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PLPBP Deficiency

Synonyms: PLPHP Deficiency, PROSC Deficiency, Pyridoxal 5'-Phosphate Homeostasis Protein Deficiency, Pyridoxal 5'-Phosphate-Binding Protein Deficiency, PDE-*PLPBP*

Hilal Al-Shekaili, PhD,[1] Jolita Ciapaite, PhD,[2] Clara van Karnebeek, MD, PhD,[3] and Izabella Pena, PhD[4]

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Summary

Clinical characteristics

PLPBP deficiency is a treatable form of vitamin B_6-dependent early-onset epileptic encephalopathy. Seizure onset is typically in the neonatal period (i.e., within the first 28 days after birth), and rarely in childhood after the neonatal period. Seizures are unresponsive to (or only partly responsive to) anti-seizure medications (ASMs) but typically show an immediate positive response to vitamin B_6, given as either pyridoxine (PN) or pyridoxal 5'-phosphate (PLP). This therapy needs to be continued lifelong. In addition to vitamin B_6 treatment, almost 60% of individuals require adjunct ASMs to achieve optimal seizure control. Although many individuals with PLPBP deficiency have normal motor, speech, and intellectual development, more than 50% have varying degrees of neurodevelopmental issues, including learning difficulties or intellectual disability (varying from mild to severe), delayed or absent speech development, or motor development abnormalities (most commonly mild hypotonia).

Diagnosis/testing

The diagnosis of PLPBP deficiency is established in a proband with suggestive findings and biallelic pathogenic variants in *PLPBP* identified by molecular genetic testing.

Management

Targeted therapies: There is no cure for PLPBP deficiency. Targeted therapy is lifelong pharmacologic treatment with either PN or PLP, and often with additional ASMs.

Author Affiliations: 1 Centre for Molecular Medicine and Therapeutics, BC Children's Hospital Research Institute, University of British Columbia, Vancouver, Canada; Email: halshekaili@bcchr.ca. 2 Department of Genetics, University Medical Center Utrecht, Utrecht, the Netherlands; Email: j.ciapaite@umcutrecht.nl. 3 Departments of Pediatrics and Human Genetics, Emma Center for Personalized Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands; Email: c.d.vankarnebeek@amsterdamumc.nl. 4 Scientist, CHEO Research Institute; Assistant Professor, Faculty of Medicine, University of Ottawa, Ottawa, Canada; Email: ipena@cheo.on.ca.

Supportive care: Supportive care for neurodevelopmental issues typically includes specialists in multiple disciplines including neurology, developmental pediatrics, speech-language therapy, physical therapy, and occupational therapy.

Surveillance: Regular examination by treating specialists is necessary to monitor existing manifestations, the individual's response to pharmacologic treatment and supportive care, and the emergence of new manifestations.

Agents/circumstances to avoid: Several ASMs (such as carbamazepine, valproate, phenytoin, and phenobarbitone) can cause a low plasma concentration of PLP.

Evaluation of relatives at risk: If the *PLPBP* pathogenic variants have been identified in an affected family member, prenatal molecular genetic testing may be performed via amniocentesis or chorionic villus sampling in future pregnancies at risk in order to facilitate postnatal treatment of the newborn.

When prenatal testing has not been performed on a pregnancy at risk, prompt diagnostic evaluation of the newborn is essential. While results of molecular genetic testing are pending, the options for management are either: (1) treatment with PN or PLP (whichever was effective in the affected sib); or (2) clinical and EEG monitoring with initiation of PN or PLP (whichever was effective in the affected sib) at the first sign of seizures or encephalopathy.

Genetic counseling

PLPBP deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PLPBP* pathogenic variant, each sib of an affected individual, irrespective of sex, 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. Once the *PLPBP* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for PLPBP deficiency have been published.

Suggestive Findings

PLPBP deficiency should be suspected in individuals with the following clinical findings, imaging findings, clinical response to a standardized vitamin B_6 trial, and family history.

Clinical Findings

Classic PLPBP deficiency (defined as neonatal onset, i.e., within the first 28 days after birth)

- Difficult-to-treat seizures irrespective of a history of fetal distress
- Epileptic encephalopathy or signs of encephalopathy (e.g., inconsolable crying, hyperalertness, jitteriness, irritability, dysregulation of muscle tone)
- Seizures and neurologic findings (e.g., roving eye movements, hypotonia, dystonia) and/or systemic signs (e.g., respiratory distress, anemia, failure to gain weight, abdominal distention, poor feeding)
- Infants with a history of fetal distress and microcephaly
- Individuals with a history of partial or complete response of seizures to pyridoxine (PN) or pyridoxal 5'-phosphate (PLP)
- Seizure recurrence following discontinuation of vitamin B_6 treatment, either incidentally or for diagnostic purposes (See Standardized Vitamin B_6 Trial.)
- Developmental delay and/or intellectual disability

- Mitochondrial encephalopathy-like presentation with lactic acidemia

Late-onset PLPBP deficiency (defined as onset after age 28 days)

- Movement disorder (opisthotonos, oculogyric crises) at age two months (one child) [Johnstone et al 2019]
- Epileptic seizures (different types) starting at age one to 14 months partially responsive to anti-seizure medications (five individuals) [Darin et al 2016, Shiraku et al 2018, Akiyama et al 2020, Espinoza et al 2021]
- Epileptic spasms without hypsarrhythmia at age four months (one individual) [Kalser et al 2022]

Imaging Findings

The following brain MRI findings have been noted in individuals with PLPBP deficiency [Johnstone et al 2019]:

- White matter abnormalities (T_2 hyperintensity and T_1 hypointensity, subcortical cystic degeneration)
- Cortical atrophy and simplified cortical gyral pattern
- Periventricular cysts
- Thinning of the corpus callosum (particularly of the posterior corpus callosum)

Standardized Vitamin B_6 Trial

A standardized vitamin B_6 trial [Wilson et al 2019] may suggest a diagnosis of PLPBP deficiency (see Figure 1).

