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

NLM Citation: Duque Lasio ML, Lehman AN, Ahmad A, et al. Pyruvate Carboxylase Deficiency. 2009 Jun 2 [Updated 2024 May 30]. 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

Maria Laura Duque Lasio, MD,[1] April N Lehman, MD,[2] Ayesha Ahmad, MD,[3] and Jirair K Bedoyan, MD, PhD[4]

Created: June 2, 2009; Updated: May 30, 2024.

Summary

Clinical characteristics

Pyruvate carboxylase (PC) deficiency is characterized in most affected individuals by failure to gain weight and/or linear growth failure, developmental delay, epilepsy, and metabolic acidosis. Three clinical phenotypes are recognized.

Type A (infantile form) is characterized by infantile onset of metabolic and lactic acidosis, delayed motor development, intellectual disability, poor linear growth and/or weight gain, and neurologic findings (apathy, hypotonia, pyramidal and extrapyramidal signs, ataxia, and seizures). Brain anomalies can be noted. Most affected children die in infancy or early childhood.

Type B (severe neonatal form) is characterized by neonatal or infantile onset of hypothermia, respiratory distress/failure, vomiting, severe lactic acidosis, hyperammonemia, and often hypoglycemia. Neurologic findings include brain abnormalities, lethargy, hypotonia, and pyramidal and extrapyramidal signs. Death typically occurs by age eight months.

Type C (intermittent/attenuated form) is characterized by relatively normal or mildly delayed neurologic development, motor and/or gait abnormalities, (rarely) seizures, episodic movement disorders, and metabolic acidosis. Life span is unknown but survival into adulthood has been reported.

Author Affiliations: 1 Division of Genetics and Genomic Medicine and Division of Laboratory and Genomic Medicine, St Louis Children's Hospital and Washington University School of Medicine, St Louis, Missouri; Email: lduque@wustl.edu. 2 Division of Genetic and Genomic Medicine, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, Ohio; Email: april.lehman2@nationwidechildrens.org. 3 Division of Genetics, Metabolism and Genomic Medicine, Department of Pediatrics, University of Michigan School of Medicine, Ann Arbor, Michigan; Email: ayeshaah@med.umich.edu. 4 Division of Genetic and Genomic Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine and UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; Email: jbedoyan@pitt.edu.

Diagnosis/testing

The diagnosis of PC deficiency is established in a proband whose newborn screening or biochemical findings suggest PC deficiency based on identification of either (1) biallelic pathogenic variants in *PC* on molecular genetic testing or (2) PC deficiency in whole blood.

Management

Treatment of manifestations: Intravenous glucose-containing fluids, hydration, and correction of metabolic acidosis; pharmacologic therapies (amino acid supplements, cofactors, and vitamins) may improve some findings but not neurologic manifestations; orthotopic liver transplantation may be indicated in some affected individuals; anaplerotic therapies, such as triheptanoin, have had variable success (primarily for individuals with PC deficiency type C) but need further evaluation.

Surveillance: A team of multidisciplinary specialists is often required to monitor existing manifestations, the individual's response to treatment, and the emergence of new manifestations.

Agents/circumstances to avoid: A ketogenic diet is contraindicated, and it is critical to avoid fasting.

Evaluation of relatives at risk: It is appropriate to clarify the genetic and/or biochemical status of apparently asymptomatic older and younger at-risk sibs of an affected individual with PC deficiency type C in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Genetic counseling

PC deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PC* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *PC* pathogenic variants. Once the *PC* pathogenic variants have been identified in an affected family member, molecular genetic carrier testing for at-risk relatives, prenatal testing, and preimplantation genetic testing are possible.

GeneReview Scope

Pyruvate Carboxylase Deficiency: Included Phenotypes

Pyruvate Carboxylase (PC) Deficiency Type	Phenotype	Proportion of Persons w/ PC Deficiency	Historical Synonyms
Type A	Infantile form; usually assoc w/early infancy or childhood death but >5-yr survival has been reported	Majority of affected persons	North American form
Type B	Severe neonatal form; assoc w/death by age 8 mos		French form
Type C	Intermittent/attenuated form; onset by age 3 yrs	<15 persons reported to date	Benign form

Diagnosis

In some newborns and states in the United States, pyruvate carboxylase (PC) deficiency can be suspected on the basis of elevated levels of citrulline during newborn screening. Since citrulline elevation is not specific to PC deficiency, it is critical to perform additional testing to identify the etiology of the citrulline elevation (see ACMG ACT algorithm).

Suggestive Findings

Pyruvate carboxylase (PC) deficiency **should be suspected in probands** with the following clinical and supportive laboratory findings and family history.

Clinical Findings

Type A (infantile)

- Poor feeding, vomiting, failure to gain weight, linear growth failure
- Respiratory distress/failure, tachypnea, Kussmaul breathing
- Hypotonia, epilepsy (or epileptic encephalopathy), ataxia, dysarthria
- Developmental delay
- Hepatomegaly (or hepatosplenomegaly)

Type B (neonatal)

- Poor feeding, vomiting, failure to gain weight
- Respiratory distress/failure, tachypnea
- Hypotonia, epilepsy, hyporeflexia, hypothermia, lethargy
- Hepatomegaly

Type C (intermittent/attenuated)

- Relatively normal or mildly delayed motor development; intellectual disability and autism
- Respiratory distress, tachypnea, Kussmaul breathing
- Episodic vomiting
- Episodic hypotonia, dystonia, ataxia, dysarthria, transient hemiparesis or acute flaccid paralysis
- Hepatomegaly

Supportive Laboratory Findings

Laboratory abnormalities by analyte. See Table 1. Note: For each of the following analytes the abnormal values overlap among PC deficiency types A, B, and C. Normal values differ by laboratory.

Table 1. Pyruvate Carboxylase Deficiency: Supportive Biochemical Laboratory Findings in Blood by Phenotype

Phenotype	Blood Concentration			Glucose /Ketone Bodies	Blood Lactate-to-Pyruvate Ratio [1] **(NL = 10-20)**	Fasting B-Hydroxybutyrate-to-Acetoacetate Ratio **(NL = 1-10)**
	Lactate **(NL = 0.8-2.4 mmol/L)**	Amino acids [1]	Ammonia			
Type A (infantile)	↑ lactate (2-15 mmol/L)	• ↑ alanine & proline • NL or intermittent ↑ citrulline [2] & lysine	Usually NL; moderate ↑ (<140 µmol/L) has been reported [3]	Hypoglycemia, ketosis, & ketonuria (rarely, mimicking diabetic ketoacidosis presentation w/ polyuria) [4]	Usually NL (<20)	Usually NL

Table 1. continued from previous page.

