



## Free Sialic Acid Storage Disorders

David Adams, MD, PhD<sup>1</sup> and Melissa Wasserstein, MD<sup>2</sup>

Created: June 13, 2003; Updated: January 23, 2020.

### Summary

#### Clinical characteristics

Free sialic acid storage disorders (FSASDs) are a spectrum of neurodegenerative disorders resulting from increased lysosomal storage of free sialic acid. Historically, FSASD was divided into separate allelic disorders: Salla disease, intermediate severe Salla disease, and infantile free sialic acid storage disease (ISSD). The mildest type was Salla disease, characterized by normal appearance and absence of neurologic findings at birth, followed by slowly progressive neurologic deterioration resulting in mild-to-moderate psychomotor delays, spasticity, athetosis, and epileptic seizures. Salla disease was named for a municipality in Finnish Lapland where a specific founder variant is relatively prevalent. However, the term Salla has been used in the literature to refer to less severe FSASD. More severe FSASD is historically referred to as ISSD, and is characterized by severe developmental delay, coarse facial features, hepatosplenomegaly, and cardiomegaly; death usually occurs in early childhood.

#### Diagnosis/testing

The diagnosis of a FSASD is established in a proband by identification of biallelic pathogenic variants in *SLC17A5* on molecular genetic testing.

#### Management

*Treatment of manifestations:* Management is symptomatic and supportive: standard treatment of seizures; feeding therapy and provision of adequate nutrition; rehabilitation to optimize mobility and communication; supplementation of calcium and vitamin D for low bone density; family and social support.

*Surveillance:* Assessment of feeding, respiratory status, seizures, development, mobility, and nutrition with each visit. Regular evaluation by a rehabilitation specialist to identify potentially helpful interventions. Annual EKG and echocardiography for cardiomegaly.

**Author Affiliations:** 1 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; Email: [dadams1@mail.nih.gov](mailto:dadams1@mail.nih.gov). 2 Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, New York; Email: [mwassers@montefiore.org](mailto:mwassers@montefiore.org).

## Genetic counseling

The FSASDs 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. Molecular genetic carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

## GeneReview Scope

Free Sialic Acid Storage Disorders: Included Phenotypes <sup>1</sup>

- Salla disease
- Infantile free sialic acid storage disease (ISSD)

For synonyms and outdated names see Nomenclature.

## Diagnosis

There are no consensus clinical diagnostic criteria for free sialic acid storage disorders (FSASDs).

## Suggestive Findings

A FSASD **should be suspected/considered** in individuals with the following clinical, imaging, and laboratory findings.

### Less Severe FSASD Including Salla Disease

#### Clinical findings

- Truncal ataxia and hypotonia apparent at approximately one year of age
- Developmental delay
- Growth deficiency (short stature)
- Intellectual disability
- Spasticity
- Facial coarsening (variable and not always present)

#### Imaging findings on brain MRI examination

- Hypomyelination of the basal ganglia
- Hypoplasia of the corpus callosum

### Severe FSASD Including Infantile Free Sialic Acid Storage Disease (ISSD)

#### Clinical findings

- Nonimmune hydrops fetalis (24%)
- Hepatosplenomegaly
- Failure to thrive
- Severe developmental delay
- Cardiomegaly
- Club feet
- Increasingly coarse facial features
- Neurologic deterioration
- Early death

**Imaging findings on skeletal survey (ISSD)** include skeletal dysostosis (e.g., irregular enlarged metaphyses, short femurs, diffuse hypomineralization with fractures, hip dysplasia, anterior beaking of the dorsal vertebrae, and hypoplasia of the distal phalanges).

## FSASD Including Less Severe and Severe Forms

### Laboratory findings

- **Free sialic acid.** Sialic acids are a family of negatively charged sugars, one of which, N-acetylneuraminic acid, is elevated in lysosomes in free sialic acid storage disorders.

Urinary excretion of free sialic acid, measured by the fluorimetric thiobarbituric acid assay, thin-layer chromatography or mass spectrometry, is elevated about tenfold in individuals with Salla disease and about 100-fold in individuals with ISSD. HPLC/tandem mass spectrometry is also able to detect free sialic acid in urine [Valianpour et al 2004].

Note: (1) In the thiobarbituric acid assay, interfering substances may lower the measurement and chromophores may contribute to absorbance, creating a false measurement. (2) In thin-layer chromatography, an elevation of free sialic acid may be overlooked.

- **Cultured fibroblasts** from individuals with all forms of FSASD show increased concentration of free sialic acid [Renlund et al 1986].

