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NLM Citation: Srivastava S, Waldman A, Naidu S. Alexander Disease. 2002 Nov 15 [Updated 2020 Nov 12]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Alexander Disease

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Created: November 15, 2002; Updated: November 12, 2020.

Summary

Clinical characteristics

Alexander disease, a progressive disorder of cerebral white matter caused by a heterozygous *GFAP* pathogenic variant, comprises a continuous clinical spectrum most recognizable in infants and children and a range of nonspecific neurologic manifestations in adults. This chapter discusses the spectrum of Alexander disease as four forms: neonatal, infantile, juvenile, and adult.

The **neonatal form** begins in the first 30 days after birth with neurologic findings (e.g., hypotonia, hyperexcitability, myoclonus) and/or gastrointestinal manifestations (e.g., gastroesophageal reflux, vomiting, failure to thrive), followed by severe developmental delay and regression, seizures, megalencephaly, and typically death within two years.

The **infantile form** is characterized by variable developmental issues: initially some have delayed or plateauing of acquisition of new skills, followed in some by a loss of gross and fine motor skills and language during in the first decade or in others a slow disease course that spans decades. Seizures, often triggered by illness, may be less frequent/severe than in the neonatal form.

The **juvenile form** typically presents in childhood or adolescence with clinical and imaging features that overlap with the other forms. Manifestations in early childhood are milder than those in the infantile form (e.g., mild language delay may be the only developmental abnormality or, with language acquisition, hypophonia or nasal speech may alter the voice, often prior to appearance of other neurologic features). Vomiting and failure to thrive as well as scoliosis and autonomic dysfunction are common.

The **adult form** is typically characterized by bulbar or pseudobulbar findings (palatal myoclonus, dysphagia, dysphonia, dysarthria or slurred speech), motor/gait abnormalities with pyramidal tract signs (spasticity, hyperreflexia, positive Babinski sign), or cerebellar abnormalities (ataxia, nystagmus, or dysmetria). Others may

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have hemiparesis or hemiplegia with a relapsing/remitting course or slowly progressive quadriparesis or quadriplegia. Other neurologic features can include sleep apnea, diplopia or disorders of extraocular motility, and autonomic dysfunction.

Diagnosis/testing

The diagnosis of Alexander disease is established in a proband with suggestive clinical and neuroimaging findings and a heterozygous pathogenic variant in *GFAP* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is supportive and focuses on management by multidisciplinary specialists to manage general care, feeding, and nutrition; anti-seizure medication; physical and occupational therapy; speech and language therapy; and appropriate educational services.

Surveillance: Monitoring for progression of neurologic manifestations, developmental progress, and educational needs as well as need for services as they relate to physical therapy and occupational therapy, nutrition and safety of oral feeding, speech and language, gastrointestinal involvement, bladder function, evidence of autonomic dysfunction, pulmonary function, psychological/psychiatric manifestations, and sleep.

Genetic counseling

Alexander disease is inherited in an autosomal dominant manner. To date, most reported individuals with molecularly confirmed Alexander disease have the disorder as the result of a *de novo GFAP* pathogenic variant; however, familial cases have been reported, including individuals with slowly progressive adult Alexander disease who have an affected parent. Individuals with Alexander disease with significant neurologic and cognitive impairment typically do not reproduce, whereas each child of an adult with slowly progressing Alexander disease has a 50% chance of inheriting the *GFAP* pathogenic variant. Once the *GFAP* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Alexander disease are possible.

GeneReview Scope

With the currently widespread use of advanced molecular genetic testing, it is apparent that heterozygous *GFAP* pathogenic variants cause a spectrum of features ranging from cerebral white matter disease manifesting most recognizably in infants and children to a range of nonspecific neurologic manifestations in adults. The scope of this *GeneReview* encompasses all individuals with a *GFAP* pathogenic variant (regardless of clinical findings that prompted molecular genetic testing), who should be evaluated for medically actionable manifestations across the entire phenotypic spectrum of Alexander disease.

Diagnosis

Suggestive Findings

Alexander disease **should be suspected** in individuals with the following age-related clinical and brain MRI findings.

Clinical Findings

Neonates

- Weak suck, feeding difficulties, hypotonia, and myoclonus

- Progressive psychomotor impairment or developmental regression
- Megalencephaly with frontal bossing

  Note: Though the terms megalencephaly and macrocephaly are sometimes used interchangeably, macrocephaly refers to head circumference that is more than two standard deviations above the mean adjusting for age and sex, whereas megalencephaly refers to increased volume of brain parenchyma. Macrocephaly – which reflects the size of intracranial contents as well as bone and scalp – may result from megalencephaly but also other medical issues, such as hydrocephalus or thickening of the skull.
- Seizures
- Occasional hydrocephalus secondary to aqueductal stenosis
- CSF protein elevation [Springer et al 2000]

Children

- Developmental delay (slow attainment of developmental milestones or failure to achieve later milestones)
- Seizures
- Megalencephaly
- Gradual loss of intellectual function
- Regression after mild head injury or seizure
- Dysarthria (in those children who attain speech)
- Failure to thrive

Juveniles

- Developmental delay
- Seizures
- Bulbar/pseudobulbar signs with nasal speech, dysphagia, dysphonia
- Failure to thrive
- Intractable vomiting
- Scoliosis
- Autonomic dysfunction

Adults

- Bulbar/pseudobulbar signs
- Pyramidal tract signs
- Cerebellar signs
- Dysautonomia
- Sleep disturbance
- Gait disturbance
- Hemiparesis/hemiplegia or quadriparesis/quadriplegia
- Diplopia or oculomotor abnormalities

Brain MRI Findings

Based on a multi-institutional retrospective survey of MRI studies of 217 individuals with leukoencephalopathy [van der Knaap et al 2001], it has been suggested that the presence of four of the five following criteria establishes an MRI-based diagnosis of Alexander disease, which can lead to targeted genetic testing:

- Extensive cerebral white matter abnormalities with a frontal preponderance

- Periventricular rim of decreased signal intensity on T_2-weighted images and elevated signal intensity on T_1-weighted images
- Abnormalities of the basal ganglia and thalami that may include one or both of the following:
  - Swelling and increased signal intensity on T_2-weighted images
  - Atrophy and increased/decreased signal intensity on T_2-weighted images
- Brain stem abnormalities, particularly involving the medulla and midbrain
- Contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, and brain stem

Table 1. Alexander Disease: MRI Features by Age of Presentation

	Neonatal	Infantile	Juvenile	Adult
Periventricular rim	+	+	+ or -	+ or -
Basal ganglia or thalamus involvement	+++	++	+ or -	+ or -
Brain stem involvement	Symmetric signal abnormality of medulla		Mass-like brain stem lesions	Medullary & cervical cord atrophy
Contrast enhancing structures	Frequent in basal ganglia	Variable	Frequently present in posterior fossa structures	+ or -
Other notes			T_2-weighted hyperintensities may be present in cerebellar white matter or hilus of dentate nuclei [van der Knaap et al 2005].	

