GeneReviews

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Pyridoxine-Dependent Epilepsy – *ALDH7A1*

Synonyms: AASADH Deficiency, ALDH7A1 Deficiency, Alpha Aminoadipic Semialdehyde (α-AASA) Dehydrogenase Deficiency, Antiquitin (ATQ) Deficiency, PDE-*ALDH7A1*

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Summary

Clinical characteristics

Pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) is characterized by seizures not well controlled with anti-seizure medication that are responsive clinically and electrographically to large daily supplements of pyridoxine (vitamin B_6). This is true across a phenotypic spectrum that ranges from classic to atypical PDE-*ALDH7A1*. Intellectual disability is common, particularly in classic PDE-*ALDH7A1*.

In classic PDE-*ALDH7A1*, untreated seizures begin within the first weeks to months of life. Dramatic presentations of prolonged seizures and recurrent episodes of status epilepticus are typical; recurrent self-limited events including partial seizures, generalized seizures, atonic seizures, myoclonic events, and infantile spasms also occur. Electrographic seizures can occur without clinical correlates.

In atypical PDE-*ALDH7A1*, findings in untreated individuals can include late-onset seizures beginning between late infancy and age three years, seizures that initially respond to anti-seizure medication and then become intractable, seizures during early life that do not respond to pyridoxine but are subsequently controlled with pyridoxine several months later, and prolonged seizure-free intervals (≤5 months) that occur after discontinuation of pyridoxine.

Diagnosis/testing

The diagnosis of PDE-*ALDH7A1* is suspected in a proband with seizures responsive to pyridoxine administration and increased concentration of alpha-aminoadipic semialdehyde (α-AASA) in urine and/or plasma. The diagnosis is established in a proband with suggestive clinical findings and biallelic pathogenic (or likely pathogenic) variants in *ALDH7A1* identified by molecular genetic testing.

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Management

Targeted therapies: Targeted therapy requires lifelong pharmacologic supplements of pyridoxine; the rarity of the disorder has precluded controlled studies to evaluate the optimal dose. The International PDE Consortium published clinical practice guidelines recommending pyridoxine doses by age (newborns: 100 mg/day; infants: 30 mg/kg/day with a maximum of 300 mg/day; children, adolescents, and adults: 30 mg/kg/day with a maximum of 500 mg/day) and dietary modifications targeted at reducing lysine intake. To prevent exacerbation of clinical seizures and/or encephalopathy during an acute illness, the daily dose of pyridoxine may be doubled for several days.

Supportive care: Supportive care for developmental delay and/or intellectual disability follows standard practice.

Prevention of secondary complications: Overuse of pyridoxine can cause a reversible sensory neuropathy.

Surveillance: Recommendations to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations include regular assessments by the treating neurologist for control of epilepsy via targeted therapy with pyridoxine, need for concomitant use of anti-seizure medications, and signs of sensory neuropathy, as well as regular assessments of developmental progress and educational needs.

Evaluation of relatives at risk: Prenatal molecular genetic testing of fetuses at risk may be performed to inform maternal pyridoxine supplementation during pregnancy and facilitate initiation of treatment at birth. If prenatal testing has not been performed on a pregnancy at risk, the neonate should receive therapeutic doses of pyridoxine until molecular genetic testing for the family-specific *ALDH7A1* variants has been completed.

Pregnancy management: Maternal supplemental pyridoxine at a dose of 50-100 mg/day throughout the last half of pregnancy and after birth may be considered if the fetus is known to be affected or, if diagnostic prenatal testing is not pursued, in an at-risk fetus and neonate until the diagnosis has been ruled out.

Genetic counseling

PDE-*ALDH7A1* is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ALDH7A1* 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. Once the *ALDH7A1* pathogenic variants have been identified in an affected family member, carrier testing for relatives at risk, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for PDE-*ALDH7A1* are possible.

Diagnosis

Suggestive Findings

Pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) **should be suspected** in individuals with the following clinical findings, response to intravenous (IV) or oral (PO) administration of pyridoxine, laboratory findings, and family history.

Suggestive clinical features

- Seizures in any child younger than age one year without an apparent brain malformation or acquired brain injury as the cause of the epilepsy
- Cryptogenic seizures in a previously normal infant without an abnormal gestational or perinatal history
- In neonates, a phenotype suggestive of hypoxic ischemic encephalopathy and with difficult-to-control seizures

- The occurrence of long-lasting focal or unilateral seizures, resistant to anti-seizure medications, often with partial preservation of consciousness
- In infants and children, seizures that are partially responsive to anti-seizure medications, in particular if associated with developmental delay and intellectual disability
- Signs of encephalopathy including irritability, restlessness, abnormal crying, and vomiting preceding and/or following the actual seizures
- A history of transient or unclear response of seizures to pyridoxine
- In infants and children, a history of seizures responsive to folinic acid