## Establishing the Diagnosis

The diagnosis of a free sialic acid storage disorder **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *SLC17A5* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SLC17A5* variants of uncertain significance (or of one known *SLC17A5* pathogenic variant and one *SLC17A5* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of free sialic acid storage disorders is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited neurodegenerative disorders are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the phenotypic and laboratory findings suggest the diagnosis of free sialic acid storage disorders, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SLC17A5* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Note: Targeted analysis for pathogenic variant p.Arg39Cys can be performed first in individuals of Finnish or Swedish ancestry [Aula et al 2000].

- A **multigene panel** that includes *SLC17A5* 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*. Of note, given the rarity of free sialic acid storage disorders some panels for developmental delay may not include this gene. (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 characterized by neurodegeneration, **comprehensive genomic testing** (which does not require the clinician to predetermine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in Free Sialic Acid Storage Disorders

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
<i>SLC17A5</i>	Sequence analysis <sup>3</sup>	90%-95% <sup>4, 5</sup>
	Gene-targeted deletion/duplication analysis <sup>6</sup>	5%-10% <sup>4, 7</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. The p.Arg39Cys variant, known as the "FIN" variant, is common in the Finnish and other Nordic populations; therefore, a higher detection rate by sequencing is expected in those populations [Peltonen et al 1999, Aula et al 2000].

5. Aula et al [2000], Froissart et al [2005], Zielonka et al [2019]

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

7. Tarailo-Graovac et al [2017], Žigman et al [2018]

## Clinical Characteristics

### Clinical Description

To date, approximately 80 individuals have been identified with biallelic pathogenic variants in *SLC17A5* [Alajoki et al 2004, Zielonka et al 2019]. (~300 individuals with free sialic acid storage disorders [FSASDs] are reported in the literature, but many reports do not include molecular data.) The following description of the phenotypic features associated with this condition is based on these reports.

**Table 2.** Select Features of Free Sialic Acid Storage Disorders

Feature <sup>1</sup>	% of Persons w/Feature	
Developmental delay / cognitive impairment	75%	
Facial dysmorphism / coarse facies <sup>2</sup>	50%-68% <sup>2</sup>	
Hepatosplenomegaly	54%	
Truncal hypotonia	54%	
Skeletal abnormalities	50%	
Spasticity	48%	
Ataxia	44%	
Failure to thrive	42%	
Short stature	27%	
Hydrops fetalis	24%	
Epilepsy	22%	
Neurodegenerative course	20%	
Neonatal ascites	19%	
Cardiomegaly	19%	
Hernias	19%	
Microcephaly	18%	
Recurrent airway infections	16%	
Nystagmus	12%	
Nephropathy	10%	
Optic atrophy	7%	
Athetosis	6%	
Ptosis	3%	
Hoarse voice	2%	
Corneal clouding	1%	
Brain MRI findings	Brain atrophy	23%
	Hypomyelination	22%
	Hypoplasia of the corpus callosum	16%

Adapted from Zielonka et al [2019]

1. Includes features reported in entire spectrum of phenotype (less severe to severe FSASD)

2. Coarse facies are more frequent in severe FSASD.

The FSASDs comprise a spectrum of neurodegenerative disorders resulting from increased lysosomal storage of free sialic acid. Historically, FSASD was divided into separate allelic disorders: Salla disease, intermediate severe Salla disease, and infantile free sialic acid storage disease (ISSD). Salla disease was named for a municipality in Finnish Lapland where a specific founder variant is relatively prevalent. However, the term Salla has been used in the literature to refer to less severe FSASD in general. Less severe FSASD is characterized by normal appearance and neurologic findings at birth followed by slowly progressive neurologic deterioration resulting in mild to moderate psychomotor delay, spasticity, athetosis, and epileptic seizures. More severe FSASD, also known as ISSD, is characterized by severe developmental delay, coarse facial features, hepatosplenomegaly, and cardiomegaly; death usually occurs in early childhood.

### **Less Severe FSASD (Salla Disease)**

Salla disease, which serves as a model for less severe FSASD, has the mildest phenotype [Varho et al 2002]. It is characterized by a normal appearance and normal neurologic findings at birth followed by slowly progressive neurologic deterioration resulting in mild-to-moderate psychomotor delay [Renlund et al 1983, Alajoki et al 2004]. Muscular hypotonia is often first recognized at approximately age six months. One third of affected children learn to walk. Expressive language development can be limited to single words but receptive speech is good. Slow developmental progress often continues until the third decade, after which regression can occur.

