydroxypropionic, 3-aminoisobutyric, and methylmalonic acids [Marcadier et al 2013].
- Bacterial overgrowth (including *Propionibacterium or Lactobacterium*) or short gut syndrome [Haan et al 1985]
- Mitochondrial disorder may enter the differential diagnosis when individuals present with hyperammonemia, metabolic acidosis, ketonuria, and hypoglycemia [Baumgartner et al 2014].

Hyperglycinemia can be seen in a wide range of clinical conditions including nonketotic hyperglycinemia, valproate treatment, ketotic hyperglycinemia, and transient glycine encephalopathy. See Glycine Encephalopathy.

Hyperammonemia in neonatal PA can prompt clinicians to consider other disorders affecting ammonia metabolism including urea cycle disorders, organic acidemias, pyruvate carboxylase deficiency, carbonic anhydrase VA deficiency, and porto-systemic shunts. Usually, the glutamine levels in hyperammonemic patients with PA are normal or low [Al-Hassnan et al 2003, Filipowicz et al 2006].

Increased anion-gap metabolic acidosis. Possible causes are numerous and may include the following:

- Those conditions included in the commonly used mnemonic MUDPILES: *m*ethanol, *u*remia (chronic renal failure), *d*iabetic ketoacidosis, *p*ropylene glycol, *i*nfection, *i*ron, *i*soniazid, *l*actic acidosis, *e*thylene glycol, *s*alicylates
- Organic acidemias

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

The optimal management of patients with propionic acidemia (PA) is best achieved by a team comprising a physician with metabolic expertise, a dietician, and a genetic counselor. Several proposed acute and chronic management guidelines have become available in recent years [Chapman et al 2012, Sutton et al 2012, Baumgartner et al 2014]. Management of symptomatic hyperammonemic patients awaiting confirmatory testing can be particularly challenging and requires pursuit of several diagnostic considerations [Häberle et al 2012]. Also see Baumgartner et al [2014]: Table 6.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with PA the following evaluations are recommended (see Figure 2) if they have not already been completed:

- Blood gas with base balance, electrolytes with anion gap, glucose, plasma ammonia, calcium, phosphorus, urine ketones
- Plasma amino acids, total and free carnitine and acylcarnitine profile, and urine organic acid analysis
- Complete blood count to evaluate for cytopenias
- Consider initiating an evaluation for sepsis if the CBC and individual's clinical signs suggest that infection is likely
- Amylase and lipase to evaluate for pancreatitis
- Consultation with a clinical geneticist and/or genetic counselor

Once the patient becomes stable, evaluations include the following:

- Clinical assessment of growth parameters, ability to feed, the need for G-tube placement, and neurologic status.
- Laboratory assessment of nutritional status (calcium, phosphorus, albumin, prealbumin, plasma amino acids, vitamin levels [including thiamine and 25-hydroxyvitamin D], iron panel, and minerals and renal function); complete blood count to monitor for cytopenias
- Clinical evaluation for cardiomyopathy and arrhythmia with EKG, 24-hour Holter monitor, echocardiogram
- EEG and brain MRI in symptomatic individuals
- Developmental evaluation
- Dilated eye examination
- Hearing evaluation
- Immunology consult

Other

- Complete adherence to regional immunization schedules and influenza vaccination is indicated [Baumgartner et al 2014].
- Maintain a high index of suspicion for endocrine, immune, and renal problems and address accordingly.

Treatment of Manifestations

Neonatal/acute 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 metabolized in PA. The goal of acute management is to reverse this process through promotion of anabolism and removal of toxic intermediates. The treatment of individuals with acutely decompensated PA is a medical emergency and requires a transfer to a

center with biochemical genetics expertise and the ability to support urgent hemodialysis, especially if hyperammonemia is present.

In-patient management

- Assess and manage ventilation and circulation as necessary.
- Treat precipitating factors (fever, infection, dehydration, pain, vomiting, and other sources of stress).
- Determine the need for sepsis workup and antibiotics.
- Reverse catabolism by giving intravenous glucose and lipids.
  - The volume, glucose content and electrolyte composition of intravenous fluids is determined by age, target glucose infusion rate, cardiovascular status, renal condition, and co-administration of other medications.
  - 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 varies by age [Baumgartner et al 2014].
  - Additional calories can be provided using parenteral lipid emulsion.
  - The use of intravenous insulin drip may be needed to maintain euglycemia and promote anabolism.
- Manage protein intake to reduce propiogenic precursors; avoidance of protein transiently for <24-36 hours may be required.
  - Transition to enteral feedings should be commenced as soon as they are tolerated (see Prevention of Primary Manifestations, **Dietary management**).
  - If transition to enteral feedings within 48 hours is not possible, total parenteral nutrition is required.
  - Parenteral amino acid solutions are prescribed based on the recommended daily intake of age-appropriate energy, protein, isoleucine, valine, methionine, and threonine and adjusted using the daily and weekly growth data and plasma amino acid concentrations.
- Remove toxic compounds.
  - Pharmacologic detoxification:
    - Nitrogen scavenger medications (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate), such as those used in urea cycle disorders to help control ammonia levels during acute decompensations, should be used with caution in the treatment of hyperammonemia associated with PA as they can accentuate frequently observed low plasma glutamine [Al-Hassnan et al 2003, Filipowicz et al 2006]. For a discussion regarding the use of sodium benzoate versus sodium phenylacetate and sodium phenylbutyrate in propionic acidemia see Baumgartner et al [2014].
    - Oral N-carbamoylglutamate (carglumic acid; 100 mg/kg divided every 6 hours in individuals <20 kg and 2.2 gm/m^2 in individuals >20 kg) can aid in the detoxification of ammonia during neonatal and acute decompensations [Filippi et al 2010, Schwahn et al 2010, Chapman et al 2012].
  - Extracorporeal detoxification is required for persistent acidosis and hyperammonemia (plasma ammonia level >250-300 µmol/L) not responding to fluid and drug treatment. Methods include (depending on age and clinical situation) continuous veno-venous hemofiltration, extracorporeal membrane oxygenation, or hemodialysis [Chapman et al 2012, Baumgartner et al 2014].
  - Carnitine supplementation (100 mg/kg/day IV divided in 3 doses) 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 and provide a benefit through this mechanism. Consult hospital pharmacy for the recommended maximum daily dose in older patients.
- Manage pancreatitis using standard practices.