Positive response to IV or PO administration of pyridoxine

- **IV.** In an acute setting, for individuals experiencing prolonged clinical seizures (i.e., status epilepticus), administer 100 mg of pyridoxine intravenously while monitoring the EEG, oxygen saturation, and vital signs [Stockler et al 2011]:
  - In individuals with pyridoxine-dependent epilepsy, clinical seizures generally cease over a period of several minutes.
  - If a clinical response is not demonstrated, the dose should be repeated up to a maximum of 500 mg.
  - A corresponding change should be observed in the EEG; in some circumstances, the change may be delayed by several hours.
  - Note: In some individuals with pyridoxine-dependent epilepsy, significant neurologic and cardiorespiratory depression follows the administration of 100 mg of pyridoxine, making close systemic monitoring essential.
- **PO.** For individuals experiencing frequent medication-resistant seizures but not status epilepticus, administer 30 mg/kg/day of pyridoxine orally. Clinical seizures should cease within three to five days [Baxter 2001, Stockler et al 2011].

Note: Treatment with pharmacologic doses of pyridoxine **should begin immediately** or be continued when concern for PDE-*ALDH7A1* has been raised while additional testing is performed to establish the diagnosis.

Supportive laboratory findings

- Elevated plasma and urinary levels of **alpha-aminoadipic semialdehyde (α-AASA)**

  Note that α-AASA is a nonspecific biomarker, as it can also be elevated in individuals with **molybdenum cofactor deficiency** and **isolated sulfate oxidase deficiency** (see Differential Diagnosis).

- Elevated concentrations of **pipecolic acid** in plasma and cerebral spinal fluid

  Note: Pipecolic acid concentrations may normalize after many years of therapy [Plecko et al 2005].

- Analysis of cerebrospinal fluid **monoamine metabolites** via high-performance liquid chromatography, with electrochemical detection demonstrating a pattern characteristic of pyridoxine-dependent epilepsy and folinic acid-responsive seizures containing two peaks of unknown identity [Gallagher et al 2009]

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: Sibs with seizures, epileptic encephalopathy, and/or epilepsy attributed to birth trauma or prematurity should be reevaluated when subsequent sibs have a similar presentation.

Establishing the Diagnosis

The diagnosis of PDE-*ALDH7A1* **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ALDH7A1* 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 any likely pathogenic variants. (2) Identification of biallelic *ALDH7A1* variants of uncertain significance (or of one known *ALDH7A1* pathogenic variant and one *ALDH7A1* variant of uncertain significance) does not itself establish or rule out the diagnosis.

Note: Previously when deletion/duplication analysis was not widely available, a diagnosis of PDE-*ALDH7A1* could be made in an individual with one *ALDH7A1* pathogenic variant detected by sequence analysis, clinical features consistent with PDE, and unequivocal elevation of the biomarker α-AASA in urine and/or plasma (i.e., the requirements for registration in the International PDE Registry).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

- **A multigene panel** (e.g., comprehensive epilepsy panel, infantile epilepsy panel, epilepsy advanced sequencing evaluation, or epileptic encephalopathy panel) that includes *ALDH7A1* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used [Costain et al 2019]; 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 Pyridoxine-Dependent Epilepsy – *ALDH7A1*

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ALDH7A1	Sequence analysis [3]	>95% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	<5% [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. Data derived from Coughlin et al [2019] and the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Deep intronic variants may be missed by sequence analysis that includes exons and flanking regions only. *ALDH7A1* variant c.696-502G>C results in introduction of a cryptic acceptor splice site, activation of a cryptic donor splice site, and introduction of a pseudoexon between exons 7 and 8 [Milh et al 2012].

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The one clinical feature characteristic of all individuals with pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) is seizures that are not well controlled with anti-seizure medication (ASM) but respond to large daily supplements of pyridoxine (vitamin B_6). This is true across the phenotypic spectrum that ranges from classic to atypical PDE-*ALDH7A1*. Intellectual disability is common.

Classic PDE-*ALDH7A1*

Seizures. Newborns with the classic neonatal presentation begin to experience seizures soon after birth. In retrospect, many mothers recount unusual intrauterine movements that may have started in the late second trimester and that likely represent fetal seizures [Baxter 2001].

Multiple types of clinical seizures have been reported in untreated infants and children. While dramatic presentations consisting of prolonged seizures and recurrent episodes of status epilepticus are typical, recurrent self-limited events including partial, generalized, and atonic seizures, myoclonic events, and infantile spasms also occur. Affected individuals may have electrographic seizures without clinical correlates. Clinical seizures may be associated with facial grimacing and abnormal eye movements [van Karnebeek et al 2016].

Untreated affected neonates frequently have periods of encephalopathy (irritability, crying, fluctuating tone, poor feeding) that precede the onset of clinical seizures. Low Apgar scores, abnormal umbilical cord blood gases, and other abnormalities of blood chemistries may also be observed. For this reason, it is not uncommon for these newborns to be initially diagnosed with hypoxic-ischemic encephalopathy [Mills et al 2010, van Karnebeek et al 2016].

Similar periods of encephalopathy may be seen in older infants, particularly prior to recurrence of clinical seizures that occur in children treated with pyridoxine whose vitamin B_6 requirement may have increased because of growth and/or intercurrent infection, particularly gastroenteritis.

