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PNPLA6 Disorders

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Summary

Clinical characteristics

PNPLA6 disorders span a phenotypic continuum characterized by variable combinations of cerebellar ataxia; upper motor neuron involvement manifesting as spasticity and/or brisk reflexes; chorioretinal dystrophy associated with variable degrees of reduced visual function; and hypogonadotropic hypogonadism (delayed puberty and lack of secondary sex characteristics). The hypogonadotropic hypogonadism occurs either in isolation or as part of anterior hypopituitarism (growth hormone, thyroid hormone, or gonadotropin deficiencies). Common but less frequent features are peripheral neuropathy (usually of axonal type manifesting as reduced distal reflexes, diminished vibratory sensation, and/or distal muscle wasting); hair anomalies (long eyelashes, bushy eyebrows, or scalp alopecia); short stature; and impaired cognitive functioning (learning disabilities in children; deficits in attention, visuospatial abilities, and recall in adults). Some of these features can occur in distinct clusters on the phenotypic continuum: Boucher-Neuhäuser syndrome (cerebellar ataxia, chorioretinal dystrophy, and hypogonadotropic hypogonadism); Gordon Holmes syndrome (cerebellar ataxia, hypogonadotropic hypogonadism, and – to a variable degree – brisk reflexes); Oliver-McFarlane syndrome (trichomegaly, chorioretinal dystrophy, short stature, intellectual disability, and hypopituitarism); Laurence-Moon syndrome; and spastic paraplegia type 39 (SPG39) (upper motor neuron involvement, peripheral neuropathy, and sometimes reduced cognitive functioning and/or cerebellar ataxia).

Diagnosis/testing

The diagnosis of a *PNPLA6* disorder is established in a proband with suggestive findings and biallelic *PNPLA6* pathogenic variants in *trans* configuration identified by molecular genetic testing.

Management

Treatment of manifestations: Management is symptomatic and individually tailored.

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- Ataxia. Continuous training of speech and swallowing, fine-motor skills, gait, and balance
- Spasticity. Interventions to improve strength and agility and to prevent contractures, such as physical therapy, assistive walking devices and/or ankle-foot orthotics, and drugs to reduce muscle spasticity
- Chorioretinal dystrophy. Low vision aids when central acuity is reduced; involvement with agencies for the visually impaired, mobility training, and skills for independent living
- Hypothyroidism. Hormone replacement therapy as soon as identified
- Growth hormone deficiency. Hormone replacement therapy during childhood and/or adolescence as indicated
- Hypogonadotropic hypogonadism. Hormone replacement therapy at the expected time of puberty

Surveillance: Periodic multidisciplinary reevaluations to assess disease progression and modify treatment strategies.

Agents/circumstances to avoid: Alcohol; obesity; inactive, sedentary lifestyle; exposure to medications or chemicals that exacerbate neuropathy.

Genetic counseling

PNPLA6 disorders are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PNPLA6* 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 *PNPLA6* pathogenic variants in the family have been identified, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

PNPLA6 Disorders: Included Phenotypes
• Boucher-Neuhäuser syndrome (BNS) • *PNPLA6* Gordon Holmes syndrome (GHS) • Oliver-McFarlane syndrome (OMCS) • *PNPLA6* Laurence-Moon syndrome (LMS) • Spastic paraplegia type 39 (SPG39)

Diagnosis

No consensus clinical diagnostic criteria for *PNPLA6* disorders have been published.

Suggestive Findings

A *PNPLA6* disorder should be suspected in individuals with a combination of the following clinical features, neuroimaging, and family history (rather than any of these features in isolation).

Clinical features

- Cerebellar ataxia (associated with cerebellar atrophy) starting before age 50 years and
- Upper motor neuron involvement presenting as spasticity and/or brisk reflexes
- Chorioretinal dystrophy starting before age 50 years and leading to variable degrees of reduced visual function, including blindness. The diagnosis of chorioretinal dystrophy may be established by ophthalmologic assessment, including visual acuity, visual field testing, fundoscopy, and optic coherence tomography (OCT) [Synofzik et al 2015]:
    - It is usually characterized by diffuse atrophy of choroidal vessels and retinal pigment epithelium on fundoscopy, leading to complete loss of the choriocapillaris layer and the retinal pigment epithelium