Prominent or distinguishing features within the van der Knaap et al [2001] criteria by phenotype include the following.

Neonatal form

- Severe white matter abnormalities with frontal predominance and extensive pathologic periventricular enhancement demonstrated on neuroradiologic contrast imaging
- Involvement of the basal ganglia and cerebellum

Infantile form

- Frontally predominant white matter T_2-weighted hyperintensity, basal ganglia involvement, and a periventricular rim are present in most individuals.
- Brain stem abnormalities are less prominent than in other forms; typical findings may include symmetric signal abnormalities of the medulla.

Juvenile form

- Significant involvement of posterior fossa structures, such as focal brain stem lesions (mimicking tumor), or T_2-weighted hyperintensities in the cerebellar white matter or hilus of the dentate nuclei [van der Knaap et al 2005]
- T_1-weighted post-contrast enhancement is frequently present in posterior fossa structures.
- Some individuals may lack other features described by van der Knaap et al [2001].
- Characteristic imaging features of this subgroup include symmetric or asymmetric lesions in the dorsal medulla that may enhance with gadolinium administration and are often initially diagnosed as tumors, especially in the absence of other imaging features of Alexander disease.
- The later onset and presence of prominent mass-like brain stem lesions and cerebellar abnormalities distinguish this phenotype from infantile cases. Such lesions account for the vomiting and cerebellar abnormalities seen in patients with this phenotype. While some individuals may have supratentorial and

infratentorial abnormalities (an intermediate phenotype described by Yoshida et al [2011]), the extensive frontal white matter involvement is not present in every individual with juvenile onset.

Adult form

- Abnormal signal intensity of the anterior portion of the medulla oblongata along with atrophy of the medulla and cervical spinal cord
- Signal abnormalities in the cerebellar white matter or hilus of the dentate nucleus [van der Knaap et al 2005]
- Supratentorial white matter findings that may include [Yoshida et al 2020]:
  - Mild-to-moderate cerebral involvement
  - T_2-weighted hyperintensities that are primarily localized around the anterior horn of the lateral ventricles
  - Cyst formation in white matter around the anterior horn of the lateral ventricles
  - Appearance of garland-like structures along the ventricular wall (ventricular garlands), reported to represent blood vessels with a high density of periventricular Rosenthal fibers [van der Knaap et al 2006]

Establishing the Diagnosis

The diagnosis of Alexander disease **is established** in a proband with suggestive clinical and neuroimaging findings and a heterozygous pathogenic variant in *GFAP* identified by molecular genetic testing (see Table 2).

Note: Identification of a heterozygous *GFAP* variant of uncertain significance does not establish or rule out the diagnosis of Alexander disease.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, 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 Alexander disease has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *GFAP* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If 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.

Note: Alexander disease occurs through a gain-of-function mechanism (see Molecular Genetics) and, thus, intragenic deletion or duplication is a rare cause of disease; however, one in-frame exon deletion has been reported (see Table 2).

A leukodystrophy multigene panel that includes *GFAP* 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.

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

Table 2. Molecular Genetic Testing Used in Alexander Disease

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GFAP	Sequence analysis [3]	98% [4]
	Deletion/duplication analysis [5]	One reported [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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Based on a summary of prior published reports in which 293 of 299 (98%) individuals tested had a *GFAP* pathogenic variant. Of note, the numerator and denominator include ten asymptomatic individuals who had a pathogenic *GFAP* variant (see Table 3 [pdf]).
5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. Deletion of exon 5, an in-frame exon, has been reported [Green et al 2018].

Clinical Characteristics

Clinical Description

Alexander disease is a progressive disorder affecting cerebral white matter. It is most readily recognized in infants and children. Adults can also be affected, but manifestations and diagnosis may be under-recognized. Life expectancy is variable. Many individuals with Alexander disease present with nonspecific neurologic manifestations.

Previous classification recognized four forms: neonatal (sometimes considered a subset of the infantile form), infantile, juvenile, and adult. Based on a prior review of reports of *GFAP* variants, the infantile form of Alexander disease accounts for 42% (124/293) of reported individuals with an identifiable *GFAP* pathogenic variant; the juvenile form accounts for 22% (63/293); and the adult form accounts for 33% (96/293) (see Table 3 [pdf]). Ten (3%) of the 293 individuals with an identifiable *GFAP* pathogenic variant were reported to be asymptomatic [Stumpf et al 2003, Shiihara et al 2004, Yoshida et al 2011, Messing et al 2012, Wada et al 2013]. The current clinical status of these individuals is unknown.

Additional case series have suggested a two-group classification system (Type I and Type II) [Prust et al 2011] or a three-group classification system (cerebral, bulbospinal, intermediate) [Yoshida et al 2011].

See Table 4 for a comparison of select features seen in the different forms (based on age of onset).

Table 4. Alexander Disease: Comparison of Forms by Select Features

	Neonatal	Infantile	Juvenile	Adult
Typical age at presentation	1st mo of life	Infancy or childhood	Childhood or adolescence	Adolescence or adulthood
Core neurologic manifestations	Lack of developmental progression; motor impairment w/o spasticity; seizures; megalencephaly; hydrocephalus	Developmental delay or developmental regression; seizures; megalencephaly	Bulbar/pseudobulbar signs w/nasal speech, dysphagia, dysphonia; failure to thrive; intractable vomiting; scoliosis; autonomic dysfunction	Pyramidal involvement; bulbar dysfunction; autonomic dysfunction
Other findings	Feeding difficulties (failure to thrive)	Failure to thrive	Short stature	Cerebellar involvement; palatal myoclonus; normocephaly

The forms described in Table 4 and below likely represent a phenotypic continuum rather than distinct classifications. However, subgrouping is intended to help clinicians care for affected individuals and explain the disorder to them and/or their families.

Neonatal form. Neurologic manifestations (e.g., hypotonia, hyperexcitability, myoclonus) and/or gastrointestinal manifestations (e.g., gastroesophageal reflux, vomiting, failure to thrive) begin within 30 days of birth [Springer et al 2000]. Affected children fail to achieve early milestones, and if they do, may show developmental regression (though developmental regression may be difficult to identify at such an early age and may manifest only as loss of sucking reflex). Following these initial findings, seizures occur during the neonatal period or infancy. Seizures may be generalized, frequent, and/or intractable. Megalencephaly, with frontal bossing or over-proportional head growth compared to weight and length, occurs over the first several months of life. In this age group specifically, children should be monitored for hydrocephalus with raised intracranial pressure, primarily caused by aqueductal stenosis. Neurologic examination is notable for severe cognitive, language, and motor delay without prominent spasticity or ataxia. Rapid progression may occur, leading to severe disability or death, typically within two years.

Infantile form. Affected children typically present with developmental delay or plateau (failure to gain additional skills). The acquisition of developmental milestones is variable. While some children learn to walk and speak in phrases or sentences, others do not achieve independent ambulation and demonstrate limited spoken language ability. Dysarthria is frequently present in individuals who achieve expressive language.

