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NLM Citation: Ganetzky R, McCormick EM, Falk MJ. Primary Pyruvate Dehydrogenase Complex Deficiency Overview. 2021 Jun 17. 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/

Primary Pyruvate Dehydrogenase Complex Deficiency Overview

Synonyms: PDH Deficiency (PDHD), PDHC Deficiency, Pyruvate Dehydrogenase Complex Deficiency Disease (PDCDD), Pyruvate Dehydrogenase Deficiency

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Created: June 17, 2021.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding primary pyruvate dehydrogenase complex deficiency (PDCD) and its genetic causes and management.

The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of primary PDCD.

Goal 2

Review the genetic causes of primary PDCD.

Goal 3

Review the differential diagnosis of primary PDCD.

Goal 4

Provide an evaluation strategy to identify the genetic cause of primary PDCD in a proband (when possible).

Goal 5

Inform (when possible) medical management of primary PDCD based on genetic cause.

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Goal 6

Inform genetic risk assessment of family members of a proband with primary PDCD.

1. Clinical Characteristics of Primary Pyruvate Dehydrogenase Complex Deficiency

Primary pyruvate dehydrogenase complex deficiency (PDCD) is a mitochondrial disorder of carbohydrate oxidation that mostly affects the brain and leads to decreased ATP production and energy deficit. Primary PDCD most commonly manifests as a syndrome of neurologic signs (congenital microcephaly, hypotonia, epilepsy, and/or ataxia), abnormal brain imaging (dysgenesis of the corpus callosum, Leigh syndrome) and metabolic abnormalities (increased plasma pyruvate, lactic acidemia, and/or metabolic acidosis). Developmental delay is nearly universal [Sofou et al 2017].

Age of onset varies. Typically, the mean age of diagnosis of primary PDCD is about 45 months (median age ~20 months) [DeBrosse et al 2012, Sofou et al 2017]. Presentation may be as early as prenatal with routine prenatal ultrasound detecting microcephaly, ventriculomegaly, paraventricular pseudocysts, cerebellar hypoplasia, delayed gyration, and/or dysgenesis of the corpus callosum. Fetal MRI may demonstrate these features, along with cerebral volume loss and/or periventricular T_2-weighted hyperintensity [Natarajan et al 2016, Pirot et al 2016]. Newborns may present with a history of intrauterine growth restriction, microcephaly, structural brain anomalies, and lactic acidosis [DeBrosse et al 2012, Sofou et al 2017]. Children may present in late infancy or early childhood with chronic neurologic symptoms. Rarely, individuals present later in childhood with intermittent ataxia [DeBrosse et al 2012], paroxysmal dystonia or dyskinesia [Barnerias et al 2010, Castiglioni et al 2015, Friedman et al 2017], or other atypical clinical findings such as alternating hemiplegia or episodic limb paralysis [Sen et al 2021].

Features of Primary PDCD

Neurologic findings [DeBrosse et al 2012]

- Developmental delay (majority of individuals)
- Hypotonia, especially axial (majority of individuals)
- Epilepsy (occasional)
- Hypertonia, especially appendicular (occasional)
- Ataxia (occasional)
- Peripheral neuropathy (occasional) [Barnerias et al 2010]
- Dystonia – may be episodic, in response to fever, stress or exercise (occasional) [McWilliam et al 2010, Castiglioni et al 2015]
- Spasticity (occasional)
- Dyskinesia – may be paroxysmal exercise-induced (rare) [Friedman et al 2017]
- Hemiplegia or episodic limb paralysis (rare) [Sen et al 2021]

Facial features may include a long philtrum, thin upper lip, and low-set ears [De Meirleir et al 1993, Patel et al 2012].

Ophthalmologic findings [Patel et al 2012]

- Optic atrophy (rare)
- Nystagmus (rare)
- Ptosis (rare) or ophthalmoplegia [Sen et al 2021]
- Strabismus (rare)

Growth

- Intrauterine growth restriction
- Shortened long bones (rare)
- Primary or acquired microcephaly (majority of individuals)

Musculoskeletal findings include acquired hip dysplasia.

Psychiatric manifestations (e.g., auditory hallucinations, delusional thoughts) may develop in mildly affected individuals in adolescence and early adulthood [Author, unpublished observation].