Some individuals with Salla disease present later in life with spasticity, athetosis, and epileptic seizures, becoming nonambulatory and nonverbal. Affected individuals are characterized as good-humored and sociable [Varho et al 2002].

T<sub>2</sub>-weighted bright cerebral white matter changes on brain MRI are typical but variable. Abnormal myelination of the basal ganglia and hypoplasia of the corpus callosum are constant and early findings [Sonninen et al 1999]. Cerebellar white matter changes are also present and can explain the ataxia [Linnankivi et al 2003, Biancheri et al 2004]. In addition to the central dysmyelination, a peripheral dysmyelination with the clinical picture of a polyneuropathy occurs with variable neurologic presentations [Varho et al 2000, Varho et al 2002].

Affected individuals do not have organomegaly, skeletal dysostosis, or abnormal eye findings. Growth hormone and gonadotropin deficiencies were observed in one individual [Grosso et al 2001].

Life expectancy appears to be shortened, although affected individuals up to age 72 years have been observed.

### **Intermediate Severe FSASD**

Since the advent of molecular studies, phenotypes with a severity between those of Salla disease and ISSD [Aula & Gahl 2001] have been attributed to compound heterozygosity for the Salla disease-causing common pathogenic variant p.Arg39Cys and another *SLC17A5* pathogenic variant [Kleta et al 2003]. Thus, the term "intermediate severe Salla disease" was proposed [Aula et al 2000].

### **Severe FSASD (Infantile Free Sialic Acid Storage Disease; ISSD)**

ISSD, the most severe phenotype, is characterized by severe developmental delay, coarse facial features, hepatosplenomegaly, and cardiomegaly. Additional reported features include early truncal hypotonia with later spasticity and ataxia, skeletal abnormalities, and seizures (see Table 2). No single feature occurs in all individuals.

ISSD can present prenatally and in the neonatal period with nonimmune hydrops fetalis (24% of individuals) [Lemyre et al 1999, Stone & Sidransky 1999, Froissart et al 2005, Zielonka et al 2019]. Some affected infants are born prematurely. Other affected infants appear normal at birth but lose developmental milestones during infancy [Kleta et al 2003, Kleta et al 2004].

Skeletal abnormalities can include irregular metaphyses, diffuse hypomineralization, club feet, short femurs, enlarged metaphyses, fractures, hip dysplasia, anterior beaking of the dorsal vertebrae, and hypoplasia of the distal phalanges [Froissart et al 2005].

Dysmorphic facial features are nonspecific and generally fall into the spectrum of "coarsened" features (e.g., epicanthal folds, ptosis, anteverted nose, gum hypertrophy).

Reported ocular findings include nystagmus, exotropia, optic atrophy, and albinoid fundi. Corneal clouding has been rarely reported.

Additional reported features include nephropathy and/or nephrotic syndrome and hernias [Lemyre et al 1999, Ishiwari et al 2004].

Death usually occurs in early childhood, typically from recurrent respiratory infections.

## Genotype-Phenotype Correlations

Correlations between the type of *SLC17A5* pathogenic variant and the severity of the lysosomal free sialic acid storage disease have been identified [Aula et al 2000, Varho et al 2000, Kleta et al 2003]:

- Homozygosity for the pathogenic missense variant p.Arg39Cys, a single Finnish founder variant, leads to Salla disease, with its slow clinical course of neurologic deterioration.
- Compound heterozygosity for the p.Arg39Cys pathogenic variant and another *SLC17A5* pathogenic variant leads to intermediate severe FSASD, as does homozygosity for the p.Lys136Glu pathogenic variant [Biancheri et al 2005].
- Compound heterozygosity for pathogenic variants other than p.Arg39Cys leads to the severe phenotype of FSASD (ISSD), with early onset and multisystemic involvement.

Variable expression has been observed among affected family members [Landau et al 2004].

## Penetrance

The FSASDs appear to be fully penetrant. However, Mochel et al [2009] reported two individuals with homozygous p.Lys136Glu pathogenic variants, no detectable urinary sialic acid abnormality, and elevated CSF free sialic acid, suggesting that penetrance based on urinary studies alone may be incomplete.

## Nomenclature

Free sialic acid storage disorders (FSASDs) have been and continue to be labeled with different terms, mainly because of the different names used to denote N-acetylneuraminic acid. The term free sialic acid storage disorder refers to the entire spectrum of disease. The form of less severe FSASD historically known as Salla disease is specific to the Finnish founder mutation, but continues to be used colloquially to refer to mild forms of FSASD. Severe, infantile onset ISSD remains in usage to refer to disease at the more severe end of the FSASD spectrum.