[Deik et al 2014, Synofzik et al 2015], including death of photoreceptors and retinal thinning accompanied by lipofuscin deposition [Kmoch et al 2015].
    - OCT can detect thinning of the retina, loss of layered retinal architecture, and effacement of the choriocapillaris and choroidal vessels.
    - Autofluorescence photographs and fluorescein angiography provide supplementary diagnostic information by revealing hyper- and hypofluorescent regions of abnormal retinal pigment epithelium and the choriocapillaris.
- Hypogonadotropic hypogonadism usually manifest in the first two decades of life

Common but less frequent features

- Other anterior pituitary hormone deficiencies:
    - Thyroid hormone deficiency may start in infancy, childhood, or adolescence. Onset in infancy may result in intellectual disability and poor growth.
    - Of note, newborn screening for congenital hypothyroidism may detect some newborns with this disorder.
    - Growth hormone deficiency onset may occur in infancy, childhood, or adolescence and may lead to short stature.
- Peripheral neuropathy (usually of axonal type) manifesting as reduced distal reflexes, diminished vibratory sensation, and/or distal muscle wasting
- Impaired cognitive functioning unrelated to hormone deficiency that may include learning disabilities in children [Yoon et al 2013] and deficits in attention, visuospatial abilities, and recall in adults
- Hair anomalies (long eyelashes, bushy eyebrows, premature graying, or scalp alopecia)

Neuroimaging showing the following:

- Cerebellar atrophy in approximately 90% of all affected individuals [Rainier et al 2011, Yoon et al 2013, Synofzik et al 2014a]
- Small pituitary in 20%-30% of all affected individuals [Yoon et al 2013, Synofzik et al 2014a, Hufnagel et al 2015]
- Thoracic cord atrophy in one individual [Rainier et al 2011]

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

Establishing the Diagnosis

The diagnosis of a *PNPLA6* disorder is established in a proband with suggestive findings and biallelic *PNPLA6* pathogenic (or likely pathogenic) variants in *trans* configuration 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 *PNPLA6* variants of uncertain significance (or of one known *PNPLA6* pathogenic variant and one *PNPLA6* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of a *PNPLA6* disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *PNPLA6* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *PNPLA6* 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

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 *PNPLA6* Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PNPLA6	Sequence analysis [3]	>97% [4]
	Deletion/duplication analysis [5]	<3% are gross deletions or duplications. [4, 6]

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. Rainier et al [2008], Synofzik et al [2014a], Hufnagel et al [2015], Kmoch et al [2015]
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.
6. An intragenic duplication of exons 14-20 in *PNPLA6* was reported in one individual with Oliver-McFarlane syndrome [Hufnagel et al 2015].

Clinical Characteristics

Clinical Description

In all affected individuals reported to date, features of the *PNPLA6* disorder are evident in the first two decades of life [Rainier et al 2011, Yoon et al 2013, Deik et al 2014, Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015, Tarnutzer et al 2015]. The initial findings include one or several of the following features: gait disturbance, visual impairment due to chorioretinal dystrophy or atrophy, anterior hypopituitarism, delayed puberty/primary amenorrhea. Gait disturbance may precede visual impairment or anterior hypopituitarism; or alternatively, gait disturbance may follow visual impairment or hypopituitarism up to 35 years later [Deik et al 2014]. Although the combination of the three most common findings (gait disturbance, visual impairment, and delayed puberty/primary amenorrhea) is highly indicative of an underlying *PNPLA6* disorder, no single feature is specific or obligatory.

Some of these features can occur in certain combinations, presenting in partly distinct/partly overlapping clusters on the phenotypic continuum of the *PNPLA6* disorders (see Table 2).

- **Boucher-Neuhäuser syndrome (BNS).** Cerebellar ataxia, chorioretinal dystrophy, and hypogonadotropic hypogonadism [Boucher & Gibberd 1969]; high predictive value (75%) for an underlying *PNPLA6* disorder [Synofzik et al 2014a, Tarnutzer et al 2015]
- **Gordon Holmes syndrome (GHS).** Cerebellar ataxia, hypogonadotropic hypogonadism, and (to a variable degree) brisk reflexes [Holmes 1907]
- **Oliver-McFarlane syndrome (OMCS).** Trichomegaly, chorioretinal dystrophy, and congenital or childhood hypopituitarism [Hufnagel et al 2015, Kmoch et al 2015]
- **Laurence-Moon syndrome (LMS).** Cerebellar ataxia, chorioretinal dystrophy, peripheral neuropathy, spastic paraplegia and congenital or childhood hypopituitarism. One family diagnosed with Laurence-Moon syndrome has been reported to have biallelic pathogenic variants in *PNPLA6* [Hufnagel et al 2015]. Several other people with the same phenotypic cluster and biallelic pathogenic variants in *PNPLA6* have been reported [Synofzik et al 2014a] and described as having "spastic Boucher-Neuhäuser syndrome," demonstrating the continuum of *PNPLA6*- associated phenotypic clusters.
- **Spastic paraplegia type 39 (SPG39).** Upper motor neuron involvement and peripheral neuropathy, and in some cases reduced cognitive functioning and/or cerebellar ataxia [Rainier et al 2008]
- **Severe retinal dystrophy with atrophy** associated with autism, reported in one child with biallelic pathogenic variants in *PNPLA6* [Kmoch et al 2015]. The child had been previously given a diagnosis of Leber congenital amaurosis (LCA). Given the age of the affected individual, it is possible that further features of one of the above clinical diagnoses could develop with time. See Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview.