Brain MRI findings [Ah Mew et al 2011, DeBrosse et al 2012]

- Cerebral atrophy (majority of individuals) [Patel et al 2012]
- Asymmetric ventriculomegaly (common)
- Dysgenesis or agenesis of the corpus callosum (common) [Barnerias et al 2010]
- T_2-weighted hyperintensities (occasional) typically involving the basal ganglia more than the brain stem and cerebellum [Patel et al 2012]
- Periventricular cysts and/or intraventricular septations (occasional)
- Hyporotation of the hippocampus (rare)

Laboratory features

- Elevated blood lactate with proportional elevation of pyruvate; normal lactate/pyruvate ratio (normal range 10-20). Peak pyruvate is typically >0.2 mmol/L [Clarke et al 2013]. Elevations of lactate and pyruvate may be intermittent and do not necessarily correlate with the severity of the clinical phenotype [Author, unpublished observation].

  Note: Pyruvate may appear artificially low in samples that are collected improperly (e.g., not drawn immediately into a perchloric acid tube, not drawn on ice, or drawn while using a tourniquet).

- Elevated plasma alanine and proline may also occur. Alanine-to-leucine and proline-to-leucine ratios are highly sensitive but not specific for primary PDCD [Bedoyan et al 2020].

- Elevated urine and CSF lactate and pyruvate

- Low pyruvate dehydrogenase complex (PDC) enzyme activity in cultured fibroblasts, lymphocytes, and/or skeletal muscle (activity levels may vary between tissues in an individual) [Shin et al 2017]. Note: The majority of primary PDCD is X-linked and *PDHA1* related, and differential involvement of various tissues is common [Shin et al 2017].

- Additional laboratory features variably present in individuals with specific molecular causes of primary PDCD (See Table 1.)

- Positive newborn screen (limited availability to date). Pilot newborn screening for primary PDCD using dried blood spots to screen for ratio of alanine:leucine >4 and/or proline:leucine >3 was used to identify three neonates with PDCD and two additional neonates with other mitochondrial diseases. This screening had a 2.8% positive predictive value and an 80% sensitivity. Pilot newborn screening is ongoing in the state of Ohio [Bedoyan et al 2020].

2. Causes of Primary Pyruvate Dehydrogenase Complex Deficiency

Table 1. Primary Pyruvate Dehydrogenase Complex Deficiency: Genes and Distinguishing Clinical Features

Gene [1, 2]	% of all PDCD	Disorder	Distinguishing Clinical Features
DLAT	1%-4%	Pyruvate dehydrogenase E2 deficiency (OMIM 245348)	• Milder phenotype w/survival into childhood/adulthood • Episodic dystonia • PDC enzyme activity below reference range but not as low as other forms of PDCD • ± abnl brain MRI, globus pallidus lesions (resembles PKAN but w/o "eye of the tiger" MRI sign) • Several w/clinical response to lipoic acid, thiamine, &/or ketogenic diet
DLD	1%-6%	Dihydrolipoamide dehydrogenase deficiency	• Present w/Leigh syndrome [3] or w/intermittent liver failure • ↑ branched-chain amino acids (i.e., mild-moderate ↑s of leucine, isoleucine & valine w/or w/o alloisoleucine) • ↑ citrulline • ↑ urine alpha-ketoglutarate • Founder variant in Ashkenazi Jewish population [4]
PDHA1	76%-85%	Pyruvate dehydrogenase E1-alpha deficiency (OMIM 312170)	• Variable phenotype: neonatal lactic acidosis, Leigh syndrome [3], or adult-onset myopathy or ataxia • Affected females have most striking abnormalities on brain MRI (e.g., asymmetric ventriculomegaly, corpus callosum dysgenesis). • Variable response to ketogenic diet; treatment w/ ketogenic diet is assoc w/↑ life span. [5]
PDHB	4%-9%	Pyruvate dehydrogenase E1-beta deficiency (OMIM 614111)	• Typically more severely affected • ± structural brain abnormalities & microcephaly • Leigh syndrome [3] & neonatal lactic acidosis • IUGR • Treatment w/ketogenic diet is assoc w/↑ life span.
PDHX	7%-11%	Pyruvate dehydrogenase E3-binding protein deficiency (OMIM 245349)	• Neonatal lactic acidosis • Non-progressive encephalopathy • Mild dysmorphic features • Founder variant in people of Roma & Moroccan ancestry [6]
PDP1	~1%	Pyruvate dehydrogenase phosphatase deficiency (OMIM 608782)	• Cardiomyopathy • Neonatal lactic acidosis • Clinical response to ketogenic diet
PDK3	<1%	CMT, X-linked dominant type 6 (OMIM 300905)	• Clinical features of CMT incl *pes cavus* foot deformity & hand wasting • Childhood/adult onset