## Prevalence

Less severe FSASD (Salla disease), has been reported in approximately 150 individuals, mainly from Finland and Sweden [Aula et al 2000, Erikson et al 2002]. Individuals with molecularly proven less severe FSASD have been identified outside of Finland and Sweden [Martin et al 2003]. The prevalence of the *SLC17A5* pathogenic variant p.Arg39Cys is high in the founder region of northeastern Finland, where the carrier frequency is in the range of 1:100 [Aula et al 2000]. Ninety-five percent of individuals of Finnish descent with FSASD have the p.Arg39Cys pathogenic variant. The prevalence of other *SLC17A5* pathogenic variants appears to be independent of the geographic origin or ethnicity of affected individuals; their presence has been documented in more than 30

individuals from several countries throughout the world [Lemyre et al 1999, Aula et al 2000, Kleta et al 2003, Martin et al 2003, Sønderby Christensen et al 2003, Kleta et al 2004].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC17A5*.

## Differential Diagnosis

### Biochemical Findings

**Increased urinary and cellular free sialic acid.** The only disorders in which significantly elevated urinary and cellular free sialic acid are known to occur are sialuria (OMIM 269921) and the free sialic acid storage disorders (Salla disease and ISSD). The clinical course of sialuria involves developmental delay and hepatomegaly but does not include severe neurologic involvement or early death. In sialuria, elevation of free sialic acid occurs in the cytoplasm rather than in the lysosome.

Based on clinical suspicion and the finding of elevated free sialic acid in urine, one of two steps is taken to distinguish these conditions:

- The cellular (cytoplasmic versus lysosomal) localization of free sialic acid can be documented; a predominantly lysosomal localization indicates a FSASD.
- Molecular genetic testing of *SLC17A5* (for FSASD) or *GNE* (for sialuria) can be performed.

Note: Other causes of mild elevation in urinary free sialic acid may exist.

**Sialic acid bound to glycoproteins or glycolipids.** If sialic acid bound to glycoproteins or glycolipids is stored, disorders such as sialidosis caused by sialidase (neuraminidase) deficiency (OMIM 256550) and galactosialidosis (OMIM 256540) caused by combined sialidase and galactosidase deficiency should be considered (see Table 3). These enzyme deficiencies involve lysosomal storage of sialic acid-containing glycoconjugates. These disorders both have features typical of lysosomal storage diseases, but they vary widely in their manifestations.

### Clinical Findings

See Table 3 for other lysosomal storage disorders that are associated with the clinical manifestation of coarse facial features and developmental delays and other causes of nonimmune hydrops fetalis. Note: All disorders included in Table 3 are inherited in an autosomal recessive manner.



**Table 3.** Other Genes of Interest in the Differential Diagnosis of Free Sialic Acid Storage Disorders (FSASDs)

Clinical Finding(s) Overlapping w/ FSASDs	Gene	Disorder	Associated Enzyme
Coarse facial features & developmental delays	<i>AGA</i>	Aspartylglucosaminuria	N(4)-(beta-N-acetylglucosaminyl)-L-asparaginase
	<i>ARSB</i>	MPS VI (OMIM 253200)	Arylsulfatase B
	<i>FUCA1</i>	Fucosidosis (OMIM 230000)	Tissue alpha-L-fucosidase
	<i>GLB1</i>	GM1 gangliosidosis (See <i>GLB1-Related Disorders</i> .)	Beta-galactosidase
	<i>GNPTAB</i>	Mucopolidosis II (I-cell disease) (See <i>GNPTAB-Related Disorders</i> .)	N-acetylglucosamine-1-phosphotransferase subunits alpha/beta
	<i>IDS</i>	MPS II	Iduronate 2-sulfatase
	<i>IDUA</i>	MPS I	Alpha-L-iduronidase
	<i>MAN2B1</i>	Alpha-mannosidosis	Lysosomal alpha-mannosidase
	<i>NEU1</i>	Sialidosis type II (OMIM 256550)	Sialidase-1
Nonimmune hydrops fetalis	<i>CTSA</i>	Galactosialidosis (OMIM 256540)	Lysosomal protective protein
	<i>GALC</i>	Krabbe disease	Galactocerebrosidase
	<i>GBA1 (GBA)</i>	Gaucher disease	Lysosomal acid glucosylceramidase
	<i>GBA2</i>	Beta-glucosidase deficiency (OMIM 614409)	Non-lysosomal glucosylceramidase
	<i>GNPTAB</i>	I-cell disease ( <i>Mucopolidosis II</i> )	N-acetylglucosamine-1-phosphotransferase subunits alpha/beta
	<i>GUSB</i>	MPS VII	Beta-glucuronidase
	<i>IDUA</i>	MPS I	Alpha-L-iduronidase
	<i>LIPA</i>	Lysosomal acid lipase deficiency	Lysosomal acid lipase/cholesteryl ester hydrolase
	<i>NEU1</i>	Sialidase deficiency (OMIM 256550)	Sialidase-1
<i>SMPD1</i>	Acid sphingomyelinase deficiency	Sphingomyelin phosphodiesterase	