Home management of metabolic status. The detection and management of metabolic decompensations at home are a critical part of the chronic management of PA. Patients 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 for the conditions of each patient and family and may include the following:

- At-home detection and monitoring of urine ketones
- Diet modification under the direction of the metabolic team
- If fever is present due to an infection, possible treatment with paracetamol and ibuprofen [Baumgartner et al 2014]
- Use of anti-emetics such as ondansetron (See precautionary considerations in Agents/Circumstances to Avoid.)

Other

- Any injury, illness, hospitalization, or surgical procedure should involve consultation with the metabolic team.
- The diagnosis and management of pancreatitis is the same as for pancreatitis of other causes.
- Neutropenia and other cytopenias usually improve with metabolic control of PA.
- Management of arrhythmias is similar to that from other causes.
- Cardiomyopathy may improve after liver transplantation in some patients [Romano et al 2010].
- Seizures are a frequent complication of PA, necessitating anti-seizure medication. The use of valproic acid in organic acidemias is often avoided; however, several authors described its use in patients with PA [Haberlandt et al 2009, Schreiber et al 2012].
- Dermatologic manifestations (e.g., persistent dermatitis or eczema) warrant a nutritional reassessment to rule out dietary deficiency of essential amino acids, essential fatty acids, vitamins, and minerals.

Prevention of Primary Manifestations

Dietary management. 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.

Important note: Dietary management needs to be directed by an experienced physician and metabolic dietician.

- Recommended protein intake depends on age of the patient (see Baumgartner et al [2014]: Table 11).
- The ratio of natural source protein to medical foods varies depending on the individual's clinical status, laboratory parameters, and growth trajectory [Sutton et al 2012].
- Laboratory parameters useful in guiding nutritional intervention can include the following:
  - Preprandial plasma essential amino acids
  - Plasma albumin
  - Prealbumin
  - Hemoglobin
  - Plasma ammonia
  - Urinary ketones, plasma lactic acid, and methylcitric acid to monitor and adjust nutritional management
  - Plasma vitamin D
  - Essential fatty acid profile
- Additional calories can be provided using protein-free formulas.
- G-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.

- Since the number of acute decompensations negatively correlates with the intellectual quotient in patients with PA [Grünert et al 2012], prevention and proactive management of metabolic crises can be an important point of intervention to maximize favorable clinical outcomes.

Medications

- **Levocarnitine.** The optimal dose of levocarnitine has not been established; doses ranging from 50 to 300 mg/kg per day have been reported [Sutton et al 2012, Baumgartner et al 2014].
  - 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 patients.
  - Levocarnitine can be given enterally and intravenously.
- **Antimicrobial therapy.** Oral metronidazole has been shown to reduce propionic acid production by intestinal gut flora [Thompson et al 1990, Mellon et al 2000]. One regimen uses a one-week-on, three-weeks-off approach [Chapman et al 2012, Sutton et al 2012].
- **Biotin supplementation.** There is no consensus regarding the use of biotin supplementation nor the optimal dose in the treatment of PA. Given biotin's favorable profile, a short therapeutic trial may be considered [Sutton et al 2012, Baumgartner et al 2014]. Whether a biotin-responsive form of PA exists is not known [Baumgartner et al 2014].

Management during episodes of metabolic decompensation includes:

- Avoidance of fasting (e.g., using intravenous dextrose).
- Increasing calorie intake to prevent catabolism (e.g., intravenous fat emulsion).

When enteral feeding cannot be provided for a prolonged period of time, judicious use of total parenteral nutrition may include standard amino acid mixes providing age-appropriate recommended daily allowance of protein [Sutton et al 2012]. In rare circumstances, specialized amino acid mixes with reduced content of isoleucine, valine, threonine and methionine are necessary.

Organ transplantation. Orthotopic liver transplantation (OLT) may be indicated in those individuals who, despite adequate medical treatment, still experience frequent metabolic decompensations, uncontrollable hyperammonemia, and poor growth [Barshes et al 2006, Charbit-Henrion et al 2015].

- Benefits of OLT include decrease in the frequency of metabolic decompensations, improved quality-adjusted life years, increased life expectancy, life-time cost savings [Vara et al 2011, Li et al 2015], and reversal of dilated cardiomyopathy [Yorifuji et al 2004, Romano et al 2010].
- Liver transplantation has been performed from unrelated donors [Barshes et al 2006, Romano et al 2010] and from heterozygous related donors [Morioka et al 2005, Vara et al 2011, Kasahara et al 2012].
- Continuous hemofiltration, extracorporeal membrane oxygenation (ECMO) [Sato et al 2009, Kasahara et al 2012], and left ventricular assist devices have been used while waiting for OLT [Ameloot et al 2011].
- OLT in patients with PA is not curative. It does not completely protect against a metabolic stroke, hyperammonemia, or metabolic decompensations.
- Life-long post-transplant management is recommended [Yorifuji et al 2004, Vara et al 2011, Kasahara et al 2012]. Continued protein restriction and L-carnitine supplementation after OLT is advocated by several authors [Saudubray et al 1999, Yorifuji et al 2004, Kasahara et al 2012].

Sedation and perioperative management. Anesthetic aspects of perioperative management of patients with PA have been infrequently discussed [Baumgartner et al 2014]. Involvement of a metabolic specialist perioperatively to ensure adequate hydration and caloric management can help minimize the risk of decompensations.

Emergency situations. Emergency letters, bracelets, and emergency information in smartphones help facilitate appropriate emergency care by healthcare providers unfamiliar with propionic acidemia.

Prevention of Secondary Complications

Regular monitoring by a biochemical geneticist and a dietitian is necessary to avoid insufficient or excessive protein restriction. Many factors should be taken into account to guide protein restriction: the individual's age and sex, the severity of PA, nutritional status, and presence of other factors such as intercurrent illness, surgery, level of physical activity, and growth spurts. The effects of excessive protein restriction can include impaired growth, essential amino acid deficiencies, and metabolic decompensations.

Acrodermatitis enteropathica, hair loss, and cutaneous *Candida* infections in patients with PA managed with medical foods can be caused by essential amino acid deficiency and require a re-appraisal of the nutritional management.

Psychotic episodes in patients with PA have been infrequently reported [Dejean de la Bâtie et al 2014]. Similar to other inborn errors of metabolism, care should be exercised when using antipsychotic medications as they can mask clinical signs of encephalopathy or cause adverse effects.

Surveillance

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.