Intellectual function. Intellectual disability, particularly with expressive language, is common. It has been suggested that an earlier onset of clinical seizures corresponds to a worse prognosis for cognitive function, and

that the length of the delay in diagnosis and initiation of effective pyridoxine treatment correlates with increased risk for intellectual disability [Baxter 2001, Basura et al 2009, de Rooy et al 2018].

Individuals in whom seizures are incompletely controlled with pyridoxine require concurrent treatment with one or more ASMs and have significant intellectual disability [Basura et al 2009, van Karnebeek et al 2016].

Some affected individuals with normal intellectual function have been reported [Basura et al 2009, Bok et al 2012, van Karnebeek et al 2016, de Rooy et al 2018].

The few formal psychometric assessments that have been performed have had inconsistent findings. Two early studies indicated that verbal skills were more impaired than nonverbal skills [Baxter et al 1996, Baynes et al 2003], whereas a more recent report suggests that verbal IQ is slightly (but not significantly) higher than performance IQ [Bok et al 2012].

Atypical PDE-*ALDH7A1*

Late-onset seizures and other atypical features of PDE-*ALDH7A1* can include the following [Basura et al 2009, van Karnebeek et al 2016].

Seizures

- Late-onset seizures (i.e., beginning after age 2 months), sometimes presenting after age one year and as late as adolescence
- Seizures that initially respond to ASM but then become intractable
- Seizures during early life that do not respond to pyridoxine but are controlled with pyridoxine several months later
- Prolonged seizure-free intervals (age ≤5 months) that occur after pyridoxine discontinuation
- In a small number of infants, intractable seizures that are either unresponsive or only partially responsive to pyridoxine but responsive to folinic acid [Gallagher et al 2009]

Intellectual function. Variable degrees of intellectual disability have been described in individuals with atypical PDE-*ALDH7A1*. The more favorable cognitive outcome that is more commonly observed in persons with the late-onset phenotype may be due to a combination of factors, most notably the lack of neonatal seizure-induced brain injury [de Rooy et al 2018].

Classic PDE-*ALDH7A1* and Atypical PDE-*ALDH7A1*

EEG. While a variety of EEG abnormalities have been described, none is pathognomonic for PDE-*ALDH7A1* [Mills et al 2010, Schmitt et al 2010].

Neuroimaging. MRI abnormalities (Figure 1) reported include the following:

- Universal thinning of the corpus callosum (greatest in the isthmus) [Friedman et al 2014, Oesch et al 2018]
- Mega cisterna magna, hydrocephalus, ventriculomegaly, and cortical dysplasia, reported in several individuals [Mills et al 2010, Friedman et al 2014, Oesch et al 2018]

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

The common c.1279G>C; p.(Glu427Gln) pathogenic variant in exon 14 accounts for approximately 33% of pathogenic variants [Coughlin et al 2019]. Homozygous p.(Glu427Gln) variants have been observed in both neonatal- and late-onset PDE-*ALDH7A1* [Bennett et al 2009].

Figure 1. Midsagittal magnetic resonance image of the brain of an adult male with PDE-*ALDH7A1* demonstrating thinning of the isthmus of the corpus callosum (red arrow) and mega cisterna magna (blue arrow)

Pathogenic missense variants that result in residual enzyme activity may be associated with a more favorable developmental phenotype [Scharer et al 2010].

Nomenclature

Pyridoxine-responsive seizures. Children with findings suggestive of pyridoxine-dependent epilepsy (i.e., children with intractable seizures who have only partially improved seizure control with the addition of pyridoxine and those in whom seizures recur after ASMs are withdrawn and pyridoxine is continued) who have not had molecular confirmation of one of the three pyridoxine-dependent epilepsies should be diagnosed with "pyridoxine-responsive seizures" rather than pyridoxine-dependent epilepsy [Baxter 1999, Basura et al 2009].

Prevalence

First described by Hunt et al [1954], pyridoxine-dependent epilepsy is generally considered to be a rare cause of intractable neonatal seizures. In addition to PDE-*ALDH7A1*, two other genetic causes of pyridoxine-dependent epilepsy (i.e., mutation of *PLPBP* and of *PNPO*) have been characterized (see Differential Diagnosis).

As of 2019, 185 individuals with PDE-*ALDH7A1* have been reported, with an estimated incidence of 1:64,352 live births [Coughlin et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ALDH7A1*.

Differential Diagnosis

Pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) must be distinguished from PNPO deficiency and PLPBP deficiency (also referred to as PLPHP deficiency), as well as other disorders associated with pyridoxine (PN)- and pyridoxal 5'-phosphate (PLP)-responsive seizures (see Table 2).