Phenotype	Blood Concentration			Glucose /Ketone Bodies	Blood Lactate-to-Pyruvate Ratio [1] **(NL = 10-20)**	Fasting B-Hydroxybutyrate-to-Acetoacetate Ratio **(NL = 1-10)**
	Lactate **(NL = 0.8-2.4 mmol/L)**	Amino acids [1]	Ammonia			
Type B (severe neonatal)	Severe lactic acidosis (>10 mmol/L)	• ↑ alanine, citrulline, lysine, & proline • ↓ glutamine	Moderate to significant ↑ (>130 µmol/L; peak 860 µmol/L) [5]	Hypoglycemia, ketosis, & ketonuria	↑ (>20)	↓ (<1)
Type C (intermittent/ attenuated)	NL to modest ↑ (2-9 mmol/L)	• ↑ alanine, lysine, & proline • NL citrulline	Usually NL, rarely mildly ↑ (<120 µmol/L)	Hypoglycemia	Usually NL (<20)	NL

NL = normal

1. Similar abnormalities of lactate and pyruvate and amino acids are seen in urine and cerebrospinal fluid (CSF) [Ahmad et al 1999, Demir Köse et al 2020, Hidalgo et al 2021, Mhanni et al 2021, Lasio et al 2023, Tsygankova et al 2022, Bernhardt et al 2023, Xue 2023].

2. In the North American Indigenous populations homozygous for the p.Ala610Thr variant, plasma citrulline may be elevated on presentation or acute illness [Mhanni et al 2021].

3. Lasio et al [2023]

4. Mangla et al [2017]

5. Demir Köse et al [2020]

Family History

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

Establishing the Diagnosis

The **biochemical enzymatic diagnosis** of PC deficiency **is established** in a proband with supportive metabolic analyte findings (see Table 1) by identification of deficiency of PC in whole blood.

The **molecular genetic diagnosis** of PC deficiency is established in a proband with supportive metabolic analyte findings (see Table 1) by identification of biallelic *PC* pathogenic (or likely pathogenic) variants on molecular genetic testing (see Table 2).

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

Of note, the turnaround time in receiving test results, which varies among laboratories, should be considered when determining the order of testing. Frequently, both types of testing are ordered together or sequentially, especially if one of the test results is ambiguous or insufficient to establish the diagnosis.

Biochemical Diagnosis

In individuals with PC deficiency, cultured fibroblast- or lymphocyte-based PC enzyme activity is usually less than 10% of that observed in controls [Almomen et al 2018, Coci et al 2019, Demir Köse et al 2020, Lasio et al 2023].

Molecular Genetic Diagnosis

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *PC* to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions could be performed first in specific situations (e.g., lack of availability of PC enzyme assay, cost of single-gene vs multigene panel, etc.). Note: Typically, if only one or no pathogenic variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

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

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome or genome sequencing** can be used. While the majority of *PC* pathogenic variants reported to date are within the coding region and are likely to be identified on exome sequencing, several pathogenic splicing variants outside the canonical splice junction, deep intronic variants, and structural variants involving *PC* have been reported that will be identified by genome sequencing [Ostergaard et al 2013, Tsygankova et al 2022]. Ordering rapid turnaround time exome or genome sequencing is necessary in cases of critically ill newborns or infants.

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

Table 2. Molecular Genetic Testing Used in Pyruvate Carboxylase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PC	Sequence analysis [3]	~100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported to date [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from Tsygankova et al [2022] and the subscription-based professional view of Human Gene Mutation Database (HGMD) [Stenson et al 2020]
5. Several pathogenic splicing variants outside the canonical splice junction, deep intronic variants, and structural variants involving *PC* have been reported that will be identified by genome sequencing [Ostergaard et al 2013, Tsygankova et al 2022]. A 12-base-pair deletion in exon 8 within the biotin-carboxylase domain of *PC* has been reported [Demir Köse et al 2020].
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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
7. One structural variant (a reciprocal translocation between chromosomes 11 and 1) disrupting *PC*, t(1;11)(p.36.32;q13.2), has been reported [Tsygankova et al 2022].

Clinical Characteristics

Clinical Description

Pyruvate carboxylase (PC) deficiency is characterized in most affected individuals by failure to gain weight and/or linear growth failure, developmental delay, epilepsy, and metabolic acidosis. Historically, three phenotypes of PC deficiency (types A, B, and C) have been recognized based on clinical presentation (see *GeneReview* Scope).

- **Type A (infantile form).** Most affected children die in infancy or early childhood. Brain anomalies can be noted.
- **Type B (severe neonatal form).** Affected infants have hepatomegaly, pyramidal tract signs, abnormal movements, brain abnormalities, and die by eight months of life.
- **Type C (intermittent/attenuated form).** Affected individuals have relatively normal or mildly delayed neurologic development, motor and/or gait abnormalities, episodic seizure, and episodic movement disorders.

These phenotypes likely represent a continuum ranging from most severe (type B) to least severe (type C) rather than distinct subtypes.

Approximately 75 individuals with PC deficiency have been reported to date, with most being either type A or type B; approximately 15 individuals have been reported with type C [Habarou et al 2014, Mangla et al 2017, Almomen et al 2018, Coci et al 2019, Demir Köse et al 2020, Bayat et al 2021, Doğulu et al 2021, Hidalgo et al 2021, Mhanni et al 2021, Sahdev et al 2021, Tao et al 2022, Tsygankova et al 2022, Bernhardt et al 2023, Lasio et al 2023, Maryami et al 2023, Xue 2023]. The following description of the phenotypic features associated with this condition is based on these reports (see Table 3).