From Saudubray & Charpentier, Chapter 86, Table 42, *Online Metabolic and Molecular Bases of Inherited Disease*. Accessed 8-23-22 (Registration required).

MPS = mucopolysaccharidosis

## Management

### Evaluations Following Initial Diagnosis

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

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with Free Sialic Acid Storage Disorders

System/Concern	Evaluation	Comment
<b>Neurologic</b>	Neurologic eval	<ul style="list-style-type: none"> <li>To incl brain MRI</li> <li>Consider EEG if seizures are a concern.</li> </ul>

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
<b>Development</b>	Developmental assessment	<ul style="list-style-type: none"> <li>To incl motor, adaptive, cognitive, &amp; speech-language eval</li> <li>Eval for early intervention / special education</li> </ul>
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT & OT eval	<p>To incl assessment of:</p> <ul style="list-style-type: none"> <li>Gross motor &amp; fine motor skills;</li> <li>Mobility, activities of daily living, &amp; need for adaptive devices;</li> <li>Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills).</li> </ul>
<b>Gastrointestinal/ Feeding</b>	Gastroenterology / nutrition / feeding team eval	<ul style="list-style-type: none"> <li>To incl eval of aspiration risk &amp; nutritional status</li> <li>Consider eval for gastrostomy tube placement in those w/dysphagia &amp;/or aspiration risk.</li> </ul>
<b>Miscellaneous/ Other</b>	Biochemical genetics or neurogenetics consultation	To incl genetic counseling
	Family support & resources	<p>Assess need for:</p> <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>Social work involvement for parental support;</li> <li>Home nursing referral.</li> </ul>

OT = occupational therapy; PT = physical therapy

## Treatment of Manifestations

The medical and psychosocial management of individuals with free sialic acid storage disorders is symptomatic and supportive.

Table 5. Treatment of Manifestations in Individuals with Free Sialic Acid Storage Disorders

Manifestation/ Concern	Treatment	Considerations/Other
<b>Epilepsy</b>	Standardized treatment w/ASM by experienced neurologist	<ul style="list-style-type: none"> <li>Many ASMs may be effective; none has been demonstrated effective specifically for FSASDs.</li> <li>Education of parents/caregivers <sup>1</sup></li> </ul>
<b>DD/ID</b>	See Developmental Delay / Intellectual Disability Management Issues.	
<b>Poor weight gain / Failure to thrive</b>	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
<b>Spasticity</b>	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
<b>Low bone density / Fractures</b>	Supplementation as necessary to provide adequate calcium & vitamin D intake	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
<b>Family/ Community</b>	<ul style="list-style-type: none"> <li>• Ensure appropriate social work involvement to connect families w/local resources, respite, &amp; support.</li> <li>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, &amp; supplies.</li> </ul>	<ul style="list-style-type: none"> <li>• Ongoing assessment of need for palliative care involvement &amp;/or home nursing</li> <li>• Consider involvement in adaptive sports or <a href="#">Special Olympics</a>.</li> </ul>

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see [Epilepsy Foundation Toolbox](#).

## Developmental Delay / Intellectual Disability Management Issues

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

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

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

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and 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.

## Motor Dysfunction

### Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox<sup>®</sup>, anti-parkinsonian medications, or orthopedic procedures.

