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NLM Citation: Wang D, De Vivo D. Pyruvate Carboxylase Deficiency. 2009 Jun 2 [Updated 2018 Mar 1]. 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/

Pyruvate Carboxylase Deficiency

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Created: June 2, 2009; Updated: March 1, 2018.

Summary

Clinical characteristics

Pyruvate carboxylase (PC) deficiency is characterized in most affected individuals by failure to thrive, developmental delay, recurrent seizures, and metabolic acidosis. Three clinical types are recognized:

- Type A (infantile form), in which most affected children die in infancy or early childhood
- Type B (severe neonatal form), in which affected infants have hepatomegaly, pyramidal tract signs, and abnormal movement and die within the first three months of life
- Type C (intermittent/benign form), in which affected individuals have normal or mildly delayed neurologic development and episodic metabolic acidosis

Diagnosis/testing

The diagnosis of PC deficiency is established in a proband by identification of PC enzyme deficiency in fibroblasts or lymphoblasts. In individuals with PC deficiency, fibroblast PC enzyme activity is usually less than 5% of that observed in controls. The diagnosis of PC deficiency can also be established in a proband by identification of biallelic pathogenic variants in *PC* on molecular genetic testing.

Management

Treatment of manifestations: Intravenous glucose-containing fluids, hydration, and correction of the metabolic acidosis are the mainstays of acute management. Correction of biochemical abnormalities and supplementation with citrate, aspartic acid, and biotin may improve somatic findings but not neurologic manifestations. Orthotopic liver transplantation may be indicated in some affected individuals. Anaplerotic therapies such as triheptanoin show some promise, especially regarding the neurologic manifestations, but need to be further evaluated.

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Prevention of primary manifestations: Parental education regarding factors that elicit a crisis and early signs of decompensation; written information on the child's disorder and appropriate emergency treatment to be carried at all times; minimization of intercurrent infections and environmental stressors; high-carbohydrate and high-protein diet with frequent feedings to prevent dependence on gluconeogenesis.

Prevention of secondary complications: Hospitalization for the management of fever, infection, dehydration, or trauma; intensive proactive medical support to prevent dehydration, hypotension, hypoglycemia, and increasing metabolic acidosis.

Surveillance: Regular monitoring of serum lactate concentrations.

Agents/circumstances to avoid: Fasting; the ketogenic diet.

Genetic counseling

PC deficiency is inherited in an autosomal recessive manner. *De novo* somatic pathogenic variants have been reported. If both parents are carriers, sibs of an individual with PC deficiency have a 25% chance of inheriting both pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being carriers, and a 25% chance of inheriting both normal genes and not being carriers. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible by molecular genetic testing if both pathogenic variants have been identified in an affected family member.

Diagnosis

There are three clinical presentations of pyruvate carboxylase (PC) deficiency:

- Type A. Infantile or North American form
- Type B. Severe neonatal or French form
- Type C. Intermittent/benign form

Suggestive Findings

PC deficiency **should be suspected** in individuals with the following clinical features and biochemical findings.

Clinical features

- Failure to thrive
- Developmental delay
- Recurrent seizures

Biochemical findings by PC deficiency type [Wang et al 2008]

- **Type A.** Infantile-onset mild to moderate lactic acidemia; normal lactate-to-pyruvate ratio despite acidemia
- **Type B.** Increased lactate-to-pyruvate ratio; decreased 3-hydroxybutyrate-to-acetoacetate ratio; elevated blood concentrations of citrulline, proline, lysine, and ammonia; low concentration of glutamine
- **Type C.** Episodic metabolic acidosis with normal plasma citrulline concentrations and elevated plasma lysine and proline concentrations

Biochemical abnormalities by analyte. Note: For each of the following analytes the abnormal values overlap among PC deficiency types A, B, and C. Normal values differ by laboratory.

- **Lactate and pyruvate.** The lack of PC enzyme activity causes the accumulation of pyruvate in the plasma, which is subsequently converted to lactate by the enzyme lactate dehydrogenase, causing an elevated plasma concentration of lactic acid. Elevated blood lactate concentrations (5.5-27.8 mmol/L; normal range

0.5-2.2) are characteristically found in PC deficiency type A (2-10 mmol/L), type B (>10 mmol/L), and type C (2-5 mmol/L). Blood pyruvate concentrations are usually elevated in PC deficiency type B (0.14-0.90 mmol/L; normal range 0.04-0.13), resulting in an elevated lactate-to-pyruvate ratio (>20). The ratio is usually normal in PC deficiency type A and C (<20).