abnl = abnormal; CMT = Charcot-Marie-Tooth; IUGR = intrauterine growth restriction; PKAN = pantothenate kinase-associated neurodegeneration

1. Genes are listed alphabetically

2. Molecular causes of **secondary** pyruvate dehydrogenase deficiency are discussed in Table 2.

3. Leigh syndrome is characterized by decompensation during intercurrent illness, lactic acidosis, and bilateral symmetric T_2-weighted hyperintensities in the basal ganglia and/or brain stem on brain MRI.

4. DLD pathogenic variant c.685G>T (p.Gly229Cys) is an Ashkenazi-Jewish founder variant.

5. Cameron et al [2004], Ah Mew et al [2011], Imbard et al [2011], Patel et al [2012], Deeb et al [2014], Sperl et al [2015], Qin et al [2016], Shin et al [2017]

6. PDHX c.1336C>T (p.Arg446Ter) is a Roma founder variant; c.1182+2T>C (p.Ile386SerfsTer13) is a Moroccan founder variant.

3. Differential Diagnosis of Primary Pyruvate Dehydrogenase Complex Deficiency

Secondary pyruvate dehydrogenase complex deficiency (PDCD). It is important to distinguish primary PDCD from secondary PDCD (i.e., dysfunction of the pyruvate dehydrogenase complex secondary to conditions that impair complex assembly, iron-sulfur cluster formation, and deficiencies of cofactors thiamine and lipoic acid). While secondary PDCD can be phenotypically similar to primary PDCD (see Table 2), secondary PDCD can have significantly different treatment implications.

Note: Multiple genes, in addition to those listed in Table 2, have been associated with secondary PDCD. These genes are associated with phenotypically distinct disorders and include *FDX2* (*FDX1L*), *GOT2, ISCU*, *LONP1*, *MPC1*, *SLC19A2, SLC19A3*, *SLC25A19*, *SUCLA2*, and *SUCLG1*.

Table 2. Genes of Interest in the Differential Diagnosis of Primary Pyruvate Dehydrogenase Complex Deficiency

Gene(s)	Disorder	MOI	Clinical Findings & Brain MRI	Laboratory Findings
Disorders assoc w/secondary PDCD that are phenotypically similar to primary PDCD				
BOLA3 *IBA57* *ISCA1* *ISCA2* *NFU1* *PMPCB*	Multiple mitochondrial dysfunction syndromes (OMIM PS605711)	AR	Leigh syndrome, seizures, spasticity, & mvmt disorder; unlike primary PDCD, MMDS is assoc w/optic atrophy, cardiomyopathy, leukodystrophy.	Neonatal lactic acidosis; ↓ PDC enzyme activity in at least fibroblasts & skeletal muscle cells for some; unlike primary PDCD, MMDS is assoc w/↑ glycine & electron transport chain enzyme activity deficiencies.
ECHS1	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D)	AR	Leigh syndrome, long philtrum, & episodic dystonia; may be a complete phenocopy of primary PDCD [1]; corpus callosum dysgenesis/agenesis	Lactic acidosis & & ↑ pyruvate (lactate:pyruvate ratio may be nl); unlike primary PDCD, ECHS1D may be assoc w/ abnl acylcarnitine profile or ↑urine organic acid w/marked 2-methyl-2,3-dihydroxybutyric acid.
HIBCH	3-hydroxyisobutyryl-CoA hydrolase deficiency (HIBCHD) (OMIM 250620)	AR	Leigh syndrome & long philtrum; corpus callosum dysgenesis/ agenesis	Lactic acidosis & ↑ pyruvate (lactate:pyruvate ratio may be nl); unlike primary PDCD, HIBCHD may be assoc w/abnl acylcarnitine profile or urine organic acids.
LIAS	Hyperglycinemia, lactic acidosis, and seizures (OMIM 614462)	AR	Epileptic encephalopathy, lactic acidosis	Lactic acidosis & ↑ pyruvate (lactate:pyruvate ratio may be nl or ↑); ↓ PDC enzyme activity (muscle, fibroblasts); unlike primary PDCD, lipoic acid synthesis defects are assoc w/↑ glycine & electron transport chain enzyme activity deficiencies.
LIPT1	Lipoyltransferase 1 deficiency (LIPT1D; OMIM 616299)			
LIPT2	Lipoyltransferase 2 deficiency (OMIM 617668)			
SLC25A1	Mitochondrial citrate carrier deficiency (combined D-2- & L-2-hydroxyglutaric aciduria; OMIM 615182)	AR	Unlike primary PDCD, MCCD is assoc w/facial dysmorphism & apnea; intracerebral cysts.	Neonatal lactic acidosis & ↑ 2-hydroxyglutaric acid
TPK1	Thiamine pyrophosphokinase deficiency (thiamine metabolism dysfunction syndrome 5 - episodic encephalopathy type; OMIM 614458)	AR	Developmental regression, ataxia, dystonia, & microcephaly; typically higher developmental achievement than in PDCD.	↑ lactate & ↑ pyruvate; nl lactate:pyruvate ratio. Note: Treatable w/high dose thiamine [2]
Other disorders (not assoc w/inhibition of PDCs) that are phenotypically similar to primary PDCD				