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

**Oral motor dysfunction** should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

**Communication issues.** Consider evaluation for alternative means of communication (e.g., [augmentative and alternative communication](#) [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

## Surveillance

**Table 6.** Recommended Surveillance for Individuals with Free Sialic Acid Storage Disorders

System/Concern	Evaluation	Frequency
<b>Feeding</b>	<ul style="list-style-type: none"> <li>• Measurement of growth parameters</li> <li>• Eval of nutritional status &amp; safety of oral intake</li> </ul>	At each visit
<b>Respiratory</b>	Monitor for evidence of aspiration, respiratory insufficiency.	
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>• Monitor those w/seizures as clinically indicated.</li> <li>• Assess for new manifestations (e.g., seizures, changes in tone, mvmt disorders).</li> </ul>	
<b>Development</b>	Monitor developmental progress & educational needs.	
<b>Musculoskeletal</b>	Physical medicine &/or rehab medicine, OT/PT assessment of mobility, self-help skills	
	Nutritional monitoring incl vitamin D intake	
<b>Cardiomegaly</b>	EKG & echocardiography	Annually for signs of cardiomegaly
<b>Nephrotic syndrome</b>	Urinalysis for protein	Annually
<b>Other</b>	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

## Evaluation of Relatives at Risk

No routine testing of apparently asymptomatic at-risk family members is recommended because adult presentations are unusual and no early interventions are available.

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

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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

The free sialic acid storage disorders are inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *SLC17A5* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *SLC17A5* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- If both parents are known to be heterozygous for an *SLC17A5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Variable expression has been observed among affected sibs [Landau et al 2004].
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Because of the severity of the disease, affected individuals are unlikely to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC17A5* pathogenic variant.

## Carrier Detection

**Molecular genetic testing.** Carrier testing for at-risk relatives requires prior identification of the *SLC17A5* pathogenic variants in the family.

**Biochemically based carrier testing** is not feasible.

## 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.
- Because the prevalence of the *SLC17A5* pathogenic variant p.Arg39Cys is high in the founder region of northeastern Finland (where the carrier frequency is in the range of 1:100; see [Genetic Disorders Associated with Founder Variants Common in the Finnish Population](#)), pre-conception testing of the partner of a known carrier may be requested if the partner is of Finnish descent.

## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the 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. 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](#).

- Salla Treatment and Research (STAR) Foundation**  
 PO Box 1051  
 Riverdale Station NY 10471  
[www.sallaresearch.org](http://www.sallaresearch.org)
- Metabolic Support UK**  
 United Kingdom  
**Phone:** 0845 241 2173  
[metabolicsupportuk.org](http://metabolicsupportuk.org)
- National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**  
**Phone:** 617-277-4463  
**Email:** [info@ntsad.org](mailto:info@ntsad.org)  
[www.ntsad.org](http://www.ntsad.org)
- Myelin Disorders Bioregistry Project**  
**Phone:** 215-590-1719  
**Email:** [sherbinio@chop.edu](mailto: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.** Free Sialic Acid Storage Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
<a href="#">SLC17A5</a>	6q13	<a href="#">Sialin</a>	<a href="#">SLC17A5</a>	<a href="#">SLC17A5</a>

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 Free Sialic Acid Storage Disorders ([View All in OMIM](#))

<a href="#">269920</a>	INFANTILE SIALIC ACID STORAGE DISEASE; ISSD
<a href="#">604322</a>	SOLUTE CARRIER FAMILY 17 (ACIDIC SUGAR TRANSPORTER), MEMBER 5; SLC17A5
<a href="#">604369</a>	SALLA DISEASE; SD

The gene product of *SLC17A5*, sialin, is an integral lysosomal membrane transporter that exports free sialic acid from lysosomes [Mancini et al 1991]. Deficient or defective sialin results in excessive lysosomal storage of the free sialic acid produced by lysosomal degradation of glycoproteins and glycolipids. How elevated intralysosomal free sialic acid causes pathology is not understood. Expression of sialin in the brain may explain part of the neurologic sequelae of Salla disease/ISSD [Aula et al 2004].

**Mechanism of disease causation.** Loss of function

**Table 7.** Notable *SLC17A5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_012434.4 NP_036566.1	c.115C>T	p.Arg39Cys	Founder variant in Finnish & other Nordic populations [Aula et al 2000]
	c.406A>G	p.Lys136Glu	Penetrance may be incomplete in some homozygous individuals [Mochel et al 2009].

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

### Author Notes

David Adams, MD, PhD is a pediatrician, medical geneticist, and biochemical geneticist who performs clinical and basic research into rare diseases at the National Institutes of Health.