Table 2. *PNPLA6* Disorders: Comparison of Phenotypic Clusters by Select Features

Phenotypic Feature	*PNPLA6* Disorder				
	BNS	GHS	OMCS	LMS	SPG39
Cerebellar ataxia	+	+		+	±
Peripheral neuropathy					+
Spasticity		+		+	+
Cognitive dysfunction					±
Chorioretinal dystrophy	+		+	+	
Hypogonadotropic hypogonadism	+	+			

Table 2. continued from previous page.

Phenotypic Feature	*PNPLA6* Disorder				
	BNS	GHS	OMCS	LMS	SPG39
Congenital/childhood anterior hypopituitarism			+	+	
Trichomegaly			+		

BNS = Boucher-Neuhäuser syndrome; GHS = *PNPLA6* Gordon Holmes syndrome; LMS = *PNPLA6* Laurence-Moon syndrome; OMCS = Oliver-McFarlane syndrome; SPG39 = spastic paraplegia type 39
Note: The clusters in this table do not constitute distinct phenotypes, as they may overlap in many affected individuals.

Given the limited number of individuals reported to date and the lack of longitudinal studies of affected individuals, a more detailed understanding of the natural history of *PNPLA6* disorders remains to be determined.

Gait disturbance is due to **ataxia**, **spasticity** (with or without paresis), **peripheral neuropathy**, or a combination thereof. Progression of the gait disturbance varies: more severely affected individuals lose the ability to walk without aid between ages 25 and 50 years and may become wheelchair dependent at this stage [Rainier et al 2011, Synofzik et al 2014a]; less affected individuals are still able to walk unaided at age 54 years [Synofzik et al 2014a].

Dysarthria and dysphagia are recurrent features in *PNPLA6* disorders, evolving throughout the disease course in almost all individuals with cerebellar ataxia. Dysarthria appears to present shortly after onset of gait ataxia, with dysphagia following years later, but detailed natural history studies corroborating this clinical impression are still lacking. Both are likely due to cerebellar dysfunction [Tarnutzer et al 2015]. Likewise, urinary urgency appears to be a recurrent feature at least in individuals with *PNPLA6*-associated ataxias, but a systematic investigation providing detailed evidence for this clinical impression is likewise still lacking.

Peripheral neuropathy (if present) is usually of the axonal motor type, including an additional sensory component (sensorimotor neuropathy) reported to date in only three individuals [Author, unpublished observation]. The motor neuropathy can be associated with severe atrophy of distal muscles, in particular the distal leg and intrinsic hand muscles, starting in the late teens [Rainier et al 2011]. Impairment of the sensory tracts (peripheral sensory neurons, dorsal columns) including diminished vibration sense and touch has been reported in different age groups [Rainier et al 2011, Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015].

Functional impairment due to **upper motor neuron involvement** varies: while some affected individuals show only increased reflexes or extensor plantar responses, others have severe spastic paraparesis of the lower extremities [Rainier et al 2011, Synofzik et al 2014a, Hufnagel et al 2015]. Electrophysiologic data available are currently insufficient to determine whether corticospinal tract involvement is axonal (with motor evoked potentials showing almost normal central motor conduction times) or demyelinating (with motor evoked potentials showing severely prolonged central motor conduction times).

Progressive **visual impairment**, which is less frequent than gait disturbances in the *PNPLA6* disorders, is typically due to chorioretinal dystrophy. Initially, these findings (which can present in the first few years of life) include nystagmus, choroidal and retinal pigment atrophy, and bitemporal central visual field defects and blind spot enlargement. In adolescence or adulthood visual acuity is often severely reduced (to perception of hand motion) such that some affected individuals meet the criteria for legal blindness [Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015, Synofzik et al 2015].