Most children are referred to neurology after an initial seizure, often leading to brain MRI that reveals characteristic features (see Table 1) and recognition of the disorder. Seizures (often triggered by illness) may be less frequent/severe than in the neonatal form.

Frontal bossing and megalencephaly are not universally present. Macrocephaly is not always noted at the time of other neurologic manifestations (e.g., seizures, developmental delay) and may be detected through serial measurement of the head circumference many years after the initial neurologic manifestations and diagnosis.

While developmental regression may occur after a seizure or mild head trauma, some individuals can regain skills over time. Disease progression is also variable, with some individuals losing gross and fine motor as well as language skills in the first decade of life, while others follow a very slow disease course that spans decades.

Juvenile form. Children may present with a combined or intermediate [Yoshida et al 2011] phenotype with clinical and imaging features overlapping those of the other forms. Onset is usually in childhood or adolescence.

Compared to the infantile form, affected children have milder manifestations in early childhood. For example, mild language delay may be the only developmental abnormality or, with language acquisition, a change in voice

(hypophonia or nasal speech) may develop, often prior to other neurologic features. Children and adolescents with this phenotype frequently have vomiting and failure to thrive as well as scoliosis and autonomic dysfunction.

Some individuals with Alexander disease present with vomiting as the only manifestation of bulbar dysfunction (i.e., dysphagia and dysphonia may not be present initially) [Namekawa et al 2012]. Anorexia is frequently present as well, and affected individuals may be diagnosed with an eating disorder. Over time, individuals have failure to thrive (poor weight gain) and delayed physical growth (short stature). Progressive scoliosis occurs in some individuals.

It is possible that this phenotype represents a spectrum of disease with other presentations. Longitudinal evaluations of individuals with Alexander disease have deidentified those with isolated brain stem lesions whose symptoms spontaneously resolved and who subsequently developed medullary and cervical cord atrophy as noted in the adult phenotype [Namekawa et al 2012].

Adult form. Adults typically present with bulbar or motor manifestations reflecting the prominent infratentorial involvement in this form. Bulbar or pseudobulbar manifestations include palatal myoclonus, dysphagia, dysphonia, dysarthria, or slurred speech. Other individuals present with gait abnormalities and are noted to have pyramidal tract signs (spasticity, hyperreflexia, positive Babinski sign) or cerebellar abnormalities (ataxia, nystagmus, or dysmetria). While some individuals have hemiparesis or hemiplegia and may have a relapsing remitting course [Ayaki et al 2010], others have a slowly progressive quadriparesis or quadriplegia. Other features include sleep apnea, diplopia or disorders of extraocular motility (impaired smooth pursuit, gaze-evoked horizontal nystagmus, slowed saccades, or ocular myoclonus) [Martidis et al 1999], and autonomic dysfunction (incontinence, constipation, pollakiuria [urinary frequency], urinary retention, impotence, sweating abnormality, hypothermia, orthostatic hypotension) [Spritzer et al 2013].

Variable expressivity is most frequently observed in affected individuals within a family in which mildly affected parents and sibs of affected individuals have a *GFAP* pathogenic variant [Messing 2018].

In contrast, in one family all three individuals with a *GFAP* pathogenic variant had mild manifestations: a boy age 16 months had macrocephaly; his mother (age 34 years) and sister (age 7 years) had normal physical and neurologic examinations, including head circumference. However, their brain MRIs showed abnormal signal intensities in the deep frontal white matter and caudate [Shiihara et al 2004]. Clinical follow up has not been reported.

EEG. Electroencephalographic studies are nonspecific. While some individuals may have a normal EEG, others may show slow waves over the frontal areas. Focal epileptiform discharges have been reported, and may be related to cortical abnormalities [Gordon 2003], although generalized patterns have also occurred, likely due to thalamic involvement.

Histologic studies. Prior to the definition of the molecular genetic basis of Alexander disease, the demonstration of enormous numbers of Rosenthal fibers on brain biopsy or at autopsy was the only method for definitive diagnosis. Rosenthal fibers are intracellular inclusion bodies composed of aggregates of glial fibrillary acidic protein, vimentin, αβ-crystallin, and heat shock protein 27 found exclusively in astrocytes. Rosenthal fibers increase in size and number during the course of the disease. Some individuals with mass-like lesions have been biopsied, and the presence of Rosenthal fibers has led to genetic confirmation of Alexander disease.

Genotype-Phenotype Correlations

A number of genotype-phenotype correlations have been observed for some recurrent variants, albeit with a limited number of affected individuals (see Table 3 [pdf] for references and Table 11). It is possible that given the variable expressivity of the disorder, exceptions may occur.

- **Infantile form.** Recurrent pathogenic variants commonly (but not necessarily exclusively) observed in this form include: p.Met73Thr (c.218T>C), p.Leu76Phe (c.226C>T), p.Asn77Ser (c.230A>G), p.Arg79Cys (c.235C>T), p.Arg88Cys (c.262C>T), p.Leu97Pro (c.290T>C), p.Arg239Cys (c.715C>T), p.Arg239His (c.716G>A), p.Arg239Leu (c.716G>T), p.Arg239Pro (c.716G>C), p.Leu352Pro (c.1055T>C), p.Glu373Lys (c.1117G>A), p.Asp417MetfsTer15 (c.1249delG).
- **Juvenile form.** Recurrent pathogenic variants commonly (but not necessarily exclusively) observed in this form include: p.Arg79Cys (c.235C>T), p.Arg88Cys (c.262C>T), p.Glu210Lys (c.628G>A), p.Leu235Pro (c.704T>C), p.Arg239Cys (c.715C>T), p.Arg416Trp (c.1246C>T).
- **Adult form.** Recurrent pathogenic variants commonly (but not necessarily exclusively) observed in this form include: p.Arg66Gln (c.197G>A), p.Arg70Trp (208C>T), p.Arg70Gln (c.209G>A), p.Met74Thr (c.221T>C), p.Glu205Lys (c.613G>A), p.Arg258Cys (c.772C>T), p.Arg276Leu (c.827G>T), p.Leu359Pro (c.1076T>C), p.Ala364Thr (c.1090G>C), p.Ser393Ile (c.1178G>T), p.Arg416Trp (c.1246C>T).

Penetrance

Penetrance appears to be nearly 100% in individuals with the infantile and juvenile forms [Li et al 2002, Messing & Brenner 2003a, Messing 2018].

Reports of molecularly confirmed familial cases support the existence of asymptomatic adults with Alexander disease [Stumpf et al 2003, Shiihara et al 2004, Messing et al 2012, Wada et al 2013].

Nomenclature

Table 5. Alexander Disease: Comparison of Classification Systems

Classification System	Typical Age at Presentation			
	First Month of Life	Infancy or Childhood	Childhood or Adolescence	Adolescence or Adulthood
4-group system by age of onset	Neonatal form	Infantile form	Juvenile form	Adult form
2-group system by symptoms at onset [1]	Type I	Type I	Type II	Type II
3-group system by MRI features [2]	Cerebral	Cerebral	Intermediate	Bulbospinal

1. Prust et al [2011] classification based on clinical findings, not age
2. Yoshida et al [2011] classification based on brain MRI findings

Prevalence

The prevalence of Alexander disease is not known, but hundreds of affected individuals with heterozygous *GFAP* pathogenic variants have been reported.