Table 3. Pyruvate Carboxylase Deficiency: Phenotypes by Select Clinical Features

Feature	Phenotype		
	Type A	Type B	Type C
Prenatal neurologic presentation [1]	+	+	–
Age of onset	Birth to age 10 mos	Within 1-3 days of birth	Age 3 mos to 2 yrs
Development	Development delay & intellectual disability	Severe developmental delay	Normal or mildly delayed motor &/or speech development & intellectual disability, autism
Growth	Poor feeding, vomiting, failure to gain weight, linear growth failure	Poor feeding, vomiting, lethargy, hypothermia	Limited information; may be normal
Hypotonia	+	+	May be episodic
Respiratory	Respiratory distress/failure, tachypnea, exertional dyspnea	Respiratory distress/failure at birth, tachypnea	Respiratory distress, tachypnea (may be episodic), Kussmaul breathing, exertional dyspnea
Hepatomegaly	+	+	+
Epilepsy	+	+	Seizure disorder described in 1 person [2]
Movement disorders	Pyramidal tract signs, ataxia, choreoathetoid movements, nystagmus	Pyramidal tract signs, high-amplitude tremor, dyskinesia, & abnormal ocular movements	Dystonia, dysarthria, transient hemiparesis, &/or acute transient flaccid paralysis
Ataxia / choreoathetoid movements	+	–	May be episodic
Nystagmus	+	+	–
Development	Severe delay w/marked speech delay if survive long term	Severe delay if survive long term	Normal or mild delay incl motor & speech, depending on frequency of metabolic acidosis
Life span	Early infant or early childhood death	Death in neonatal period	Unknown but long-term survival reported

Habarou et al [2014], Mangla et al [2017], Almomen et al [2018], Coci et al [2019], Demir Köse et al [2020], Bayat et al [2021], Doğulu et al [2021], Hidalgo et al [2021], Mhanni et al [2021], Tao et al [2022], Tsygankova et al [2022], Bernhardt et al [2023], Lasio et al [2023], Maryami et al [2023], Xue [2023]

+ = present; – = not reported

1. Includes brain anomalies in fetuses homozygous for the North American Indigenous population founder variant p.Ala610Thr [Mhanni et al 2021].

2. Stern et al [1995]

PC Deficiency Type A

PC deficiency type A is characterized by infantile onset with metabolic acidosis, lactic acidosis, delayed motor development, intellectual disability, failure to gain weight and/or linear growth failure, apathy, hypotonia, pyramidal tract signs, ataxia, chorea-like movements, nystagmus, and seizures.

Episodes of acute vomiting, tachypnea, and lactic acidosis with a compensated metabolic acidosis are usually precipitated by metabolic or infectious stress. Some individuals may require gastrostomy tube placement.

Prognosis. Most affected children die in infancy or early childhood following an acute illness. Development of uncontrolled severe metabolic acidosis during a hospital course with continued deterioration despite hemodialysis can be followed by death [Tao et al 2022]. Survival to early childhood and use of liver

transplantation have been reported [Lasio et al 2023]. Some may survive to teenage years or young adulthood, and manifest varying degrees of cognitive impairment [Mangla et al 2017, Bayat et al 2021, Lasio et al 2023].

PC Deficiency Type B

PC deficiency type B is characterized by affected neonates and infants presenting with hypothermia (neonates), lethargy, respiratory distress/failure, vomiting, severe lactic acidosis, and hyperammonemia; presenting individuals are likely to develop hypoglycemia. Some affected individuals may require gastrostomy tube placement. Other features include hepatomegaly (or hepatosplenomegaly), epilepsy, and neurologic findings, including hypotonia, pyramidal tract signs, and abnormal movements (including high-amplitude tremor and dyskinesia). Motor development is severely delayed and affected infants have marked developmental delay.

Prognosis. Most affected neonates/infants die within the neonatal period or within the first eight months of life [Breen et al 2014, Mochel 2017, Lasio et al 2023]. Unrecoverable renal tubular acidosis despite massive bicarbonate replacement or multiorgan (liver) failure have been causes of death [Demir Köse et al 2020]. Death due to respiratory and hepatic failure with hepatomegaly and histopathologic findings of balloon dystrophy of hepatocytes was reported [Tsygankova et al 2022]. An individual who underwent liver transplantation at age 6.5 months was alive at age 20 years [Lasio et al 2023].

PC Deficiency Type C

In the approximately 15 individuals with PC deficiency type C reported to date, development has ranged from relatively normal (e.g., individuals who walk independently and have some speech and slight cognitive delays) to others with mild developmental delays involving motor skills, speech, and/or cognition; other individuals have had speech delay, a broad-based toe-walking or unsteady gait, and autism spectrum disorder with stereotypic movements (hand flapping) with an otherwise normal neurologic examination [Almomen et al 2018, Coci et al 2019, Doğulu et al 2021, Tsygankova et al 2022, Bernhardt et al 2023, Lasio et al 2023].

Other findings reported in some individuals have included exertional dyspnea, seizures, and episodic metabolic acidosis. In one report, the initial clinical presentation mimicked diabetic ketoacidosis [Doğulu et al 2021]. Acute transient flaccid paralysis with ketoacidosis was reported in a previously healthy and developmentally normal 11-month-old girl [Almomen et al 2018].

Prognosis. Life span is unknown, but survival into adulthood has been reported [Sahdev et al 2021].

Other

Neuroimaging findings. Several largely nonspecific brain abnormalities have been reported.

- **Seen in PC deficiency types A, B, and C.** Abnormal white matter signal intensities on T_2-weighted imaging have been reported in all three types of PC deficiency [Coci et al 2019, Mhanni et al 2021, Lasio et al 2023]. Choroid plexus cysts are also seen, as well as cystic dilatation of the lateral ventricles [Demir Köse et al 2020, Lasio et al 2023].
- **Seen most commonly in PC deficiency types A and B**
  - Septated or nonseptated inter- or periventricular or caudothalamic groove cysts [Ostergaard et al 2013, Coci et al 2019, Hidalgo et al 2021, Mhanni et al 2021, Bernhardt et al 2023, Lasio et al 2023]
  - Periventricular leukopathy, abnormal diffuse white matter edema involving the frontal temporoparietal, occipital deep, and subcortical white matter, corpus callosum atrophy/agenesis, and brain stem hypoplasia [Ostergaard et al 2013, Coci et al 2019, Lasio et al 2023]
  - Moderate or severe cortical atrophy, white matter loss, periventricular focal infarctions, ischemic-like brain lesions, subdural hemorrhage / hematomas of differing age, or subarachnoid hemorrhage [Ostergaard et al 2013, Bernhardt et al 2023, Lasio et al 2023]

- Abnormal myelination in the cerebral hemispheres, posterior limbs of the internal capsules, cerebral peduncles, midbrain, and cerebellum [Stern et al 1995, Demir Köse et al 2020, Bernhardt et al 2023, Lasio et al 2023]

- **Magnetic resonance spectroscopy (MRS).** Increased lactate peaks in sampled frontal white matter and basal ganglia [Coci et al 2019, Lasio et al 2023]

Genotype-Phenotype Correlations

The pathogenic variant **p.Ala610Thr** is a founder variant in the native North American Ojibwa, Cree, and Mi'kmaq tribes of the Algonquin-speaking peoples in northwestern Ontario and northeastern Manitoba, Canada [Haworth et al 1991, Carbone et al 1998]. In all 14 affected individuals of Ojibwa and Cree origin, homozygous p.Ala610Thr pathogenic variants were identified. Brain anomalies were identified at age ten days, suggesting that these changes were present in utero [Mhanni et al 2021].