Note: The classic approach to confirm the clinical diagnosis of the different forms of pyridoxine-dependent epilepsy (PDE) was based on withdrawal of anti-seizure medications, followed by withdrawal of daily vitamin B_6 supplementation, and then successful treatment of recurrent seizures with vitamin B_6 [Stockler et al 2011] (see Pyridoxine-Dependent Epilepsy – *ALDH7A1*). However, trial withdrawal in the neonatal period or early infancy is not recommended [Wilson et al 2019], and daily vitamin B_6 treatment should be continued in an infant with suspected PDE while molecular genetic testing is pursued.

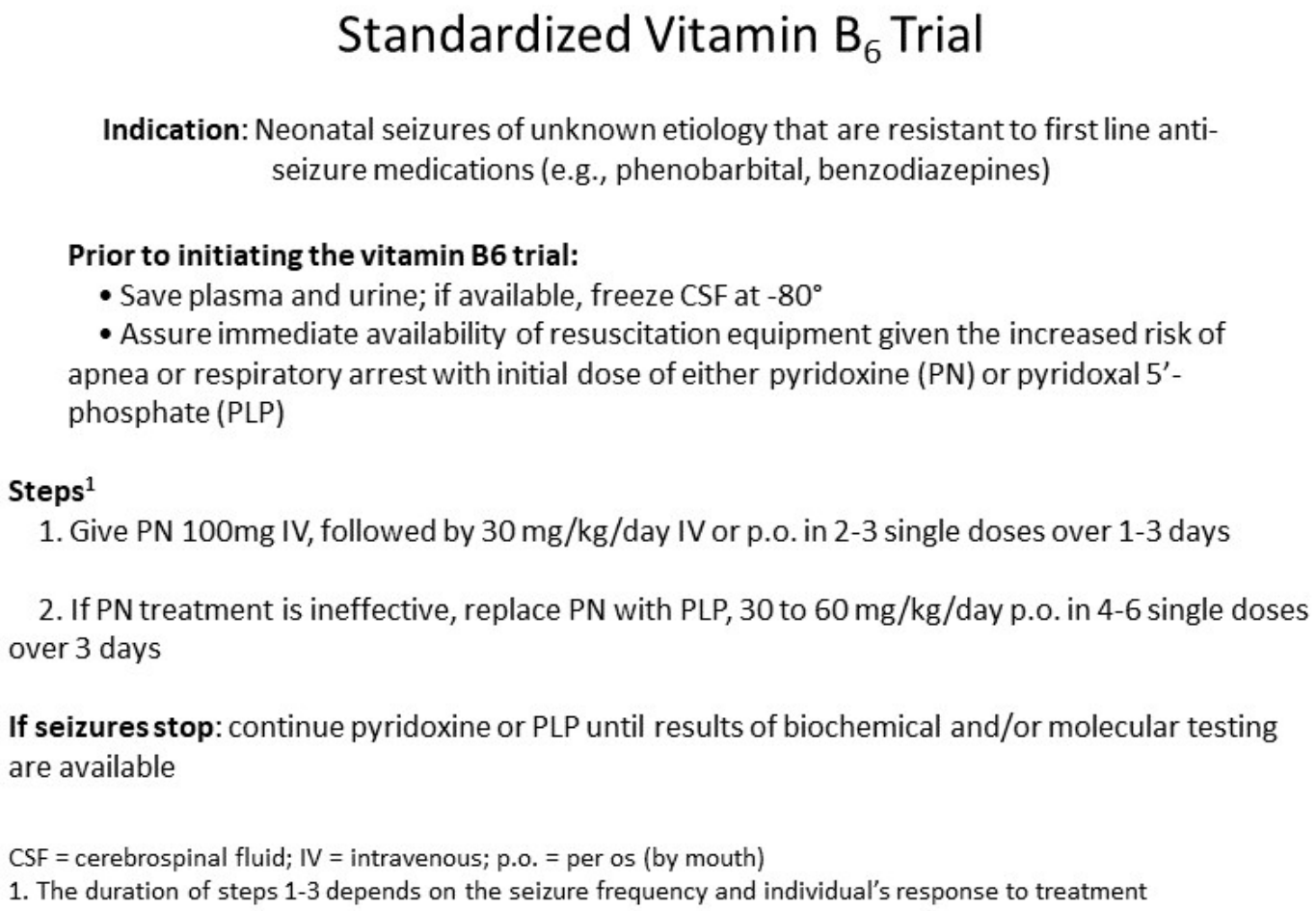

Figure 1. Stages of a standardized vitamin B_6 trial (See PNPO Deficiency.)

Based on Wilson et al [2019]

Note: (1) Because the first administration of either PN or PLP may lead to apnea or respiratory arrest, the vitamin B_6 trial must be performed in an intensive care environment with availability of full resuscitation equipment. (2) While simultaneous EEG recording is informative, it may not be practical, as improvement may take hours to days. (3) In the event of a favorable clinical or EEG response to either PN or PLP, treatment with pharmacologic doses of PN or PLP should be continued pending definitive diagnosis (see Establishing the Diagnosis).

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.

Note: (1) Sibs with seizures, epileptic encephalopathy, and/or epilepsy attributed to birth trauma or prematurity should be reevaluated when subsequent sibs have a similar presentation. (2) Families segregating pathogenic variants associated with autosomal recessive epileptic encephalopathy may have a history of infertility and miscarriage [Mills et al 2014].

Establishing the Diagnosis

The diagnosis of PLPBP deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PLPBP* identified by molecular genetic testing (see Table 1).

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 *PLPBP* variants of uncertain significance (or of one known *PLPBP* pathogenic variant and one *PLPBP* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted 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

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

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

Option 2

When the diagnosis of PLPBP deficiency has not been considered because an individual has atypical clinical findings, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) can 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.

Table 1. Molecular Genetic Testing Used in PLPBP Deficiency

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

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. All variants reported to date have been detected by sequence analysis [Darin et al 2016, Plecko et al 2017, Kernohan et al 2018, Shiraku et al 2018, Jensen et al 2019, Johannsen et al 2019, Johnstone et al 2019, Koul et al 2019, Ahmed et al 2020, Heath et al 2020, Jiao et al 2020, Espinoza et al 2021, Mittal et al 2021, Pal et al 2021].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

PLPBP deficiency, first identified in 2016, causes a rare, treatable form of vitamin B_6-dependent early-onset epileptic encephalopathy [Darin et al 2016].

