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Sandhoff Disease

Synonym: Type II GM2 Gangliosidosis

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Summary

Clinical characteristics

Sandhoff disease comprises a phenotypic continuum encompassing acute infantile, subacute juvenile, and late-onset disease. Although classification into these phenotypes is somewhat arbitrary, it is helpful in understanding the variation observed in the timing of disease onset, presenting manifestations, rate of progression, and life span.

- **Acute infantile Sandhoff disease** (onset age <6 months). Infants are generally normal at birth followed by progressive weakness and slowing of developmental progress, then developmental regression and severe neurologic impairment. Seizures are common. Death usually occurs between ages two and three years.
- **Subacute juvenile Sandhoff disease** (onset age 2-5 years). After attaining normal developmental milestones, developmental progress slows, followed by developmental regression and neurologic impairment (abnormal gait, dysarthria, and cognitive decline). Death (usually from aspiration) typically occurs in the early to late teens.
- **Late-onset Sandhoff disease** (onset older teen years or young adulthood). Nearly normal psychomotor development is followed by a range of neurologic findings (e.g., weakness, spasticity, dysarthria, and deficits in cerebellar function) and psychiatric findings (e.g., deficits in executive function and memory). Life expectancy is not necessarily decreased.

Diagnosis/testing

In a proband, the diagnosis of Sandhoff disease is established by: (1) enzymatic testing that identifies abnormally low activity of the enzymes beta-hexosaminidase A (HEX A) and beta-hexosaminidase B (HEX B) combined with an increased contribution from HEX A; and (2) identification biallelic pathogenic variants in *HEXB* on molecular testing.

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Management

Treatment of manifestations: Treatment is symptomatic. Supportive care in acute infantile Sandhoff disease focuses on providing adequate nutrition and hydration, managing infectious disease, protecting the airway to reduce aspiration risk, controlling seizures, supporting motor development, and preventing deformities. Supportive care in subacute juvenile and late-onset Sandhoff disease focuses on maximizing motor function and speech and language as well as providing aids for activities of daily living and communication.

Surveillance: Periodic multidisciplinary evaluations to monitor existing disease manifestations and identify new manifestations requiring modification of supportive care.

Agents/circumstances to avoid: In **acute infantile** Sandhoff disease, avoid positioning that increases aspiration risk during feedings; and seizure medication dosages that result in excessive sedation. In **subacute juvenile** Sandhoff disease, avoid situations that increase the likelihood of contractures or pressure sores, such as extended periods of immobility; and circumstances that increase the risk of falling. In **late-onset** Sandhoff disease, avoid situations that increase the risk of falling (e.g., walking on uneven or unstable surfaces); and psychiatric medications that have been associated with worsening disease in late-onset Tay-Sachs disease, a similar disorder (e.g., haloperidol, risperidone, chlorpromazine).

Genetic counseling

Sandhoff disease is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *HEXB* 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 inheriting neither of the familial pathogenic variants. Once the *HEXB* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

Sandhoff Disease: Clinical Phenotypic Spectrum	
Biochemical Phenotype	Clinical Phenotypes [1]
Deficient activity of enzymes beta-hexosaminidase A & beta-hexosaminidase B	• Acute infantile Sandhoff disease • Subacute juvenile Sandhoff disease • Late-onset Sandhoff disease

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

No consensus clinical diagnostic criteria for Sandhoff disease have been published.

Suggestive Findings

Sandhoff disease should be suspected in individuals with the following findings by phenotype.

Acute Infantile Sandhoff Disease (onset age <6 months)

Clinical findings

- **Neurologic**
  - Progressive weakness or loss of motor skills
  - Decreased attentiveness

- Exaggerated startle response
- Hypotonia
- Hyperreflexia
- Seizures

- **Other**
  - Cherry-red macula (seen in virtually all children with infantile disease)
  - Progressive macrocephaly
  - Hepatosplenomegaly

Brain MRI findings

- Hyperintense T_1-weighted signal in the thalami and basal ganglia; hyperintense T_2-weighted signal in the external capsule and cerebellar white matter [Yüksel et al 1999, Beker-Acay et al 2016]
- Cortical atrophy, thinning of the corpus callosum, and abnormal MRI signal intensity in the caudate, globus pallidus, putamen, cerebellum, and brain stem [Yüksel et al 1999]

Subacute Juvenile Sandhoff Disease (onset age 2-5 years)

Clinical findings

- Developmental plateauing followed by regression
- Progressive spasticity, dysarthria, and dysphagia
- Seizures
- Absence of hepatosplenomegaly

Brain MRI findings. Global brain atrophy [Tallaksen & Berg 2009]

Late-Onset Sandhoff Disease (onset later teens – young adulthood)