Classes of pathogenic variants. Disease severity has been loosely correlated with the class of *PC* pathogenic variant. Pathogenic missense and intronic variants are more often associated with PC deficiency types A and C, whereas truncating or nonsense variants are more often associated with PC deficiency type B [Coci et al 2019, Demir Köse et al 2020, Tsygankova et al 2022, Lasio et al 2023]. Whether disease-modifying factors for specific *PC* pathogenic variants exist is not known.

Of note, in general, there is no significant correlation between the clinical phenotype and level of fibroblast- or lymphocyte-based residual PC enzyme activity, although no detectable or low PC activity (<2% of unaffected control mean) is more often associated with PC deficiency type B [Ostergaard et al 2013, Coci et al 2019, Lasio et al 2023].

Prevalence

About 75 individuals with PC deficiency have been reported, with most being either type A or type B. Because type C may be under reported, the prevalence of PC deficiency in most populations may be higher.

In most populations, the birth incidence of PC deficiency is considered low (1 in 250,000), but prospective studies evaluating the incidence in newborns in most populations have not been completed.

In the native North American Ojibwa, Cree, and Mi'kmaq tribes of the Algonquin-speaking peoples in northwestern Ontario and northeastern Manitoba, Canada, the carrier frequency of the founder variant p.Ala610Thr may be as high as 1 in 10 [Haworth et al 1991, Carbone et al 1998].

Nomenclature

PC deficiency type A is also referred to as the infantile or North American form.

PC deficiency type B is also referred to as the severe neonatal or French form.

PC deficiency type C is also referred to as the intermittent/attenuated form.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Many inborn errors of metabolism have features similar to those of pyruvate carboxylase (PC) deficiency. As listed in Table 4, the differential diagnosis includes biotinidase deficiency, holocarboxylase synthase deficiency,

pyruvate dehydrogenase deficiency, respiratory chain disorders, tricarboxylic acid cycle disorders, and gluconeogenic defects.

Table 4. Disorders in the Differential Diagnosis of Pyruvate Carboxylase Deficiency

Gene(s)	Disorder	MOI	Selected Features / Comments
>350 genes [1]	Primary mitochondrial disorders	AD AR Mat XL	Lactate & pyruvate concentrations are ↑; lactate-to-pyruvate ratio is ↑, often >20
BTD	Biotinidase deficiency	AR	• Can present in neonatal period or later in infancy w/neurologic symptoms such as lethargy, seizures w/metabolic acidosis, hearing loss, alopecia, & perioral/facial dermatitis • Laboratory findings incl metabolic ketolactic acidosis, organic aciduria, & hyperammonemia • If diagnosed through newborn screening, usually asymptomatic w/lifelong treatment of oral biotin
CA5A	Carbonic anhydrase VA deficiency	AR	Neonatal, infantile, or early-childhood metabolic hyperammonemic encephalopathy combined w/lactic acidosis
>30 genes	Organic acidemias (incl propionic acidemia, isolated methylmalonic acidemia, disorders of intracellular cobalamin metabolism, & other organic acidemias)	AR XL	• Can present in neonatal period or later in infancy w/neurologic symptoms such as lethargy, encephalopathy, seizure, & metabolic acidosis &/or metabolic stroke • Lactic acidemia, hypoglycemia, hyperammonemia, ketosis • Multiorgan system involvement
DLAT *DLD* *PDHA1* *PDHB* *PDHX* *PDK3* *PDP1*	Primary pyruvate dehydrogenase complex deficiency (PDCD)	AR XL	• Lactic acidemia w/progressive or intermittent neurologic features (poor acquisition or loss of motor milestones, hypotonia, epilepsy, ataxia), nystagmus, & dystonia • ↑ blood & CSF lactate concentrations & ↑ blood & CSF concentrations of pyruvate & alanine • Blood ketone bodies usually not detectable & normal lactate-to-pyruvate ratio in plasma, unlike PC deficiency
Disorders assoc w/secondary PDCD that are phenotypically similar to primary PDCD			
OLA3 *IBA57* *ISCA1* *ISCA2* *NFU1* *PMPCB*	Multiple mitochondrial dysfunction syndromes (MMDS) (See *ISCA1*-MMDS & *ISCA2*-MMDS.)	AR	• Neonatal lactic acidosis • ↑ glycine concentration • Electron transport chain enzyme activity deficiencies
ECHS1	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency	AR	• Lactic acidosis • ↑ pyruvate concentration (lactate-to-pyruvate ratio may be normal) • May be assoc w/abnormal acylcarnitine profile &/or ↑ urine organic acid w/marked 2-methyl-2,3-dihydroxybutyric acid
HIBCH	3-hydroxyisobutyryl-CoA hydrolase deficiency (OMIM 250620)	AR	• Lactic acidosis • ↑ pyruvate concentration (lactate-to-pyruvate ratio may be normal) • May be assoc w/abnormal acylcarnitine profile &/or urine organic acids

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Selected Features / Comments
LIAS	Lipoic acid synthetase deficiency (OMIM 614462)	AR	• Lactic acidosis & seizures • ↑ pyruvate concentration (lactate-to-pyruvate ratio may be normal or elevated) • ↑ glycine concentration • Electron transport chain enzyme activity deficiencies
LIPT1	Lipoyltransferase 1 deficiency (OMIM 616299)		
LIPT2	Lipoyltransferase 2 deficiency (OMIM 617668)		
SLC25A1	Mitochondrial citrate carrier deficiency (combined D-2- & L-2-hydroxyglutaric aciduria) (OMIM 615182)	AR	• Neonatal lactic acidosis • ↑ 2-hydroxyglutaric acid concentration
TPK1	Thiamine pyrophosphokinase deficiency (thiamine metabolism dysfunction syndrome 5, episodic encephalopathy type) (OMIM 614458)	AR	• ↑ lactate & pyruvate concentrations (normal lactate-to-pyruvate ratio) • Treatable w/high-dose thiamine [2]
Gluconeogenic disorders			
FBP1	Fructose-1,6-bisphosphatase deficiency	AR	• ↑ blood lactate, pyruvate, & alanine concentrations w/clinical symptoms • Hypoglycemia • ↑ ketone bodies
G6PC3	G6PC3 deficiency (ubiquitous glucose-6-phosphatase deficiency)		
PCK1	Phosphoenolpyruvate carboxykinase deficiency, cytosolic (OMIM 261680)		
Tricarboxylic acid cycle (TCA) disorders			
FH	Fumarate hydratase deficiency	AR	• ↑ lactate & pyruvate concentrations • ↑ lactate-to-pyruvate ratio • ↑ fumaric acid or other TCA cycle intermediates
OGDH	Oxoglutarate dehydrogenase deficiency (OMIM 203740)		
SDHA *SDHAF1* *SDHB* *SDHD*	Mitochondrial complex II deficiency, nuclear type (OMIM PS252011)		
SUCLA2	*SUCLA2*-related mitochondrial DNA depletion syndrome, encephalomyopathic form w/ methylmalonic aciduria		
Defects of ketone body utilization or transport			
OXCT1	Succinyl-CoA:3-oxoacid CoA transferase (SCOT) (OMIM 245050)	AR	• Severe ketoacidosis, metabolic acidosis, tachypnea (due to acidosis), vomiting • May have seizures • May be hypo- or hyperglycemic or have mild hyperammonemia
ACAT1	Mitochondrial acetoacetyl-CoA thiolase (T2) (OMIM 203750)		
SLC16A1	Moncarboxylate transporter (MCT1) deficiencies (OMIM 616095)		