Clinical evaluation should include assessment of the following:

- Linear growth, weight gain, head circumference, and body mass index
- Interval assessment for the need of G-tube
- Neurologic evaluation including survey for seizures and movement disorders
- Interval ophthalmologic evaluation including dilated eye examination
- Audiology evaluation
- Evaluation for clinical signs of cardiomyopathy (e.g., tachycardia, tachypnea, shortness of breathy, hepatomegaly)
- Evaluation of integumentary system (skin, hair, G-tube, and central line insertion sites)
- Developmental and neurocognitive progress, as age-appropriate

Laboratory evaluation should include the following:

- Metabolic studies: urine organic acids, pre-prandial plasma amino acids (especially, isoleucine, leucine, valine, threonine, and methionine), plasma ammonia concentration, plasma free and total carnitine, and quantitative plasma acylcarnitine profile
- Nutritional studies: electrolytes, mineral panel, albumin, prealbumin, hemoglobin, vitamin D, iron studies, essential fatty acids, and trace minerals (selenium and zinc)
- Complete blood count and differential to monitor for cytopenias
- Renal function tests; serum cystatin C can be more sensitive than plasma creatinine in identifying early evidence of chronic renal failure.
- Amylase and lipase as needed to evaluate for pancreatitis

Other evaluations:

- Cardiology evaluation, screening for cardiomyopathy and arrhythmias by echocardiogram, EKG, and Holter monitor, annual and as needed
- Ophthalmologic evaluation to assess optic nerve and retinal changes, annually and as needed
- DXA (dual-energy x-ray absorptiometry) scan
- Brain MRI, MRS, and EEG as clinically indicated
- Physical, occupational, and speech therapy services to determine need

Agents/Circumstances to Avoid

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

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

In patients with QT 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 patients with PA who have cardiomyopathy and QT interval abnormalities.

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 patients 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 the 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 obligate heterozygotes (i.e., carriers of one *PCCA* or *PCCB* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

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

Offspring of a proband. The offspring of an individual with PA are obligate heterozygotes (carriers) for a pathogenic variant in *PCCA* or *PCCB*.

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

Carrier (Heterozygote) Detection

Molecular genetic testing. Carrier testing for at-risk family members is possible if the pathogenic variants in the family have been identified.

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 relatives for the purpose of early diagnosis and treatment.

Family planning

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

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *PCCA* or *PCCB* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for PA and preimplantation genetic testing are possible [Alberola et al 2011].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal 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.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  PA
- **Propionic Acidemia Foundation**
  Phone: 877-720-2192
  Email: paf@pafoundation.com
  www.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
  www.newbornscreening.hrsa.gov/your-state
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Fax: 866-539-4060 (toll-free)
  Email: kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml

Molecular Genetics

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

Table A. 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

Table A. continued from previous page.

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 an organic acidemia caused by deficiency of propionyl-CoA carboxylase (PCC), a biotin-dependent carboxylase located in the mitochondrial inner space.

PCC is a heterododecamer (α6β6) composed of six α-subunits encoded by *PCCA* and six β-subunits encoded by *PCCB* [Huang et al 2010]. The β-subunits form a central core and each of the α-subunits attaches to a β-subunit (see Figure 1).

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 cholesterol. Gut bacteria (i.e., *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.

PCCA

Gene structure. *PCCA* is composed of 24 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Most *PCCA* pathogenic variants are private [Kraus et al 2012]. Approximately 50% of molecularly diagnosed individuals with propionic acidemia harbor pathogenic variants in *PCCA*. Copy number variants are responsible for 18% of the reported variants [Campeau et al 2001, Yang et al 2004, Kaya et al 2008, Desviat et al 2009, Aradhya et al 2012].

Table 5. Selected *PCCA* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.412G>A	p.Ala138Thr [1]	NM_000282.3 NP_000273.2 NC_000013.10
c.491T>C	p.Ile164Thr [1]	
c.862A>G	p.Arg288Gly [1]	
c.937C>T	p.Arg313Ter [1]	
c.1685C>G	p.Ser562Ter [1]	

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.
See cbs.lf1.cuni.cz for an updated list of *PCCA* pathogenic variants and polymorphisms.
1. Desviat et al [2004]

Normal gene product. The alpha subunit of PCC has ATP, bicarbonate, and biotin-binding domains, and is responsible for transferring bicarbonate to form carboxybiotin, the first step in the PCC reaction [Campeau et al 2001].

Abnormal gene product. Most pathogenic variants in *PCCA* cause protein instability [Desviat et al 2004].

PCCB

Gene structure. *PCCB* comprises 15 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Approximately 50% of molecularly diagnosed cases of propionic acidemia have pathogenic variants in *PCCB*. Three percent of reported variants in *PCCB* are deleterious copy number variants [Desviat et al 2006, Kraus et al 2012, Chiu et al 2014].

- The pathogenic variant c.1218_1231del14ins12 is reported to account for approximately 30% of disease-causing alleles in individuals of northern European origin [Desviat et al 2004].
- The pathogenic variant c.1304T>C, associated with a milder form of propionic acidemia, accounts for 25% of mutated alleles in Japanese individuals.
- Homozygous c.1606A>G (p.Asn536Asp) variant has been identified in Amish and Mennonite communities, in individuals who can initially present with cardiomyopathy.

Table 6. Selected *PCCB* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.280G>T	p.Gly94Ter	NM_000532.4 NP_000523.2 NC_000003.11
c.335G>A	p.Gly112Asp	
c.457G>C	p.Ala153Pro [2]	
c.502G>A	p.Glu168Lys [3]	
c.1218del14ins12 [4]	p.Gly407fs	
c.1228C>T	p.Arg410Trp [2]	
c.1283C>T	p.Thr428Ile [2]	
c.1304A>G	p.Tyr435Cys [5]	
c.1495C>T	p.Arg499Ter	
c.1534C>T	p.Arg512Cys	
c.1539_1540dupCCC (1540insCCC)	p.Arg514ProfsTer38 [6] (513insP)	
c.1556T>C	p.Leu519Pro	
c.1606A>G [7]	p.Asn536Asp	

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.

See cbs.lf1.cuni.cz for an updated list of *PCCB* pathogenic variants and polymorphisms.

1. Variant designation that does not conform to current naming conventions

2. Common in Japan [Yang et al 2004]

3. Common in Spanish populations [Desviat et al 2004]

4. Most frequent mutated allele reported in individuals of northern European origin (~30%)

5. Detected in asymptomatic newborns through newborn screening in Japan; long-term effects are yet to be determined [Yorifuji et al 2002].