To date, 56 individuals have been identified with biallelic pathogenic variants in *PLPBP* [Darin et al 2016, Plecko et al 2017, Kernohan et al 2018, Shiraku et al 2018, Jensen et al 2019, Johannsen et al 2019, Johnstone et al 2019, Koul et al 2019, Ahmed et al 2020, Akiyama et al 2020, Heath et al 2020, Jiao et al 2020, Espinoza et al 2021, Mittal et al 2021, Pal et al 2021, McLean et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

In PLPBP deficiency, seizures that have not been responsive – or only partly responsive – to anti-seizure medications (ASMs) show an immediate positive response to vitamin B_6 (given as either pyridoxine [PN] or pyridoxal 5'-phosphate [PLP]), a therapy that needs to be continued lifelong. In addition to vitamin B_6 treatment, almost 60% of individuals require adjunct ASMs to achieve optimal seizure control [Heath et al 2020]. Although many individuals with PLPBP deficiency have normal motor, speech, and intellectual development, more than 50% have varying degrees of neurodevelopmental issues, including learning difficulties or intellectual disability (varying from mild to severe), delayed or absent speech development, or motor development abnormalities (most commonly mild hypotonia). Brain white matter abnormalities and progressive microcephaly are common in individuals with more severe manifestations.

Classic PLPBP Deficiency

Classic PLPBP deficiency is defined as neonatal onset (i.e., within the first 28 days after birth).

Birth is often at term; however, preterm to late preterm birth is reported. Perinatal distress, reported in some instances, included abnormal intrauterine movements and fetal distress, suggesting fetal seizures [Heath et al 2020].

Seizures. In 43 children with known age of onset of seizures, around 50% of seizures were evident within 24 hours of birth, 23% between age one and seven days, and 14% between age one and four weeks.

The various types of seizures included tonic, clonic, generalized tonic-clonic, myoclonic, lip smacking, and/or grimacing. Initial EEG recordings vary from normal to abnormal, including burst suppression, reduced background activity, focal discharges, and multifocal spikes.

In most instances, seizures that were nonresponsive or only partially responsive to ASMs responded well to PN or PLP. In a few instances, seizure control improved with discontinuation of PN and initiation of PLP [Darin et al 2016, Johnstone et al 2019, Heath et al 2020]. In addition to PN or PLP treatment, the majority of affected individuals still require ASMs.

Withdrawal of PN or PLP (either incidentally or for diagnostic purposes before establishing the diagnosis with molecular genetic testing) led to reoccurrence of seizures, highlighting vitamin B_6 dependency in this disorder [Darin et al 2016, Plecko et al 2017, Shiraku et al 2018, Johnstone et al 2019, Jiao et al 2020].

Breakthrough seizures during illness/fever are fairly common.

Neurodevelopmental outcomes vary widely (reviewed in Heath et al [2020]). Although some affected individuals have normal motor, speech, and intellectual development, more than 50% of individuals experience varying degrees of neurodevelopmental issues, including learning difficulties or intellectual disability (varying from mild to severe), delayed or absent speech development, or motor development abnormalities, most commonly (mild) hypotonia [Johnstone et al 2019].

Other features

- Head circumference at birth varies widely from low (<10%) to normal. While progressive microcephaly is common, it is not the rule [Heath et al 2020].
- Some individuals had minor dysmorphic features [Darin et al 2016, Plecko et al 2017, Johnstone et al 2019].
- In one individual with an early-onset seizure disorder (at age 15 days), PLPBP deficiency was not diagnosed until age 16 years. His seizures were relatively well controlled with ASMs; he had a mild learning disability. Prior to the diagnosis of PLPBP deficiency and initiation of PN treatment, he experienced excessive seizure clusters and intermittent states of anxiety, suggesting that these may be typical features of untreated PLPBP deficiency in adolescents [Johannsen et al 2019]. Consistent with this observation, one individual reported hallucinations and panic attacks upon PN withdrawal [Plecko et al 2017].

Brain imaging findings. Many affected individuals have brain MRI abnormalities including white matter abnormalities (variable T_2 hyperintensity and T_1 hypointensity, subcortical cystic degeneration), cortical abnormalities (atrophy and/or simplified cortical gyral pattern), periventricular cysts, and/or thinning of the corpus callosum and the posterior limb of the internal capsule (PLIC). Of note, brain MRI findings at seizure onset vary from normal in 12/29 (41%) of individuals to abnormal in 17/29 (59%) (reviewed in Heath et al [2020]). Abnormalities in the 17 individuals were white matter changes (11), simplified sulcation (10), cysts (7), and poor myelination in the PLIC (3).

Late-Onset PLPBP Deficiency

Late-onset PLPBP deficiency is defined as onset after the neonatal period (i.e., after age 28 days).

To date six individuals (14% of affected individuals) have been reported with late-onset PLPBP deficiency, five with seizures [Akiyama et al 2020, Espinoza et al 2021, McLean et al 2022] and one without seizures [Johnstone et al 2019]. The phenotype of these individuals is broad and includes the following observations.