Table 2. Selected Disorders of Interest in the Differential Diagnosis of Pyridoxine-Dependent Epilepsy – *ALDH7A1*

Gene	Disorder	Laboratory Features	Response to PN/PLP	Clinical Features
Pyridoxine (vitamin B$_6$)-dependent epilepsy [1]				
PLPBP	PLPBP (PLPHP) deficiency [2]	Secondary biochemical abnormalities suggesting abnormal vitamin B$_6$ metabolism may be present, as may lactic acidosis.	Szs in affected children respond to supraphysiologic doses of PN (or PLP).	Majority have sz onset w/in 1st wk of life; some children present as late as 6 mos. [3] Acquired microcephaly, structural brain abnormalities, & DD/ID are variable.
PNPO	PNPO deficiency [2]	Low CSF & plasma levels of PLP when measured prior to administration of PN or PLP. Biochemical changes in CSF, plasma, & urine prior to treatment w/PN or PLP indicative of ↓ activity of PLP-dependent enzymes (e.g., aromatic acid decarboxylase or glycine cleavage enzyme).	Szs in affected children respond to supraphysiologic doses of PLP (60% of affected persons) or PN (40% of affected persons).	~90% have sz onset in neonatal period (often age <2 wks); some children present as late as age 3 yrs. ≥60% have DD/ID.
Pyridoxine (vitamin B$_6$)-responsive seizures [4]				
ALDH4A1	Hyperprolinemia type II [2] (OMIM 239510)	Markedly ↑ plasma proline levels as well as ↑ P5C in urine	Szs may respond to ASM & PN.	Szs usually manifest beyond neonatal period, may occur w/ febrile infections, & may respond to common ASM. Persons may have ID or normal intelligence.

Table 2. continued from previous page.

Gene	Disorder	Laboratory Features	Response to PN/PLP	Clinical Features
ALPL	Infantile hypophosphatasia [5]	Suspected in presence of ↓ serum ALP enzyme activity (based on appropriate pediatric normative reference values)	Vitamin B_6-responsive seizures may occur.	Clinical signs resembling rickets may be recognized between birth & age 6 mos. Prior to availability of ERT, ~50% died of respiratory failure caused by undermineralization of ribs. Intractable szs may precede biochemical or radiographic manifestations of rickets.
CACNA1A	Developmental & epileptic encephalopathy 42 [6] (OMIM 617106)	No assoc biochemical abnormalities	A female w/*CACNA1A*-related absence epilepsy & ataxia responded dramatically to PN. [7]	
KCNQ2	KCNQ2-related disorders [6]	No assoc biochemical abnormalities	Some w/neonatal epilepsy are vitamin B_6 responsive. [8]	May present w/benign familial neonatal epilepsy or severe neonatal epileptic encephalopathy. Szs are tonic & often asymmetric.
MOCS2	*MOSC2*-related molybdenum cofactor deficiency [2]	When present, ↑ α-AASA is secondary to ALDH7A1 inhibition by accumulated S-sulfocysteine.	A clear but transient response of szs to PN observed in 2 affected sibs [9]	
PGAP3	Hyperphosphatasia w/ID syndrome 4 [2] (OMIM 615716)	↑ serum ALP	Szs may respond to PN.	DD/ID, structural brain anomalies, dysmorphic facies, & szs
PIGA	Multiple congenital anomalies-hypotonia-seizures syndrome 2 [10] (OMIM 300868)	↑ serum ALP in some persons	Heterogeneous effect of PN on szs	Dysmorphic features, hypotonia, early-onset myoclonic seizures, & variable congenital anomalies
PIGL	CHIME syndrome [2] (OMIM 280000)	↑ 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 [2] (OMIM 614749)	↑ serum ALP	Szs w/variable response to PN	Moderate-to-severe DD/ID; facial dysmorphism & brachytelephalangy ± szs
PIGS	Developmental & epileptic encephalopathy 95 [2] (OMIM 618143)	Normal serum ALP (except mildly ↑ in 1 person)	Szs may be PN responsive.	Severe DD/ID, ataxia, hypotonia, coarse facies, & intractable szs

Table 2. continued from previous page.

Gene	Disorder	Laboratory Features	Response to PN/PLP	Clinical Features
PIGV	Hyperphosphatasia w/ID syndrome 1 [2] (OMIM 239300)	↑ serum ALP	Variable neurologic features incl szs that may respond to PN	Distinct facial phenotype, DD, & brachytelephalangy ± anorectal malformations

α-AASA = alpha-aminoadipic semialdehyde; ALP = alkaline phosphatase; ASM = anti-seizure medication; CSF = cerebrospinal fluid; DD = developmental delay; ERT = enzyme replacement therapy; ID = intellectual disability; P5C = pyrroline-5-carboxylate; PLP = pyridoxal 5'-phosphate; PN = pyridoxine; sz = seizure

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. Autosomal recessive mode of inheritance

3. Jiao et al [2022]

4. 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.