The only population-based prevalence estimate is one in 2.7 million [Yoshida et al 2011].

The disorder is known to occur in diverse ethnic and racial groups [Gorospe & Maletkovic 2006].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Alexander disease is usually considered in the differential diagnosis of infants who present with megalencephaly, developmental delay, spasticity, and seizures, or in older individuals who have a preponderance of brain stem signs and spasticity with or without megalencephaly or seizures.

Differential Diagnosis in Neonates, Infants, and Juveniles

Table 6. Genes of Interest in the Differential Diagnosis of the Neonatal, Infantile, and Juvenile Forms of Alexander Disease

Gene(s)	Disorder	Features of Differential Diagnosis Disorder	
		Overlapping w/ Alexander disease	Distinguishing from Alexander disease
ABCD1	X-linked adrenoleukodystrophy (X-ALD)	• Male children present w/ regression in motor & cognitive skills. • Spasticity & gait abnormalities	MRI: mostly sparing of subcortical WM; involvement of deep WM primarily (most severe in parietal & occipital lobes w/anterior progression); leading edge enhancement of involved WM
ARSA	Arylsulfatase A deficiency (metachromatic leukodystrophy, MLD) [1]	• Developmental regression in early childhood • Spasticity w/preserved cognitive function	MRI: involvement of deep WM primarily w/sparing of subcortical WM early in disease course; enhancement of cranial nerves; tigroid pattern (stripes/spots of spared perivascular WM) w/o abnormal periventricular WM
ASPA	Canavan disease [1]	• Hypotonia, head lag, macrocephaly, & difficulties w/ suck & swallow • DD ± regression • MRI: involvement of subcortical WM & globus pallidus & thalami	• Elevation in N-acetylcysteine on MR spectroscopy • MRI: diffuse WM changes w/o frontal predominance; sparing of putamen
GALC	Krabbe disease [1]	• Early feeding difficulties, hypotonia, & irritability • Developmental regression & seizures • MRI: involvement of thalami & cerebellar WM	• Macrocephaly not present • MRI: involvement of deep WM primarily w/sparing of subcortical WM until later in disease course; thickening/enhancement of optic nerves & peripheral nerves
GCDH	Glutaric acidemia type 1 [1]	• Macrocephaly, DD, extrapyramidal signs (often preceded by an acute encephalopathy during infancy) • MRI: involvement of basal ganglia	MRI: lack of enhancement of affected structures; widening of sylvian fissures & expansion of CSF spaces
HEPACAM *MLC1*	Megalencephalic leukoencephalopathy w/ subcortical cysts 1 & 2A [1]	• Megalencephaly during infancy, DD, seizures • MRI: involvement of subcortical WM	MRI: subcortical cysts, relative sparing of cerebellar WM, sparing of basal ganglia

Table 6. continued from previous page.

Gene(s)	Disorder	Features of Differential Diagnosis Disorder	
		Overlapping w/ Alexander disease	Distinguishing from Alexander disease
L2HGDH	L-2-hydroxyglutaric aciduria (OMIM 236792) [1]	• DD, seizures, dysarthria, ataxia (often w/insidious progression) • MRI: involvement of subcortical, WM & basal ganglia; anterior to posterior involvement of WM	MRI: sparing of brain stem & cerebellum; no enhancement
PEX1 *PEX6* *PEX12* (13 assoc genes) [2]	Zellweger spectrum disorder (ZSD)	• Neonatal-infantile onset: hypotonia, feeding difficulties, & seizures • Childhood onset: hypotonia, DD, regression, & diffuse involvement of WM incl cerebrum, brain stem, & cerebellum • Adolescent-adult onset: variable ID, pyramidal signs, & ataxia	• May be assoc w/liver, heart, kidney, & skeletal system dysfunction; distinct facial features • Neonatal-infantile onset of ZSD MRI findings: cortical dysplasia, generalized ↓ in WM volume, delayed myelination, & ventricular dilatation • Childhood onset of ZSD MRI findings: involvement of parietooccipital WM progressing to entire cerebral WM

CSF = cerebrospinal fluid; DD = developmental delay; ID = intellectual disability; WM = white matter

1. Mode of inheritance is autosomal recessive.

2. Biallelic pathogenic variants in *PEX1*, *PEX6*, *PEX12* account for 60.5%, 14.5%, and 7.6% of Zellweger spectrum disorder (ZSD), respectively. ZSD is also known to be caused by biallelic pathogenic variants in *PEX2*, *PEX3*, *PEX10*, *PEX5*, *PEX11β*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, or *PEX26*. ZSD is typically inherited in an autosomal recessive manner. One *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state.

Differential Diagnosis in Adults

Multiple sclerosis (MS). Similar to Alexander disease, MS is characterized by relapsing and remitting hemiparesis or hemiplegia, dysarthria, and ataxia. On MRI, MS is associated with mild frontal white matter involvement, periventricular rim, and brain stem or cervical cord signal abnormalities. Unlike Alexander disease, MS is not inherited in an autosomal dominant manner and, on MRI, MS is associated with generalized brain atrophy (rather than symmetric brain stem signal abnormalities with medullary and cord atrophy as in Alexander disease).

Hereditary disorders in the differential diagnosis of the adult form of Alexander disease are summarized in Table 7.

Table 7. Genes of Interest in the Differential Diagnosis of the Adult Form of Alexander Disease

Gene(s)	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/ Alexander disease	Distinguishing from Alexander disease
ABCD1	X-linked adrenoleukodystrophy (X-ALD)	XL	• Progressive gait disorder, spasticity or weakness, & abnormalities of sphincter control • MRI: cerebellar lesions & demyelination	• Abnormal VLCFAs • MRI: T_2-weighted hyperintensity in CC, occipital periventricular WM, & internal capsule

Table 7. continued from previous page.