- At age two months, the child without seizures presented with a movement disorder (opisthotonos, oculogyric crisis), findings that resembled aromatic L-amino acid decarboxylase (AADC) deficiency [Johnstone et al 2019].
- At age four months, a girl presented with paroxysmal episodes of abnormal multidirectional eye-head movements, followed at age five months by almost daily epileptic spasms without hypsarrhythmia [Kalser et al 2022]. No developmental plateauing or regression was observed. She experienced mild-to-moderate gastroesophageal reflux disease (GERD). After initiation of PN treatment, the seizures and GERD resolved.
- At age 14 months, a boy with normal development and a normal brain MRI presented with recurring prolonged myoclonic seizures, after which speech regression was observed [Espinoza et al 2021]. Subsequently, tonic-clonic seizures occurred with more prominent developmental regression within each seizure cluster. His brain MRI at age 22 months showed bilateral mesial temporal sclerosis. Following diagnosis of PLPBP deficiency at age three years, PN treatment was initiated.
- At age three months, a boy presented with focal and generalized tonic seizures and no neurologic abnormalities [Akiyama et al 2020]. Brain MRI showed structural abnormalities including broad gyri and shallow sulci, underdevelopment of white matter, and microcephaly. At age seven years, he had moderate intellectual disability.
- Shiraku et al [2018] described two boys with seizure onset at ages three months and 34 days, respectively. Seizures (including tonic, clonic, generalized tonic-clonic, and myoclonic) were partially responsive to ASMs. Seizures ceased following initiation of PN treatment at ages eight years and five years, five months, respectively. Both boys had delayed motor and speech development and moderate-to-profound intellectual disability. Brain MRI showed broad gyri and shallow sulci, underdevelopment of white matter, and microcephaly.

Other

Biomarkers not effective in identifying PLPBP deficiency. Biochemical alterations previously reported in individuals with PLPBP deficiency are nonspecific, as they are seen in other metabolic and neonatal seizure disorders (see Table 2).

Table 2. Summary of Nonspecific Biochemical Findings Reported in PLPBP Deficiency

Metabolic Feature [1]	Incidence [2]
Blood/Plasma	
Acidosis	11/26
High lactate	16/28
Anemia at birth	3/12
High glycine	10/22
High alanine	4/22
High threonine	1/22
High PLP (on vitamin B_6 treatment)	4/7
High PL (on vitamin B_6 treatment)	4/7
CSF	
High lactate	2/6
High glycine	7/11
High alanine	2/11

Table 2. continued from previous page.

Metabolic Feature [1]	Incidence [2]
High threonine	2/11
High tryptophan	1/11
High tyrosine	1/11
Low homovanillic acid	2/10
High 3-O-methyldopa	3/9
High L-dopa	1/9
High 5-hydroxytryptophan	2/9
Low PLP	2/3
Low PL	1/1
Urine	
High vanillactic acid	5/20
High vanilpyruvic acid	1/20
High N-acetylvanilalanine	1/20
High lactic acid	2/20

Based on the review in Heath et al [2020]
CSF = cerebrospinal fluid
1. Unless otherwise noted, these results are from samples obtained before initiation of vitamin B_6 therapy.
2. Refers to number of individuals with specific finding / total number of individuals in whom the analyte was measured

Genotype-Phenotype Correlations

Since the number of individuals with PLPBP deficiency is small, it is difficult to establish true genotype-phenotype correlations. Nonetheless, the following observations about vitamin B_6 responsiveness may be helpful in guiding clinical management.

Johnstone et al [2019], who used an adapted clinical severity score to classify phenotypes and variants in 23 individuals with PLPBP deficiency, suggested that severe phenotypes and/or early mortality are usually associated with:

- Truncating *PLPBP* pathogenic variants leading to complete loss of function of the pyridoxal phosphate-binding protein (PLPBP) (e.g., c.207+1G>A, c.320-2A>G, c.233C>G [p.Ser78Ter], c.211C>T [p.Gln71Ter], c.370_373delGACA [p.Asp124LysfsTer2]);
- Missense *PLPBP* variants that are predicted or experimentally proven to affect residues surrounding the PLP binding sites (e.g., c.722G>A [p.Arg241Gln]).

Mild-to-moderate phenotypes may be associated with missense variants that decrease, but do not abolish, PLP binding or protein stability.

Nomenclature

Pyridoxine (PN) and pyridoxal 5'-phosphate (PLP) responsive seizures. Children with findings suggestive of PN- or PLP-responsive epilepsy (i.e., children with intractable seizures who have only partially improved seizure control with the addition of PN or PLP, and children in whom seizures do not recur after PN or PLP is withdrawn) who have not had molecular confirmation of PNPO deficiency, pyridoxine-dependent epilepsy –

ALDH7A1, or PLPBP deficiency should be diagnosed with "PN- or PLP-responsive seizures" rather than PN- or PLP-dependent epilepsy (see Differential Diagnosis).

Prevalence

Currently, there are no data on the prevalence of PLPBP deficiency. To date, a total of 56 individuals with PLPBP deficiency have been reported in more than 15 publications [Darin et al 2016, Plecko et al 2017, Kernohan et al 2018, Shiraku et al 2018, Jensen et al 2019, Johannsen et al 2019, Johnstone et al 2019, Ahmed et al 2020, Akiyama et al 2020, Heath et al 2020, Jiao et al 2020, Espinoza et al 2021, Pal et al 2021, McLean et al 2022].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

In addition to other vitamin B_6-dependent epilepsies and disorders associated with pyridoxine (PN)- and pyridoxal 5'-phosphate (PLP)-responsive seizures, PLPBP deficiency must be distinguished from the following:

- **Mitochondrial epileptic encephalopathy.** Lactic and metabolic acidosis along with severe neonatal encephalopathy in infants with PLPBP deficiency has led previously to the misdiagnosis of mitochondrial encephalopathy and, without PN or PLP trial, resulted in early death [Jensen et al 2019, Johnstone et al 2019].
- **Glycine encephalopathy.** Increased glycine concentration in plasma and cerebrospinal fluid has led previously to misdiagnosis of glycine encephalopathy and early demise [Jensen et al 2019].
- **Aromatic L-amino acid decarboxylase (AADC) deficiency.** Movement disorder features (opisthotonos, oculogyric crisis) compatible with AADC deficiency were described in a two-month-old child with PLPBP deficiency who did not have seizures [Johnstone et al 2019]. The biochemical profile of this child was also consistent with AADC deficiency.

Early targeted therapy with PN or PLP is critical in individuals with a vitamin B_6-dependent epilepsy. Some of the few deceased infants with vitamin B_6-dependent epilepsy reported to date were misdiagnosed with a mitochondrial disorder or glycine encephalopathy and, consequently, vitamin B_6 treatment was not considered or was introduced late [Heath et al 2020].