- **Amino acids.** In serum and urine: high alanine, citrulline, and lysine; low aspartic acid and glutamine. Amino acid concentrations vary with the general metabolic state of the individual:
  - Hyperalaninemia as a result of pyruvate shunting
  - Hypercitrullinemia and hyperlysinemia caused by the block in the urea cycle secondary to a low aspartic acid
  - Low aspartic acid and glutamine as a result of deficiency in the oxaloacetate precursor
- **Ketonemia.** 3-hydroxybutyrate and acetoacetate concentrations are increased in blood. In PC deficiency type B, the ratio of acetoacetate to 3-hydroxybutyrate is increased, reflecting a low NADH-to-NAD ratio inside the mitochondria. Lack of oxaloacetate prevents the liver from oxidizing acetyl-CoA derived from pyruvate and fatty acids. The expanded acetyl-CoA pool results in hepatic ketone body synthesis [De Vivo et al 1977].
- **Hypoglycemia.** Oxaloacetate deficiency limits gluconeogenesis. Note: Hypoglycemia is not a consistent finding despite the fact that PC is the first rate-limiting step in gluconeogenesis.
- **Hyperammonemia** results from poor ammonia disposal and decreased urea cycle function.
- **Cerebrospinal fluid (CSF)**
  - Elevated lactate and pyruvate concentrations
  - Markedly reduced glutamine concentration
  - Elevated glutamic acid and proline concentrations

Establishing the Diagnosis

The diagnosis of PC deficiency **is established** in a proband by identification of PC enzyme deficiency in fibroblasts or lymphoblasts by PC enzyme assay. In individuals with PC deficiency, fibroblast PC enzyme activity is usually less than 5% of that observed in controls [Wang et al 2008]. Note: Muscle PC activity is quite low in control tissue. Therefore, PC enzyme assay on muscle tissue is not recommended.

The diagnosis of PC deficiency can also be **established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *PC* on molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *PC* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

  Note: (1) Pathogenic variants have been found to be mosaic, an unusual occurrence in an autosomal recessive disorder (see Genotype-Phenotype Correlations and Molecular Genetics). (2) Since PC deficiency occurs through a loss-of-function mechanism, testing for intragenic deletions or duplication could identify a disease-causing variant; such a variant has not been reported.

- **A multigene panel** that includes *PC* 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 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, mitochondrial sequencing, and genome sequencing may be considered. 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 Pyruvate Carboxylase Deficiency

Gene [1]	Method [2]	Proportion of Probands with Pathogenic Variants [3] Detectable by Method
PC	Sequence analysis [4]	95% [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. The presence of mosaicism may complicate molecular testing; see Genotype-Phenotype Correlations, Table 2, and Wang et al [2008].
3. See Molecular Genetics for information on allelic variants detected in this gene.
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. Sequence analysis of the *PC* coding region and promoter detects pathogenic variants in 95% of affected individuals, including the most common pathogenic variants: p.Ala610Thr, p.Arg631Gln, and p.Ala847Val.
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Most individuals with pyruvate carboxylase (PC) deficiency present with failure to thrive, developmental delay, recurrent seizures, and metabolic acidosis. Hypoglycemia is an inconsistent finding.

Three types of PC deficiency have been recognized, based on clinical presentation.

Type A (infantile form) is characterized by infantile onset with mild metabolic acidosis, delayed motor development, intellectual disability, failure to thrive, apathy, hypotonia, pyramidal tract signs, ataxia, nystagmus, and convulsions.

Episodes of acute vomiting, tachypnea, and acidosis are usually precipitated by metabolic or infectious stress.

Most affected children die in infancy or early childhood, although some may survive to maturity. Older individuals function at a lower-than-average level and need special care and schooling [Wang et al 2008].

