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ASAH1-Related Disorders

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Summary

Clinical characteristics

The spectrum of *ASAH1*-related disorders ranges from Farber disease (FD) to spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME).

- Classic FD is characterized by onset in the first weeks of life of painful, progressive deformity of the major joints; palpable subcutaneous nodules of joints and mechanical pressure points; and a hoarse cry resulting from granulomas of the larynx and epiglottis. Life expectancy is usually less than two years. In the other less common types of FD, onset, severity, and primary manifestations vary.
- SMA-PME is characterized by early-childhood-onset progressive lower motor neuron disease manifest typically between ages three and seven years as proximal lower-extremity weakness, followed by progressive myoclonic and atonic seizures, tremulousness/tremor, and sensorineural hearing loss. Myoclonic epilepsy typically begins in late childhood after the onset of weakness and can include jerking of the upper limbs, action myoclonus, myoclonic status, and eyelid myoclonus. Other findings include generalized tremor, and cognitive decline. The time from disease onset to death from respiratory complications is usually five to 15 years.

Diagnosis/testing

The diagnosis of an *ASAH1*-related disorder is established in a proband with suggestive clinical findings by identification of biallelic pathogenic variants in *ASAH1* and/or decreased activity of the enzyme acid ceramidase in peripheral blood leukocytes or cultured skin fibroblasts.

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Management

Treatment of manifestations is symptomatic and multidisciplinary.

- For FD: Management may include gastrostomy tube placement, surgical removal of oral and airway granulomas, and treatment of seizures as per standard practice. Hematopoietic stem cell transplantation may be an option in affected individuals who do not have significant neurologic involvement.
- For SMA-PME: Management may include standard treatment for hearing loss, scoliosis, seizures, and tremor. Weakness can be mitigated with the use of orthotics, wheelchairs, or other assistive devices.

Surveillance:

- For FD: At each visit assess growth with emphasis on feeding and nutritional status; airway, joint mobility, and developmental milestones.
- For SMA-PME: At each visit monitor growth with emphasis on feeding and nutritional status, pulmonary function, back for evidence of scoliosis, strength, seizure control, functional capacity (e.g., mobility, communication); assess hearing annually.

Genetic counseling

ASAH1-related disorders are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Sibs with the same two pathogenic variants would be expected to have the same (or very similar) phenotype. Once the *ASAH1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

ASAH1-Related Disorders: Included Phenotypes
• Farber disease • Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) [1] • Spinal muscular atrophy without epilepsy • Progressive adult-onset brachydactyly due to osteolysis

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of this phenotype, see Differential Diagnosis.

Diagnosis

Suggestive Findings

The following phenotypes of the *ASAH1*-related disorders **should be suspected** based on the following age-related clinical and associated findings.

Farber disease (FD) **should be strongly suspected** in a **neonate or toddler** with the following:

Clinical findings

- Subcutaneous nodules located at pressure points and joints
- Swollen, painful joints with progressive limitation of range of motion resulting in contractures
- Hoarse voice/cry

Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME)should be suspected in a previously well **child** with the following:

Clinical findings

- Normal motor and intellectual milestones
- Childhood-onset progressive, proximal muscle weakness at a mean age of five years
- Epilepsy characterized by myoclonic and atonic seizures that are refractory to treatment. Other seizure types include absence seizures and the occasional generalized tonic-clonic seizure.

Other

- Electromyography (EMG): evidence of chronic denervation
- Electroencephalography (EEG): generalized polyspike and wave discharges
- Muscle biopsy: evidence of a neurogenic process; absence of mitochondrial-related pathology
- Absence of biallelic pathogenic variants in *SMN1* (the cause of the most common form of SMA)

Establishing the Diagnosis

The diagnosis of an *ASAH1*-related disorder **is established** in a proband with suggestive clinical findings by identification of biallelic pathogenic variants in *ASAH1* (see Table 1) and/or decreased activity of the enzyme acid ceramidase in peripheral blood leukocytes or cultured skin fibroblasts.