AD = autosomal dominant; AR = autosomal recessive; CSF = cerebrospinal fluid; Mat = maternal; MOI = mode of inheritance; PC deficiency = pyruvate carboxylase deficiency; PDCD = pyruvate dehydrogenase complex deficiency; XL = X-linked

1. See Primary Mitochondrial Disorders Overview.

2. Marcé-Grau et al [2019]

Management

No clinical practice guidelines for pyruvate carboxylase (PC) deficiency have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

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

Table 5. Pyruvate Carboxylase Deficiency: Recommended Evaluations Following Initial Diagnosis in a Neonate/Infant or Child

System/Concern	Evaluation	Comment
Metabolic decompensation	Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases is strongly recommended. • Hospitalization at center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for metabolic crises)
Laboratory studies	• Blood lactate & pyruvate • Blood ammonia • Blood chemistry panel incl glucose & liver enzymes • Arterial or venous blood gas • Beta-hydroxybutyrate • Blood amino acids • Urine organic acids	Baseline laboratory studies to monitor for metabolic acidosis
Neurologic	• Neurology consultation • Brain MRI (and MRS if available) • Electroencephalogram	In all persons w/PC deficiency types A & B; as needed in those w/type C
Nutrition/Feeding	Eval of feeding skills, anthropometric measures, & nutritional status	
Development	Baseline developmental assessment; referral to therapy services (speech, feeding, occupational, & physical) as clinically warranted	Neuropsychological testing recommended at least prior to school entrance for those w/PC deficiency type C
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of PC deficiency to facilitate medical & personal decision making
Palliative care	Consider early involvement of palliative care team for discussions re goals of care short term & long-term prognosis	In all persons w/PC deficiency types A & B

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

MOI = mode of inheritance; PC deficiency = pyruvate carboxylase deficiency
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for PC deficiency. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Pyruvate Carboxylase Deficiency: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Acute decompensation	• Reverse catabolism w/IV dextrose administration. • Metabolic acidosis may require IV sodium bicarbonate. • Treat precipitating stressors (dehydration, fever, infection, vomiting) • Initiate anaplerotic therapy.	Hospitalization is indicated for mgmt of fever, infection, dehydration, &/or trauma.
Diet mgmt / Correction of biochemical abnormality	• Provide a high-carbohydrate & high-protein diet w/frequent feedings to help prevent dependence on gluconeogenesis. • Ketogenic diet is contraindicated.	Can reverse some manifestations, but not CNS involvement, which progresses regardless of treatment
	Liver transplantation [1]	Improves lactic acidosis, ketoacidosis, & renal tubular acidosis; does not reverse neurologic involvement
Poor feeding / Inadequate nutrition	• Feeding therapy • Nasogastric tube or gastrostomy tube	Needed almost universally in those w/PC deficiency types A & B
Anaplerotic therapy	Citrate supplementation (2.5-7.5 mmol/kg/day, as sodium citrate-citric acid)	↓ acidosis & provides substrate for citric acid cycle energy; substrate deficits could be improved by providing alternative substrate for both the citric acid cycle and the electron transport chain for enhanced ATP production
	Aspartate supplementation (2.5-10 mmol/kg/day)	Allows urea cycle to proceed to help reduce urine & plasma ammonia concentrations but has little effect on the brain, as aspartic acid does not enter the brain freely
Cofactor supplementation	Biotin (5-30 mg/day)	Usually of little efficacy

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Anticipatory guidance for prevention of metabolic decompensation	Educate parents/caregivers about factors that elicit a crisis & early signs of decompensation	Carry written information re child's disorder & appropriate treatment in emergency setting

CNS = central nervous system
1. Liver transplantation between ages 6.5 months and 2.5 years has been tried as a treatment option for PC deficiency types A and B, with long survival reported [Lasio et al 2023].

Therapies include pharmacologic doses of cofactors involved in the metabolism of pyruvate and the substitution of the missing end-products. Aspartic acid is needed because in PC deficiency, oxaloacetate biosynthesis and the Krebs cycle are impaired. Depletion of aspartate disrupts the urea cycle; therefore, it is necessary for affected individuals to receive aspartic acid. Thiamine (coenzyme for pyruvate dehydrogenase), biotin (regulator of pyruvate carboxylase activity), and citrate (which reduces acidosis and provides the substrate in the citric acid cycle) are also needed. Studies have suggested that exogenous lipoic acid, while beneficial as an antioxidant and with very low toxicity, is not utilized for mitochondrial lipoylation [Mayr et al 2014]; thus, the utility of lipoic acid supplementation in PC deficiency is unclear. Aspartic acid lowers ammonia levels, letting the urea cycle take place. In general, treatments that affected individuals receive can include thiamine, aspartic acid, biotin, citric acid / sodium citrate, clobazam, and levocarnitine [Ahmad et al 1999, Nyhan et al 2002, Mochel et al 2005, Roe & Mochel 2006, Breen et al 2014, Mochel 2017, Coci et al 2019, Demir Köse et al 2020, Doğulu et al 2021, Hidalgo et al 2021, Bernhardt et al 2023, Lasio et al 2023].