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Findings & Brain MRI	Laboratory Findings
~90 genes	Other Leigh syndromes (See Nuclear Gene-Encoded Leigh Syndrome Overview & mtDNA-Associated Leigh Syndrome & NARP.)	AR AD XL Mat	Dystonia & developmental regression; T_2-weighted hyperintensity of the basal ganglia	Lactic acidosis. Note: Electron transport chain defects typically → nl pyruvate. If pyruvate is ↑, lactate:pyruvate ratio is > nl (>20) due to dysfunction of electron transport chain.
FBXL4	*FBXL4*-related encephalomyopathic mtDNA depletion syndrome	AR	Leigh syndrome & long philtrum; corpus callosum dysgenesis/ agenesis	Lactic acidosis & ↑ pyruvate; hyperammonemia may be more striking than in primary PDCD.
PANK2	Pantothenate kinase-associated neurodegeneration (PKAN)	AR	Dystonia, spasticity, dysarthria, intellectual impairment; "eye of the tiger" MRI sign (classic for PKAN) is absent in primary PDCD (Globus pallidus lesions in DLAT-PDCD resemble PKAN but DLAT-PDCD is not assoc w/eye of the tiger MRI sign.)	Unlike primary PDCD, PKAN is assoc w/ acanthocytosis & low/absent plasma pre-beta lipoprotein fraction.

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA; nl = normal; PDCD = pyruvate dehydrogenase complex deficiency; PDC = pyruvate dehydrogenase complex; XL = X-linked

1. Bedoyan et al [2017], Nouguès et al [2017]

2. Marcé-Grau et al [2019]

Acquired disorders of interest in the differential diagnosis of primary pyruvate dehydrogenase complex deficiency (PDCD) include the following:

- **Dietary thiamine deficiency** – which may develop in children who are critically ill for other reasons – results in an acquired decrease in PDC enzyme activity, resulting in biochemical findings (elevated lactate and pyruvate with a normal ratio) similar to those of primary PDCD [Murali & Ganetzky 2020].
- **Fetal alcohol syndrome.** Similar to primary PDCD, the facial appearance in individuals with fetal alcohol syndrome may include a short nose, a long and smooth philtrum, and a thin upper lip as well as primary microcephaly and agenesis of the corpus callosum.

  Unlike primary PDCD, fetal alcohol syndrome is associated with normal lactate and pyruvate and a fetal history suggestive of in utero alcohol exposure. In addition, children with fetal alcohol syndrome typically have more advanced development compared to children with primary PDCD.

4. Evaluation Strategies to Identify the Genetic Cause of Primary Pyruvate Dehydrogenase Complex Deficiency in a Proband

Establishing a specific genetic cause of primary pyruvate dehydrogenase complex deficiency (PDCD):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/ genetic testing.