Gene(s)	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/ Alexander disease	Distinguishing from Alexander disease
DARS2	Leukoencephalopathy w/brain stem & spinal cord involvement & lactate elevation	AR	• Spastic paraplegia or progressive gait impairment • Ataxia • Cognitive decline • MRI: abnormalities in medulla & upper cervical cord	• ↓ position & vibratory sensation • MRI: abnormalities visualized in dorsal columns & lateral corticospinal tracts of spinal cord, splenium of CC, posterior limb of internal capsule, intraparenchymal part of trigeminal nerve, & mesencephalic trigeminal tracts [2]
EIF2B1 *EIF2B2* *EIF2B3* *EIF2B4* *EIF2B5*	Vanishing WM disease (See CACH/VWM.)	AR	Ataxia & cognitive decline	MRI: bilateral confluent T_2-weighted hyperintensities w/WM rarefaction & global atrophy
NOTCH3	Cerebral autosomal dominant arteriopathy w/subcortical infarcts & leukoencephalopathy (CADASIL)	AD	Mild cognitive decline	• Ischemic stroke & migraine w/aura • MRI: T_2-weighted hyperintense lesions in temporal poles
PLP1	Pelizaeus-Merzbacher disease (See *PLP1* Disorders.)	XL	Spastic gait, ataxia, bowel & bladder dysfunction	MRI: patchy T_2-weighted hyperintensities or more diffuse hypomyelination

AD = autosomal dominant; AR = autosomal recessive; CACH/VWM = childhood ataxia with central nervous system hypomyelination / vanishing white matter; CC = corpus callosum; MOI = mode of inheritance; VLCFA = very long chain fatty acid; WM = white matter; XL = X-linked

1. de Beer et al [2014]

2. Lynch et al [2017]

Management

No clinical practice guidelines for Alexander disease have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Alexander disease, the evaluations summarized in Table 8 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 8. Recommended Evaluations Following Initial Diagnosis in Individuals with Alexander Disease

System/Specialist	Evaluation	Comment
Neurologic	Complete neurologic assessment incl history, physical exam, & eval of head circumference	• Review clinical & MRI findings w/affected individual & caregivers. • Perform formal, age-appropriate developmental assessment (in children). • Discuss symptomatic therapy. • Determine if EEG is needed.
Primary care physician	History & physical exam	To facilitate care coordination after receiving info about diagnosis & mgmt plan
Genetic counseling	Discussion led by genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of Alexander disease to facilitate medical & personal decision making

Table 8. continued from previous page.

System/Specialist	Evaluation	Comment
Family support/ resources	Discussion w/patient, family, & caregivers	To assess family & social structure to determine availability of adequate support system, need for social work involvement & parental or caregiver support, need for home nursing referral, & use of community or online resources such as Parent to Parent
Speech/language pathologist or feeding specialist	Swallow eval	Some programs may offer a clinical eval while others may recommend a study, such as videofluoroscopic swallowing study (also called modified barium swallow) or fiberoptic endoscopic eval.
Speech/language pathologist	Speech/language eval	To identify impairments in receptive & expressive language & determine if speech/language therapy &/or AAC would help improve communication skills
Physical therapist	Physical eval	To evaluate range of motion, strength, coordination, & tone; & develop a plan for improving gross motor function (e.g., ambulation, mobility)
Occupational therapist	Physical eval	To evaluate fine motor activities (incl dexterity & handwriting) & develop plan to improve self-care skills (e.g., dressing, toileting, & grooming)
Physiatrist (rehab doctor)	History & physical exam	To evaluate function & guide team in maximizing abilities
Orthopedic specialist	History & physical exam	To evaluate scoliosis & hip dislocation (may be done in conjunction w/ physiatry)
Gastroenterologist	History & physical exam	To assess feeding/eating, digestive problems (incl constipation & gastroesophageal reflux), & nutrition using history, growth measurements, & (if needed) gastrointestinal investigations
Nutritionist	Review caloric intake & expended energy	To determine nutritional & fluid needs to ensure adequate growth
Pulmonologist (or sleep medicine physician)	Lung & breathing eval	To determine whether respiratory compromise is present (from weakness, scoliosis, or aspiration) & assess for sleep apnea (often central in etiology)
Urologist	Review bladder function	To determine if upper or lower motor neuron involvement of bladder requires intervention
Psychologist	Discussion of medical diagnosis	Psychological assessment for older patients to determine awareness & understanding of disease & its consequences
Neuropsychologist	Formal eval (when age appropriate) to incl standardized metrics of cognition & other areas of brain development	To determine impact of disrupted cerebral pathways on learning & cognitive development, as well as develop plan to optimize learning strategies

AAC = augmentative alternative communication; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

No specific therapy is currently available for Alexander disease; however, clinicians and families should routinely check ClinicalTrials.gov or other experts regarding potential experimental therapies [Hagemann et al 2018].

Management is supportive and includes attention to general care, feeding and nutrition, anti-seizure medication (ASM) for seizure control, physical and occupational therapy, speech and language therapy, and appropriate educational services. The management by multidisciplinary specialists as outlined in Table 9 is recommended.

Table 9. Treatment of Manifestations in Individuals with Alexander Disease

Manifestation/ Concern	Treatment	Considerations
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Seizures	ASM	Neurologists may wish to consider initiating ASM even in setting of provoked seizures (by illness) or a single seizure w/normal EEG, given high risk for epilepsy & regression.
Speech/ Language	Speech/language therapy	Consider need for assistive communication devices.
Vomiting	Reflux medications, valproic acid	Follow nutritional status & growth.
Nutritional support	Additional calories, medications that stimulate appetite	Consider gastrostomy tube for persons w/significant dysphagia.
Constipation	Motility agents, stool softeners, enemas	Constipation may contribute to vomiting & should be considered in persons for whom vomiting is major symptom.
Tone	Spasticity medications for ↑ tone	Botox/phenol injections may also be considered for targeted approach.
	Treatment for scoliosis	Particularly in those w/low tone
Tremor	Various medications can be tried to ↓ tremor, incl but not limited to carbidopa/levodopa.	Consultation w/OT for non-medical strategies may be considered.
UTI or other bacterial illness	Antibiotics if appropriate	Additional prevention strategies may be considered.
Bone health	Vitamin D	Consider checking serum levels of vitamin D 25-OH.

ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; OT = occupational therapist; UTI = urinary tract infection

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 specialists 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.
    - Hearing consultants should be a part of the child's IEP team to support access to academic material.
    - 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.

Surveillance

Table 10. Recommended Surveillance for Individuals with Alexander Disease

System/Concern	Evaluation	Frequency
Growth parameters	Height, weight, head circumference, heart rate, vital signs	Every 6 mos
Neurology	Neurologic exam	Every 3-6 mos (Younger persons & those early in disease course may require more frequent assessment.)
Development	Monitor developmental progress & educational needs.	At each visit
PT/OT	Gross & fine motor rating scales	Per therapist
Swallow eval	Clinical or radiologic eval	Annually [1]
Speech/ Language	Expressive & receptive language skills	Per therapist

Table 10. continued from previous page.

System/Concern	Evaluation	Frequency
Gastrointestinal	History & eval of GI tract for esophageal dysfunction, reflux, vomiting, & constipation	Annually [1]
Orthopedics	Clinical or radiographic assessment for scoliosis	
Orthostatic vitals	Measurement of heart rate & blood pressure while lying, sitting, & standing	
Psychiatry/ Psychology	Discussion of impact of diagnosis on patient's physical & mental health	
Pulmonary	Assessment of respiratory function	
Sleep medicine	Discussion about sleep apnea & sleep study, if indicated	
Urology	Review of urinary tract symptoms & bladder scan or other testing, if indicated	

GI = gastrointestinal; OT = occupational therapy; PT = physical therapy
1. Active issues may require more frequent evaluations

Evaluation of Relatives at Risk

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

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

Alexander disease is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, most reported individuals with molecularly confirmed Alexander disease have the disorder as the result of a *de novo GFAP* pathogenic variant, though familial cases have occurred [Messing 2018].
- A study on unrelated individuals with Alexander disease revealed that the *GFAP* pathogenic variant was on the paternal chromosome in a majority of individuals (24/28), suggesting that most instances of *de novo* mutation occur during spermatogenesis rather than in the embryo [Li et al 2006].