Acid ceramidase activity varies in peripheral blood leukocytes or cultured skin fibroblasts from complete loss often observed in Farber disease [Levade et al 2009] to modest decrease (6%-32%) in SMA-PME [Zhou et al 2012, Gan et al 2015]. Note: The level of acid ceramidase activity can overlap in FD and SMA-PME.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Farber disease is relatively specific, young children with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1). In contrast, children within the phenotypic spectrum of SMA with PME – which can in its early stages be indistinguishable from other inherited disorders with lower motor neuron weakness and/or epilepsy – are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of an *ASAH1*-related disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ASAH1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis should be performed as multiexon and whole-gene deletions have been reported.
- **A multigene panel** that includes *ASAH1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders with lower motor neuron weakness and/or epilepsy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. **Exome array** (when clinically available) may be considered if exome sequencing is nondiagnostic.

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 *ASAH1*-Related Disorders

Gene [1]	Method	Proportion of Probands by Phenotype with Pathogenic Variants [2] Detectable by Method	
		Farber disease	SMA-PME
ASAH1	Sequence analysis [3]	35/36	12/13
	Gene-targeted deletion/duplication analysis [4]	1/36 [5]	1/13 [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. One proband was a compound heterozygote for an intronic pathogenic variant (c.917+4A>G) and a deletion of exons 3-5 [Alves et al 2013] (see Molecular Genetics, **Pathogenic variants**).
6. One proband was a compound heterozygote for the recurrent pathogenic variant (c.125C>T) and a whole-gene deletion [Zhou et al 2012] (see Molecular Genetics, **Pathogenic variants**).

Clinical Characteristics

Clinical Description

ASAH1-related disorders comprise a spectrum that ranges from Farber disease (FD) to spinal muscular atrophy (SMA) with or without epilepsy. *ASAH1*-related disorders vary in the age of onset of manifestations, the systems affected, and severity and progression of the disease. While Farber disease has been recognized clinically and diagnosed for decades based on enzyme analysis [Farber 1952, Abul-Haj et al 1962], the recognition of *ASAH1*-related SMA and associated findings is a recent discovery based on the use of genomic testing; thus, the understanding of the latter *ASAH1*-related phenotype is still evolving.

Furthermore, although to date SMA-PME and FD have been considered to be two distinct phenotypes with differences in age of onset and primary involvement of different organ systems, a girl with features of both phenotypes illustrates the phenotypic continuum of *ASAH1*-related disorders that is possible [Teoh et al 2016]. The individual presented at age three years with polyarticular arthritis (without subcutaneous nodules) followed

by progressive motor neuron disease without seizures. At age seven years she developed cognitive deficits and a hoarse voice.

Farber Disease (FD)

Farber disease in its classic form is an early-onset, progressive, and fatal disease. With better understanding of the natural history of FD over time, investigators have suggested categorization into several types based on age of onset, severity, and primary manifestations [Levade et al 2009]. Nonetheless, these Farber disease phenotypes can realistically be considered part of a continuum.

Type 1 FD (classic FD) is characterized by the triad of (1) painful, progressive deformity of the joints of the elbows, wrists, hands, knees, and feet; (2) palpable subcutaneous nodules that tend to occur at joints and mechanical pressure points, but can occur elsewhere; and (3) a hoarse cry resulting from granulomas of the larynx and epiglottis. These findings often manifest in the first weeks of life.

Neurologic involvement, reported in a significant proportion of children, can be difficult to assess given the extent of contractures and joint deformity. Many children with type 1 FD have a lower motor neuron disease that manifests as hypotonia and muscle atrophy; EMG studies show chronic denervation [Levade et al 2009]. A minority of children can have infantile spasms [Levade et al 2009].

Other features can include a cherry red spot of the macula [Cogan et al 1966].