Type B (severe neonatal form). Affected infants present with biochemical abnormalities, hypoglycemia, hyperammonemia, hypernatremia, anorexia, hepatomegaly, convulsions, stupor, hypotonia, pyramidal tract signs, abnormal movements (including high-amplitude tremor and dyskinesia), and abnormal ocular behavior.

Motor development is severely retarded and affected individuals have intellectual disability [Wang et al 2008].

The majority of affected infants die within the first three months of life [García-Cazorla et al 2006]; however, two affected individuals were alive at ages nine and 20 years, likely because of mosaicism [Wang et al 2008] (see Genotype-Phenotype Correlations).

Type C (intermittent/benign form) is characterized by normal or mildly delayed neurologic development and episodic metabolic acidosis. Five affected individuals have been reported [Van Coster et al 1991, Stern et al 1995, Vaquerizo Madrid et al 1997, Arnold et al 2001, Wang et al 2008]. The first individual described had normal mental and motor development at age 12 years despite several earlier episodes of metabolic acidosis [Van Coster et al 1991].

Brain MRI. Symmetric cystic lesions and gliosis in the cortex, basal ganglia, brain stem, or cerebellum; generalized hypomyelination; and hyperintensity of the subcortical frontoparietal white matter were described in some individuals with type A.

Ventricular dilatation, cerebrocortical and white matter atrophy, or periventricular white matter cysts have been reported in some individuals with type B [García-Cazorla et al 2006].

Magnetic resonance spectroscopy (MRS). Brain MRS shows high levels for lactate and choline and low levels for *N*-acetylaspartate.

Pathophysiology. The glutamine-glutamate cycle in astrocytes requires a continuous supply of oxaloacetate provided by the reaction catalyzed by PC enzyme activity.

Genotype-Phenotype Correlations

Type A. Seven pathogenic variants (p.Arg62Cys, p.Val145Ala, p.Arg451Cys, p.Ala610Thr, p.Arg631Gln, p.Met743Ile, and p.Ala847Val) have been identified in five individuals [Wang et al 2008].

Type B. Missense variants, deletions, and splice donor site pathogenic variants occur in homozygotes, compound heterozygotes, and individuals with mosaicism (see Table 2) [Wang et al 2008].

Type C. A heterozygous variant (p.Ser266Ala) and somatic mosaic variant (p.Ser705Ter) were observed in the first individual described [Wang et al 2008]; compound heterozygosity for the pathogenic variants p.Thr569Ala and p.Leu1137ValfsTer34 was observed in the second individual described [Wang et al 2008].

Mosaicism (see Molecular Genetics) was found in five individuals [Wang et al 2008: Table 2 (type A: #6; type B: #2, #5, and #7; type C: #1)]. Four had prolonged survival; the fifth (type B: #7) died from unrelated medical complications.

Homozygous pathogenic variants. The deaths of the more severely affected individuals with type B correlated with homozygous variants, which produced very low amounts (2% and 3%) of fibroblast PC protein [Wang et al 2008: Table 2].

Prevalence

In most populations, the birth incidence of PC deficiency is low (1:250,000).

PC deficiency is more prevalent in particular ethnic groups:

- **Type A.** Incidence is increased among the native North American Ojibwa, Cree, and Micmac tribes of the Algonquin-speaking peoples. The p.Ala610Thr pathogenic variant was identified in all 13 affected individuals of Ojibwa and Cree origin. In those populations the carrier frequency may be as high as 1:10 [Carbone et al 1998].
- **Type B.** Incidence is increased in Europe (France especially, but also Germany and England).

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Biotinidase deficiency results from the inability to recycle endogenous biotin and to use protein-bound biotin from the diet. Biotin binds to propionyl-coenzyme A-carboxylase, pyruvate carboxylase (PC), beta-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase. Deficiency affects all biotinylated enzymes and can present in the neonatal period or later in infancy with neurologic symptoms such as lethargy, seizures with metabolic acidosis, hearing loss, alopecia, and perioral/facial dermatitis. It can be effectively treated with biotin.

In the untreated state, profound biotinidase deficiency during infancy is usually characterized by neurologic and cutaneous findings that include seizures, hypotonia, and rash, often accompanied by hyperventilation, laryngeal stridor, and apnea. Older children may also have alopecia, ataxia, developmental delay, sensorineural hearing loss, optic atrophy, and recurrent infections. Individuals with partial biotinidase deficiency may have hypotonia, skin rash, and hair loss, particularly during times of stress.