6. Common pathogenic variant among Inuits in Greenland with a carrier frequency in that community of ~5% [Ravn et al 2000]

7. A less severe form of PA is seen in some Amish and Mennonite communities.

Normal gene product. The beta subunit of PCC has a propionyl-CoA binding site and is responsible for transferring the carboxyl group to propionyl-CoA.

Abnormal gene product. Most pathogenic variants are predicted to alter the active site and reduce the enzymatic activity. A smaller percent of pathogenic variants affect subunit interactions, and thus, the assembly of the heterododecamer of PCC [Desviat et al 2004].

References

Literature Cited

Alberola TM, Bautista-Llácer R, Vendrell X, García-Mengual E, Pardo M, Vila M, Calatayud C. Case report: birth of healthy twins after preimplantation genetic diagnosis of propionic acidemia. J Assist Reprod Genet. 2011;28:211–6. PubMed PMID: 21125326.

Al Essa M, Rahbeeni Z, Jumaah S, Joshi S, Al Jishi E, Rashed MS, Al Amoudi M, Ozand PT. Infectious complications of propionic acidemia in Saudia Arabia. Clin Genet. 1998;54:90–4. PubMed PMID: 9727749.

Al-Hassnan ZN, Boyadjiev SA, Praphanphoj V, Hamosh A, Braverman NE, Thomas GH, Geraghty MT. The relationship of plasma glutamine to ammonium and of glycine to acid-base balance in propionic acidaemia. J Inherit Metab Dis. 2003;26:89–91. PubMed PMID: 12872849.

Al-Shamsi A, Hertecant JL, Al-Hamad S, Souid AK, Al-Jasmi F. Mutation spectrum and birth prevalence of inborn errors of metabolism among Emiratis: a study from Tawam Hospital Metabolic Center, United Arab Emirates. Sultan Qaboos Univ Med J. 2014;14:e42–9. PubMed PMID: 24516753.

Ameloot K, Vlasselaers D, Dupont M, Meersseman W, Desmet L, Vanhaecke J, Vermeer N, Meyns B, Pirenne J, Cassiman D, De Laet C, Goyens P, Malekzadeh-Milan SG, Biarent D, Meulemans A, Debray FG. Left ventricular assist device as bridge to liver transplantation in a patient with propionic acidemia and cardiogenic shock. J Pediatr. 2011;158:866–7. PubMed PMID: 21324476.

Aradhya S, Lewis R, Bonaga T, Nwokekeh N, Stafford A, Boggs B, Hruska K, Smaoui N, Compton JG, Richard G, Suchy S. Exon-level array CGH in a large clinical cohort demonstrates increased sensitivity of diagnostic testing for Mendelian disorders. Genet Med. 2012;14:594–603. PubMed PMID: 22382802.

Arias C, Raimann E, Peredo P, Cabello JF, Castro G, Valiente A, de la Parra A, Bravo P, Okuma C, Cornejo V. Propionic acidemia and optic neuropathy: a report of two cases. JIMD reports. 2014;12:1–4. PubMed PMID: 23818179.

Barshes NR, Vanatta JM, Patel AJ, Carter BA, O'Mahony CA, Karpen SJ, Goss JA. Evaluation and management of patients with propionic acidemia undergoing liver transplantation: a comprehensive review. Pediatr Transplant. 2006;10:773–81. PubMed PMID: 17032422.

Baumgartner D, Scholl-Bürgi S, Sass JO, Sperl W, Schweigmann U, Stein JI, Karall D. Prolonged QTc intervals and decreased left ventricular contractility in patients with propionic acidemia. J Pediatr. 2007;150:192–7. PubMed PMID: 17236900.

Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, Huemer M, Hochuli M, Assoun M, Ballhausen D, Burlina A, Fowler B, Grünert SC, Grünewald S, Honzik T, Merinero B, Pérez-Cerdá C, Scholl-Bürgi S, Skovby F, Wijburg F, MacDonald A, Martinelli D, Sass JO, Valayannopoulos V, Chakrapani A. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014;9:130. PubMed PMID: 25205257.

Bergman AJ, Van der Knaap MS, Smeitink JA, Duran M, Dorland L, Valk J, Poll-The BT. Magnetic resonance imaging and spectroscopy of the brain in propionic acidemia: clinical and biochemical considerations. Pediatr Res. 1996;40:404–9. PubMed PMID: 8865276.

Broomfield A, Gunny R, Prabhakar P, Grunewald S. Spontaneous rapid resolution of acute basal ganglia changes in an untreated infant with propionic acidemia: a clue to pathogenesis? Neuropediatrics. 2010;41:256–60. PubMed PMID: 21445815.

Campeau E, Desviat LR, Leclerc D, Wu X, Pérez B, Ugarte M, Gravel RA. Structure of the PCCA gene and distribution of mutations causing propionic acidemia. Mol Genet Metab. 2001;74:238–47. PubMed PMID: 11592820.

Chace DH, DiPerna JC, Kalas TA, Johnson RW, Naylor EW. Rapid diagnosis of methylmalonic and propionic acidemias: quantitative tandem mass spectrometric analysis of propionylcarnitine in filter-paper blood specimens obtained from newborns. Clin Chem. 2001;47:2040–4. PubMed PMID: 11673377.

Chapman KA, Gropman A, MacLeod E, Stagni K, Summar ML, Ueda K, Ah Mew N, Franks J, Island E, Matern D, Pena L, Smith B, Sutton VR, Urv T, Venditti C, Chakrapani A. Acute management of propionic acidemia. Mol Genet Metab. 2012;105:16–25. PubMed PMID: 22000903.

Charbit-Henrion F, Lacaille F, McKiernan P, Girard M, de Lonlay P, Valayannopoulos V, Ottolenghi C, Chakrapani A, Preece M, Sharif K, Chardot C, Hubert P, Dupic L. Early and late complications after liver transplantation for propionic acidemia in children: a two centers study. Am J Transplant. 2015;15:786–91. PubMed PMID: 25683683.

Chiu YH, Liu YN, Liao WL, Chang YC, Lin SP, Hsu CC, Chiu PC, Niu DM, Wang CH, Ke YY, Chien YH, Hsiao KJ, Liu TT. Two frequent mutations associated with the classic form of propionic acidemia in Taiwan. Biochem Genet. 2014;52:415–29. PubMed PMID: 24863100.