Anterior hypopituitarism manifests either in infancy or childhood (micropenis and cryptorchidism in males, and thyroid and growth hormone deficiency) or in adolescence (hypogonadotropic hypogonadism and growth hormone deficiency) [Hufnagel et al 2015].

- Congenital hypothyroidism and growth hormone deficiency can result in global developmental delay, severe cognitive impairment, and short stature.
- Hypogonadotropic hypogonadism usually becomes manifest during the second decade of life with delayed puberty and lack of secondary sexual characteristics including primary amenorrhea in females, small penis and testes in males, and absent pubic hair and/or breast development.

Cognitive functioning appears to be impaired in many (albeit not all) individuals with a *PNPLA6* disorder, including learning disabilities in children [Yoon et al 2013] and deficits in attention, visuospatial abilities, and recall in adults.

The relationship of white matter lesions and cortical and cerebellar degeneration with cognitive disability has not been explored in *PNPLA6* disorders; thus, the substrate or network mechanism underlying the cognitive dysfunction is not yet understood.

Genotype-Phenotype Correlations

No obvious genotype-phenotype correlation exists, as the same *PNPLA6* pathogenic variant can lead to different presentations (e.g., ataxia plus hypogonadism in one individual, and spastic ataxia in another) and to different degrees and rates of progression of manifestation (e.g., loss of ambulation in an individual age 44 years with a 17-year history of ataxia vs full ambulation in an individual age 42 years with a 36-year history of ataxia) [Synofzik et al 2014a]. Correspondingly, manifestations and disease progression differ not only between but also within families.

Nor does the phenotype appear to depend on either the location of the pathogenic variant or the pathogenic variant type (e.g., missense and frameshift variants) [Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015].

Prevalence

PNPLA6 disorders are rare in cohorts with unselected neurologic findings. Synofzik et al [2014a] identified two affected persons among 538 unrelated individuals with ataxia, spastic paraplegia, and/or neuropathy.

In contrast, *PNPLA6* pathogenic variants are a common cause of Boucher-Neuhäuser syndrome (BNS) and Oliver-McFarlane syndrome (OMCS): individuals in four of six families with BNS and 11 of 12 families with OMCS had biallelic pathogenic variants in *PNPLA6* [Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015]. Given that clinical descriptions of more than 50 index cases with BNS or OMCS have been reported to date, the number of individuals with this phenotype who are found to have biallelic *PNPLA6* pathogenic variants is likely to increase in the near future. (For meta-analysis of index cases see Wu et al [2021].)

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PNPLA6*.

Differential Diagnosis

Disorders with Ataxia

Table 3. Disorders with Ataxia in the Differential Diagnosis of *PNPLA6* Disorders