Vitamin B_6-Dependent Epilepsies and Disorders with PN- or PLP-Responsive Seizures

Pyridoxine-dependent epilepsy – *ALDH7A1* (also referred to as PDE-*ALDH7A1*, *ALDH7A1* deficiency, or antiquitin deficiency), PNPO deficiency, and PLPBP deficiency are the most common genetic causes of vitamin B_6-dependent and vitamin B_6-responsive epilepsies presenting in neonates, infants, and children for which an underlying lesion (i.e., symptomatic epilepsy) has not been identified.

Prematurity has been reported in the vitamin B_6-dependent epilepsies, with a frequency of 18% in PDE-*ALDH7A1*, 46%-50% in PNPO deficiency, and 27% in PLPBP deficiency. Onset of seizures tends to occur earlier in premature infants who are PLPBP deficient, usually within the first 24 hours of life [Heath et al 2020].

See Table 3 for additional features that may help distinguish between PLPBP deficiency and disorders associated with PN- and PLP-responsive seizures.

Table 3. Other Vitamin B_6-Dependent Epilepsies and Selected Disorders with PN- or PLP-Responsive Seizures in the Differential Diagnosis of PLPBP Deficiency

Gene	Disorder	MOI	Laboratory Features	Response to PN/PLP	Clinical Features
Vitamin B_6-dependent epilepsy disorders [1]					
ALDH7A1	Pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) [2]	AR	• ↑ levels of α-AASA irrespective of treatment w/PN or PLP • May also have ↑ levels of pipecolic acid • Low PLP levels in plasma & CSF prior to vitamin B_6 supplementation	Szs in affected children respond to supraphysiologic doses of PN (or PLP).	• Although most newborns have szs soon after birth, some have late-onset szs (i.e., age >2 mos or as late as adolescence). • ID is common, w/more favorable outcomes observed in those w/late-onset szs.
PNPO	PNPO deficiency	AR	• ↓ CSF & plasma levels of PLP when measured prior to administration of PN or PLP • ↑ CSF glycine • ↑ urinary vanillactic acid. [3] • ↑ plasma PM, ↑ PM:PA ratio. [4]	Szs respond to supraphysiologic doses of PLP (~60% of affected persons) or PN (~40% of affected persons).	• The vast majority of infants w/classic PNPO deficiency have szs before age 2 wks, w/30% presenting on day 1 of life. • As w/other forms of vitamin B^6-dependent epilepsy, if untreated, PNPO deficiency is usually fatal. • Motor delay has been reported, likely due to long periods of poor sz control before introduction of PLP/PN treatment. [5]
Vitamin B_6-responsive seizures [6]					
ALDH4A1	Hyperprolinaemia type II	AR	Markedly ↑ plasma proline levels as well as ↑ P5C in urine	• ~50% of persons develop szs. • PN leads to cessation &/or prevention of szs (esp during infection) [2]	• Szs usually manifest after neonatal period, may occur w/febrile infections, & may respond to common ASMs. • Persons may have ID or normal intellectual ability.
ALPL	Infantile hypophosphatasia (See Hypophosphatasia.)	AR [7]	Using appropriate pediatric normative reference values, this disorder is suspected w/low serum ALP enzyme activity.	Vitamin B_6-responsive szs may occur.	• Clinical signs may be recognized between birth & age 6 mos & resemble rickets. • Prior to availability of enzyme replacement therapy, ~50% succumbed to respiratory failure caused by undermineralization of ribs. • Intractable szs may precede biochemical or radiographic manifestations of rickets.

Table 3. continued from previous page.

Gene	Disorder	MOI	Laboratory Features	Response to PN/PLP	Clinical Features
CACNA1A	Developmental & epileptic encephalopathy 42 (OMIM 617106)	AD	No assoc biochemical abnormalities	A female w/ *CACNA1A*-related absence epilepsy & ataxia responded dramatically to PN. [8]	
GOT2	Developmental & epileptic encephalopathy 82 (OMIM 618721)	AR	↑ serum lactate & ammonia	Combined PN & serine resulted in clinical improvement & amelioration of sz frequency.	• Early-onset metabolic epileptic encephalopathy • Severely impaired intellectual development w/absent speech & spastic tetraplegia • Microcephaly, cerebral atrophy, thin corpus callosum, cerebellar hypoplasia, & white matter abnormalities. [9]
KCNQ2	*KCNQ2*-related disorders	AD	No assoc biochemical abnormalities	Some persons w/ neonatal epilepsy are vitamin B_6-responsive. [10]	• May present w/benign familial neonatal epilepsy or severe neonatal epileptic encephalopathy • Szs are tonic & often asymmetric.
MOCS2	*MOSC2*-related molybdenum cofactor deficiency	AR	When present, ↑ α-AASA is secondary to ALDH7A1 inhibition by accumulated sulfocysteine.	A clear but transient response of szs to PN has been observed in 2 affected sibs. [11]	
PGAP3	Hyperphosphatasia w/ID syndrome 4 (OMIM 615716)	AR	↑ serum ALP	Szs may respond to PN.	DD, ID, structural brain anomalies, dysmorphic facies, & szs
PIGA	Multiple congenital anomalies-hypotonia-seizures syndrome 2 [4] (OMIM 300868)	XL	↑ serum ALP in some persons	Heterogeneous effect of PN on szs	Dysmorphic features, hypotonia, early-onset myoclonic seizures, & variable congenital anomalies
PIGL	CHIME syndrome (OMIM 280000)	AR	↑ serum ALP	Szs may respond to PN (but much more slowly than in PDE-*ALDH7A1*).	Coloboma, congenital heart disease, ichthyosiform dermatosis, ID, & ear anomalies
PIGO	Hyperphosphatasia w/ID syndrome 2 (OMIM 614749)	AR	↑ serum ALP	Szs w/variable response to PN	Moderate-to-severe DD, facial dysmorphism, & brachytelephalangy ± szs
PIGS	Developmental & epileptic encephalopathy 95 (OMIM 618143)	AR	Normal serum ALP (except mildly ↑ in 1 person)	Szs may be PN responsive.	Severe DD, ataxia, hypotonia, coarse facies, & intractable szs

Table 3. continued from previous page.