Couce ML, Castiñeiras DE, Bóveda MD, Baña A, Cocho JA, Iglesias AJ, Colón C, Alonso-Fernández JR, Fraga JM. Evaluation and long-term follow-up of infants with inborn errors of metabolism identified in an expanded screening programme. Mol Genet Metab. 2011;104:470–5. PubMed PMID: 22000754.

de Baulny HO, Benoist JF, Rigal O, Touati G, Rabier D, Saudubray JM. Methylmalonic and propionic acidaemias: management and outcome. J Inherit Metab Dis. 2005;28:415–23. PubMed PMID: 15868474.

de Keyzer Y, Valayannopoulos V, Benoist JF, Batteux F, Lacaille F, Hubert L, Chrétien D, Chadefeaux-Vekemans B, Niaudet P, Touati G, Munnich A, de Lonlay P. Multiple OXPHOS deficiency in the liver, kidney, heart, and skeletal muscle of patients with methylmalonic aciduria and propionic aciduria. Pediatr Res. 2009;66:91–5. PubMed PMID: 19342984.

Dejean de la Bâtie C, Barbier V, Valayannopoulos V, Touati G, Maltret A, Brassier A, Arnoux JB, Grévent D, Chadefaux B, Ottolenghi C, Canouï P, de Lonlay P. Acute psychosis in propionic acidemia: 2 case reports. J Child Neurol. 2014;29:274–9. PubMed PMID: 24334345.

Delgado C, Macías C, de la Sierra García-Valdecasas M, Pérez M, del Portal LR, Jiménez LM. Subacute presentation of propionic acidemia. J Child Neurol. 2007;22:1405–7. PubMed PMID: 18174561.

Desviat LR, Clavero S, Pérez-Cerdá C, Navarrete R, Ugarte M, Perez B. New splicing mutations in propionic acidemia. J Hum Genet. 2006;51:992–7. PubMed PMID: 17051315.

Desviat LR, Pérez B, Pérez-Cerdá C, Rodríguez-Pombo P, Clavero S, Ugarte M. Propionic acidemia: mutation update and functional and structural effects of the variant alleles. Mol Genet Metab. 2004;83:28–37. PubMed PMID: 15464417.

Desviat LR, Sanchez-Alcudia R, Pérez B, Pérez-Cerdá C, Navarrete R, Vijzelaar R, Ugarte M. High frequency of large genomic deletions in the PCCA gene causing propionic acidemia. Mol Genet Metab. 2009;96:171–6. PubMed PMID: 19157943.

Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis. 2006;29:383–9. PubMed PMID: 16763906.

Dionisi-Vici C, Rizzo C, Burlina AB, Caruso U, Sabetta G, Uziel G, Abeni D. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr. 2002;140:321–7. PubMed PMID: 11953730.

Domínguez-Cruz JJ, Bueno-Delgado M, Pereyra J, Bernabeu-Wittel J, Conejo-Mir J. Acrodermatitis enerophatica-like skin lesions secondary to isoleucine deficiency. Eur J Dermatol. 2011;21:115–6. PubMed PMID: 21224187.

Filipowicz HR, Ernst SL, Ashurst CL, Pasquali M, Longo N. Metabolic changes associated with hyperammonemia in patients with propionic acidemia. Mol Genet Metab. 2006;88:123–30. PubMed PMID: 16406646.

Filippi L, Gozzini E, Fiorini P, Malvagia S, la Marca G, Donati MA. N-carbamylglutamate in emergency management of hyperammonemia in neonatal acute onset propionic and methylmalonic aciduria. Neonatology. 2010;97:286–90. PubMed PMID: 19887858.

Griffin TA, Hostoffer RW, Tserng KY, Lebovitz DJ, Hoppel CL, Mosser JL, Kaplan D, Kerr DS. Parathyroid hormone resistance and B cell lymphopenia in propionic acidemia. Acta Paediatr. 1996;85:875–8. PubMed PMID: 8819559.

Grünert SC, Müllerleile S, de Silva L, Barth M, Walter M, Walter K, Meissner T, Lindner M, Ensenauer R, Santer R, Bodamer OA, Baumgartner MR, Brunner-Krainz M, Karall D, Haase C, Knerr I, Marquardt T,

Hennermann JB, Steinfeld R, Beblo S, Koch HG, Konstantopoulou V, Scholl-Bürgi S, van Teeffelen-Heithoff A, Suormala T, Sperl W, Kraus JP, Superti-Furga A, Schwab KO, Sass JO. Propionic acidemia: neonatal versus selective metabolic screening. J Inherit Metab Dis. 2012;35:41–9. PubMed PMID: 22134541.

Haan E, Brown G, Bankier A, Mitchell D, Hunt S, Blakey J, Barnes G. Severe illness caused by the products of bacterial metabolism in a child with a short gut. Eur J Pediatr. 1985;144:63–5. PubMed PMID: 4018104.

Haberlandt E, Canestrini C, Brunner-Krainz M, Möslinger D, Mussner K, Plecko B, Scholl-Bürgi S, Sperl W, Rostásy K, Karall D. Epilepsy in patients with propionic acidemia. Neuropediatrics. 2009;40:120–5. PubMed PMID: 20020396.

Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, Karall D, Martinelli D, Crespo PS, Santer R, Servais A, Valayannopoulos V, Lindner M, Rubio V, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;7:32. PubMed PMID: 22642880.

Hoffman M. Scientific sleuths solve a murder mystery. Science. 1991;254:931. PubMed PMID: 1948075.

Hsia YE, Scully KJ, Rosenberg LE. Defective propionate carboxylation in ketotic hyperglycinaemia. Lancet. 1969;1:757–8. PubMed PMID: 4180220.

Huang CS, Sadre-Bazzaz K, Shen Y, Deng B, Zhou ZH, Tong L. Crystal structure of the alpha(6)beta(6) holoenzyme of propionyl-coenzyme A carboxylase. Nature. 2010;466:1001–5. PubMed PMID: 20725044.

Jameson E, Walter J. Cardiac arrest secondary to long QT(C) in a child with propionic acidemia. Pediatr Cardiol. 2008;29:969–70. PubMed PMID: 18058159.

Karimzadeh P, Jafari N, Ahmad Abadi F, Jabbedari S, Taghdiri MM, Alaee MR, Ghofrani M, Tonekaboni SH, Nejad Biglari H. Propionic acidemia: diagnosis and neuroimaging findings of this neurometabolic disorder. Iran J Child Neurol. 2014;8:58–61. PubMed PMID: 24665329.

Kasahara M, Sakamoto S, Kanazawa H, Karaki C, Kakiuchi T, Shigeta T, Fukuda A, Kosaki R, Nakazawa A, Ishige M, Nagao M, Shigematsu Y, Yorifuji T, Naiki Y, Horikawa R. Living-donor liver transplantation for propionic acidemia. Pediatr Transplant. 2012;16:230–4. PubMed PMID: 22151065.