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	Distinguishing Features
ANGPTL3 *APOB* *MTTP* [1]	Abetalipoproteinemia & familial hypobetalipoproteinemia (OMIM 615558, 605019)	AR	RP, progressive ataxia, steatorrhea, demyelinating neuropathy, dystonia, extrapyramidal signs, spastic paraparesis (rare) [2]	*PNPLA6* disorders w/retinopathy typically incl anterior pituitary hormone deficiency.
ATXN7	SCA7	AD	Progressive cerebellar ataxia (incl dysarthria & dysphagia) & a cone-rod retinal dystrophy w/progressive central visual loss → blindness in affected adults [3]	*PNPLA6* disorders present w/ widespread rod-cone or cone-rod retinal degeneration & can incl hypogonadism.
MT-ATP6 *MT-ND6* *MT-TV*	NARP (See mtDNA-Associated Leigh Syndrome Spectrum.)	Mat	Childhood-onset disease most often characterized by proximal neurogenic muscle weakness w/sensory neuropathy, ataxia, learning difficulties, & pigmentary retinopathy	*PNPLA6* disorders w/retinopathy typically incl anterior pituitary hormone deficiency.
OTUD4 *RNF216* [4]	*RNF216*/*OTUD4* ataxia-hypogonadism	AR	Ataxia w/hypogonadism & dementia	*PNPLA6* disorders do not typically incl dementia.
PEX7 *PHYH*	Refsum disease	AR	Anosmia (a universal finding) & early-onset RP w/variable combinations of chronic polyneuropathy, deafness, cerebellar ataxia, & ichthyosis; cardiac conduction disorders are common.	Hearing loss has not been reported in *PNPLA6* disorders.
POLR3A *POLR3B* *POLR1C*	*POLR3* leukodystrophy	AR	Hypomyelinating leukodystrophy w/ neurologic (cerebellar, extrapyramidal, pyramidal, & cognitive) & non-neurologic (dental, endocrine, & ocular) features	*PNPLA6* disorders are not assoc w/dental abnormalities or leukodystrophy.
SIL1	Marinesco-Sjögren syndrome (MSS)	AR	Cerebellar ataxia w/cerebellar atrophy, early-onset cataracts, mild-to-severe ID, hypotonia, muscle weakness, & hypergonadotropic hypogonadism; after age 7 yrs. MSS is invariably assoc w/the combination of a cerebellar syndrome, chronic myopathy, & cataracts. [5]	Myopathy & cataracts have not been reported in *PNPLA6* disorders.
SPART	Troyer syndrome	AR	Progressive spastic paraparesis, dysarthria, pseudobulbar palsy, distal amyotrophy, motor & cognitive delays, short stature, & subtle skeletal abnormalities	Skeletal abnormalities have not been reported in *PNPLA6* disorders.
STUB1	Autosomal recessive SCA 16 (See Hereditary Ataxia Overview.)	AR	Ataxia w/cerebellar atrophy & variable cognitive impairment, hypogonadism, &/or pyramidal tract involvement [6]	*PNPLA6* disorders are characterized by more rapid disease progression & incl chorioretinal dystrophy.
TTPA	Ataxia w/vitamin E deficiency (AVED)	AR	Early-onset progressive ataxia, clumsiness of the hands, loss of proprioception (esp of vibration & joint position sense), areflexia [7]	*PNPLA6* disorders often have less severe loss of proprioception & can incl hypogonadism.

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	Distinguishing Features
TWNK	Infantile-onset SCA (IOSCA) (OMIM 271245)	AR	Severe, progressive neurodegenerative disorder w/normal development until age 1 yr, followed by onset of ataxia, muscle hypotonia, loss of deep-tendon reflexes, & athetosis; hypergonadotropic hypogonadism becomes evident in females by adolescence.	IOSCA usually starts in early childhood & is mostly accompanied by athetosis, deafness, ophthalmoplegia, &/or epilepsy.

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; ID = intellectual disability; Mat = Maternal; MOI = mode of inheritance; NARP = neurogenic muscle weakness, ataxia, and retinitis pigmentosa; RP = retinitis pigmentosa; SCA = spinocerebellar ataxia

1. Abetalipoproteinemia is caused by biallelic pathogenic variants in *MTTP*; familial hypobetalipoproteinemia is caused by biallelic pathogenic variants in *APOB* or *ANGPTL3*.

2. Hypocholesterolemia and reduced lipid-soluble vitamins in serum are due to defective intestinal absorption of lipids.

3. Onset of SCA7 in early childhood or infancy has an especially rapid & aggressive course often associated with failure to thrive & regression of motor milestones.

4. Biallelic pathogenic variants in *RNF216* or, in one family, biallelic pathogenic variants in both *RNF216* and *OTUD4*, are causative [Margolin et al 2013].

5. Krieger et al [2013]

6. Shi et al [2014], Synofzik et al [2014b]

7. The principal criterion for diagnosis of AVED is a Friedreich ataxia-like neurologic phenotype combined with markedly reduced plasma vitamin E (α-tocopherol) concentration in the absence of known causes of malabsorption.

Ataxia with hypergonadotropic hypogonadism due to coenzyme Q_{10} deficiency [Gironi et al 2004]. In contrast to coenzyme Q_{10} deficiency, *PNPLA6* disorders may present with hypogonadotropic hypogonadism, often also with spasticity, findings not known to be frequently associated with CoQ_{10} deficiency.

See also Hereditary Ataxia Overview.

Chorioretinal Dystrophy / Leber Congenital Amaurosis (LCA) / Early-Onset Severe Retinal Dystrophy (EOSRD)

Chorioretinal dystrophy / LCA / EOSRD comprises a spectrum of inherited retinal disorders with onset in infancy and early childhood. LCA is characterized by severe visual impairment from birth or the first few months of life, roving eye movements or nystagmus, poor pupillary light responses, oculodigital sign (poking, rubbing, and/or pressing of the eyes), and undetectable or severely abnormal full-field electroretinogram (ERG). EOSRD is characterized by the onset of visual impairment typically after infancy but before age five years, with variably preserved visual acuity and minimally preserved full-field ERG. Persons with *PNPLA6* disorders can have evidence of widespread retinal degeneration and vision loss in infancy or throughout childhood and adolescence. Nystagmus is rarely noted in *PNPLA6* disorders.