Biotinidase deficiency is caused by pathogenic variants in *BTD*. Individuals with profound biotinidase deficiency have less than 10% of mean normal serum biotinidase activity; individuals with partial biotinidase deficiency have 10%-30% of mean normal serum biotinidase activity.

Biotinidase deficiency is inherited in an autosomal recessive manner.

Pyruvate dehydrogenase complex (PDHC) deficiency results from deficiency of either one of three catalytic components (E1, E2, and E3) or the regulatory component of PDHC (pyruvate dehydrogenase phosphate phosphatase). The diagnosis of PDHC deficiency is suspected in individuals with lactic acidemia who have a progressive or intermittent neurologic syndrome including: poor acquisition or loss of motor milestones, poor muscle tone, new-onset seizures, periods of incoordination (i.e., ataxia), abnormal eye movements, poor response to visual stimuli, and episodic dystonia. Blood and CSF lactate concentrations are elevated and are associated with elevations of blood and CSF concentrations of pyruvate and alanine. Blood glucose values are normal and decline only slowly with fasting because of increased pyruvate carboxylation and gluconeogenesis. Blood ketone bodies are usually not detectable, unlike PC deficiency. Also, unlike PC deficiency, PDHC deficiency usually presents with a normal lactate-to-pyruvate ratio in plasma. Typically, the CSF lactate elevations are higher than those in the blood, giving rise to the term "cerebral lactic acidosis."

Brain MRI may show varying combinations of ventricular dilatation; cerebral atrophy; hydrocephaly; partial or complete absence of the corpus callosum; absence of the medullary pyramids; abnormal and ectopic inferior olives; symmetric cystic lesions; gliosis in the cortex, basal ganglia, brain stem, or cerebellum; and generalized hypomyelination.

Brain MRS shows high lactate concentrations (giving rise to the term "cerebral lactic acidosis") and low *N*-acetylaspartate and choline concentrations consistent with hypomyelination.

PDHC enzyme assay, immunoblotting analysis, and molecular genetic testing of the genes known to be associated with this disorder (see Primary Pyruvate Dehydrogenase Complex Deficiency Overview) can help establish the diagnosis.

Respiratory chain disorder may result from pathogenic variants in nuclear genes or mitochondrial genes that encode any one of the five respiratory chain complexes. Lactate and pyruvate concentrations are elevated, and the lactate/pyruvate ratio is elevated, often above 20. Biopsied skeletal muscle may reveal ragged-red fibers, cytochrome *c*-oxidase negative fibers, and succinate dehydrogenase intensely positive fibers. These histologic abnormalities are commonly seen with pathogenic nuclear DNA variants causing intergenomic signaling defects and pathogenic mitochondrial DNA variants affecting protein synthesis genes. Brain MRI may reveal distinctive abnormalities, as described with Leigh syndrome or mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [DiMauro & Schon 2008]. Nuclear gene variants are inherited in an autosomal recessive or dominant manner; mitochondrial DNA variants are inherited as maternal, non-mendelian traits.

Krebs cycle disorders are rare and the enzymyopathies are partial. Lactate and pyruvate concentrations are elevated and the lactate/pyruvate ratio is normal. Urine organic acid profile may reveal distinctive elevation of fumaric acid or other Krebs cycle intermediates, reflecting the site of the enzyme deficiency.

Gluconeogenic defects may be aggravated clinically by fasting. Blood lactate, pyruvate, and alanine concentrations are classically elevated with clinical symptoms, and blood glucose concentration is low, indicating glycogen depletion and gluconeogenic pathway block. Ketone bodies are elevated, reflecting a physiologic response to fasting, stress, and hypoglycemia.