Infiltrative pulmonary disease causes respiratory insufficiency that typically results in death before age two years [Ehlert et al 2007, Levade et al 2009].

Type 2 FD ("Intermediate FD") is characterized by age of onset of approximately eight months. Although the classic triad is present, the neurologic involvement is considered less severe than that of type 1 FD [Burck et al 1985, Al Jasmi 2012, Chedrawi et al 2012, Kostik et al 2013]. Seizures become relatively more common over time [Levade et al 2009].

Life expectancy is to mid-childhood.

Type 3 FD (mild FD) is characterized by joint swelling, pain, and contractures with onset after age one year. Many of these children will be mistakenly diagnosed with a juvenile idiopathic arthritis [Schuchman 2014]. Neurologic findings are observed in approximately half of affected children [Levade et al 2009]. Approximately 30% (8/25) of individuals with either type 2 FD or type 3 FD show marked cognitive deficits (IQ<80).

Life expectancy is into the teen years [Samuelsson & Zetterström 1971, Pavone et al 1980, Fiumara et al 1993].

Type 4 FD (neonatal-visceral FD) is characterized by neonatal severe hepatosplenomegaly without the classic triad [Cartigny et al 1985, Qualman et al 1987, Kattner et al 1997].

Death occurs within the first days to weeks of life.

Type 5 FD (neurologic FD) is characterized by six to 12 months of normal development followed by refractory seizures, progressive paraparesis, and speech regression [Eviatar et al 1986, Jameson et al 1987].

Subcutaneous nodules can be present, but are usually mild. Lung infiltration and hepatosplenomegaly do not occur.

Diagnosis of FD prior to the availability of *ASAH1* molecular genetic testing. The diagnosis of FD was formerly based on histologic and biochemical findings in individuals with a typical clinical presentation [Levade et al 2009]. Biopsy of the subcutaneous nodules can show characteristic curvilinear granulomatous infiltrations or "Farber bodies" under light microscopy in macrophages, histiocytes, foam cells, and fibroblasts [Schmoeckel 1980, Burck et al 1985].

Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy (SMA-PME)

SMA-PME is characterized by early-childhood onset of progressive proximal weakness followed by progressive myoclonic and atonic seizures, tremulousness/tremor, and sensorineural hearing loss [Zhou et al 2012, Gan et al 2015, Topaloglu & Melki 2016].

Lower motor neuron disease, the first manifestation in the majority of affected individuals (16/17), is typically evident as weakness between ages three and seven years (median 5 years; range 17 months [Rubboli et al 2015] to 15 years [Dyment et al 2014]). Initially weakness is proximal, and progresses from initial clumsiness/frequent falls to a waddling gait and need for assistive devices for walking.

The lower motor neuron disease also involves the muscles of respiration; thus, recurrent aspiration pneumonias are common (6/16).

Epilepsy. Although seizures often begin in late childhood, after the onset of weakness, exceptions occur [Filosto et al 2016, Topaloglu & Melki 2016].

Myoclonic seizures, which begin as jerking of the upper limbs, are more proximal than distal. Action myoclonus, myoclonic status, and eyelid myoclonus have also been reported [Rubboli et al 2015, Oguz Akarsu et al 2016]. Progressive increase in frequency of the myoclonus contributes significantly to the decreasing motor function [Dyment et al 2014, Rubboli et al 2015].

Atonic seizures of the head and/or torso are also an early presenting seizure type.

Absence seizures are observed in more than half of affected individuals [Gan et al 2015].

Although reported, generalized tonic-clonic seizures are less common than the other types.

Seizures vary in frequency from a few per day initially to a few per minute as the disease evolves. Over time, seizures become refractory to treatment.

Brain MRI is normal.

A generalized tremor, sometimes described as overall tremulousness, has been observed in eight of 16 affected individuals reported to date.