To date, pathogenic variants of 24 genes account for 70%-80% of individuals with LCA/EOSRD. LCA/EOSRD is typically inherited in an autosomal recessive manner; rarely, LCA/EOSRD is inherited in an autosomal dominant manner as a result of a heterozygous pathogenic variant in *CRX*, *OTX2*, or *IMPDH1*.

See also Retinitis Pigmentosa Overview.

Other Types of Disorders

Multisystem mitochondrial diseases with retinopathy. See Mitochondrial Disorders Overview.

Peripheral neuropathies with additional multisystem disease, including retinopathies. See Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Complicated hereditary spastic paraplegias. See Hereditary Spastic Paraplegia Overview.

Management

No clinical practice guidelines for *PNPLA6* disorder have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *PNPLA6* disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with a *PNPLA6* Disorder

System/Concern		Evaluation	Comment
Neurologic	**Ataxia**	By neurologist for cerebellar motor dysfunction: gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit	Use standardized scale to establish baseline for ataxia (SARA). [1]
	LMN involvement (motor & sensory neuropathy)	Weakness, amyotrophy, fasciculations, sensory involvement	Nerve conduction studies & EMG to determine presence & extent of peripheral neuropathy
	UMN involvement (spasticity)	Spasticity, Babinski signs, hyperreflexia	Use standardized scale to establish baseline for spasticity (SPRS). [2]
	Neuro-imaging	MRI of the cerebrum (incl pituitary), cerebellum, spinal cord (incl thoracic cord)	To establish extent of atrophy in the different brain regions & exclude secondary causes of clinical features
Musculoskeletal/ADL		OT/PT/rehab specialist	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices, ongoing need for PT & OT
Feeding		If frequent choking or severe dysphagia, assessment of: • Nutritional status • Aspiration risk	Consider involving gastroenterology/ nutrition/feeding team, incl formal swallowing eval
Speech		For those w/dysarthria: speech-language eval	Consider referral to speech & language pathologist.
Bladder dysfunction		Hx of spastic bladder symptoms: urgency, frequency, difficulty voiding	Referral to urologist; consider urodynamic eval.
Cognitive dysfunction		Neuropsychological investigation	Incl assessment of IQ, attention span, visuospatial abilities, recall
Chorioretinal dystrophy		By ophthalmologist	Best corrected visual acuity, visual field testing, fundoscopy, retinal imaging, OCT

Table 4. continued from previous page.

System/Concern		Evaluation	Comment
Anterior pituitary deficiency	**Hypogonadotropic hypogonadism**	• Males: for cryptorchidism, micropenis, delayed puberty • Females: for hx of primary amenorrhea	Refer to endocrinologist for complete workup.
	Hypothyroidism	For hx of congenital hypothyroidism or delayed growth	
	Growth hormone deficiency	For hx of delayed growth	
Genetic counseling		By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of a *PNPLA6* disorder to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	See Resources.

ADL = activities of daily living; hx = history; LMN = lower motor neuron; MOI= mode of inheritance; OCT= optical coherence tomography; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; SPRS = Spastic Paraplegia Rating Scale; UMN = upper motor neuron

1. Schmitz-Hübsch et al [2006]

2. Schüle et al [2006]

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

No disease-modifying drug treatment exists for *PNPLA6* disorders. Given the great phenotypic variability and broad spectrum of the disorders, management must be tailored to the needs of the individual.

Management by multidisciplinary specialists including a neurologist, ophthalmologist, endocrinologist, physical, occupational, and speech therapists, and neuropsychologist is recommended.

Table 5. Treatment of Manifestations in Individuals with a *PNPLA6* Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Ataxia	PT & OT; self-directed exercise	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL (incl use of adaptive devices, e.g., weighted eating utensils, dressing hooks) • Consider adaptive devices to maintain / improve independence in mobility (e.g., canes, walkers, motorized chairs). • Provide continuous training in the form of active speech, fine-motor, & gait exercises [Fonteyn et al 2014, Ilg et al 2014, Synofzik & Ilg 2014] incl: daily regimen w/PT exercises focusing on active, physically demanding tasks [Ilg et al 2009, Ilg et al 2010]; videogame-based whole-body training ("exergames") w/ games designed to improve coordination & rapid adaptation to changing environments [Ilg et al 2012, Synofzik et al 2013].