Medical history. A careful history should be taken, particularly for neurologic features (e.g., epilepsy, dystonia, hypotonia, microcephaly, structural brain anomalies, and/or spasticity). Attention should be paid to whether there is exacerbation of symptoms in response to stress, fever, and/or illness, which is highly suggestive of primary PDCD. Care should also be taken to elicit a history of intermittent/episodic/paroxysmal symptoms including ataxia, dystonia, flaccid paralysis, and Kussmaul respirations (see also Table 1).

Physical examination. Physical examination is notable for microcephaly, which may be primary or acquired, dysmorphic facial features (e.g., thin upper lip, long, smooth philtrum). Ptosis or ophthalmoplegia may occur. Neurologic examination typically shows truncal hypotonia with spasticity in the limbs. Dystonia, dyskinesia, and ataxia may also be present on examination. Sensory examination may show a peripheral sensory neuropathy (see also Table 1).

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of primary PDCD and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel or serial single-gene testing) and comprehensive genomic testing (exome sequencing or genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **Serial single-gene testing** can be considered if clinical findings and/or family history indicate that pathogenic variants in a particular gene are most likely (see Table 1).
- **A multigene panel** that includes some or all of the genes listed in Table 1 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by clinical 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 clinical 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.
- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

5. Management of Pyruvate Dehydrogenase Complex Deficiency Based on Genetic Cause

This section provides information regarding recommendations for evaluations following initial diagnosis (Table 3), medical management based (when possible) on the genetic cause (Table 4), and recommended surveillance for individuals with primary pyruvate dehydrogenase complex deficiency (PDCD) and family members at risk of primary PDCD (Table 5).

Evaluations Following Initial Diagnosis

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Primary Pyruvate Dehydrogenase Complex Deficiency

System/Concern	Evaluation	Comment
Metabolic decompensation	Consultation w/metabolic physician or biochemical geneticist & specialist metabolic dietitian [1]	Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended)
	STAT blood gas (arterial or venous), blood lactic acid, & glucose, comprehensive metabolic panel, serum beta-hydroxybutyrate (while on ketogenic diet), urinalysis, plasma acylcarnitines incl free & total carnitine (while on ketogenic diet)	Urgent labs to be obtained if an acute metabolic crisis is suspected
Neurologic	Eval for seizures	EEG
	Eval for structural brain abnormalities	Brain MRI if not previously performed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of primary PDCD in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing or therapy (speech, PT &/or OT) referral.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There are no FDA-approved therapies for primary PDCD, thus, treatment recommendations are based on open-label case reports and small trials.

Table 4. Pyruvate Dehydrogenase Complex Deficiency: Management by Genetic Cause

Gene	Treatment	References / *GeneReview*
DLAT	• Ketogenic diet • Thiamine (300-1000 mg/day) has been used w/limited success. [1]	Friedman et al [2017]
PDHA1		Fouque et al [2003], DeBrosse et al [2012], Patel et al [2012]
PDHB		Okajima et al [2008]
PDHX		Tajir et al [2012]
PDP1		Bedoyan et al [2019]
DLD	• Branched-chain amino acid restriction • Dextrose-containing IV fluids • Riboflavin (220-400 mg/day) • Acetaminophen & ethanol are contraindicated.	See also Dihydrolipoamide Dehydrogenase Deficiency.

1. Sedel et al [2008]

Ketogenic diet is the gold-standard therapy for individuals with primary PDCD [Bedoyan et al 2017, Shin et al 2017, Bedoyan et al 2020]. The underlying rationale for the ketogenic diet is that individuals with primary PDCD do not metabolize carbohydrates effectively. Therefore, carbohydrates may precipitate lactic acidosis. On the basis of this rationale and many open-label studies, high-fat, low-carbohydrate diets ("ketogenic diet") are

used [Sofou et al 2017]. Ketogenic diet has been shown to be particularly beneficial in decreasing seizures and improving ataxia, lactic acidosis, and sleep habits [Wexler et al 1997, Sofou et al 2017]. Half of individuals with primary PDCD-related epilepsy achieve epileptic remission within one year of starting a ketogenic diet; studies have also shown improvement of language, social, cognitive, and motor development on the ketogenic diet. The developmental benefit appears to be the most pronounced in individuals with relatively mild presentations, such as childhood-onset ataxia [Sofou et al 2017].