Sensorineural hearing loss (SNHL) that ranges from mild to profound hearing loss at high frequencies has been reported in four of 16 affected individuals [Dyment et al 2014, Gan et al 2015]. The hearing loss was not present at birth.

Musculoskeletal. Scoliosis, observed in five of 16 individuals, ranged from mild [Rubboli et al 2015] to more severe [Zhou et al 2012].

Cognition. Early developmental milestones are typically achieved on time. Cognition is described as normal; however, one child with intellectual disability has been reported [Rubboli et al 2015].

A decline in cognitive ability has been described in children in the last weeks of disease.

In one child progressive cognitive decline was the first manifestation [Sathe & Pearson 2013].

Life expectancy is shortened. The time from disease onset to death has ranged from five to 15 years. Although most affected children die in their late teens [Zhou et al 2012], some individuals who have been symptomatic for more than two decades have lived into their twenties [Gan et al 2015, Filosto et al 2016, Kernohan et al 2017]

ASAH1-Related Spinal Muscular Atrophy without Epilepsy

Two sibs in one family have been reported with childhood-onset *ASAH1*-related spinal muscular atrophy [Filosto et al 2016] without any history of seizures or myoclonus. As adults, the sibs had mild proximal weakness that caused difficulty with walking. Both had scoliosis and a postural tremor. Fasciculation, contractures, and pulmonary disease/respiratory insufficiency were not observed. Sensorineural hearing loss was not reported [Filosto et al 2016].

Progressive Adult-Onset Brachydactyly Due to Osteolysis

A progressive adult-onset brachydactyly due to osteolysis has been reported in a single family with three affected family members who had progressive shortening of the fingers and toes due to severe osteolysis. Both reduced acid ceramidase activity and biallelic *ASAH1* pathogenic variants segregated with the phenotype in the family [Bonafé et al 2016].

Genotype-Phenotype Correlations

No obvious genotype-phenotype correlations have been observed in *ASAH1*-related disorder to date despite a predominance of nonsense and splice-site variants in SMA-PME and a predominance of missense variants in FD.

While recurrent pathogenic variants have been observed in the FD phenotype (e.g., c.703G>C) and the SMA-PME phenotype (e.g., c.125C>T), to date the only *ASAH1* pathogenic variants observed in both phenotypes are those that result in skipping of exon 6 [Bär et al 2001, Bashyam et al 2014, Dyment et al 2014].

There is a correlation in FD between age of death, in situ acid ceramidase activity, and the amount of ceramide accumulation [Levade et al 1995].

Nomenclature

Farber disease may also be referred to as "acid ceramidase deficiency," "Farber lipogranulomatosis," or "disseminated lipogranulomatosis."

Spinal muscular atrophy with progressive myoclonic epilepsy may also be referred to as "myoclonus with progressive distal muscular atrophy."

Prevalence

No known specific prevalence estimates exist for *ASAH1*-related disorders (recognized primarily as FD or SMA-PME). The disorders are ultra-rare and estimated to occur in fewer than one per million (www.orpha.net).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ASAH1*.

Differential Diagnosis

Table 2. Inherited Disorders to Consider in the Differential Diagnosis of *ASAH1*-Related Disorder: Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy (SMA-PME)

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Spinal muscular atrophy (SMA)	*SMN1*	AR	Lower MND w/onset age similar to SMA III	Earlier onset of weakness in SMA I & II; no seizures or hearing loss in SMA
Progressive myoclonus epilepsy, Lafora type	*EPM2* *NHLRC1*	AR	Progressive myoclonic seizures	No MND in Lafora disease
Unverricht-Lundborg disease	*CSTB*	AR	Progressive myoclonic jerks, tremor	Ataxia & lack of MND in Unverricht-Lundborg disease
MERRF	*MT-TK* [1]	mt	Myoclonic epilepsy, weakness, hearing loss	Ataxia, optic atrophy, & characteristic muscle biopsy (ragged red fibers) in MERRF