### Author History

David Adams, MD, PhD (2008-present)

William A Gahl, MD, PhD; National Human Genome Research Institute (2003-2020)

Robert Kleta, MD, PhD; National Human Genome Research Institute (2003-2008)

Melissa Wasserstein, MD (2020-present)

### Revision History

- 23 January 2020 (sw) Comprehensive update posted live
- 6 June 2013 (me) Comprehensive update posted live
- 3 July 2008 (me) Comprehensive update posted live
- 4 October 2005 (me) Comprehensive update posted live
- 13 June 2003 (ca) Review posted live
- 28 February 2003 (wg) Original submission

## References

### Literature Cited

- Alajoki L, Varho T, Posti K, Aula P, Korhonen T. Neurocognitive profiles in Salla disease. *Dev Med Child Neurol.* 2004;46:832-7. PubMed PMID: 15581157.
- Aula N, Kopra O, Jalanko A, Peltonen L. Sialin expression in the CNS implicates extralysosomal function in neurons. *Neurobiol Dis.* 2004;15:251-61. PubMed PMID: 15006695.
- Aula N, Salomäki P, Timonen R, Verheijen F, Mancini G, Mansson JE, Aula P, Peltonen L. The spectrum of *SLC17A5*-gene mutations resulting in free sialic acid-storage diseases indicates some genotype-phenotype correlation. *Am J Hum Genet* 2000;67:832-40. PubMed PMID: 10947946.
- Aula P, Gahl WA. Disorders of free sialic acid storage. In: Scriver CR, Beaudet AL, Valle D, Sly WS, eds. *The Metabolic & Molecular Bases of Inherited Disease.* 8 ed. New York, NY: McGraw-Hill; 2001:5109-20.
- Biancheri R, Rossi A, Mancini MG, Minetti C. Cerebellar white matter involvement in Salla disease. *Neuroradiology.* 2004;46:587-8. PubMed PMID: 15179531.



- Biancheri R, Rossi A, Verbeek HA, Schot R, Corsolini F, Assereto S, Mancini GMS, Verheijen FW, Minetti C, Filocamo M. Homozygosity for the p.K136E mutation in the SLC15A5 gene as cause of an Italian severe Salla disease. *Neurogenetics*. 2005;6:195-9. PubMed PMID: 16170568.
- Erikson A, Aula N, Aula P, Mansson JE. Free sialic acid storage (Salla) disease in Sweden. *Acta Paediatr*. 2002;91:1324-7. PubMed PMID: 12578289.
- Froissart R, Cheillan D, Bouvier R, Tourret S, Bonnet V, Piraud M, Maire I. Clinical, morphological and molecular aspects of sialic acid storage disease manifesting in utero. *J Med Genet*. 2005;42:829-36. PubMed PMID: 15805149.
- Grosso S, Berardi R, Farnetani MA, Margollicci M, Mancini MG, Morgese G, Balestri P. Multiple neuroendocrine disorder in Salla disease. *J Child Neurol*. 2001;16:775-7. PubMed PMID: 11669356.
- Ishiwari K, Kotani M, Suzuki M, Pumbo E, Suzuki A, Kobayashi T, Ueno T, Fukushige T, Kanzaki T, Imada M, Itoh K, Akioka S, Tajima Y, Sakuraba H. Clinical, biochemical, and cytochemical studies on a Japanese Salla disease case associated with a renal disorder. *J Hum Genet*. 2004;49:656-63. PubMed PMID: 15635485.
- Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. *Nature*. 2017;549:519-22. PubMed PMID: 28959963.
- Kleta R, Aughton DJ, Rivkin MJ, Huizing M, Strovel E, Anikster Y, Orvisky E, Natowicz M, Krasnewich D, Gahl WA. Biochemical and molecular analyses of infantile free sialic acid storage disease in North American children. *Am J Med Genet*. 2003;120A:28-33. PubMed PMID: 12794688.
- Kleta R, Morse RP, Orvisky E, Krasnewich D, Alroy J, Ucci AA, Bernardini I, Wenger DA, Gahl WA. Clinical, biochemical, and molecular diagnosis of a free sialic acid storage disease patient of moderate severity. *Mol Genet Metab*. 2004;82:137-43. PubMed PMID: 15172001.
- Landau D, Cohen D, Shalev H, Pinsk V, Yerushalmi B, Zeigler M, Birk OS. A novel mutation in the SLC17A5 gene causing both severe and mild phenotypes of free sialic acid storage disease in one inbred Bedouin kindred. *Mol Genet Metab*. 2004;82:167-72. PubMed PMID: 15172005.
- Lemyre E, Russo P, Melancon SB, Gagne R, Potier M, Lambert M. Clinical spectrum of infantile free sialic acid storage disease. *Am J Med Genet*. 1999;82:385-91. PubMed PMID: 10069709.
- Linnankivi T, Lonnqvist T, Autti T. A case of Salla disease with involvement of the cerebellar white matter. *Neuroradiology*. 2003;45:107-9. PubMed PMID: 12592494.
- Mancini GM, Beerens CE, Aula PP, Verheijen FW. Sialic acid storage diseases. A multiple lysosomal transport defect for acidic monosaccharides. *J Clin Invest*. 1991;87:1329-35. PubMed PMID: 2010546.
- Martin RA, Slauch R, Natowicz M, Pearlman K, Orvisky E, Krasnewich D, Kleta R, Huizing M, Gahl WA. Sialic acid storage disease of the Salla phenotype in American monozygous twin female sibs. *Am J Med Genet A*. 2003;120A:23-7. PubMed PMID: 12794687.
- Mochel F, Yang B, Barritault J, Thompson JN, Engelke UF, McNeill NH, Benko WS, Kaneski CR, Adams DR, Tsokos M, Abu-Asab M, Huizing M, Seguin F, Wevers RA, Ding J, Verheijen FW, Schiffmann R. Free sialic acid storage disease without sialuria. *Ann Neurol*. 2009;65:753-7. PubMed PMID: 19557856.
- Peltonen L, Jalanko A, Varilo T. Molecular genetics of the Finnish disease heritage. *Hum Mol Genet*. 1999;8:1913-23. PubMed PMID: 10469845.
- Renlund M, Aula P, Raivio KO, Autio S, Sainio K, Rapola J, Koskela SL. Salla disease: a new lysosomal storage disorder with disturbed sialic acid metabolism. *Neurology*. 1983;33:57-66. PubMed PMID: 6681560.
- Renlund M, Tietze F, Gahl WA. Defective sialic acid egress from isolated fibroblast lysosomes of patients with Salla disease. *Science*. 1986;232:759-62. PubMed PMID: 3961501.