Carbonic anhydrase VA deficiency is suspected in children with neonatal, infantile, or early-childhood metabolic hyperammonemic encephalopathy combined with hyperlactatemia and metabolites suggestive of multiple carboxylase deficiency. The diagnosis is established in a proband with these metabolic findings and biallelic pathogenic variants in *CA5A*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with pyruvate carboxylase (PC) deficiency, the evaluations summarized in this section are recommended (if not performed as part of the evaluation that led to the diagnosis):

- Blood, urine, and CSF measures of organic and amino acids; brain MRI and MRS analysis
- Evaluation by a pediatric neurologist skilled in metabolic and genetic disorders to confirm the diagnosis, guide the treatment, and determine the prognosis
- Genetic counseling for the parents regarding the risk of recurrence in future pregnancies
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment focuses on providing alternative energy sources, hydration, and correction of the metabolic acidosis during acute decompensation. Stimulating residual PC enzyme activity is an important goal for long-term stable metabolic status. Correction of the biochemical abnormality can reverse some symptoms, but central nervous system damage progresses regardless of treatment [DiMauro & De Vivo 1999].

"Anaplerotic therapy" is based on the concept that an energy deficit in these diseases could be improved by providing alternative substrate for both the citric acid cycle and the electron transport chain for enhanced ATP production [Roe & Mochel 2006].

- Citrate supplementation reduces the acidosis and provides substrate for the citric acid cycle [Ahmad et al 1999].
- Aspartic acid supplementation allows the urea cycle to proceed and reduces the plasma and urine ammonia concentrations but has little effect on the neurologic disturbances as the aspartate does not enter the brain freely [Ahmad et al 1999]. Lowering the body ammonia burden may mitigate the neurologic insult.
- Biotin supplementation is given to help optimize the residual PC enzyme activity but is usually of little efficacy.
- Triheptanoin, an odd-carbon triglyceride, providing a source for acetyl-CoA and anaplerotic propionyl-CoA, has been tried in one individual with biotin-unresponsive PC deficiency type B with immediate reversal (<48 h) of major hepatic failure and full correction of all biochemical abnormalities [Mochel et al 2005, Mochel 2017]. Triheptanoin provides C5-ketone bodies that can cross the blood-brain barrier, therefore providing substrates for the brain. Dietary intervention with triheptanoin is the only therapeutic approach that showed improvement of brain metabolism. However, this observation needs to be confirmed in additional affected individuals.
- Orthotopic liver transplantation has reversed the biochemical abnormalities in two affected individuals [Nyhan et al 2002].

Prevention of Primary Manifestations

Educate parents about the factors that elicit a crisis and the early signs of decompensation.

Carry written information regarding the child's disorder and appropriate treatment in an emergency setting.

Minimize intercurrent infections and environmental stressors.

Provide a high-carbohydrate and high-protein diet with frequent feedings to help prevent dependence on gluconeogenesis.

Prevention of Secondary Complications

Individuals with PC deficiency are very brittle metabolically. Intensive medical support is indicated proactively to prevent dehydration, hypotension, hypoglycemia, and increasing metabolic acidosis. Hospitalization is indicated for the management of fever, infection, dehydration, or trauma. The ketogenic diet is an absolute contraindication, shown to worsen the acidosis into a life-threatening range.

Surveillance

Monitor lactate levels regularly.

Agents/Circumstances to Avoid

Avoid the following:

- Fasting
- The ketogenic diet, which aggravates life-threatening metabolic acidosis

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnancy in a woman with PC deficiency has not been reported. However, women with the benign form (type C) could become pregnant; such a pregnancy should be closely monitored for any metabolic derangements including dehydration and acidosis.

Therapies Under Investigation

Thiamine and lipoic acid could optimize pyruvate dehydrogenase complex (PDHC) activity, which could help reduce the plasma and urine pyruvate and lactate concentrations through an alternate route of pyruvate metabolism. Theoretically, this intervention could increase the acetyl-CoA pool and worsen the ketonemia.

- An individual with PC deficiency was responsive to treatment with thiamine.
- Two sisters with PC deficiency, severe intellectual disability and motor retardation, and Leigh syndrome improved clinically and biochemically after treatment with thiamine and lipoic acid. The precise molecular diagnosis in these individuals is uncertain.

Based on reports from the literature [Nyhan et al 2002, Mochel et al 2005], it has been suggested that a combination of orthotopic liver transplantation and anaplerotic diet be used in order to obtain both (i) long-term metabolic stability and (ii) improvement/correction of brain energy metabolism, myelination, and neurotransmission.