The recommended ratio varies from as low as a 1:1 fat-to-carbohydrate & protein ratio ("modified" ketogenic diet) to as high as a 4:1 ratio. There are no studies that definitively demonstrate the superiority of any particular ratio. The recommended amount of dietary fat can vary widely, from ~55% to 80%, with variable proportions of unsaturated and saturated fats. The best outcomes are associated with maintaining plasma or serum beta-hydroxybutyrate levels at about 3.0-3.5 mEq/L [Sofou et al 2017]. Tolerance of the ketogenic diet varies and treatment must be individualized.

Ketogenic diet is the most beneficial in individuals with a milder pre-treatment disease course, disease onset after the neonatal period, higher baseline developmental functioning, and absence of structural brain anomalies [Sofou et al 2017]; although the effect of early implementation of ketogenic diet such as in the neonatal period is not well understood or investigated because of the delayed diagnosis of individuals with PDCD. The most favorable developmental outcomes are associated with early implementation of the diet [Wexler et al 1997].

Thiamine (vitamin B_1) is routinely used in individuals with primary PDCD, at doses of 300-1000 mg/day divided in three doses, although only a minority of individuals have shown biochemical or neurologic response [Pastoris et al 1996, Sedel et al 2008, Barnerias et al 2010, Sofou et al 2017]. Genotype-phenotype correlation exists for thiamine responsiveness in primary PDCD, with missense variants – especially those in exon 3 or the thiamine pyrophosphate binding site of the E1-alpha subunit (*PDHA1*) – being the most amenable to treatment [Sedel et al 2008, Castiglioni et al 2015].

Therapies. For all individuals, physical therapy and occupational therapy are essential, with a goal of maintaining mobility for those with spasticity.

Table 5. Treatment of Manifestations in Individuals with Primary Pyruvate Dehydrogenase Complex Deficiency

Manifestation	Treatment	Comments
Dystonia (paroxysmal)	• Minimize stressors (e.g., fever). • Benzodiazepines	
Dystonia (chronic)	Botulinum toxin injections	
Spasticity	PT, OT	
Seizures	• Ketogenic diet • Standard anti-seizure therapy as needed [1]	
Ataxia	Vestibular therapy	
Inadequate nutrition	• Nasogastric tube or gastrostomy tube • Feeding therapy w/speech therapist	Many persons require gastrostomy tube to achieve & maintain a ketogenic diet.
Optic atrophy	Low-vision support for educational settings	
Acidosis	Bicarbonate or buffer therapy (e.g. citrate, acetate) for correction	Metabolic acidosis may be secondary to lactic acidosis or ketogenic diet. In persons w/ significant lactic acidosis, ketogenic diet may be helpful; however, care needs to be taken to buffer acid/base status before acutely initiating the ketogenic diet. Continue monitoring of acid/base status while on ketogenic diet.
Hip dysplasia	Surgical correction or supportive bracing	

Table 5. continued from previous page.

Manifestation	Treatment	Comments
Psychiatric manifestations	Standard psychiatric care; may be responsive to ↑ ketosis	

OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Other

- **Lipoic acid.** Lipoic acid supplementation is theoretically of benefit (and has very low toxicity). However, studies have suggested that exogenous lipoic acid, while beneficial as an antioxidant, is not utilized for mitochondrial lipoylation [Mayr et al 2014].
- **N-acetylcysteine.** As mitochondrial disorders (including primary PDCD) commonly have increased oxidative stress, antioxidant therapy may be considered. In particular, blood glutathione testing may reveal deficiency of the major cellular antioxidant defense system, glutathione, which may be responsive to N-acetylcysteine to boost endogenous glutathione production [Barcelos et al 2020].
- **L-carnitine (if on ketogenic diet).** Supplementation with L-carnitine (sugar free) is utilized to protect against secondary carnitine deficiency, which is associated with long-term use of ketogenic diet.

Surveillance

For individuals with primary PDCD, comprehensive neurologic examination and developmental assessment are recommended every six to 12 months to assess for new neurologic symptoms and epilepsy control. Repeat brain MRI and EEG are warranted only if new symptoms develop.