AR = autosomal recessive; MERRF = *m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers; MND = motor neuron disease; MOI = mode of inheritance; mt = mitochondrial

1. MT-TK, a mitochondrial DNA gene, is the gene most commonly associated with MERRF. Pathogenic variants in *MT-TF, MT-TL1, MT-TI*, and *MT-TP* have also been described in a subset of individuals with MERRF.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *ASAH1*-related disorder, the evaluations summarized in Table 3a and Table 3b (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3a. Recommended Evaluations Following Initial Diagnosis of an *ASAH1*-Related Disorder: Farber Disease

System/Concern	Evaluation	Comment
Constitutional	Assessment for evidence of failure to thrive	
Respiratory	Airway & pulmonary assessment for evidence of decreased pulmonary function due to granulomatous infiltrations	
Gastrointestinal	Assessment of swallowing, feeding, & nutritional status, particularly in later stages of disease	
Musculoskeletal	Referral to specialist in pediatric pain management	Pain due to deforming joint contractures
	Referral to rehabilitation specialist	Evaluate for functional disability in mobility & ADL.
Neurologic	Referral to pediatric neurologist	Assess for evidence of lower motor neuron disease or seizure activity.
Hematologic	Assessment for possible hematopoietic stem cell transplantation	For those w/type 2 or 3 FD, as non-CNS symptoms may be improved
Miscellaneous/ Other	Consultation w/clinical geneticist or genetic counselor	
	Referral to palliative care specialist	When deemed appropriate by family & care providers

ADL = activities of daily living

Table 3b. Recommended Evaluations Following Initial Diagnosis of an *ASAH1*-Related Disorder: Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy (SMA-PME)

System/Concern	Evaluation	Comment
Constitutional	Assessment for evidence of poor growth	
ENT	Audiology eval	Assess for sensorineural hearing loss.
Respiratory	Assessment for pulmonary disease secondary to recurrent aspiration	
Gastrointestinal	Assessment of feeding & nutritional status, esp in later stages of disease	
Musculoskeletal	Referral to rehabilitation specialist	Evaluate for functional disability in mobility & ADL.
	Assessment for scoliosis	
Neurologic	Referral to neurologist	To document extent of any weakness or other neurologic manifestations of SMA-PME & to evaluate for evidence of seizures
Miscellaneous/ Other	Consultation w/clinical geneticist or genetic counselor	
	Referral to palliative care specialist	When deemed appropriate by family & care providers

ADL = activities of daily living

Treatment of Manifestations

Treatment for those with FD and SMA-PME is symptomatic and multidisciplinary.

There is no curative treatment; measures that can improve the individual's quality of life are summarized in Table 4a and Table 4b. Depending on the age and presenting problems of the individual with an *ASAH1*-related disorder, a multidisciplinary evaluation involving health care providers from the following specialties is often necessary:

- **FD.** Rheumatology, neurology, general pediatrics, pain specialists, ENT and palliative care
- **SMA-PME.** Neurology, physical medicine and rehabilitation, feeding/gastroenterology, general pediatrics, audiology, clinical genetics, ophthalmology, and palliative care

Table 4a. Treatment of Manifestations in Individuals with *ASAH1*-Related Disorder: Farber Disease

Manifestation/ Concern	Treatment	Considerations/Other
Aspiration pneumonia	Gastrostomy tube placement	
Compromised airway	Tracheostomy	Consider if airway compromised due to presence of granulomas or for those who are ventilator dependent
	Surgical removal of granulomas in airway & oral cavity	In 1 case, surgical removal of granulomas resulted in improved oral intake & ↓ airway obstruction [Haraoka et al 1997].
Seizures	Standard AED as determined by treating neurologist	
Cutaneous & joint-related symptoms of FD	Bone marrow transplantation (BMT)	BMT does not alter progression of motor neuron disease or other neurologic manifestations [Yeager et al 2000, Torcoletti et al 2014, Cappellari et al 2016].
	Hematopoietic stem cell transplantation	Shown to improve only the peripheral manifestations of FD [Ehlert et al 2007, Jarisch et al 2014]