- Some individuals with slowly progressive adult Alexander disease have an affected parent [Namekawa et al 2002, Okamoto et al 2002, Stumpf et al 2003, Thyagarajan et al 2004, van der Knaap et al 2006, Messing et al 2012].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., a proband who appears to be the only affected family member).
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. * Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism. Sib recurrence of neuropathologically and molecularly proven Alexander disease in families in which the parents are neurologically intact suggest the possibility of germline mosaicism in one of the parents [Messing et al 2012, Messing 2018].

      * An individual with somatic and germline mosaicism for a *GFAP* pathogenic variant may be mildly/minimally affected [Flint et al 2012].
- Some individuals with Alexander disease may appear to be the only affected family member because of failure to recognize the disorder in other family members, early death of the parent before the onset of symptoms, late onset of the disease in the affected parent, or reduced penetrance.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Variable expressivity may occur in heterozygous family members (see Genotype-Phenotype Correlations and Penetrance).
- If the *GFAP* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Messing 2018].
- If the parents have not been tested for the *GFAP* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband with Alexander disease appears to be lower than 1:200 (i.e., <0.5%) because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband

- Individuals with Alexander disease with significant neurologic and cognitive impairment typically do not reproduce.
- Each child of an adult with slowly progressing Alexander disease has a 50% chance of inheriting the *GFAP* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *GFAP* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

Predictive testing for Alexander disease (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *GFAP* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of Alexander disease, it is appropriate to consider testing of symptomatic individuals regardless of age.

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 or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e. the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *GFAP* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Alexander disease 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.

- **End Alexander Disease**
  www.endaxd.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  MD
  Alexander Disease Information Page
- **National Library of Medicine Genetics Home Reference**
  Alexander disease
- **Waisman Center for Alexander Disease**
  University of Wisconsin-Madison
  1500 Highland Avenue
  Room 277
  Madison WI 53705
  Phone: 608-263-5776
  Fax: 608-263-0529
  www.waisman.wisc.edu/alexander/index.html
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  ulf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

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. Alexander Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GFAP	17q21.31	Glial fibrillary acidic protein	Human Intermediate Filament Database GFAP GFAP database	GFAP	GFAP

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 Alexander Disease (View All in OMIM)

137780	GLIAL FIBRILLARY ACIDIC PROTEIN; GFAP
203450	ALEXANDER DISEASE; ALXDRD

Molecular Pathogenesis

GFAP encodes glial fibrillary acidic protein, the main intermediate filament protein expressed in mature astrocytes of the central nervous system. GFAP is a homotetramer, consisting of two dimers of paired alpha-helices and stabilized by a vast array of intermolecular interactions [Kim et al 2018]. As a cytoskeletal protein

providing structural stability, GFAP appears to be important in modulating the morphology and motility of astrocytes [Eng et al 2000, Messing & Brenner 2003b]; however, it may have other as-yet unknown functions.

Mechanism of disease causation. Gain of function. The cellular mechanism causing the Alexander disease phenotype remains unresolved; however, abnormal protein oligomerization that alters either the oligomerization or the solubility of the protein has been proposed [Hsiao et al 2005, Der Perng et al 2006]. Proteins encoded by pathogenic variants in *GFAP* may interfere with the intermolecular interactions necessary to stabilize the protein, leading to increased protein aggregation [Kim et al 2018, Viedma-Poyatos et al 2018]. Expression of an abnormal protein may result in disturbance of the normal interaction between astrocytes and oligodendrocytes, resulting in hypomyelination or demyelination. See Messing et al [2001], Gorospe & Maletkovic [2006], and Sosunov et al [2018].

Consistent with a gain-of-function mechanism, the majority of disease-associated variants are missense or in-frame variants [Li et al 2005, van der Knaap et al 2006, Murakami et al 2008, Ayaki et al 2010, Flint et al 2012, Schmidt et al 2013].

***GFAP*-specific laboratory technical considerations.** The most common pathogenic variants occur at three amino acid residues (p.Arg79, p.Arg88, and p.Arg239).

Most *GFAP* pathogenic variants have been reported on transcript NM_002055.4; however, a heterozygous variant (p.Arg430His) presently only on the transcript NM_001131019.2 has been identified in multiple individuals [Melchionda et al 2013, Karp et al 2019, Helman et al 2020] (see Table 11).

Table 11. Notable *GFAP* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change [1]	Comment [Reference]
NM_002055.4 NP_002046.1	c.218T>C	p.Met73Thr	Recurrent pathogenic variants commonly (but not necessarily exclusively) observed in the infantile form (See Table 3 [pdf].)
	c.226C>T	p.Leu76Phe	
	c.230A>G	p.Asn77Ser	
	c.235C>T	p.Arg79Cys	
	c.262C>T	p.Arg88Cys	
	c.290T>C	p.Leu97Pro	
	c.715C>T	p.Arg239Cys	
	c.716G>A	p.Arg239His	
	c.716G>T	p.Arg239Leu	
	c.716G>C	p.Arg239Pro	
	c.1055T>C	p.Leu352Pro	
	c.1117G>A	p.Glu373Lys	
	c.1249delG	p.Asp417MetfsTer15	
	c.235C>T	p.Arg79Cys	Recurrent pathogenic variants commonly (but not necessarily exclusively) observed in the juvenile form (See Table 3 [pdf].)
	c.262C>T	p.Arg88Cys	
	c.628G>A	p.Glu210Lys	
	c.704T>C	p.Leu235Pro	
	c.715C>T	p.Arg239Cys	
	c.1246C>T	p.Arg416Trp	

Table 11. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change [1]	Comment [Reference]
	c.197G>A	p.Arg66Gln	Recurrent pathogenic variants commonly (but not necessarily exclusively) observed in the adult form (See Table 3 [pdf].)
	c.208C>T	p.Arg70Trp	
	c.209G>A	p.Arg70Gln	
	c.221T>C	p.Met74Thr	
	c.613G>A	p.Glu205Lys	
	c.772C>T	p.Arg258Cys	
	c.827G>T	p.Arg276Leu	
	c.1076T>C	p.Leu359Pro	
	c.1090G>C	p.Ala364Thr	
	c.1178G>T	p.Ser393Ile	
	c.1246C>T	p.Arg416Trp	
NM_001131019.2 NP_001124491.1	c.1289G>A	p.Arg430His	Recurrent pathogenic variant reported on alternate transcript [Melchionda et al 2013, Karp et al 2019, Helman et al 2020]

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. The most common pathogenic variants occur at the three amino acid residues p.Arg79, p.Arg88, and p.Arg239.