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Peripheral neuropathy (weakness)	PT	Orthotics
Upper motor involvement (spasticity)	PT	Daily PT to maintain & improve coordination, muscle strength, & gait; ↓ spasticity; & prevent contractures
	Pharmacologic treatment to ↓ muscle spasticity	Consider baclofen (oral or intrathecal), tolperison; Botox® injections.
Dysphagia	Feeding therapy programs to improve nutrition & dysphagia & ↓ aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration
Dysarthria	Speech & language therapy	Consider alternative communication methods (e.g., writing pads, digital devices) as needed.
Bladder dysfunction	Per treating urologist	Incl pharmacologic treatment (e.g., oxybutynin) to ↓ urinary urgency
Cognitive dysfunction	Neuropsychiatric eval & educ plan per developmental pediatrician	
Chorioretinal dystrophy	Low vision aids	Per low vision clinic
	Vocational training, mobility training, skills for independent living	In the US, state-level publicly funded agencies for the visually impaired
Hypogonadotropic hypogonadism	Hormone replacement therapy; per treating endocrinologist	Usually at puberty
Hypothyroidism	Thyroid hormone replacement as per treating endocrinologist	
Growth hormone deficiency	Growth hormone replacement; per treating endocrinologist	
Family support & resources	Social work referral	To assist in identifying sources for in-home or local community support

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist
1. Martineau et al [2014]

Surveillance

Affected individuals require periodic multidisciplinary reevaluations to assess disease progression and modify treatment strategies (Table 6).

Note that the frequency of recommended surveillance is at the discretion of treating specialists (usually annually or as symptoms change or as medication needs change).

Table 6. Recommended Surveillance for Individuals with a *PNPLA6* Disorder

System/Concern	Evaluation
Neurologic	• Neurologic assessment for progression of ataxia; UMN or LMN signs • Monitor ataxia progression w/standardized scale (SARA). [1] • Physiatry, OT/PT assessment of mobility, self-help skills as they relate to ataxia, spasticity, weakness
Dysphagia	Assess aspiration risk & feeding methods.

Table 6. continued from previous page.

System/Concern	Evaluation
Weight / Nutritional status	• Monitor BMI. • Consult nutritionist. • Assess need for high-calorie supplementation.
Dysarthria	Assess need for alternative communication method or speech therapy.
Bladder dysfunction	Per treating urologist
Cognitive dysfunction	Per treating developmental pediatrician
Chorioretinal dystrophy	Per treating ophthalmologist & low vision clinic
Hypogonadotropic hypogonadism	Per treating endocrinologist
Hypothyroidism	
Growth hormone deficiency	
Social support	Assess needs of affected person & care provider(s).

OT/PT = occupational therapy / physical therapy; SARA = Scale for the Assessment and Rating of Ataxia
1. Schmitz-Hübsch et al [2006]

Agents/Circumstances to Avoid

Avoid the following:

- Alcohol
- Obesity
- Inactive, sedentary lifestyle
- Exposure to medications or chemicals that exacerbate neuropathy. See the Charcot-Marie-Tooth Association website (pdf) for an up-to-date list of medications that are potentially toxic to persons with CMT or a related neuropathy.

Evaluation of Relatives at Risk

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

Pregnancy Management

Anecdotally, ataxia may sometimes appear for the first time or worsen during pregnancy. Note: While some individuals with ataxia report a worsening of coordination after general anesthesia, no increased risk has been reported specifically with obstetric anesthesia.

Spasticity generally does not change significantly with pregnancy.

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

PNPLA6 disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *PNPLA6* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PNPLA6* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PNPLA6* 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.
- Although affected sibs usually share most of the same *PNPLA6* phenotypic features, some features may be missing or additionally present. For example, within the same family, one sib may have all features of Boucher-Neuhäuser syndrome and another sib may have either spastic ataxia with hypogonadism or chorioretinal dystrophy, but not both. The degree and progression of impairment may also differ among sibs.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with a *PNPLA6* disorder are obligate heterozygotes (carriers) for a pathogenic variant in *PNPLA6*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PNPLA6* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PNPLA6* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PNPLA6* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for a *PNPLA6* disorder are possible. However, given the possibility of intrafamilial variability, the results of such testing do not necessarily predict the phenotype, age of onset, and/or severity of findings.