5. Perinatal and most infantile cases of hypophosphatasia are inherited in an autosomal recessive manner.

6. Autosomal dominant mode of inheritance

7. Du et al [2017]

8. Reid et al [2016]

9. Struys et al [2012]

10. X-linked mode of inheritance

Note: In the Far East, PLP has been used as an anticonvulsant when anti-seizure medications have failed, and to control seizures in children with infantile spasms and generalized and focal epilepsy in cohorts that had not undergone molecular genetic testing [Ohtahara et al 1993, Nakagawa et al 1997, Ito et al 2000, Wang et al 2005, Ohtahara et al 2011]. Specifically, PLP responsiveness was reported in 20.2% of 119 individuals with West syndrome of unknown etiology and 10.7% of individuals with West syndrome of known etiology, such as birth asphyxia or brain malformation [Ohtahara et al 2011], and PLP or PN responsiveness was reported in 11.7% of 94 children with idiopathic intractable epilepsy, including West syndrome [Wang et al 2005]. (International guidelines do not generally recommend a standardized trial of PN or PLP in infants with infantile spasms; recently, however, consideration of a therapeutic trial with PN or PLP has been proposed in children with West syndrome when infantile spasms are associated with other seizure types or have started before age two months [Gibaud et al 2021].)

Other Considerations in the Differential Diagnosis of PDE-*ALDH7A1*

Inborn pyridoxine dependency states. While other inborn pyridoxine dependency states have been described – for example, pyridoxine-dependent anemia and pyridoxine-dependent forms of homocystinuria (see Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency), xanthurenic aciduria (OMIM 236800), and cystathioninuria (OMIM 219500) – these conditions are not genetically related to pyridoxine-dependent epilepsy and are phenotypically distinct disorders.

Mitochondrial disorders. PDE-*ALDH7A1* may present with lactic acidosis. Lactate acid elevation can be an important (albeit nonspecific) marker of mitochondrial disease and mislead clinicians toward other less treatable inborn errors of metabolism.

Hypoxic ischemic encephalopathy (HIE). About 15% of individuals with PDE-*ALDH7A1* have fetal distress followed by poor adaptation and low Apgar scores. This presentation can mislead clinicians toward symptomatic seizures as a sign of HIE. Resistance to common anticonvulsants, a history of prematurity, and severely pathologic or persistent EEG changes should lead to reevaluation for genetic causes of neonatal seizures.

Pyridoxine-responsive seizures. Some children with intractable seizures may have only partial improvement in seizure control with the addition of pyridoxine. In this situation, or in instances in which seizures recur after

seizure medications are withdrawn and pyridoxine is continued, individuals who have not had molecular confirmation of one of the three pyridoxine-dependent epilepsies or any of the other disorders listed in Table 2 should be diagnosed with "pyridoxine-responsive seizures" [Baxter 1999, Basura et al 2009].

Other causes of neonatal seizures in which elevated levels of alpha-aminoadipic semialdehyde may be present include the following:

- **Molybdenum cofactor deficiency.** This heterogeneous group of conditions can be distinguished from pyridoxine-responsive epilepsy by the presence of increased urinary xanthine, hypoxanthine, and S-sulfocysteine [Mills et al 2012, Struys et al 2012]. Molybdenum cofactor deficiency is caused by biallelic pathogenic variants in *GPHN*, *MOCS1*, *MOCS2*, or *MOCS3* and inherited in an autosomal recessive manner.
- **Isolated sulfite oxidase deficiency.** This condition can be distinguished from pyridoxine-responsive epilepsy by increased urinary sulfite and decreased urinary sulfate [Mills et al 2012]. Isolated sulfite oxidase deficiency is caused by biallelic pathogenic variants in *SUOX* and inherited in an autosomal recessive manner.

Management

Clinical practice guidelines for pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) have been published [Coughlin et al 2021].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PDE-*ALDH7A1*, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neurologic examination to evaluate cranial nerve function, muscle strength, tone (for hypotonia or rigidity), and symmetry, and to describe seizure semiology
- EEG including sleep and wake cycles
- As congenital brain developmental abnormalities may occur in PDE-*ALDH7A1*, brain MRI when clinically indicated (e.g., macrocephaly, incomplete control of seizures to pyridoxine)
- Developmental assessment including motor, adaptive, cognitive, and speech-language evaluation
- Evaluation for early intervention programs / special education
- 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 PDE-*ALDH7A1* in order to facilitate medical and personal decision making

Treatment of Manifestations

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

Pyridoxine

There is no cure for PDE-*ALDH7A1*. Affected individuals are metabolically dependent on pyridoxine (rather than pyridoxine deficient); therefore, they require lifelong pharmacologic supplements of pyridoxine. Compliance with pyridoxine supplementation is critical, as status epilepticus may develop within days of discontinuation of pyridoxine.

Dosage. The International PDE Consortium [Coughlin et al 2021] presently recommend the following:

- Newborns: 100 mg/day of pyridoxine (vitamin B_6)
- Infants: 30 mg/kg/day of pyridoxine (maximum dose 300 mg/day)
- Children, adolescents, and adults: 30 mg/kg/day of pyridoxine (maximum dose 500 mg/day)

Because affected individuals may have exacerbations of clinical seizures and/or encephalopathy during an acute illness (such as gastroenteritis or a febrile respiratory infection), the daily dose of pyridoxine may be doubled for several days until the acute illness resolves.