Gene	Disorder	MOI	Laboratory Features	Response to PN/PLP	Clinical Features
PIGV	Hyperphosphatasia w/ID syndrome 1 (OMIM 239300)	AR	↑ serum ALP	Variable neurologic features incl szs that are ± PN responsive.	Distinct facial phenotype, DD, & brachytelephalangy ± anorectal malformations

α-AASA = alpha-aminoadipic semialdehyde; AD = autosomal dominant; ALP = alkaline phosphatase; AR = autosomal recessive; ASM = anti-seizure medication; CSF = cerebrospinal fluid; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; P5C = pyrroline-5-carboxylate; PA = pyridoxic acid; PLP = pyridoxal 5'-phosphate; PM = pyridoxamine; PN = pyridoxine; sz = seizure; XL = X-linked

1. Epilepsies that respond to treatment with vitamin B_6 long term. In this context vitamin dependency indicates a need for lifelong supplementation of supraphysiologic doses of a respective vitamin.

2. See Mills et al, "Vitamin B6 Metabolism and Inborn Errors," in *The Online Metabolic and Molecular Bases of Inherited Disease*. Accessed 6-19-22 (registration required).

3. Alghamdi et al [2021]

4. Mathis et al [2016]

5. Mills et al [2014]

6. Epilepsies that may respond to treatment with vitamin B_6 transiently. In this context vitamin responsiveness may be a transient effect and may not be directly linked to vitamin B_6 metabolism.

7. Perinatal and infantile hypophosphatasia are typically inherited in an autosomal recessive manner.

8. Du et al [2017]

9. van Karnebeek et al [2019]

10. Mefford et al [2012], Reid et al [2016], Klotz et al [2017]

11. Struys et al [2012]

Management

No clinical practice guidelines for PLPBP deficiency have been published.

Evaluations Following Initial Diagnosis

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

- Full neurologic examination, including evaluation of eye movements and muscle tone (for hypotonia or rigidity) and description of seizure semiology
- EEG, including sleep and wake cycles (preferably with a recording time of two hours)
- Physical examination, including measurement of weight, length, and head circumference
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of PLPBP deficiency in order to facilitate medical and personal decision making

To support the family of an individual diagnosed with PLPBP deficiency, review of the following options is recommended:

- Use of community or online resources (e.g., Parent to Parent)
- Social work involvement for parental support
- Home nursing referral (if needed)
- Ethics consultation (clinical ethics services) to assess health care decisions in the context of the best interest of the child and the values and preferences of the family

Treatment of Manifestations

There is no cure for PLPBP deficiency.

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Individuals with PLPBP deficiency require pharmacologic treatment with vitamin B_6 for life [Hoytema van Konijnenburg et al 2021]. The two forms of vitamin B_6 used in treating PLPBP deficiency are pyridoxine (PN) and pyridoxal 5'-phosphate (PLP).

PN is the first-line therapy. The majority of individuals have a favorable response to PN: 79% were seizure free and 10% had good seizure control [Heath et al 2020]. Of the remainder, 3% had only partial control and 8% had no improvement.

When the therapy in about 25% of these previously reported individuals was changed from PN to PLP due either to suspected PNPO deficiency or seizure recurrence during the first 2.5 years of life, the majority showed seizure control that was complete or good [Heath et al 2020].

Pyridoxine (PN)

Dosage. The rarity of PLPBP deficiency has precluded controlled studies to evaluate the optimal dose of pyridoxine. The guidelines for pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) recommend the age-related doses in Table 4.

Table 4. Recommended Daily Oral Dose of Pyridoxine

Age	Dose	Maximum Dose	Comment
Newborn	100 mg/day		See footnotes 1 & 2.
Infant	30 mg/kg/day	300 mg/day	
Children & adolescents	20 mg/kg/day (range: 5-30 mg/kg/day)	500 mg/day	See footnote 2.
Adults	200-500 mg/day	500 mg/day	See footnote 2.

Data from Coughlin et al [2021]; see Pyridoxine-Dependent Epilepsy – *ALDH7A1*

1. Because severe apnea and respiratory insufficiency as well as prolonged somnolence can occur with the first administration of either form of vitamin B_6, affected infants should be treated initially and monitored in a neonatal intensive care unit over the first three days of high-dose supplementation of either form of vitamin B_6.

2. To prevent exacerbation of clinical seizures and/or encephalopathy during an acute illness, the daily dose of pyridoxine may be doubled to a maximum dose of 60 mg/kg/day (in children) or 500 mg/day (in adolescents and adults) for up to three days [Coughlin et al 2021].

Individuals clinically responsive to PN should receive 30 mg/kg/day of PN intravenously or orally in three to four single doses (up to a total dose of 300 mg/day or, if needed, 500 mg/day) [Mills et al 2014, Plecko et al 2014, Ware et al 2014]. Once the diagnosis of PLPBP deficiency is confirmed, consider lowering the dosage of PN to 15-20 mg/kg/day in two to three doses [Coughlin et al 2021]. Doses rarely exceed 500 mg/day, and modification over time is rarely warranted [Authors, personal experience]. In individuals with PN-dependent epilepsy, clinical seizures generally cease over a period of several minutes.

Nearly 57% of reported individuals required additional anti-seizure medications (ASMs) during breakthrough seizures (often described with fever) [Johnstone et al 2019, Ahmed et al 2020].

Side effects. PN side effects can include sensory (or motor) neuropathy, which is usually reversible with dose reduction.

Pyridoxal 5'-Phosphate (PLP)

Dosage. PLP is the active form of vitamin B_6. Individuals with PLPBP deficiency receive 30-60 mg/kg/day PLP orally, divided into four to six single doses following guidelines proposed by Mills et al [2014]. The lowest effective PLP dose should be used.

PLP is only available as a nonlicensed compound outside of Asia. Recent studies have raised major concerns about the dose accuracy, stability, and safety of food-grade PLP supplements [Mohamed-Ahmed et al 2017, Stolwijk et al 2022].

Because PLP is a photosensitive compound that can rapidly degrade when in solution (which could reduce its effectiveness and produce unwanted byproducts), it should be dissolved immediately prior to administration to avoid buildup of photochemical degradation products.