AED = antiepileptic drug

Table 4b. Treatment of Manifestations in Individuals with *ASAH1*-Related Disorder: Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy (SMA-PME)

Manifestation/ Concern	Treatment	Considerations/Other
Hearing loss	Standard treatment	See Hereditary Hearing Loss and Deafness Overview.
Aspiration pneumonia	Gastrostomy tube placement	
Scoliosis	Standard treatment	Consider referral to orthopedist.
Seizures	Standard antiepileptic medication as determined by treating neurologist	Improvement w/valproic acid observed in case reports, but ↓ in seizure frequency is temporary [Dyment et al 2014, Kernohan et al 2017]
Weakness	PT, OT, &/or physiatrist can assist w/use of orthotics, wheelchairs, or other assistive devices for mobility.	
Tremor	Standard pharmacologic treatment for tremors to ↓ severity	
Respiratory insufficiency	Respiratory therapy; standard treatments for recurrent pneumonias	Consider: • Noninvasive ventilatory support (CPAP/BiPAP); • Tracheostomy if ventilator dependent.

OT = occupational therapist; PT = physical therapist

Adaptive Disabilities

Note: The following information represents typical management recommendations for individuals with adaptive disabilities in the United States; standard recommendations may vary from country to country.

Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Surveillance

No guidelines have been published for the surveillance of *ASAH1*-related disorder.

Table 5a. Recommended Surveillance for Individuals with *ASAH1*-Related Disorder: Farber Disease

System/Concern	Evaluation	Frequency of Assessment / Comments
Constitutional	Monitor growth for evidence of failure to thrive.	At every visit, consider referral for feeding assessment if poor weight gain.
	Monitor general health & immunization status.	At each visit
Respiratory	Assessment of airway & for evidence of infiltrative pulmonary disease	Routinely
Musculoskeletal	Assessment of joints	Routinely
Developmental	Monitor achievement of developmental milestones.	Child psychologist or developmental pediatrician can assess for cognitive & behavioral issues. [1]

1. Surveillance relevant to the milder forms of Farber disease (i.e., type 1 FD and type 2 FD)

Table 5b. Recommended Surveillance for Individuals with *ASAH1*-Related Disorder: SMA-PME

System/Concern	Evaluation	Frequency/Comments
Constitutional	Monitor growth w/emphasis on feeding & nutritional status.	At each visit
	Monitor general health & immunization status.	
ENT	Audiologic eval	At least annually
Respiratory	Pulmonary function tests	Routinely
Musculoskeletal	Monitor for development of scoliosis.	Annually
Neurologic	Evaluate disease progression (extent of lower motor neuron disease; status of seizure control).	Routinely
Miscellaneous / Other	Assess for functional capacity & equipment needs (mobility, communication).	At each visit

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Acid ceramidase cDNA introduced into mice in a viral vector has been shown to be expressed over an extended period of time [Ramsubir et al 2008]. Further, the expressed acid ceramidase was able to ameliorate the manifestations in a mouse model of Farber disease [Alayoubi et al 2013].

Acid ceramidase introduced safely into in non-human, myelo-ablated primates using a lentiviral vector was successfully expressed in hematopoietic cells [Walia et al 2011].

Enzyme replacement therapy

- Human recombinant acid ceramidase reduced ceramide levels in the fibroblasts of an individual with Farber disease [He et al 2017].
- Recombinant acid ceramidase treatment of the mouse model resulted in no further accumulation of ceramide and improved survival [He et al 2017].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

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

Mode of Inheritance

ASAH1-related disorders are inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ASAH1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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. Sibs with the same two pathogenic variants would be expected to have the same (or very similar) phenotype.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with an *ASAH1*-related disorder would be expected to be obligate heterozygotes (carriers) for a pathogenic variant in *ASAH1*. However, fertility is unknown, as the only affected individual known to have reproduced to date was a woman with atypical SMA without seizures, diagnosed in the first trimester of pregnancy [Filosto et al 2016].