Once seizures come under control with the addition of daily pyridoxine monotherapy in pharmacologic doses, all anti-seizure medication (ASM) can be withdrawn in the majority of individuals.

Side effects. The dosage of pyridoxine should not exceed 500 mg/day [Stockler et al 2011], as a reversible sensory neuropathy (ganglionopathy) caused by pyridoxine neurotoxicity can develop. While primarily reported in adults who have received "megavitamin therapy" with pyridoxine, sensory neuropathy has been reported in two persons with pyridoxine-dependent epilepsy [McLachlan & Brown 1995, Rankin et al 2007], one of whom was an adolescent who developed a secondary cause of epilepsy and received a pyridoxine dose of 2 g/day [McLachlan & Brown 1995].

Dietary Modifications

ALDH7A1 encodes the enzyme alpha-aminoadipic semialdehyde dehydrogenase (antiquitin), which is involved in cerebral lysine catabolism. For this reason, dietary modifications targeted at reducing lysine intake have been recommended.

- **Lysine-restricted medical diet.** It has been proposed that persons with pyridoxine-dependent epilepsy may benefit from a lysine-restricted diet. Improvements in development and behavior along with decreased biomarker levels have been described in affected individuals on such diets [Stockler et al 2011, van Karnebeek et al 2012].
- **L-arginine supplementation.** L-arginine competitively inhibits lysine transport and can therefore reduce lysine levels. Some individuals with pyridoxine-dependent epilepsy have difficulty tolerating a lysine-restricted medical diet; in such individuals, L-arginine supplementation has been offered as an alternative method of lowering lysine levels [Mercimek-Mahmutoglu et al 2014].

"Triple therapy." The effectiveness of treating pyridoxine-dependent epilepsy with "triple therapy" (a combination of pyridoxine supplementation, lysine restriction, and L-arginine supplementation) has been demonstrated [Coughlin et al 2015, Mahajnah et al 2016].

The combination of pyridoxine and lysine-reduction therapies improves the developmental profile of individuals with PDE-*ALDH7A1*. This was particularly noticeable in families with multiple affected sibs when the younger sib began treatment at an earlier age [Tseng et al 2022a]. A clinically significant improvement in developmental test scores has been shown when these therapies are started within the first six months of life [Coughlin et al 2022].

Supportive Care

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).

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 are common in PDE-*ALDH7A1*, 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 supportive care, and the emergence of new manifestations, the following evaluations are recommended:

- Regular assessment by treating neurologist for:
  - Control of epilepsy via targeted therapy with pyridoxine, and need for concomitant use of ASM
  - Development of clinical signs of a sensory neuropathy including regular assessments of joint-position sense, ankle jerks, gait, and station [Baxter 2001, Stockler et al 2011, Coughlin et al 2021]
- Assessment for developmental progress and educational needs at each visit
- If lysine reduction therapies are used, regular follow up by a biochemical geneticist and/or medical dietician

Agents/Circumstances to Avoid

Avoid overuse of pyridoxine (see Targeted Therapies, Pyridoxine, **Side effects**).

Evaluation of Relatives at Risk

Prenatal testing of a fetus at risk. Molecular genetic prenatal testing of fetuses at risk may be performed via amniocentesis or chorionic villus sampling to inform maternal pyridoxine supplementation (see Pregnancy Management) and facilitate institution of treatment at birth.

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

- Prophylactic treatment with pyridoxine until molecular genetic testing clarifies whether the newborn is affected

  Note: At least one newborn at risk for PDE-*ALDH7A1* developed status epilepticus after being given high-dose pyridoxine 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 pyridoxine at the first sign of seizures or encephalopathy

Note: It would be unlikely for the proband's older sibs who have not experienced seizures to be pyridoxine dependent; however, testing to determine the genetic status of asymptomatic sibs should be considered, as late-onset seizures (developing in adolescence) have been reported. If an older sib has neurodevelopmental disabilities, biomarker screening for alpha-aminoadipic semialdehyde in urine or plasma and/or molecular genetic testing should be considered.

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 a child with PDE-*ALDH7A1* is 25%, there is justification to treat the mother empirically with supplemental pyridoxine at a dose of 50-100 mg/day throughout the last half of her subsequent pregnancies and to treat the newborn with supplemental pyridoxine to prevent seizures and reduce the risk of neurodevelopmental disability [Stockler et al 2011]. It is important to emphasize, however, that at least one severe phenotype has been described in a family in which prenatal treatment of an at-risk sib did not result in an improved neurodevelopmental outcome [Rankin et al 2007].

Prenatal testing for the family-specific *ALDH7A1* pathogenic variants can be performed; if both pathogenic variants are present, supplemental pyridoxine should be continued during pregnancy and postnatally. If one or none of the family-specific *ALDH7A1* pathogenic variants are detected, supplemental pyridoxine can be discontinued.

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.

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

Pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ALDH7A1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ALDH7A1* 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 an *ALDH7A1* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.
- Note: Once a molecular diagnosis has been established in the proband, testing to determine the genetic status of asymptomatic sibs of the proband should be considered, as late-onset seizures developing during adolescence have been reported. For those who inherited both *ALDH7A1* pathogenic variants, treatment should be initiated (see Evaluation of Relatives at Risk).