Kaya N, Al-Owain M, Albakheet A, Colak D, Al-Odaib A, Imtiaz F, Coskun S, Al-Sayed M, Al-Hassnan Z, Al-Zaidan H, Meyer B, Ozand P. Array comparative genomic hybridization (aCGH) reveals the largest novel deletion in PCCA found in a Saudi family with propionic acidemia. Eur J Med Genet. 2008;51:558–65. PubMed PMID: 18790721.

Kölker S, Cazorla AG, Valayannopoulos V, Lund AM, Burlina AB, Sykut-Cegielska J, Wijburg FA, Teles EL, Zeman J, Dionisi-Vici C, Barić I, Karall D, Augoustides-Savvopoulou P, Aksglaede L, Arnoux JB, Avram P, Baumgartner MR, Blasco-Alonso J, Chabrol B, Chakrapani A, Chapman K. I Saladelafont EC, Couce ML, de Meirleir L, Dobbelaere D, Dvorakova V, Furlan F, Gleich F, Gradowska W, Grünewald S, Jalan A, Häberle J, Haege G, Lachmann R, Laemmle A, Langereis E, de Lonlay P, Martinelli D, Matsumoto S, Mühlhausen C, de Baulny HO, Ortez C, Peña-Quintana L, Ramadža DP, Rodrigues E, Scholl-Bürgi S, Sokal E, Staufner C, Summar ML, Thompson N, Vara R, Pinera IV, Walter JH, Williams M, Burgard P. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: the initial presentation. J Inherit Metab Dis. 2015a;38:1155–6. PubMed PMID: 26077420.

Kölker S, Valayannopoulos V, Burlina AB, Sykut-Cegielska J, Wijburg FA, Teles EL, Zeman J, Dionisi-Vici C, Barić I, Karall D, Arnoux JB, Avram P, Baumgartner MR, Blasco-Alonso J, Boy SP, Rasmussen MB, Burgard P, Chabrol B, Chakrapani A, Chapman K, Cortès I, Saladelafont E, Couce ML, de Meirleir L, Dobbelaere D, Furlan F, Gleich F, González MJ, Gradowska W, Grünewald S, Honzik T, Hörster F, Ioannou H, Jalan A, Häberle J, Haege G, Langereis E, de Lonlay P, Martinelli D, Matsumoto S, Mühlhausen C, Murphy E, de Baulny HO, Ortez C, Pedrón CC, Pintos-Morell G, Pena-Quintana L, Ramadža DP, Rodrigues E, Scholl-Bürgi S, Sokal E, Summar ML, Thompson N, Vara R, Pinera IV, Walter JH, Williams M, Lund AM, Garcia-

Cazorla A. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis. 2015b;38:1059–74. PubMed PMID: 25875216.

Kraus JP, Spector E, Venezia S, Estes P, Chiang PW, Creadon-Swindell G, Müllerleile S, de Silva L, Barth M, Walter M, Walter K, Meissner T, Lindner M, Ensenauer R, Santer R, Bodamer OA, Baumgartner MR, Brunner-Krainz M, Karall D, Haase C, Knerr I, Marquardt T, Hennermann JB, Steinfeld R, Beblo S, Koch HG, Konstantopoulou V, Scholl-Bürgi S, van Teeffelen-Heithoff A, Suormala T, Ugarte M, Sperl W, Superti-Furga A, Schwab KO, Grünert SC, Sass JO. Mutation analysis in 54 propionic acidemia patients. J Inherit Metab Dis. 2012;35:51–63. PubMed PMID: 22033733.

Laemmle A, Balmer C, Doell C, Sass JO, Häberle J, Baumgartner MR. Propionic acidemia in a previously healthy adolescent with acute onset of dilated cardiomyopathy. Eur J Pediatr. 2014;173:971–4. PubMed PMID: 24916042.

Lam C, Desviat LR, Pérez-Cerdá C, Ugarte M, Barshop BA, Cederbaum S. 45-Year-old female with propionic acidemia, renal failure, and premature ovarian failure; late complications of propionic acidemia? Mol Genet Metab. 2011;103:338–40. PubMed PMID: 21549625.

Langendonk JG, Roos JC, Angus L, Williams M, Karstens FP, de Klerk JB, Maritz C, Ben-Omran T, Williamson C, Lachmann RH, Murphy E. A series of pregnancies in women with inherited metabolic disease. J Inherit Metab Dis. 2012;35:419–24. PubMed PMID: 21918856.

Lee TM, Addonizio LJ, Barshop BA, Chung WK. Unusual presentation of propionic acidaemia as isolated cardiomyopathy. J Inherit Metab Dis. 2009;32 Suppl 1:S97–101. PubMed PMID: 19238581.

Lehnert W, Sperl W, Suormala T, Baumgartner ER. Propionic acidaemia: clinical, biochemical and therapeutic aspects. Experience in 30 patients. Eur J Pediatr. 1994;153:S68–80. PubMed PMID: 7957390.

Li M, Dick A, Montenovo M, Horslen S, Hansen R. Cost-effectiveness of liver transplantation in methylmalonic and propionic acidemias. Liver Transpl. 2015;21:1208–18. PubMed PMID: 25990417.

Manoli I, Myles JG, Sloan JL, Shchelochkov OA. Venditti CP. A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 1: isolated methylmalonic acidemias. Genet Med. 2016;18:386–95. PubMed PMID: 26270765.

Marcadier JL, Smith AM, Pohl D, Schwartzentruber J, Al-Dirbashi OY; FORGE Canada Consortium. Majewski J, Ferdinandusse S, Wanders RJ, Bulman DE, Boycott KM, Chakraborty P, Geraghty MT. Mutations in ALDH6A1 encoding methylmalonate semialdehyde dehydrogenase are associated with dysmyelination and transient methylmalonic aciduria. Orphanet J Rare Dis. 2013;8:98. PubMed PMID: 23835272.

Martín-Hernández E, Lee PJ, Micciche A, Grunewald S, Lachmann RH. Long-term needs of adult patients with organic acidaemias: outcome and prognostic factors. J Inherit Metab Dis. 2009;32:523–33. PubMed PMID: 19629744.

Martinez Alvarez L, Jameson E, Parry NR, Lloyd C, Ashworth JL. Optic neuropathy in methylmalonic acidemia and propionic acidemia. Br J Ophthalmol. 2016;100:98–104. PubMed PMID: 26209586.