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

Genetic Counseling

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

Mode of Inheritance

Pyruvate carboxylase (PC) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- In most instances, the parents of a proband are heterozygotes (i.e., carriers of one *PC* pathogenic variant).
- In rare cases, a proband has one *de novo* somatic pathogenic variant and one pathogenic variant inherited from a carrier parent [Wang et al 2008]; in these families, presumably only one parent is heterozygous for a *PC* pathogenic variant.
- Heterozygotes are asymptomatic.

Sibs of a proband

- If both parents are carriers, each sib of an affected individual has at conception a 25% chance of inheriting both pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither pathogenic variant.

- If only one parent is a carrier (i.e., the proband is compound heterozygous for an inherited pathogenic variant and a *de novo* somatic pathogenic variant), the sibs of a proband have a 50% chance of inheriting one pathogenic variant and a 50% chance of not inheriting a pathogenic variant.
- Sibs who inherit two pathogenic variants will be affected. Sibs who inherit one pathogenic variant (heterozygotes) are expected to be asymptomatic. A sib who is heterozygous for an inherited pathogenic variant could be affected if the sib has a *de novo* somatic *PC* pathogenic variant.

Offspring of a proband. The offspring of a proband are typically heterozygous for a pathogenic variant.

Other family members. Each sib of a heterozygous parent is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PC* pathogenic variants in the family.

Biochemical genetic testing for carrier status is not reliable.

Related Genetic Counseling Issues

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

Molecular genetic testing. Once the *PC* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for PC and preimplantation genetic testing are possible.

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.

- **Kiana Research Foundation for Pyruvate Carboxylase**
  Phone: 949-280-1455
  Email: pcdeficiency@gmail.com
- **MedlinePlus**
  Pyruvate carboxylase deficiency
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org

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. Pyruvate Carboxylase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PC	11q13.2	Pyruvate carboxylase, mitochondrial	PC database	PC	PC

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 Pyruvate Carboxylase Deficiency (View All in OMIM)

266150	PYRUVATE CARBOXYLASE DEFICIENCY
608786	PYRUVATE CARBOXYLASE; PC

Molecular Pathogenesis

Pyruvate carboxylase (PC) [EC 6.4.1.1] is a biotin-dependent mitochondrial enzyme that plays an important role in energy production and anaplerotic pathways. PC catalyzes the conversion of pyruvate to oxaloacetate (see Figure 1).

Gene structure. *PC* contains 20 coding exons and four noncoding exons at the 5'-UTR [Wang et al 2008]. All four noncoding exons are involved in alternative splicing, resulting in three tissue-specific PC transcripts carrying the same coding region: variant 1 (4004 bp, NM_000920.3), variant 2 (3959 bp, NM_022172.2), and variant 3 (4192 bp, NM_001040716.1) (Figure 2). Southern blotting of human genomic DNA showed that *PC* exists in a single copy and no pseudogenes are detected. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Missense, nonsense, frameshift, and splice site variants in *PC* are associated with PCD. Mosaicism, in which the abnormal allele was typically present in a greater proportion than the normal allele, was found in five individuals [Wang et al 2008]. Four had prolonged survival.

Of note, two substitutions – c.1892G>A (p.Arg631Gln) and c.2549C>T (p.Ala847Val) – were found in a mosaic state on the same allele in three individuals [Wang et al 2008].

Table 2. *PC* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.184C>T	p.Arg62Cys	NM_000920.4 NP_000911.2
c.434T>C	p.Val145Ala	
c.796T>A	p.Ser266Ala	
c.1351C>T	p.Arg451Cys	
c.1705A>G	p.Thr569Ala	
c.1828G>A	p.Ala610Thr	
c.1892G>A	p.Arg631Gln [1, 2]	
c.2114C>A	p.Ser705Ter [1]	
c.2229G>T	p.Met743Ile	
c.2540C>T	p.Ala847Val [1, 2]	
c.3409_3410delCT	p.Leu1137ValfsTer34	

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. Indicates the mosaic state of this allele
2. These variants have been observed *in cis*.