Offspring of a proband

- Unless an affected individual's reproductive partner also has PDE-*ALDH7A1* or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ALDH7A1*.
- Note: Adults diagnosed with PDE-*ALDH7A1* are being followed, but the fertility status of these individuals is not known, and there are no published reports concerning the offspring of individuals with PDE-*ALDH7A1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ALDH7A1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ALDH7A1* 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

- As the recurrence risk for couples who have a child with PDE-*ALDH7A1* is 25%, the mother of a child with PDE-*ALDH7A1* should receive counseling regarding empiric pyridoxine supplementation in subsequent pregnancies (see Pregnancy Management).
- 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ALDH7A1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for PDE-*ALDH7A1* 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.

- **American Epilepsy Society**
  www.aesnet.org

- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org

- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  www.epilepsy.ca

- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.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. Pyridoxine-Dependent Epilepsy - ALDH7A1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALDH7A1	5q23.2	Alpha-aminoadipic semialdehyde dehydrogenase	ALDH7A1 database	ALDH7A1	ALDH7A1

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 Pyridoxine-Dependent Epilepsy - ALDH7A1 (View All in OMIM)

107323	ALDEHYDE DEHYDROGENASE 7 FAMILY, MEMBER A1; ALDH7A1
266100	EPILEPSY, EARLY-ONSET, 4, VITAMIN B6-DEPENDENT; EPEO4

Molecular Pathogenesis

ALDH7A1 encodes the protein alpha-aminoadipic semialdehyde (α-AASA) dehydrogenase (also referred to as antiquitin), an aldehyde dehydrogenase that functions as a Δ^1-piperideine-6-carboxylate (P6C)-α-AASA dehydrogenase within the saccharopine pathway of L-lysine metabolism (Figure 2). Decreased activity of antiquitin results in increased levels of P6C, which is the cyclic Schiff base of α-AASA; these two substances are in equilibrium with one another. P6C, in turn, inactivates pyridoxal-5'-phosphate (PLP) by condensing with the cofactor, likely resulting in abnormal metabolism of neurotransmitters [Mills et al 2006].

Additional novel metabolites, 6-oxo-pipecolate (6-oxo-PIP) and two diastereomers of 2-oxopropylpiperidine-2-carobylic acid (2-OPP), have been detected [Wempe et al 2019, Engelke et al 2021]. Importantly, these two metabolites are more stable than α-AASA at room temperature and can be detected via newborn screening techniques. Of note, 2-OPP may contribute to progressive neurotoxicity in PDE-*ALDH7A1*, as 2-OPP induces epilepsy-like behavior in a zebra fish model [Engelke et al 2021]. α-AASA, P6C, 6-oxo-PIP, and 2-OPP can be detected via next-generation metabolic screening [Tseng et al 2022b].

Antiquitin localizes to radial glia, astrocytes, and ependymal cells but not to neurons. Deficiency of antiquitin in pyridoxine-dependent epilepsy – *ALDH7A1* (PDE-*ALDH7A1*) is associated with neuronal migration abnormalities and other forms of brain dysgenesis, such as thinning of the corpus callosum [Friedman et al 2014, Jansen et al 2014, Marguet et al 2016, Oesch et al 2018]. These neurodevelopmental aspects of antiquitin deficiency are not reversible with pyridoxine treatment, lysine restriction, or L-arginine supplementation.

Mechanism of disease causation. Loss of function

***ALDH7A1*-specific laboratory technical considerations.** Deep intronic variants may be missed by sequence analysis that only includes exons and flanking regions. *ALDH7A1* variant c.696-502G>C results in introduction of a cryptic acceptor splice site, activation of a cryptic donor splice site, and introduction of a pseudoexon between exons 7 and 8 [Milh et al 2012].

Table 3. Notable *ALDH7A1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001182.5	c.696-502G>C [1]	--	Milh et al [2012]