Triheptanoin. Several groups have evaluated the use of triheptanoin (Doljovi®) treatment for PC deficiency. Triheptanoin is an odd-carbon triglyceride (source for acetyl-CoA and anaplerotic propionyl-CoA converted to succinyl-CoA) that provides C5-ketone bodies that can cross the blood-brain barrier, thereby providing substrates for the brain. The goal is reduction in lactate and improvement of other metabolic parameters. Improvements in development and myelination have been reported. Overall, variable treatment outcomes have been reported with additional studies needed [Lasio et al 2023]. Beneficial effect of triheptanoin treatment (1.5-2.0 g/kg of body weight per day, providing up to 35% of daily caloric intake per package insert) for PC deficiency type C with certain genotypes has been reported [Bernhardt et al 2023]. Triheptanoin is not approved by the FDA for treatment of PC deficiency but may be available through an investigational compassionate use protocol.

Surveillance

To monitor existing manifestations, the individual's response to treatment, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Pyruvate Carboxylase Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Abnormal growth / Nutritional deficiencies / Feeding issues	• Measurement of growth parameters (incl head circumference) • Assessment of feeding skills in infants/toddlers • Assessment by metabolic dietitian	At each visit
Abnormal biochemical laboratory parameters	• Plasma ammonia, if clinically warranted • Plasma lactic acid • Plasma amino acids • Comprehensive metabolic panel • Liver function tests • CBC, ferritin, & urinalysis for ketones	At each visit dependent on diet mgmt recommendations

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic status	Neurologic exam, clinical history assessing for new movement disorder or seizures	At each visit
	• EEG • MRI	As clinically indicated by neurologist
Triheptanoin-related surveillance	• Monitor for GI adverse reactions. • If receiving via feeding tube, monitor integrity of feeding tube. • Monitor plasma acylcarnitine profile.	At each visit, if affected person is receiving triheptanoin
Development	Assess developmental milestones & educational needs.	At each visit
Supportive care	Assess need for referrals for social work, palliative care, respite care, & home nursing.	

CBC = complete blood count; GI = gastrointestinal

Agents/Circumstances to Avoid

Ketogenic diet is contraindicated, as it adds to the metabolic acidosis and ketosis from ketone bodies.

Avoid fasting, which induces a catabolic state.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic and/or biochemical status of apparently asymptomatic older and younger at-risk sibs of an affected individual with PC deficiency type C in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

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, should a woman with PC deficiency type C become pregnant, such a pregnancy would be considered high risk and should be closely monitored for any metabolic derangements including dehydration and metabolic acidosis.

Therapies Under Investigation

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. 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

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are typically heterozygous for a *PC* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *PC* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a postzygotic *de novo* event in a mosaic parent or proband. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity.
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PC* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *PC* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has PC deficiency or is a carrier, offspring will be obligate heterozygotes for a pathogenic variant in *PC*.

Other family members. Each sib of a heterozygous parent is at a 50% risk of being a carrier of a pathogenic variant in *PC*.

Carrier Detection

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known carriers, particularly if both partners are of the same ancestry. In the native North American Ojibwa, Cree, and Mi'kmaq tribes of the Algonquin-speaking peoples in northwestern Ontario and northeastern Manitoba, Canada, the carrier frequency of the founder variant p.Ala610Thr may be as high as 1 in 10 (see Table 8).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

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

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.

- **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) deficiency was first described in 1968 in an individual with Leigh encephalopathy [Hommes et al 1968]. PC deficiency is caused by pathogenic variants in *PC*, which encodes for pyruvate carboxylase (PC), a biotin-dependent mitochondrial homotetrameric enzyme that plays an important role in energy production and anaplerotic pathways. The enzyme is localized within the mitochondrial matrix in many tissues, with expression highest in the liver and kidney.

PC catalyzes the ATP-dependent irreversible two-step carboxylation of pyruvate to oxaloacetate (see Figure 1). It is the rate-limiting enzyme controlling the first step in gluconeogenesis. The anaplerotic function of PC is important for the biosynthesis of neurotransmitters (glutamate and GABA) 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 purpose of aspartate use in management of PC deficiency is to provide oxaloacetate, the missing product of PC (see Figure 1), and for citrulline utilization in the urea cycle, with consequent amelioration of hyperammonemia. Aspartate is also important in purine synthesis.

Mechanism of disease causation. Loss of PC protein function may occur from loss of mRNA expression or loss or reduction of functional activity of PC, which could in part be due to partial or complete deletion of *PC*. For further information, see Lasio et al [2023].

Mosaicism. Mosaic (or postzygotic) *PC* variants have been reported in a few individuals with PC deficiency [Wang et al 2008]. These studies were done prior to next-generation sequencing technologies, with parental studies not included. Therefore, attention to the sensitivity of the diagnostic method used (e.g., next-generation sequencing or array CGH) is recommended.

Noncoding variants. Intronic pathogenic *PC* variants beyond the canonical splice junction and in deeper intronic regions, as well as structural variants, have been reported [Ostergaard et al 2013, Tsygankova et al 2022]. Thus, genome sequencing should be considered for individuals with features consistent with PC deficiency who do not have biallelic pathogenic variants detected by multigene panel testing or exome sequencing.

Table 8. *PC* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Protein Change	Comment [Reference]
NM_000920.4 NP_000911.2	c.1828G>A	p.Ala610Thr	Founder variant in North American Ojibwa, Cree, and Mi'kmaq tribes of Algonquin-speaking peoples in northwestern Ontario & northeastern Manitoba, Canada, w/estimated carrier frequency as high as 1 in 10 [Haworth et al 1991, Carbone et al 1998, Mhanni et al 2021]

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.

Chapter Notes

Author Notes

Jirair K Bedoyan (www.pediatrics.pitt.edu; email: jbedoyan@pitt.edu) is actively involved in clinical research regarding individuals with disorders of pyruvate metabolism including pyruvate carboxylase (PC) deficiency and