Normal gene product. The protein consists of 1,178 amino acids with a molecular weight of approximately 125 kd. It consists of a homotetramer of polypeptides, each covalently bound to a biotin molecule and processing both the catalytic and regulatory functions.

PC (EC 6.4.1.1, PC) normally serves an anaplerotic function by replenishing the Krebs cycle intermediates. PC catalyzes the conversion of pyruvate to oxaloacetate; this reaction is allosterically activated by elevated acetyl-coenzyme A levels (Figure 1). The anaplerotic function of PC is important for the biosynthesis of neurotransmitters in the central nervous system, as well as energy metabolism. PC also controls the first step of hepatic gluconeogenesis and is important in lipogenesis.

The enzyme is localized within the mitochondrial matrix in many tissues. Expression is highest in the liver, kidney, adipose tissue, pancreatic islets, and lactating mammary gland. Expression is moderate in brain, heart, and adrenal gland, and lowest in white blood cells and skin fibroblasts [Jitrapakdee & Wallace 1999].

Abnormal gene product. Loss of protein function may occur from loss of mRNA expression or loss or reduction of functional activity of PC. Individuals with mosaic pathogenic variants retained greater enzyme activity than those with non-mosaic pathogenic variants [Wang et al 2008].

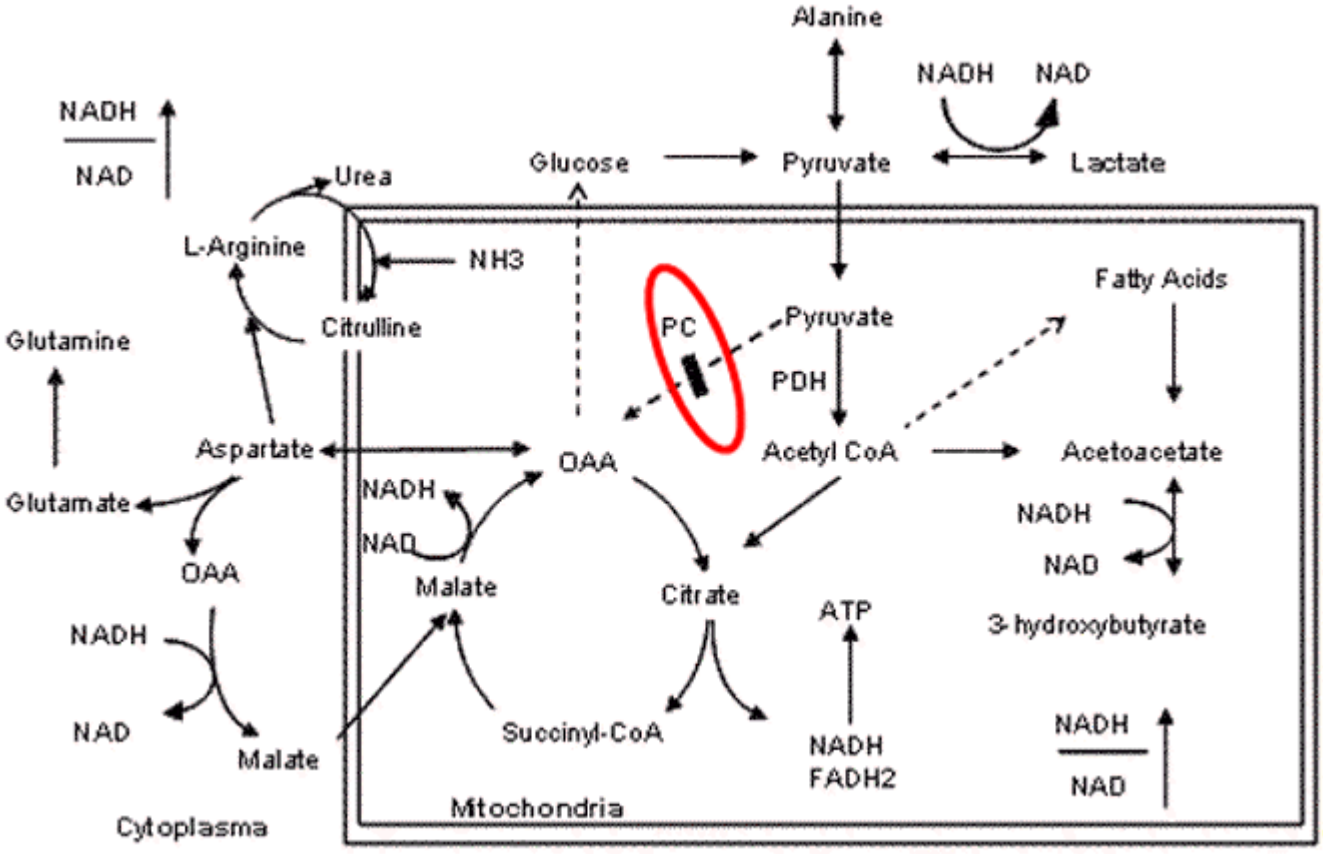

Figure 1. Diagrammatic representation of metabolic pathway affected by PC deficiency. The PC enzyme is indicated by the red oval; the dotted arrow lines represent absent pathways.

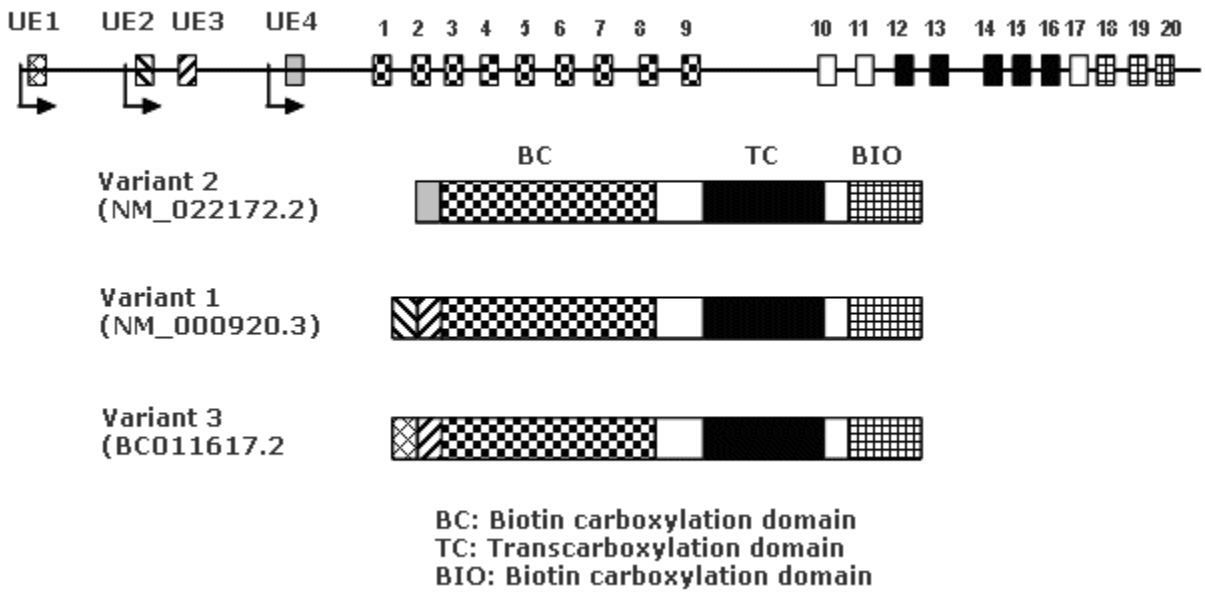

Figure 2. *PC* structure and three transcript variants. The coding exons of *PC* are represented by rectangles with different patterns and Arabic numbers on the top. The four untranslated exons (UEs) are labeled UE1-UE4 (top left). The arrows before UE1, UE2, and UE4 represent the transcription initiation sites. Three transcript variants are shown with the same coding region and different noncoding exons in the 5'-UTR and the reference sequences for the three splice variants are given.

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Chapter Notes

Revision History

- 1 March 2018 (sw) Comprehensive update posted live
- 30 July 2015 (bp/ctf) Revision: CA-VA added to Differential Diagnosis
- 24 July 2014 (me) Comprehensive update posted live
- 21 July 2011 (me) Comprehensive update posted live
- 2 June 2009 (et) Review posted live
- 7 March 2005 (ddv) Original submission

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