Mellon AF, Deshpande SA, Mathers JC, Bartlett K. Effect of oral antibiotics on intestinal production of propionic acid. Arch Dis Child. 2000;82:169–72. PubMed PMID: 10648377.

Morioka D, Kasahara M, Takada Y, Corrales JP, Yoshizawa A, Sakamoto S, Taira K, Yoshitoshi EY, Egawa H, Shimada H, Tanaka K. Living donor liver transplantation for pediatric patients with inheritable metabolic disorders. Am J Transplant. 2005;5:2754–63. PubMed PMID: 16212637.

Müller S, Falkenberg N, Mönch E, Jakobs C. Propionacidaemia and immunodeficiency. Lancet. 1980;1:551–2. PubMed PMID: 6102279.

Muro S, Perez B, Desviat LR, Rodríguez-Pombo P, Pérez-Cerdá C, Clavero S, Ugarte M. Effect of PCCB gene mutations on the heteromeric and homomeric assembly of propionyl-CoA carboxylase. Mol Genet Metab. 2001;74:476–83. PubMed PMID: 11749052.

Nizon M, Ottolenghi C, Valayannopoulos V, Arnoux JB, Barbier V, Habarou F, Desguerre I, Boddaert N, Bonnefont JP, Acquaviva C, Benoist JF, Rabier D, Touati G, de Lonlay P. Long-term neurological outcome of a cohort of 80 patients with classical organic acidurias. Orphanet J Rare Dis. 2013;8:148. PubMed PMID: 24059531.

North KN, Korson MS, Gopal YR, Rohr FJ, Brazelton TB, Waisbren SE, Warman ML. Neonatal-onset propionic acidemia: neurologic and developmental profiles, and implications for management. J Pediatr. 1995;126:916–22. PubMed PMID: 7539836.

Noval S, López-Rodríguez M, González-Sánchez E, Contreras I, Royo A, Boto-De-los-Bueis A. Late optic neuropathy in propionic acidemia following surgical intervention. J Neuroophthalmol. 2013;33:90–1. PubMed PMID: 23149616.

Nyhan WL, Bay C, Beyer EW, Mazi M. Neurologic nonmetabolic presentation of propionic acidemia. Arch Neurol. 1999;56:1143–7. PubMed PMID: 10488817.

Ottolenghi C, Abermil N, Lescoat A, Aupetit J, Beaugendre O, Morichon-Delvallez N, Ricquier D, Chadefaux-Vekemans B, Rabier D. Gestational age-related reference values for amniotic fluid organic acids. Prenat Diagn. 2010;30:43–8. PubMed PMID: 19950217.

Pena L, Burton BK. Survey of health status and complications among propionic acidemia patients. Am J Med Genet A. 2012;158A:1641–6. PubMed PMID: 22678880.

Pérez-Cerdá C, Merinero B, Rodríguez-Pombo P, Pérez B, Desviat LR, Muro S, Richard E, García MJ, Gangoiti J, Ruiz Sala P, Sanz P, Briones P, Ribes A, Martínez-Pardo M, Campistol J, Pérez M, Lama R, Murga ML, Lema-Garrett T, Verdú A, Ugarte M. Potential relationship between genotype and clinical outcome in propionic acidaemia patients. Eur J Hum Genet. 2000;8:187–94. PubMed PMID: 10780784.

Raby RB, Ward JC, Herrod HG. Propionic acidaemia and immunodeficiency. J Inherit Metab Dis. 1994;17:250–1. PubMed PMID: 7526032.

Rashed MS. Clinical applications of tandem mass spectrometry: ten years of diagnosis and screening for inherited metabolic diseases. J Chromatogr B Biomed Sci Appl. 2001;758:27–48. PubMed PMID: 11482732.

Ravn K, Chloupkova M, Christensen E, Brandt NJ, Simonsen H, Kraus JP, Nielsen IM, Skovby F, Schwartz M. High incidence of propionic acidemia in greenland is due to a prevalent mutation, 1540insCCC, in the gene for the beta-subunit of propionyl CoA carboxylase. Am J Hum Genet. 2000;67:203–6. PubMed PMID: 10820128.

Romano S, Valayannopoulos V, Touati G, Jais JP, Rabier D, de Keyzer Y, Bonnet D, de Lonlay P. Cardiomyopathies in propionic aciduria are reversible after liver transplantation. J Pediatr. 2010;156:128–34. PubMed PMID: 19818452.

Rousson R, Guibaud P. Long term outcome of organic acidurias: survey of 105 French cases (1967-1983). J Inherit Metab Dis. 1984;7 Suppl 1:10–2. PubMed PMID: 6434836.

Sarafoglou K, Rodgers J, Hietala A, Matern D, Bentler K. EXpanded newborn screening for detection of vitamin b12 deficiency. JAMA. 2011;305:1198–200. PubMed PMID: 21427371.

Sass JO, Hofmann M, Skladal D, Mayatepek E, Schwahn B, Sperl W. Propionic acidemia revisited: a workshop report. Clin Pediatr (Phila). 2004;43:837–43. PubMed PMID: 15583780.

Sato S, Kasahara M, Fukuda A, Mizuguchi K, Nakagawa S, Muguruma T, Saito O, Karaki C, Nakagawa A, Yoshii K, Horikawa R. Liver transplantation in a patient with propionic acidemia requiring extra corporeal membrane oxygenation during severe metabolic decompensation. Pediatr Transplant. 2009;13:790–3. PubMed PMID: 19207227.

Saudubray JM, Touati G, Delonlay P, Jouvet P, Schlenzig J, Narcy C, Laurent J, Rabier D, Kamoun P, Jan D, Revillon Y. Liver transplantation in propionic acidaemia. Eur J Pediatr. 1999;158 Suppl 2:S65–9. PubMed PMID: 10603102.

Schoderbeck M, Auer B, Legenstein E, Genger H, Sevelda P, Salzer H, Marz R, Lohninger A. Pregnancy-related changes of carnitine and acylcarnitine concentrations of plasma and erythrocytes. J Perinat Med. 1995;23:477–85. PubMed PMID: 8904477.

Scholl-Bürgi S, Haberlandt E, Gotwald T, Albrecht U, Baumgartner Sigl S, Rauchenzauner M, Rostásy K, Karall D. Stroke-like episodes in propionic acidemia caused by central focal metabolic decompensation. Neuropediatrics. 2009;40:76–81. PubMed PMID: 19809936.