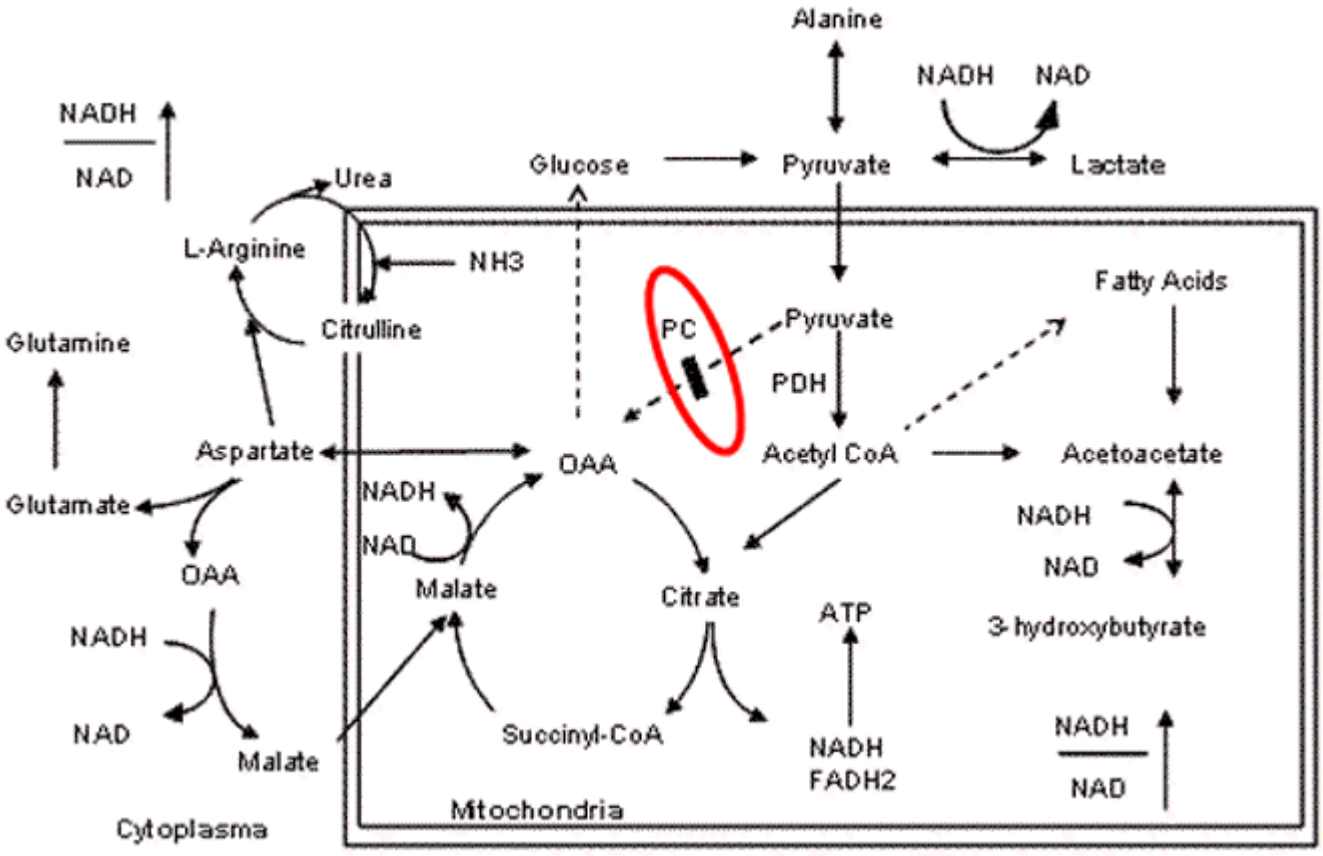

Figure 1. Diagrammatic representation of the metabolic pathways affected by pyruvate carboxylase (PC) deficiency. The PC enzyme is indicated by the red oval; the dotted arrow lines represent absent pathways.

pyruvate dehydrogenase complex deficiency (PDCD). Dr Bedoyan would be happy to communicate with persons who have any questions regarding diagnosis of PC deficiency, PDCD, or other considerations.

Dr Bedoyan is also interested in hearing from clinicians treating families affected by various disorders of pyruvate metabolism in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Bedoyan to inquire about review of *PC*, *PDHA1*, *PDHB*, *DLAT*, *PDHX*, and *PDP1* variants of uncertain significance.

Acknowledgments

JKB was supported in part by NIH 2U54NS078059-09 RDCRN NAMDC Project 4 grant.

Author History

Ayesha Ahmad, MD (2024-present)
Jirair K Bedoyan, MD, PhD (2024-present)
Darryl De Vivo, MD; Columbia University (2009-2024)
Maria Laura Duque Lasio, MD (2024-present)
April N Lehman, MD (2024-present)
Dong Wang, MD; Georgia Neurodiagnostic & Treatment Center (2009-2024)

Revision History

- 30 May 2024 (gf) Comprehensive update posted live
- 1 March 2018 (sw) Comprehensive update posted live
- 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

References

Literature Cited

Ahmad A, Kahler SG, Kishnani PS, Artigas-Lopez M, Pappu AS, Steiner R, Millington DS, Van Hove JL. Treatment of pyruvate carboxylase deficiency with high doses of citrate and aspartate. Am J Med Genet. 1999;87:331–8. PubMed PMID: 10588840.

Almomen M, Sinclair G, Stockler-Ipsiroglu SG, Horvath GA. Pyruvate carboxylase deficiency type C: A rare cause of acute transient flaccid paralysis with ketoacidosis. Neuropediatrics. 2018;49:369-72. PubMed PMID: 30045381.

Bayat R, Koohmanaee S, Mahdieh N, Kharaee F, Shahrokhi M, Rad AH, Chakoosari SN, Dalili S, Nouri SAH. A case of pyruvate carboxylase deficiency with longer survival and normal laboratory findings. Acta Medica Iranica. 2021;59:625–28.

Bernhardt I, Van Dorp L, Dixon M, McSweeney M, Gan C, Baruteau J, Chakrapani A. Pyruvate carboxylase deficiency type C; variable presentation and beneficial effect of triheptanoin. JIMD Rep. 2023;65:10-16. PubMed PMID: 38186850.

Breen C, White FJ, Scott CA, Heptinstall L, Walter JH, Jones SA, Morris AA. Unsuccessful treatment of severe pyruvate carboxylase deficiency with triheptanoin. Eur J Pediatr. 2014;173:361–6. PubMed PMID: 24114256.

Carbone MA, MacKay N, Ling M, Cole DE, Douglas C, Rigat B, Feigenbaum A, Clarke JT, Haworth JC, Greenberg CR, Seargeant L, Robinson BH. Amerindian pyruvate carboxylase deficiency is associated with two distinct missense mutations. Am J Hum Genet. 1998;62:1312–9. PubMed PMID: 9585612.

Coci EG, Gapsys V, Shur N, Shin-Podskarbi Y, Bert L. de Groot BL, Miller K, Vockley J, Sondheimer N, Ganetzky R, Freisinger P. Pyruvate carboxylase deficiency type A and type C: Characterization of five novel pathogenic variants in PC and analysis of the genotype–phenotype correlation. Hum Mutat. 2019;40:816–27. PubMed PMID: 30870574.