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ASAH1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ASAH1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ASAH1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **National Library of Medicine Genetics Home Reference**
  Farber lipogranulomatosis
- **American Epilepsy Society (AES)**
  www.aesnet.org
- **Epilepsy Foundation**
  3540 Crain Highway
  Suite 675
  Bowie MD 20716
  Phone: 800-332-1000 (toll-free)
  Email: ContactUs@efa.org
  www.epilepsy.com
- **Metabolic Support UK**
  5 Hilliards Court, Sandpiper Way
  Chester Business Park
  Chester CH4 9QP
  United Kingdom
  Phone: 0845 241 2173
  Email: contact@metabolicsupportuk.org
  www.metabolicsupportuk.org
- **Muscular Dystrophy Association (MDA) - USA**
  161 North Clark
  Suite 3550
  Chicago IL 60601
  Phone: 800-572-1717
  Email: ResourceCenter@mdausa.org
  www.mda.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. ASAH1-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

ASAH1	8p22	Acid ceramidase	ASAH1 database	ASAH1	ASAH1

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 ASAH1-Related Disorders (View All in OMIM)

159950	SPINAL MUSCULAR ATROPHY WITH PROGRESSIVE MYOCLONIC EPILEPSY; SMAPME
228000	FARBER LIPOGRANULOMATOSIS; FRBRL
613468	N-ACYLSPHINGOSINE AMIDOHYDROLASE 1; ASAH1

Gene structure. The primary *ASAH1* transcript (NM_177924.4) comprises 14 exons spanning 30 kb [Li et al 1999]. Multiple transcript variants that encode different isoforms are known. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. To date 46 pathogenic variants have been reported [Stenson et al 2014].

Two reported gross deletions include:

- A 55-kb deletion including all of *ASAH1* [Zhou et al 2012];
- A 9,471-bp deletion including exons 3-5 (c.126-3941_382+1358del) [Alves et al 2013].

Cellular ceramide levels, which are increased from two- to fivefold for *ASAH1*-related disorders, can provide further evidence that variants identified by *ASAH1* sequencing are pathogenic [Levade et al 2009, Kernohan et al 2017].

Table 6. *ASAH1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.125C>T	p.Thr42Met	NM_177924.4 NP_808592.2
c.703G>C	p.Gly235Arg	
c.917+4A>G [1]		

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. rs397509415

Normal gene product.*ASAH1* encodes a 395-amino acid protein, N-acylsphingosine amidohydrolase (acid ceramidase) [Koch et al 1996] (NP_808592.2). The 53-55 kd precursor protein is self-cleaved into both an alpha and beta subunit at position Cys143. The alpha subunit is 13 kd and not glycosylated; the beta subunit is 27 kd and glycosylated [Shtraizent et al 2008]. The Cys143 is then able to serve as a site for the hydrolysis of ceramide [Shtraizent et al 2008].

Acid ceramidase catalyzes the breakdown of ceramide into sphingosine and fatty acid within the acidic lysosome; it can also perform the reverse reaction and synthesize ceramide at neutral pH. The substrate, ceramide, is an important sphingolipid with a role in signal transmission and cell recognition [Alayoubi et al 2013].

Abnormal gene product. Absence of or reduction in acid ceramidase activity results in an accumulation of ceramide in the lysosomes of most tissues [Koga et al 1992, Levade et al 2009]. The expected downstream consequences of accumulated ceramide include increased levels of monocyte chemotactic protein-1 (MCP1), a pro-inflammatory chemokine that attracts monocytes to sites of tissue infection and injury [Alayoubi et al 2013].

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