Schreiber J, Chapman KA, Summar ML, Ah Mew N, Sutton VR, MacLeod E, Stagni K, Ueda K, Franks J, Island E, Matern D, Peña L, Smith B, Urv T, Venditti C, Chakarapani A, Gropman AL. Neurologic considerations in propionic acidemia. Mol Genet Metab. 2012;105:10–5. PubMed PMID: 22078457.

Schulze A, Lindner M, Kohlmüller D, Olgemöller K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. Pediatrics. 2003;111:1399–406. PubMed PMID: 12777559.

Schwahn BC, Pieterse L, Bisset WM, Galloway PG, Robinson PH. Biochemical efficacy of N-carbamylglutamate in neonatal severe hyperammonaemia due to propionic acidaemia. Eur J Pediatr. 2010;169:133–4. PubMed PMID: 19680687.

Shuaib T, Al-Hashmi N, Ghaziuddin M, Megdad E, Abebe D, Al-Saif A, Doubi A, Aldhalaan H, Abouzied ME, Al-Owain M. Propionic acidemia associated with visual hallucinations. J Child Neurol. 2012;27:799–803. PubMed PMID: 22156789.

Sipahi T, Yilmaz D, Tavil B. Propionic acidemia with myelodysplasia and neutropenia in a Turkish child. J Pediatr Hematol Oncol. 2004;26:154–5. PubMed PMID: 15125606.

Stork LC, Ambruso DR, Wallner SF, Sambrano JE, Moscinski LC, Wilson HL, McCabe ER. Pancytopenia in propionic acidemia: hematologic evaluation and studies of hematopoiesis in vitro. Pediatr Res. 1986;20:783–8. PubMed PMID: 3737292.

Surtees RA, Matthews EE, Leonard JV. Neurologic outcome of propionic acidemia. Pediatr Neurol. 1992;8:333–7. PubMed PMID: 1418175.

Sutton VR, Chapman KA, Gropman AL, MacLeod E, Stagni K, Summar ML, Ueda K, Ah Mew N, Franks J, Island E, Matern D, Peña L, Smith B, Urv T, Venditti C, Chakarapani A. Chronic management and health supervision of individuals with propionic acidemia. Mol Genet Metab. 2012;105:26–33. PubMed PMID: 21963082.

Tay KY, Ewald MB, Bourgeois FT. Use of QT-prolonging medications in US emergency departments, 1995-2009. Pharmacoepidemiol Drug Saf. 2014;23:9–17. PubMed PMID: 23696066.

Thompson GN, Walter JH, Bresson JL, Bonnefont JP, Saudubray JM, Leonard JV, Halliday D. In vivo propionate oxidation as a prognostic indicator in disorders of propionate metabolism. Eur J Pediatr. 1990;149:408–11. PubMed PMID: 2332010.

Touati G, Valayannopoulos V, Mention K, de Lonlay P, Jouvet P, Depondt E, Assoun M, Souberbielle JC, Rabier D, Ogier de Baulny H, Saudubray JM. Methylmalonic and propionic acidurias: management without or with a few supplements of specific amino acid mixture. J Inherit Metab Dis. 2006;29:288–98. PubMed PMID: 16763890.

Van Calcar SC, Harding CO, Davidson SR, Barness LA, Wolff JA. Case reports of successful pregnancy in women with maple syrup urine disease and propionic acidemia. Am J Med Genet. 1992;44:641–6. PubMed PMID: 1481826.

van der Meer SB, Poggi F, Spada M, Bonnefont JP, Ogier H, Hubert P, Depondt E, Rapoport D, Rabier D, Charpentier C, Parvy P, Bardet J, Kamoun P, Saudubray JM. Clinical outcome and long-term management of 17 patients with propionic acidaemia. Eur J Pediatr. 1996;155:205–10. PubMed PMID: 8929729.

Vara R, Turner C, Mundy H, Heaton ND, Rela M, Mieli-Vergani G, Champion M, Hadzic N. Liver transplantation for propionic acidemia in children. Liver Transpl. 2011;17:661–7. PubMed PMID: 21618686.

Vernon HJ, Bagnasco S, Hamosh A, Sperati CJ. Chronic kidney disease in an adult with propionic acidemia. JIMD Rep. 2014;12:5–10. PubMed PMID: 23756992.

Woolf AD, Wynshaw-Boris A, Rinaldo P, Levy HL. Intentional infantile ethylene glycol poisoning presenting as an inherited metabolic disorder. J Pediatr. 1992;120:421–4. PubMed PMID: 1538289.

Yang X, Sakamoto O, Matsubara Y, Kure S, Suzuki Y, Aoki Y, Yamaguchi S, Takahashi Y, Nishikubo T, Kawaguchi C, Yoshioka A, Kimura T, Hayasaka K, Kohno Y, Iinuma K, Ohura T. Mutation spectrum of the PCCA and PCCB genes in Japanese patients with propionic acidemia. Mol Genet Metab. 2004;81:335–42. PubMed PMID: 15059621.

Yorifuji T, Kawai M, Mamada M, Kurokawa K, Egawa H, Shigematsu Y, Kohno Y, Tanaka K, Nakahata T. Living-donor liver transplantation for propionic acidaemia. J Inherit Metab Dis. 2004;27:205–10. PubMed PMID: 15159651.

Yorifuji T, Kawai M, Muroi J, Mamada M, Kurokawa K, Shigematsu Y, Hirano S, Sakura N, Yoshida I, Kuhara T, Endo F, Mitsubuchi H, Nakahata T. Unexpectedly high prevalence of the mild form of propionic acidemia in Japan: presence of a common mutation and possible clinical implications. Hum Genet. 2002;111:161–5. PubMed PMID: 12189489.

Zayed H. Propionic acidemia in the Arab World. Gene. 2015;564:119–24. PubMed PMID: 25865301.

Chapter Notes

Author Notes

Dr Oleg A Shchelochkov, Dr Carrillo, and Dr Venditti are physicians at the NIH Clinical Center and specialize in pediatrics and biochemical genetics. Dr Carrillo leads the Clinical Section of the Therapeutics for Rare and Neglected Diseases (TRND) Program at the NIH and Dr Venditti is the Director of the Organic Acid Disorder Research Unit at the National Human Genome Research Institute.

Revision History

- 6 October 2016 (ha) Comprehensive update posted live
- 17 May 2012 (me) Review posted live
- 28 October 2011 (ncc) Original submission

Note: Pursuant to 17 USC Section 105 of the United States Copyright Act, the *GeneReview* "Propionic Acidemia" is in the public domain in the United States of America.

License