Demir Köse M, Colak R, Yangin Ergon E, Kulali F, Yildiz M, Alkan S, Atilgan T, Aslan F, Brown R, Brown G, Serdaroğlu E, Çalkavur S. Challenges in the management of an ignored cause of hyperammonemic encephalopathy: pyruvate carboxylase deficiency. J Pediatr Endocrinol Metab. 2020;33:569-74. PubMed PMID: 32145058.

Doğulu N, Oncul U, Köse E, Aycan Z, Eminoglu FT. Pyruvate carboxylase deficiency typ C as a differential diagnosis of diabetic ketoacidosis. J Pediatr Endocrinol Metab. 2021;34:947-50. PubMed PMID: 33860652.

Habarou F, Brassier A, Rio M, Chrétien D, Monnot S, Barbier V, Barouki R, Bonnefont JP, Boddaert N, Chadefaux-Vekemans B, Le Moyec L, Bastin J, Ottolenghi C, de Lonlay P. Pyruvate carboxylase deficiency: an underestimated cause of lactic acidosis. Mol Genet Metab Rep. 2014;2:25-31. PubMed PMID: 28649521.

Haworth JC, Dilling L, Seargeant L. Increased prevalence of hereditary metabolic diseases among native Indians in Manitoba and northwestern Ontario. CMAJ. 1991;145:123-29. PubMed PMID: 1650287.

Hidalgo J, Campoverde L, Ortiz J, Ruxmonhan S, Eissa-Garces A. A unique case of pyruvate carboxylase deficiency. Cureus 2021;13: e15042. PubMed PMID: 34150393.

Hommes FA, Polman HA, Reerink JD. Leigh's encephalomyelopathy: an inborn error of gluconeogenesis. Arch Dis Child. 1968;43:423–26. PubMed PMID: 4873809.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Lasio MLD, Leshinski AC, Ducich NH, Flore LA, Lehman A, Shur N, Jayakar PB, Hainline BE, Basinger AA, Wilson WG, Diaz GA, Erbe RW, Koeberl DD, Vockley J, Bedoyan JK. Clinical, biochemical and molecular characterization of 12 patients with pyruvate carboxylase deficiency treated with triheptanoin. Mol Genet Metab. 2023;139 :107605. PubMed PMID: 37207470.

Mangla P, Gambhir PS, Sudhanshu S, Srivastava P, Rai A, Bhatia V, Phadke SR. Pyruvate carboxylase deficiency mimicking diabetic ketoacidosis. Indian J Pediatr. 2017;84:959-60. PubMed PMID: 28831725.

Marcé-Grau A, Martí-Sánchez L, Baide-Mairena H, Ortigoza-Escobar JD, Pérez-Dueñas B. Genetic defects of thiamine transport and metabolism: a review of clinical phenotypes, genetics, and functional studies. J Inherit Metab Dis. 2019;42:581–97. PubMed PMID: 31095747.

Maryami F, Rismani E, Davoudi-Dehaghani E, Khalesi N, Talebi S, Mahdian R, Zeinali S. In silico analysis of two novel variants in the pyruvate carboxylase (*PC*) gene associated with the severe form of PC deficiency. Iran Biomed J. 2023;27:307-19. PubMed PMID: 37873728.

Mayr JA, Feichtinger RG, Tort F, Ribes A, Sperl W. Lipoic acid biosynthesis defects. J Inherit Metab Dis. 2014;37:553–63. PubMed PMID: 24777537.

Mhanni AA, Rockman-Greenberg C, Ryner L, Bunge M. Prenatal onset of the neuroradiologic phenotype of pyruvate carboxylase deficiency due to homozygous PC c.1828G>A mutations. JIMD Rep. 2021;61:42–7. PubMed PMID: 34485016.

Mochel F. Triheptanoin for the treatment of brain energy deficit: a 14-year experience. J Neurosci Res. 2017;95:2236-43. PubMed PMID: 28688166.

Mochel F, DeLonlay P, Touati G, Brunengraber H, Kinman RP, Rabier D, Roe CR, Saudubray JM. Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy. Mol Genet Metab. 2005;84:305–12. PubMed PMID: 15781190.

Nyhan WL, Khanna A, Barshop BA, Naviaux RK, Precht AF, Lavine JE, Hart MA, Hainline BE, Wappner RS, Nichols S, Haas RH. Pyruvate carboxylase deficiency--insights from liver transplantation. Mol Genet Metab. 2002;77:143–9. PubMed PMID: 12359142.

Ostergaard E, Duno M, Møller LB, Kalkanoglu-Sivri HS, Dursun A, Aliefendioglu D, Leth H, Dahl M, Christensen E, Wibrand F. Novel mutations in the PC gene in patients with type B Pyruvate carboxylase deficiency. JIMD Rep. 2013;9:1–5. PubMed PMID: 23430542.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Roe CR, Mochel F. Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential. J Inherit Metab Dis. 2006;29:332–40. PubMed PMID: 16763896.

Sahdev N, Oji O, Babu A, Roy SM. Case report of Takotsubo syndrome following seizures in a patient with pyruvate carboxylase deficiency. Eur Heart J Case Rep. 2021;5:ytab011. PubMed PMID: 34109288.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Stern HJ, Nayar R, Depalma L, Rifai N. Prolonged survival in pyruvate carboxylase deficiency: lack of correlation with enzyme activity in cultured fibroblasts. Clin Biochem. 1995;28:85–9. PubMed PMID: 7720232.

Tao D, Zhang H, Yang J, Niu H, Zhang J, Zeng M, Cheng S. *PC* splice-site variant c.1825+5G>A caused intron retention in a patient with pyruvate carboxylase deficiency: a case report. Front. Pediatr. 2022;10:825515. PubMed PMID: 35573952.

Tsygankova P, Bychkov I, Minzhenkova M, Pechatnikova N, Bessonova L, Buyanova G, Naumchik I, Beskorovainiy N, Tabakov V, Itkis Y, Shilova N, Zakharova E. Expanding the genetic spectrum of the pyruvate carboxylase deficiency with novel missense, deep intronic and structural variants. Mol Genet Metab Rep. 2022;32:100889. PubMed PMID: 35782291.

Wang D, Yang H, De Braganca KC, Lu J, Yu Shih L, Briones P, Lang T, De Vivo DC. The molecular basis of pyruvate carboxylase deficiency: mosaicism correlates with prolonged survival. Mol Genet Metab. 2008;95:31–8. PubMed PMID: 18676167.

Xue M. Case report: prenatal neurological injury in a neonate with pyruvate carboxylase deficiency type B. Front Endocrinol (Lausanne). 2023;14:1199590. PubMed PMID: 37484962.

License