Clinical findings

- Progressive lower motor neuronopathy with progressive lower-extremity weakness (primarily knee extensors and hip flexors) with atrophy, fasciculations, balance issues, tremors, and/or ataxia
- Distal sensory neuropathy
- Progressive dysarthria
- Neurocognitive decline including cognition
- Absence of hepatosplenomegaly

Brain MRI findings

- Cerebellar atrophy, less prominent than in *HEXA* disorders [Rowe et al 2021]
- Mild cortical atrophy [Masingue et al 2020]
- Generalized spinal cord atrophy and normal imaging [Schnorf et al 1995, Stephen et al 2020]

Family History

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

Establishing the Diagnosis

The diagnosis of Sandhoff disease **is established** in a proband with:

- Abnormally low activity of the enzymes beta-hexosaminidase A (HEX A) and beta-hexosaminidase B (HEX B) combined with elevated-percent contribution from HEX A; and

- Biallelic pathogenic (or likely pathogenic) variants in *HEXB* identified by molecular genetic testing (see Table 1).

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

Enzymatic Activity Testing

In individuals with Sandhoff disease, testing of enzymatic activity of HEX A and HEX B in serum, white blood cells, or other tissues reveals absent to near-absent activity of HEX A and HEX B (i.e., total hexosaminidase), and a normal- or elevated-percent contribution from HEX A [Hall et al 2014].

- Individuals with acute infantile Sandhoff disease have absent to near-absent HEX A and HEX B activity.
- Individuals with subacute juvenile or late-onset Sandhoff disease have some residual HEX A and HEX B activity.

Molecular Genetic Testing

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Sandhoff disease is broad, infants with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1). In contrast, those (especially older individuals) with a phenotype indistinguishable from many other disorders with later-onset neurodegeneration or neurocognitive decline are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Single-gene testing can be considered for individuals with a HEX B enzyme profile consistent with Sandhoff disease. Sequence analysis of *HEXB* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** for GM2 gangliosidoses, lysosomal storage diseases, neurometabolic diseases, or neurodevelopmental diseases would be an appropriate initial test when seeking a molecular diagnosis in most individuals suspected clinically of having Sandhoff disease. Such panels include *HEXB* and other genes of interest (see Differential Diagnosis) and are 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

When the phenotype is indistinguishable from many other inherited disorders characterized by slowly progressive neurodegeneration, **comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, is appropriate. **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 1. Molecular Genetic Testing Used in Sandhoff Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
HEXB	Sequence analysis [3]	~90% [4]
	Gene-targeted deletion/duplication analysis [5]	<10% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The phenotypes of Sandhoff disease comprise a continuum ranging from acute infantile to subacute juvenile and late-onset Sandhoff disease. Although classification into these phenotypes is somewhat arbitrary, the classification is helpful in understanding the variation observed in the timing of disease onset, presenting manifestations, rate of progression, and life span.

Despite numerous case reports of individuals with Sandhoff disease from specific ethnic backgrounds, few prospective studies have delineated the progression of disease by phenotype.

Acute Infantile Sandhoff Disease

Affected infants are generally normal at birth. Progressive weakness, exaggerated startle, and slowing of developmental progress is typically noted between ages three and six months. Decreasing visual attentiveness and unusual eye movements including poor fix-and-follow, typically noted at age three to six months, may be the first signs prompting parents to seek medical attention; subsequent ophthalmologic evaluation reveals the characteristic cherry-red macula seen in virtually all children with infantile-onset disease.

Affected infants reach a developmental plateau followed by developmental regression typically between ages six to ten months. After age eight to ten months, disease progression is rapid. Voluntary movements diminish and the infant becomes progressively less responsive. Vision deteriorates rapidly.

Seizures and myoclonic jerks are common by age 12 months. Partial complex seizures or absence seizures that are initially subtle typically become more severe and more frequent.

Typically, progressive enlargement of the head resulting from reactive cerebral gliosis beginning by age 18 months is eventually followed by ventriculomegaly [Nestrasil et al 2018].

Further deterioration in the second year of life results in decerebrate posturing, difficulty in swallowing, worsening seizures, and finally an unresponsive, vegetative state. Death from respiratory complications usually occurs between ages two and three year; however, the use of a gastrostomy tube to minimize aspiration events and the use of vibrating vests to improve pulmonary hygiene have extended the life span by five to seven years [Bley et al 2011, Regier et al 2016].

Subacute Juvenile Sandhoff Disease

Children attain developmental milestones normally until about age two years. Between ages two and five years, the rate of motor and speech development slows and eventually plateaus. Abnormal gait and/or dysarthria begin to emerge, followed by loss of previously acquired skills and cognitive decline.

Spasticity, dysphagia, and seizures are present by age ten years [Maegawa et al 2006].

Decreased visual acuity occurs much later than in the acute infantile form. A cherry-red macula is rarely observed. Optic atrophy and retinal pigmentation may be seen late in the disease course.