Variants listed in the table have been provided by the author. *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.
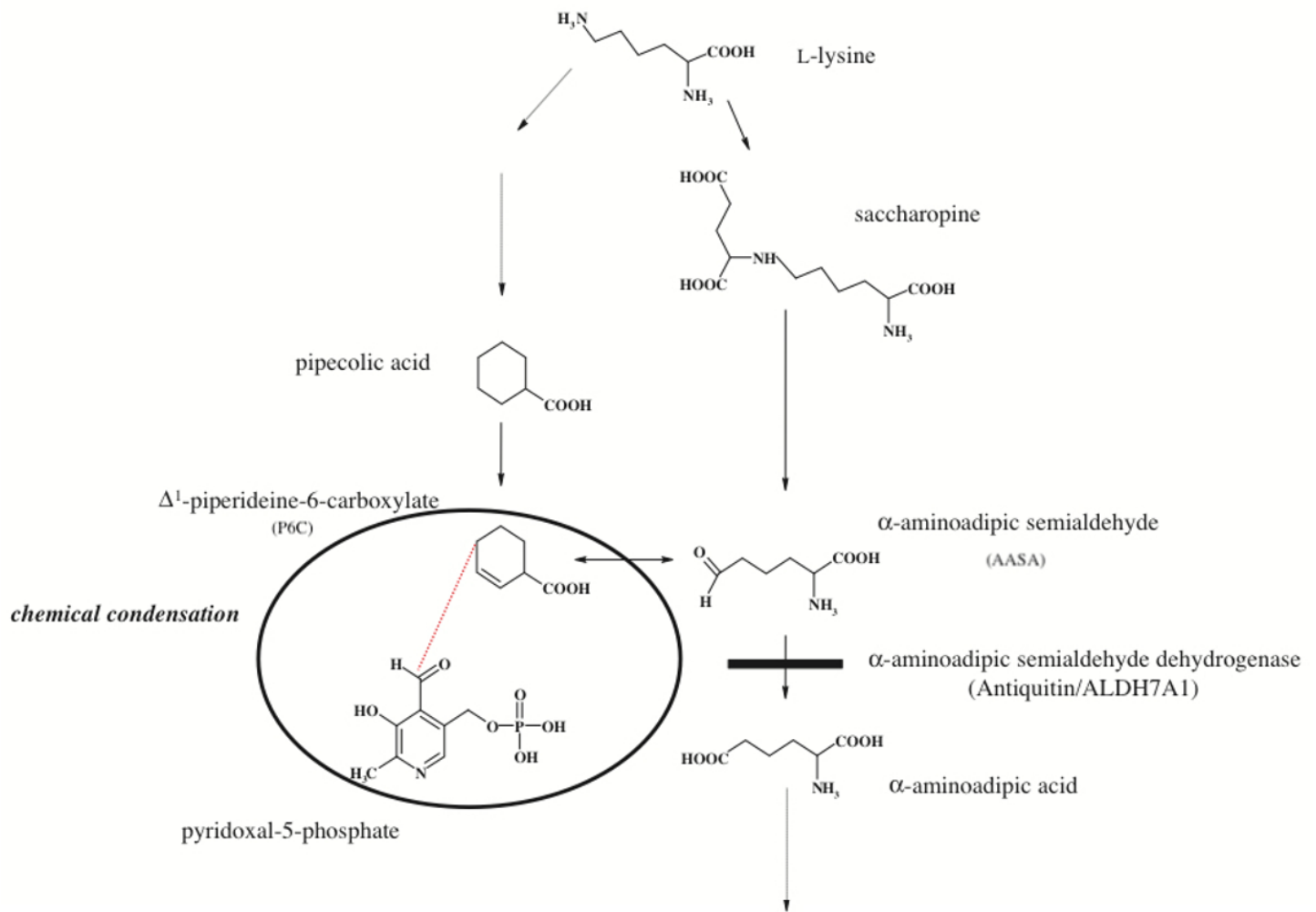
1. Results in introduction of pseudoexon between exons 7 & 8

Chapter Notes

Author Notes

Pyridoxine-Dependent Epilepsy Patient Registry

For diagnosed patients, operated by the PDE Consortium. Information about the registry may be obtained through the author or Dr Clara van Karnebeek (email: c.d.vankarnebeek@amsterdamumc.nl).

Figure 2. Outline of the metabolism of L-lysine via the saccharopine and pipecolic acid pathways and biochemical pathophysiology of PDE-*ALDH7A1*

The two pathways converge where L-Δ^1-piperideine 6-carboxylate (P6C), produced via the pipecolic acid pathway, and alpha-aminoadipic semialdehyde (α-AASA), produced via the saccharopine pathway, are in equilibrium. α-AASA is then converted to alpha-aminoadipic acid by α-AASA dehydrogenase (antiquitin/ALDH7A1). In antiquitin deficiency, P6C and α-AASA accumulate due to a block in α-AASA dehydrogenase. P6C undergoes chemical condensation with pyridoxal-5'-phosphate (PLP), resulting in PLP deficiency. Pipecolic acid accumulates due to back pressure from the enzymatic block.

Reprinted from Stockler et al [2011]

Revision History

- 22 September 2022 (bp) Comprehensive update posted live
- 29 July 2021 (bp) Comprehensive update posted live
- 13 April 2017 (ma) Comprehensive update posted live
- 19 June 2014 (me) Comprehensive update posted live

- 7 June 2012 (sg) Revision: Table 1 updated
- 26 April 2012 (sg) Revision: additions to molecular genetic testing table (Table 1); references added
- 1 March 2012 (me) Comprehensive update posted live
- 10 November 2009 (me) Comprehensive update posted live
- 24 July 2007 (cd) Revision: clinical testing available: analyte and sequence analysis; prenatal diagnosis
- 9 June 2006 (sg) Revision: mutations in *ALDH7A1* found to be causative
- 8 March 2006 (me) Comprehensive update posted live
- 18 December 2003 (me) Comprehensive update posted live
- 7 December 2001 (me) Review posted live
- 17 September 2001 (sg) Original submission

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