Individuals may require a physical medicine and rehabilitation specialist to guide their therapy and advise on the use of orthotic devices. Physical examination to assess for neuromuscular scoliosis and acquired hip dysplasia should be performed every six to 12 months, accompanied by radiographic imaging if there is clinical concern.

Annual ophthalmologic examination to assess for eye movement and ptosis is recommended.

Serum bicarbonate and lactate levels to monitor for acidosis should be performed as needed with illness and metabolic stressors, as well as with initiation of and modifications in ketogenic diet regimen.

Beta-hydroxybutyrate levels should be monitored routinely for children on the ketogenic diet, with a goal of maintenance above 3.0-3.5 mmol/L.

For individuals with pathogenic variants in *DLD*, liver monitoring includes physical examination and imaging to assess for liver size, as well as measurement of liver transaminases and synthetic liver function both routinely and when acutely ill. Like other mitochondrial hepatopathies, a theoretic risk exists of developing hepatocellular carcinoma – for which annual monitoring of alpha-fetoprotein and liver ultrasound may be considered; however, hepatocellular carcinoma has not been reported in *DLD*-related disease to date [Schady et al 2015]. See the *GeneReview* Dihydrolipoamide Dehydrogenase Deficiency for further guidance.

Therapies Under Investigation

Dichloroacetate (DCA) and phenylbutyrate both inhibit pyruvate dehydrogenase kinase 1 (PDK1), which is the major inhibitor of PDC. Inhibition of PDK1 results in enhanced residual PDC enzyme activity. DCA is reportedly a pan PDK inhibitor, although the inhibition varies among isoforms.

Clinical trials with DCA are ongoing (ClinicalTrials.gov NCT02616484). DCA may also reduce degradation of E1a. Therefore, it may have the most clinical efficacy in individuals with pathogenic variants that result in

residual protein expression [Fouque et al 2003]. DCA has also shown in vitro promise in treating gain-of-function variants in *PDK3*, as expected [Perez-Siles et al 2020]. DCA dosing is titrated to the haplotype of the pharmacogenetic modifier gene, *GSTZ1* [James et al 2017].

Phenylbutyrate has been shown in vitro to increase PDC enzyme activity in cell lines from individuals with *DLAT*, *DLD*, *PDHA1*, *PDHB*, *PDHX*, and *PDP1* pathogenic variants, particularly in individuals with pathogenic variants associated with residual enzyme activity [Ferriero et al 2014].

6. Genetic Risk Assessment of Family Members of a Proband with Primary Pyruvate Dehydrogenase Complex Deficiency

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

PDHA1- and *PDK3*-related primary pyruvate dehydrogenase complex deficiency (PDCD) are inherited in an X-linked manner.

Unlike many X-linked disorders, an equal frequency of clinically affected males and females has been observed in *PDHA1*-related primary PDCD; however, affected females tend to have insertion/deletion pathogenic variants, while affected males are more likely to have missense pathogenic variants. Females with missense *PDHA1* pathogenic variants are more likely to be asymptomatic [Lissens et al 2000].

Primary PDCD caused by pathogenic variants in *DLAT*, *DLD*, *PDHB*, *PDHX*, or *PDP1* is inherited in an autosomal recessive manner.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor be hemizygous for the *PDHA1* or *PDK3* pathogenic variant; therefore, he does not require further evaluation or testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the familial pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the mother may have somatic/germline mosaicism, or the affected male may have a *de novo* pathogenic variant (in which case the mother is not a heterozygote). About 60%-63% of males with *PDHA1*-related primary PDCD have the disorder as the result of a *de novo* pathogenic variant [Lissens et al 2000, Imbard et al 2011]. *De novo PDK3* pathogenic variants have not been reported but are theoretically possible.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Parents of a female proband

- A female proband may have *PDHA1*-related primary PDCD as the result of a *de novo* pathogenic variant or she may have the disorder as the result of a *PDHA1* pathogenic variant inherited from her mother or,

theoretically, from her father (to date, there are no reports of paternal inheritance [Author, personal observation]). *De novo PDHA1* pathogenic variants are more common in female probands than in male probands: about 85%-95% of females with *PDHA1*-related primary PDCD have the disorder as the result of a *de novo* pathogenic variant [Lissens et al 2000, Imbard et al 2011].