Another concern is that PLP content in a number of dietary supplements differed from the expected amount, reflecting inconsistencies in PLP dose accuracy. In a recent report, three individuals with PLP-dependent seizures experienced clinical complications (the most serious of which was status epilepticus) due to food supplement quality issues and possible PLP intoxication [Stolwijk et al 2022].

Side effects. In contrast to PN, there is no FDA statement on a safety limit for PLP.

PLP side effects include possible liver toxicity, which has been observed in a few individuals with PNPO deficiency.

- Porri et al [2014] reported mild elevation of transaminases in an individual treated with 50 mg/kg/day of PLP.
- Two individuals with unstable epilepsy had liver cirrhosis at ages four years and eight years, respectively, following long-term use of PLP in doses ranging from 50-100 mg/kg/day [Sudarsanam et al 2014, Coman et al 2016].
- Stolwijk et al [2022] reported three individuals with PLP-dependent seizures with elevated transaminases that normalized or improved upon PLP dosage reduction.
- One individual age 15 years underwent liver transplantation because of hepatocellular carcinoma [Webster et al 2021].

Because of this reported toxicity, it might be reasonable to avoid high doses of PLP by adding ASMs in those individuals who do not become seizure free or who do not stay seizure free on PLP monotherapy, especially in the presence of elevated transaminases. Likewise, in persons who are PLP dependent who have recurrent seizures, it may be necessary to modify/adjust the dose to weight [Authors, personal experience].

Although PLP inhibits platelet function, no bleeding diathesis has been reported with its use in PLPBP deficiency. Bleeding was reported in one boy with PNPO deficiency who also had mild hemophilia A (factor VIII activity of 14%) [Borst & Tchapyjnikov 2018].

Possible Drug Interactions

Several ASMs (such as carbamazepine, valproate, phenytoin, and phenobarbital) can cause a low plasma concentration of PLP [Footitt et al 2011].

D-cycloserine can act as a PN antagonist and increases renal excretion of PN [Donald 2010, Kuhrau et al 2023].

PLP interacts with various small molecules:

- PLP undergoes a condensation reaction with hydrazines, leading to an increased requirement for vitamin B_6 in individuals taking drugs such as hydralazine and isoniazid [Biehl & Vilter 1954, Standal et al 1974, Snider 1980, Wason et al 1981, Shigetomi & Kuchel 1993, Alvarez & Guntupalli 1995, Donald & McIlleron 2009].

  When an individual with PLPBP deficiency needs treatment with either hydralazine (an antihypertensive medication) or isoniazid (a tuberculostatic drug), the respective dose of PLP or PN may need to be increased. When the actual dose of vitamin B_6 supplementation is low, the dose could be increased as a precaution; however, when the actual dose of vitamin B_6 supplementation is high, increasing the dose should only be considered if seizure frequency increases.

- PLP can also react with -SH groups such as that in penicillamine [Tu et al 1964, Rumsby & Shepherd 1979, Matsui & Rozovski 1982].

PN and presumably also PLP supplementation antagonizes the therapeutic effect of L-dopa.

Other

Absence of seizures in an individual treated with PN precludes a change to PLP.

Seizures can recur during febrile episodes and/or with delayed or missed doses.

To cover their overnight sleep, some individuals need higher doses in the evening (e.g., 30%-35% of the total daily dose).

Supportive Care

Supportive care often includes specialists in multiple disciplines, including neurology, developmental pediatrics, speech-language therapy, physical therapy, and occupational therapy.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. For individuals with delays in gross motor function, physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation). Individuals with dystonia may need additional medication per their treating neurologist.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained.

Communication issues. As expressive language difficulties have been reported in PLPBP deficiency, consider evaluation by a speech-language pathologist. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of speech therapy. This may include alternative means of communication (e.g., augmentative and alternative communication [AAC]) AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to pharmacologic treatment and supportive care, and the emergence of new manifestations, see Table 5.

Table 5. Recommended Surveillance for Individuals with PLPBP Deficiency

System/Concern	Evaluation		Frequency
Seizure control	In outpatient epilepsy clinic		• 1st yr of life: every 3-6 mos • Children & adults: every 3-12 mos
	EEG follow up in case of poor seizure control or periods of encephalopathy		• 1st yr of life: every 3-6 mos • Thereafter: every 6 mos OR not required in those who are seizure free
Growth	Assess body weight, height, & head circumference.		Children: at each visit
Neurologic findings	Neurologic exam (incl assessment of deep tendon reflexes) for emergence of new findings &/or response to medications used in symptomatic treatment		At each visit
Adverse effects of PN therapy	Sensory (or motor) neuropathy eval (deep tendon reflexes, & if indicated nerve conduction studies)		
Adverse effects of PLP therapy	Complete blood count		1st yr of life: every 3-6 mos
	Liver assessment	Transaminases & clotting factors	• Age <10 yrs: transaminases every 3-6 mos • If transaminases are >3x normal, also assess clotting factors
		Ultrasound	• Annually (or more frequently as needed) • Age >4 yrs: incl elastography
Development / Educational needs	Assessment		• Children age <6 yrs: every 4-6 mos • Children age >6 yrs: annually
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).		At each visit

PLP = pyridoxal 5'-phosphate; PN = pyridoxine

Agents/Circumstances to Avoid

Several ASMs (such as carbamazepine, valproate, phenytoin, and phenobarbitone) can cause a low plasma concentration of PLP [Footitt et al 2011].

PLP interacts with various small molecules. See Targeted Therapies, Pyridoxal 5'-Phosphate (PLP).

Evaluation of Relatives at Risk

Prenatal testing of a fetus at risk. If the *PLPBP* pathogenic variants have been identified in an affected family member, prenatal molecular genetic testing may be performed via amniocentesis or chorionic villus sampling on future pregnancies at risk in order to facilitate postnatal treatment of the newborn.