Chapter Notes

Author Notes

Website for Amy Waldman at the Children's Hospital of Philadelphia
www.chop.edu/doctors/waldman-amy

Website for Siddharth Srivastava at Boston Children's Hospital
www.childrenshospital.org/directory/physicians/s/siddharth-srivastava

Clinical trial pertaining to outcome measures of Alexander disease at the Children's Hospital of Philadelphia
www.research.chop.edu/axd-outcomes

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Revision History

- 12 November 2020 (bp) Comprehensive update posted live
- 8 January 2015 (me) Comprehensive update posted live
- 22 April 2010 (me) Comprehensive update posted live
- 9 March 2007 (cd,jrg) Revision: sequence analysis of select exons and targeted mutation analysis no longer clinically available

- 2 October 2006 (me) Comprehensive update posted live
- 28 September 2004 (me) Comprehensive update posted live
- 5 May 2003 (cd,jrg) Revision: molecular genetic testing clinically available
- 15 November 2002 (me) Review posted live
- 24 April 2002 (jrg) Original submission

References

Literature Cited

Ayaki T, Shinohara M, Tatsumi S, Namekawa M, Yamamoto T. A case of sporadic adult Alexander disease presenting with acute onset, remission and relapse. J Neurol Neurosurg Psychiatry. 2010;81:1292–3. PubMed PMID: 20562394.

de Beer M, Engelen M, van Geel BM. Frequent occurrence of cerebral demyelination in adrenomyeloneuropathy. Neurology. 2014;83:2227–31. PubMed PMID: 25378668.

Der Perng M, Su M, Wen SF, Li R, Gibbon T, Prescott AR, Brenner M, Quinlan RA. The Alexander disease-causing glial fibrillary acidic protein mutant, R416W, accumulates into Rosenthal fibers by a pathway that involves filament aggregation and the association of alpha B-crystallin and HSP27. Am J Hum Genet. 2006;79:197–213. PubMed PMID: 16826512.

Eng LF, Ghirnikar RS, Lee YL. Glial fibrillary acidic protein: GFAP-thirty-one years (1969-2000). Neurochem Res. 2000;25:1439–51. PubMed PMID: 11059815.

Flint D, Li R, Webster LS, Naidu S, Kolodny E, Percy A, van der Knaap M, Powers JM, Mantovani JF, Ekstein J, Goldman JE, Messing A, Brenner M. Splice site, frameshift, and chimeric GFAP mutations in Alexander disease. Hum Mutat. 2012;33:1141–8. PubMed PMID: 22488673.

Gordon N. Alexander disease. Eur J Paediatr Neurol. 2003;7:395–9. PubMed PMID: 14623218.

Gorospe JR, Maletkovic J. Alexander disease and megalencephalic leukoencephalopathy with subcortical cysts: leukodystrophies arising from astrocyte dysfunction. Ment Retard Dev Disabil Res Rev. 2006;12:113–22. PubMed PMID: 16807904.

Green L, Berry IR, Childs AM, McCullagh H, Jose S, Warren D, Craven I, Camm N, Prescott K, van der Knaap MS, Sheridan E, Livingston JH. Whole exon deletion in the GFAP gene is a novel molecular mechanism causing Alexander disease. Neuropediatrics. 2018 Apr;49:118–22. PubMed PMID: 29253910.

Hagemann TL, Powers B, Mazur C, et al. Antisense suppression of glial fibrillary acidic protein as a treatment for Alexander disease. Ann Neurol. 2018;83:27–39. PubMed PMID: 29226998.

Helman G, Takanohashi A, Hagemann TL, Perng MD, Walkiewicz M, Woidill S, Sase S, Cross Z, Du Y, Zhao L, Waldman A, Haake BC, Fatemi A, Brenner M, Sherbini O, Messing A, Vanderver A, Simons C, Type II. Alexander disease caused by splicing errors and aberrant overexpression of an uncharacterized GFAP isoform. Hum Mutat. 2020;41:1131–7. PubMed PMID: 32126152.

Hsiao VC, Tian R, Long H, Der Perng M, Brenner M, Quinlan RA, Goldman JE. Alexander-disease mutation of GFAP causes filament disorganization and decreased solubility of GFAP. J Cell Sci. 2005;118:2057–65. PubMed PMID: 15840648.

Karp N, Lee D, Shickh S, Jenkins ME. c. 1289G>A (p.Arg430His) variant in the epsilon isoform of the GFAP gene in a patient with adult onset Alexander disease. Eur J Med Genet. 2019;62:235–8. PubMed PMID: 30048824.

Kim B, Kim S, Jin MS. Crystal structure of the human glial fibrillary acidic protein 1B domain. Biochem Biophys Res Commun. 2018;503:2899–905. PubMed PMID: 30126635.

Li R, Johnson AB, Salomons G, Goldman JE, Naidu S, Quinlan R, Cree B, Ruyle SZ, Banwell B, D'Hooghe M, Siebert JR, Rolf CM, Cox H, Reddy A, Gutierrez-Solana LG, Collins A, Weller RO, Messing A, van der Knaap MS, Brenner M. Glial fibrillary acidic protein mutations in infantile, juvenile, and adult forms of Alexander disease. Ann Neurol. 2005;57:310–26. PubMed PMID: 15732097.

Li R, Johnson AB, Salomons GS, van der Knaap MS, Rodriguez D, Boespflug-Tanguy O, Gorospe JR, Goldman JE, Messing A, Brenner M. Propensity for paternal inheritance of de novo mutations in Alexander disease. Hum Genet. 2006;119:137–44. PubMed PMID: 16365765.

Li R, Messing A, Goldman J, Brenner M. GFAP mutations in Alexander disease. Int J Dev Neurosci. 2002;20:259–68. PubMed PMID: 12175861.

Lynch DS, Rodrigues Brandão de Paiva A, Zhang WJ, Bugiardini E, Freua F, Tavares Lucato L, Macedo-Souza LI, Lakshmanan R, Kinsella JA, Merwick A, Rossor AM, Bajaj N, Herron B, McMonagle P, Morrison PJ, Hughes D, Pittman A, Laurà M, Reilly MM, Warren JD, Mummery CJ, Schott JM, Adams M, Fox NC, Murphy E, Davagnanam I, Kok F, Chataway J, Houlden H. Clinical and genetic characterization of leukoencephalopathies in adults. Brain. 2017;140:1204–11. PubMed PMID: 28334938.

Martidis A, Yee RD, Azzarelli B, Biller J. Neuro-ophthalmic, radiographic, and pathologic manifestations of adult- onset Alexander disease. Arch Ophthalmol. 1999;117:265–7. PubMed PMID: 10037578.

Melchionda L, Fang M, Wang H, Fugnanesi V, Morbin M, Liu X, Li W, Ceccherini I, Farina L, Savoiardo M, D'Adamo P, Zhang J, Costa A, Ravaglia S, Ghezzi D, Zeviani M. Adult-onset Alexander disease, associated with a mutation in an alternative GFAP transcript, may be phenotypically modulated by a non-neutral HDAC6 variant. Orphanet J Rare Dis. 2013;8:66. PubMed PMID: 23634874.