- 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.
- Sønderby Christensen P, Kaad PH, Ostergaard JR. Two cases of Salla disease in Danish children. *Acta Paediatr*. 2003;92:1357-8. PubMed PMID: 14696864.
- Sonninen P, Autti T, Varho T, Hamalainen M, Raininko R. Brain involvement in Salla disease. *AJNR Am J Neuroradiol*. 1999;20:433-43. PubMed PMID: 10219409.
- Stone DL, Sidransky E. Hydrops fetalis: lysosomal storage disorders in extremis. *Adv Pediatr*. 1999;46:409-40. PubMed PMID: 10645471.
- Tarailo-Graovac M, Drögemöller BI, Wasserman WW, Ross CJ, van den Ouweland AM, Darin N, Kollberg G, van Karnebeek CD, Blomqvist M. Identification of a large intronic transposal insertion in SLC17A5 causing sialic acid storage disease. *Orphanet J Rare Dis*. 2017;12:28. PubMed PMID: 28187749.
- Valianpour F, Abeling NG, Duran M, Huijmans JG, Kulik W. Quantification of free sialic acid in urine by HPLC-electrospray tandem mass spectrometry: a tool for the diagnosis of sialic acid storage disease. *Clin Chem*. 2004;50:403-9. PubMed PMID: 14684624.
- Varho T, Jaaskelainen S, Tolonen U, Sonninen P, Vainionpaa L, Aula P, Sillanpaa M. Central and peripheral nervous system dysfunction in the clinical variation of Salla disease. *Neurology*. 2000;55:99-104. PubMed PMID: 10891913.
- Varho TT, Alajoki LE, Posti KM, Korhonen TT, Renlund MG, Nyman SR, Sillanpaa ML, Aula PP. Phenotypic spectrum of Salla disease, a free sialic acid storage disorder. *Pediatr Neurol*. 2002;26:267-73. PubMed PMID: 11992753.
- Zielonka M, Garbade SF, Kölker S, Hoffmann GF, Ries M. A cross-sectional quantitative analysis of the natural history of free sialic acid storage disease-an ultra-orphan multisystemic lysosomal storage disorder. *Genet Med*. 2019;21:347-52. PubMed PMID: 29875421.
- Žigman T, Petković Ramadža D, Lušić M, Zekušić M, Ninković D, Gardijan D, Potočki K, Omerza L, Beljan L, Žarković K, Kerkhof J, Ljubojević M, de Sain-van der Velden M, Vuković J, Fumić K, Sadiković B, Barić I. Hypogammaglobulinemia and imaging features in a patient with infantile free sialic acid storage disease (ISSD) and a novel mutation in the SLC17A5 gene. *J Pediatr Endocrinol Metab*. 2018;31:1155-9. PubMed PMID: 30243016.

## License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: [admasst@uw.edu](mailto:admasst@uw.edu).