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.

- **Ataxia UK**

  United Kingdom

  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)

  Email: help@ataxia.org.uk

  ataxia.org.uk

- **EuroAtaxia**

  www.euroataxia.org

- **National Ataxia Foundation**

  Phone: 763-553-0020

  Email: naf@ataxia.org

  ataxia.org

- **National Institute of Neurological Disorders and Stroke (NINDS)**

  Hereditary Spastic Paraplegia

- **Spastic Paraplegia Foundation, Inc.**

  Phone: 877-773-4483

  Email: information@sp-foundation.org

  sp-foundation.org

- **Autosomal Recessive Cerebellar Ataxia (ARCA) Registry**

  The ARCA Registry is a collaborative global platform for advancing trial readiness in autosomal recessive cerebellar ataxias.

  Email: andreas.traschuetz@uni-tuebingen.de

www.arca-registry.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. PNPLA6 Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PNPLA6	19p13.2	Patatin-like phospholipase domain-containing protein 6	PNPLA6 database	PNPLA6	PNPLA6

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 PNPLA6 Disorders (View All in OMIM)

212840	GORDON HOLMES SYNDROME; GDHS
215470	BOUCHER-NEUHAUSER SYNDROME; BNHS
245800	LAURENCE-MOON SYNDROME; LNMS
275400	OLIVER-MCFARLANE SYNDROME; OMCS
603197	PATATIN-LIKE PHOSPHOLIPASE DOMAIN-CONTAINING PROTEIN 6; PNPLA6
612020	SPASTIC PARAPLEGIA 39, AUTOSOMAL RECESSIVE; SPG39

Molecular Pathogenesis

PNPLA6 encodes the neuropathy target esterase, which belongs to a protein family of nine patatin-like phospholipase domain-containing proteins. Apart from its phospholipid esterase domain (EST; also sometimes called "patatin domain"), the modular architecture of PNPLA6 protein comprises three CNB domains (CNB1, CNB2, CNB3).

The most important functional domain is the EST domain, which de-esterifies phosphatidylcholine (a major component of biologic membranes) into its constituent fatty acids and glycerophosphocholine [Strickland et al 1995, Atkins et al 2002, van Tienhoven et al 2002, Zaccheo et al 2004]. Glycerophosphocholine is a precursor for the biosynthesis of acetylcholine, a key neurotransmitter involved in mediating cellular signaling in the nervous system. Moreover, it has been suggested that the EST domain has a role in lysophospholipase activity [van Tienhoven et al 2002] and functions in lipid membrane metabolism [Tesson et al 2012].

Current knowledge suggests that biallelic *PNPLA6* pathogenic variants cause disease by impairing the capacity of the EST domain to perform **one** of two functions:

- De-esterify phosphatidylcholine into fatty acids and glycerophosphocholine. (The lack of adequate glycerophosphocholine may disturb development and maintenance of synaptic connections in a variety of neuronal networks.)
- Catalyze 2-arachidonoyl lysophosphatidylinositol, thus disturbing the metabolism of lipid membranes [Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015].

Mechanism of disease causation. Loss of function

Table 7. Notable *PNPLA6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_006702.5 NP_006693.3	c.2944_2947dupAGCC	p.Arg983GlnfsTer38	Reported across the *PNPLA6* disorders phenotypic spectrum [Rainier et al 2008, Synofzik et al 2014a, Hufnagel et al 2015, Kmoch et al 2015]
	c.2990C>T	p.Ser997Leu	To date reported only in compound heterozygotes w/Boucher-Neuhauser syndrome [Deik et al 2014, Synofzik et al 2014a]
	c.3034A>G	p.Met1012Val	To date reported only in homozygotes or compound heterozygotes w/SPG39 [Rainier et al 2008]
	c.3152G>A	p.Arg1051Gln	To date reported only in compound heterozygotes w/Oliver-McFarlane syndrome [Hufnagel et al 2015]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Matthis Synofzik is a professor for translational genomics of neurodegenerative diseases, following the concept to map the full translational pipeline from mapping disease genes via identifying biomarkers to establishing trial-readiness for rare neurologic diseases.
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Robert B Hufnagel is a physician-scientist specializing in clinical care, molecular diagnostics, and gene discovery for syndromic ocular disorders.
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Stephan Züchner is professor of human genomics, with a dedicated interest of mapping disease genes and genomic variation that is related to disease.
Website

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