Messing A. Alexander disease. Handb Clin Neurol. 2018;148:693–700. PubMed PMID: 29478608.

Messing A, Brenner M. Alexander disease: GFAP mutations unify young and old. Lancet Neurol. 2003a;2:75. PubMed PMID: 12849260.

Messing A, Brenner M. GFAP: functional implications gleaned from studies of genetically engineered mice. Glia. 2003b;43:87–90. PubMed PMID: 12761871.

Messing A, Goldman JE, Johnson AB, Brenner M. Alexander disease: new insights from genetics. J Neuropathol Exp Neurol. 2001;60:563–73. PubMed PMID: 11398833.

Messing A, Li R, Naidu S, Taylor JP, Silverman L, Flint D, van der Knaap MS, Brenner M. Archetypal and new families with Alexander disease and novel mutations in GFAP. Arch. Neurol. 2012;69:208–14. PubMed PMID: 21987397.

Murakami N, Tsuchiya T, Kanazawa N, Tsujino S, Nagai T. Novel deletion mutation in GFAP gene in an infantile form of Alexander disease. Pediatr Neurol. 2008;38:50–2. PubMed PMID: 18054694.

Namekawa M, Takiyama Y, Aoki Y, Takayashiki N, Sakoe K, Shimazaki H, Taguchi T, Tanaka Y, Nishizawa M, Saito K, Matsubara Y, Nakano I. Identification of GFAP gene mutation in hereditary adult-onset Alexander's disease. Ann Neurol. 2002;52:779–85. PubMed PMID: 12447932.

Namekawa M, Takiyama Y, Honda J, Sakoe K, Naoi T, Shimazaki H, Yamagata T, Momoi MY, Nakano I. A novel adult case of juvenile-onset Alexander disease: complete remission of neurologic symptoms for over 12 years, despite insidiously progressive cervicomedullary atrophy. Neurol Sci. 2012;33:1389–92. PubMed PMID: 22198646.

Okamoto Y, Mitsuyama H, Jonosono M, Hirata K, Arimura K, Osame M, Nakagawa M. Autosomal dominant palatal myoclonus and spinal cord atrophy. J Neurol Sci. 2002;195:71–6. PubMed PMID: 11867077.

Prust M, Wang J, Morizono H, Messing A, Brenner M, Gordon E, Hartka T, Sokohl A, Schiffmann R, Gordish-Dressman H, Albin R, Amartino H, Brockman K, Dinopoulos A, Dotti MT, Fain D, Fernandez R, Ferreira J, Fleming J, Gill D, Griebel M, Heilstedt H, Kaplan P, Lewis D, Nakagawa M, Pedersen R, Reddy A, Sawaishi Y,

Schneider M, Sherr E, Takiyama Y, Wakabayashi K, Gorospe JR, Vanderver A. GFAP mutations, age at onset, and clinical subtypes in Alexander disease. Neurology. 2011;77:1287–94. PubMed PMID: 21917775.

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

Schmidt H, Kretzschmar B, Lingor P, Pauli S, Schramm P, Otto M, Ohlenbusch A, Brockmann K. Acute onset of adult Alexander disease. J Neurol Sci. 2013;331:152–4. PubMed PMID: 23706596.

Shiihara T, Sawaishi Y, Adachi M, Kato M, Hayasaka K. Asymptomatic hereditary Alexander's disease caused by a novel mutation in GFAP. J Neurol Sci. 2004;225:125–7. PubMed PMID: 15465095.

Sosunov A, Olabarria M, Goldman JE. Alexander disease: an astrocytopathy that produces a leukodystrophy. Brain Pathol. 2018;28:388–98. PubMed PMID: 29740945.

Springer S, Erlewein R, Naegele T, Becker I, Auer D, Grodd W, Krageloh-Mann I. Alexander disease – classification revisited and isolation of a neonatal form. Neuropediatrics. 2000;31:86–92. PubMed PMID: 10832583.

Spritzer SD, Zarkou S, Ireland SP, Carter JL, Goodman BP. Autonomic dysfunction in adult-onset alexander disease: a case report and review of the literature. Clin Auton Res. 2013;23:333–8. PubMed PMID: 23925719.

Stumpf E, Masson H, Duquette A, Berthelet F, McNabb J, Lortie A, Lesage J, Montplaisir J, Brais B, Cossette P. Adult Alexander disease with autosomal dominant transmission: a distinct entity caused by mutation in the glial fibrillary acid protein gene. Arch Neurol. 2003;60:1307–12. PubMed PMID: 12975300.

Thyagarajan D, Chataway T, Li R, Gai WP, Brenner M. Dominantly-inherited adult-onset leukodystrophy with palatal tremor caused by a mutation in the glial fibrillary acidic protein gene. Mov Disord. 2004;19:1244–8. PubMed PMID: 15390001.

van der Knaap MS, Naidu S, Breiter SN, Blaser S, Stroink H, Springer S, Begeer JC, van Coster R, Barth PG, Thomas NH, Valk J, Powers JM. Alexander disease: diagnosis with MR imaging. AJNR Am J Neuroradiol. 2001;22:541–52. PubMed PMID: 11237983.

van der Knaap MS, Ramesh V, Schiffmann R, Blaser S, Kyllerman M, Gholkar A, Ellison DW, van der Voorn JP, van Dooren SJ, Jakobs C, Barkhof F, Salomons GS. Alexander disease: ventricular garlands and abnormalities of the medulla and spinal cord. Neurology. 2006;66:494–8. PubMed PMID: 16505300.

van der Knaap MS, Salomons GS, Li R, Franzoni E, Gutierrez-Solana LG, Smit LM, Robinson R, Ferrie CD, Cree B, Reddy A, Thomas N, Banwell B, Barkhof F, Jakobs C, Johnson A, Messing A, Brenner M. Unusual variants of Alexander's disease. Ann Neurol. 2005;57:327–38. PubMed PMID: 15732098.

Viedma-Poyatos Á, de Pablo Y, Pekny M, Pérez-Sala D. The cysteine residue of glial fibrillary acidic protein is a critical target for lipoxidation and required for efficient network organization. Free Radic Biol Med. 2018;120:380–94. PubMed PMID: 29635011.

Wada Y, Yanagihara C, Nishimura Y, Namekawa M. Familial adult-onset Alexander disease with a novel mutation (D78N) in the glial fibrillary acidic protein gene with unusual bilateral basal ganglia involvement. J Neurol Sci. 2013;331:161–4. PubMed PMID: 23743246.

Yoshida T, Sasaki M, Yoshida M, Namekawa M, Okamoto Y, Tsujino S, Sasayama H, Mizuta I, Nakagawa M, et al. Nationwide survey of Alexander disease in Japan and proposed new guidelines for diagnosis. J Neurol. 2011;258:1998–2008. PubMed PMID: 21533827.

Yoshida T, Mizuta I, Yasuda R, Nakagawa M, Mizuno T. Characteristics of cerebral lesions in adult-onset Alexander disease. Neurol Sci. 2020;41:225–7. PubMed PMID: 31422506.

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