- To date, all reported female probands with *PDK3*-related primary PDCD whose parents have undergone molecular genetic testing have had the disorder as the result of an inherited *PDK3* pathogenic variant. There are reports of both maternal and paternal transmission. *De novo PDK3* pathogenic variants have not been reported but are theoretically possible.
- Detailed evaluation of the parents and review of the extended family history may help to distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father either concurrently or subsequently if the mother's testing is unrevealing) can help to determine if the pathogenic variant was inherited.

Sibs of a proband

- The risk to sibs of a male proband of inheriting a *PDHA1* or *PDK3* pathogenic variant depends on the genetic status of the mother: if the mother of the proband has a *PDHA1* or *PDK3* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
- The risk to sibs of a female proband of inheriting a *PDHA1* or *PDK3* pathogenic variant depends on the genetic status of the mother and the father.
  - If the mother of the proband has a *PDHA1* or *PDK3* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - If the father of the proband has a *PDHA1* or *PDK3* pathogenic variant, he will transmit it to all his daughters and none of his sons (paternal transmission of a *PDHA1* pathogenic variant has not been reported to date [Author, personal observation]).
- The risk that a sib who inherits a *PDHA1* or *PDK3* pathogenic variant will have manifestations of the disorder cannot be fully predicted. The risk of manifestations is influenced by the sex of the sib, the sex of the proband, and, to an extent, the type of pathogenic variant segregating in the family (i.e., an insertion/deletion pathogenic variant or a missense pathogenic variant).
  - **Sex of the sib.** Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and their clinical manifestations may range from asymptomatic to as severely affected as hemizygous males (see Clinical Characteristics).
  - **Sex of the proband and type of pathogenic variant.** As a result of the difference in pathogenic variants typically identified in male and female probands, it is difficult to fully predict what clinical manifestations may occur in a heterozygous or hemizygous sib who is a different sex from the proband. Theoretically, the female sibs of a male proband with a missense pathogenic variant may be asymptomatic or have milder manifestations than the proband, whereas an insertion/deletion pathogenic variant in a female proband may not be compatible with life in a hemizygous male fetus. Conclusive data regarding these possibilities are not available as there are few known families in which both male and female relatives are known to have a *PDHA1* pathogenic variant (with the exception of male probands born to asymptomatic heterozygous mothers).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and the pathogenic variant cannot be detected in the leukocyte DNA of the mother (or, if the proband is female and the pathogenic variant cannot be detected in the leukocyte DNA of the mother or the father), the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism. Possible maternal germline mosaicism is suggested in a family described by Chun et al [1993] in which two female sibs were heterozygous for a *PDHA1* pathogenic variant that was not identified in their mother, although their father was unable to be tested.

Offspring of a proband

- Affected males with *PDHA1*-related primary PDCD are not known to reproduce.
- Affected males with *PDK3*-related primary PDCD transmit the *PDK3* pathogenic variant to all of their daughters and none of their sons.
- Females with a *PDHA1* or *PDK3* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child. The severity of manifestations in offspring who inherit a *PDHA1* or *PDK3* pathogenic variant cannot be fully predicted and is influenced by several factors including the sex of the offspring (see **Sibs of a proband**).

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a primary PDCD-causing pathogenic variant, the parent's family members may be at risk.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *DLAT*, *DLD, PDHB*, *PDHX*, or *PDP1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a primary PDCD-causing pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- 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 primary PDCD-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial clinical variability may be observed between sibs who inherit biallelic primary PDCD-causing pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with autosomal recessive primary PDCD are not known to reproduce.

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

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *DLAT*, *DLD*, *PDHB*, *PDHX*, or *PDP1* pathogenic variants in the family.

Prenatal Testing and Preimplantation Genetic Testing

Once the primary PDCD-causing pathogenic variant(s) have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk 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.

- **National Library of Medicine Genetics Home Reference**
  Pyruvate Dehydrogenase 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
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

Chapter Notes

Author Notes

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Acknowledgments

This work was funded in part by the Mitochondrial Medicine Frontier Program at Children's Hospital of Philadelphia and the National Institutes of Health (R35-GM134863, U24-HD093483, K08-DK113250). The

content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors or the National Institutes of Health.

Revision History

- 17 June 2021 (sw) Review posted live
- 22 March 2021 (rg) Original submission

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