When prenatal testing has not been performed on a pregnancy at risk, prompt evaluation of the newborn is essential to determine if treatment with PN or PLP is necessary. While pending results of molecular genetic testing, two options for management of an at-risk newborn are:

- Prophylactic treatment with either PN or PLP (whichever was effective in the affected sib) until molecular genetic testing clarifies whether or not the newborn is affected

  Note: At least one newborn at risk for PDE-*ALDH7A1* developed status epilepticus after being given high-dose PN treatment before molecular genetic testing determined that the child was not affected [Hartmann et al 2011].

- Clinical and EEG monitoring with initiation of treatment with PN or PLP (whichever was effective in the affected sib) at the first sign of seizures or encephalopathy

Symptomatic younger sib. If a younger sib (without prior molecular genetic testing) of a proband presents with encephalopathy or a nonfebrile seizure, PN or PLP – depending on the drug to which the proband responded – should be administered acutely (ideally under EEG monitoring if the child is in status epilepticus or is experiencing serial seizures) for both diagnostic and therapeutic purposes. Note: It would be unlikely for the proband's older sibs who have not experienced seizures to have PLPBP deficiency.

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

Pregnancy Management

As recurrence risk for couples who have had a child with PLPBP deficiency is 25%, there has been discussion about the utility of empiric supplementation of PN during pregnancies in women carrying an at-risk fetus. In contrast to reports on PN supplementation in pregnancies at risk for PDE-*ALDH7A1*, to date there are no reports on vitamin B_6 supplementation in pregnancies at risk for PLPBP deficiency.

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

PLPBP deficiency is inherited in an autosomal recessive manner. The families of probands with PLPBP deficiency are often consanguineous.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *PLPBP* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PLPBP* 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 *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. 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 *PLPBP* pathogenic variant, each sib of an affected individual, irrespective of sex, 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.
- 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 PLPBP deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *PLPBP.*
- If an individual with PLPBP deficiency has children with an individual who is heterozygous for a *PLPBP* pathogenic variant, offspring have a 50% risk of being affected by PLPBP deficiency. The carrier frequency of PLPBP deficiency in the general population is unknown. Genetic counseling and *PLPBP* molecular genetic testing of the unaffected reproductive partner may be warranted.

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

Carrier Detection

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk 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.
- *PLPBP* molecular genetic testing for reproductive partners of known carriers is appropriate, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PLPBP* 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Epilepsy Society**
  aesnet.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **International Pyridoxine-Dependent Epilepsy Registry**
  PDE Consortium
  www.pdeonline.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. PLPBP Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PLPBP	8p11.23	Pyridoxal phosphate homeostasis protein	PLPBP	PLPBP

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 PLPBP Deficiency (View All in OMIM)

604436	PYRIDOXAL PHOSPHATE-BINDING PROTEIN; PLPBP
617290	EPILEPSY, EARLY-ONSET, 1, VITAMIN B6-DEPENDENT; EPEO1

Molecular Pathogenesis

PLPBP, previosly known as proline synthetase co-transcribed homologue (*PROSC*), codes for pyridoxal phosphate-binding protein (PLPBP) (also referred to as pyridoxal phosphate homeostasis protein, or PLPHP). Pyridoxal 5'-phosphate (PLP), the biologically active form of vitamin B_6, has an important role in maintaining the biochemical homeostasis of the body [Lee et al 2008]. PLP is required as a cofactor for more than 140 enzymatic activities in humans, mainly those associated with synthesis, degradation, and interconversion of

amino acids as well as neurotransmitter metabolism [Dakshinamurti & Dakshinamurti 2007, Sorolla et al 2010, Nichols & Gaiteri 2014, Plecko et al 2014].

PLPBP belongs to a highly conserved family of proteins known to bind PLP, but their function in humans as well as other species is not understood. Because biochemical analysis of samples from individuals with PLPBP deficiency showed a widely deranged vitamin B_6 vitamer profile, it has been suggested that this protein plays an important role in vitamin B_6 homeostasis [Darin et al 2016, Johnstone et al 2019]. However, the specific mechanism of how PLPBP dysfunction disrupts PLP homeostasis and causes the observed epileptic encephalopathy is still not well recognized. PLP is a very reactive compound that can undergo spontaneous complexation and form adducts with other molecules within the cell [Al-Shekaili et al 2021]. It has been hypothesized that PLPBP acts as a PLP carrier that prevents the highly reactive cofactor from forming chemical complexes with other cellular molecules, protects it from degradative enzymes like phosphatases, and/or safely delivers it to PLP-dependent enzymes [Darin et al 2016].

Mechanism of disease causation. Loss of function

Table 6. Notable *PLPBP* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_007198.4	c.207+1G>A	--	Predicted loss of function; severe disease [1]
	c.320-2A>G	--	
NM_007198.4 NP_009129.1	c.211C>T	p.Gln71Ter	
	c.233C>G	p.Ser78Ter	
	c.370_373delGACA	p.Asp124LysfsTer2	
	c.199G>A	p.Glu67Lys	Missense variants predicted to abolish/affect PLP binding sites; severe disease
	c.260C>T	p.Pro87Leu	
	c.524T>C	p.Leu175Pro	
	c.722G>A	p.Arg241Gln	
	c.119C>T	p.Pro40Leu	Missense variants predicted to decrease but not abolish PLP binding or protein stability; mild-to-moderate disease [2]
	c.206A>G	p.Tyr69Cys	
	c.260C>T	p.Pro87Leu	
	c.614G>A	p.Arg205Gln	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Other proven or predicted loss-of-function variants including splicing and truncating variants can be associated with severe phenotypes and/or early mortality [Tremiño et al 2018, Johnstone et al 2019].
2. Other missense variants that decrease but do not abolish PLP binding or protein stability are expected to cause mild-to-moderate phenotypes.

Chapter Notes

Author Notes

Prof Clara van Karnebeek is actively involved in clinical research regarding individuals with PLPBP deficiency. She would be happy to communicate with persons who have any questions regarding diagnosis of PLPBP deficiency or other considerations.

Contact Drs Izabella Pena and/or Jolita Ciapaite to inquire about review of *PLPBP* variants of uncertain significance.

Prof van Karnebeek is also interested in hearing from clinicians treating families affected by a pyridoxine-dependent epilepsy in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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