Episodic neuropathic pain or dysesthesia especially in the fingers and toes (acroparesthesia), neuropathy, and dysautonomia are common, and can be presenting manifestations [Modigliani et al 1994, Gomez-Lira et al 1995, Schnorf et al 1995, Grunseich et al 2015].

By age ten to 15 years, many individuals are in a vegetative state with decerebrate posturing, followed within a few years by death usually from aspiration. Newer measures in supportive care that protect airways and improve pulmonary hygiene may extend the life span.

In some individuals, the disease course is particularly rapid, culminating in death within two to four years of initial manifestations.

Late-Onset Sandhoff Disease

Affected individuals present with a slowly progressive spectrum of neurologic and psychiatric manifestations as older teenagers or young adults. Following diagnosis, many affected individuals and/or parents/caregivers describe earlier nonspecific subtle manifestations, such as clumsiness or developmental concerns.

Most affected individuals achieve nearly normal milestones into adulthood and the disorder progresses slowly over decades. The presentation may resemble that of other neurodegenerative conditions of adults, especially late-onset Tay-Sachs disease. The widespread central nervous system involvement includes the following clinical findings:

- Progressive motor neuronopathy, experienced by most (if not all) affected individuals, leads to muscle weakness and wasting. Muscle cramps, atrophy, and fasciculations are common. Early weakness primarily involves the lower extremities, particularly the knee extensors and hip flexors. Affected individuals have progressive difficulty in climbing steps or long flights of stairs, eventually requiring the aid of handrails. As knee extensor weakness progresses, affected individuals hyperextend ("lock") their knees to support their

weight, producing a characteristic gait. Failure to maintain the locked knees results in collapse and injury, which frequently leads to early need for assistive devices or knee braces.

- Upper-extremity strength may be affected years later with a predilection for triceps weakness, which affects elbow extension.
- Long tract findings including spasticity, extensor plantar reflexes, and brisk reflexes can be present, but may be obscured by lower motor neuron weakness.
- A peripheral sensory neuropathy that starts distally but can expand proximally is common [Toro et al 2021]. Proprioceptive defects from neuropathy can contribute to balance difficulties.
- Dysarthria. The speech rate is fast and almost "pressured," which, together with poor articulation, affects speech intelligibility. While poor articulation results primarily from cerebellar dysfunction, associated features can include focal laryngeal dystonia (spasmodic dysphonia), leading to a "strangled" voice and overflow activation of neck and facial muscles. Some individuals do not develop dysarthria despite substantial weakness.

  Note: Dysphagia and aspiration events are not common.
- Cerebellar dysfunction. Decreased balance can be associated with a wide base of support, decreased dexterity, and tremors. These findings plus saccadic dysmetria and abnormal saccadic gain during formal extraocular movement examination are attributed – at least in part – to cerebellar dysfunction [Stephen et al 2020]. Cerebellar dysfunction, rather than motor neuronopathy, is the predominant manifestation in some individuals [Delnooz et al 2010].
- Deficits in executive function and memory, reported in some individuals, can be associated with progressive brain volume loss; however, decline in higher cortical functioning develops slowly, often over decades after onset of disease manifestations.
- Psychiatric manifestations such as psychosis and mania have exclusively been reported in the context of hexosaminidase A (HEX A) deficiency (in contrast to other GM2 gangliosidoses) [Masingue et al 2020].

  Affective manifestations such as depression and/or anxiety, which can be present in individuals with Sandhoff disease as well, may represent part of a cerebellar affective syndrome [Stephen et al 2020].

In the absence of dysphagia or frequent falls, life expectancy is not necessarily reduced.

Genotype-Phenotype Correlations

The following *HEXB* variants are associated with acute infantile Sandhoff disease in the homozygous state or in a compound heterozygous state with null variants:

- c.76delA; p.Met26CysfsTer5
- c.115delG; p.Val39TrpfsTer25
- c.445+1G>A

In general, individuals with two null (nonexpressing) variants have the acute infantile phenotype, individuals with one null variant and one missense variant have the subacute juvenile phenotype, and individuals with two missense variants have the late-onset phenotype. This reflects the inverse correlation of the level of the residual hexosaminidase B (HEX B) enzyme activity with disease severity: the lower the enzymatic activity, the more severe the phenotype is likely to be. Nonetheless, clinical variability can be observed among family members with the subacute juvenile and late-onset phenotypes.

Nomenclature

Sandhoff disease was one of several disorders, including Tay-Sachs disease and GM2 activator deficiency, formerly referred to collectively as "amaurotic idiocy." Once GM2 ganglioside was identified as the major accumulating substrate, the terms "infantile ganglioside lipidosis" and "GM2 gangliosidosis" were introduced. Likewise, when the relationship between the enzymatic activity of HEX A and HEX B was identified, the terms "hexosaminidase B deficiency" and "hexosaminidase A and B deficiency" were introduced.

To distinguish Sandhoff disease from Tay-Sachs disease and GM2 activator deficiency – both of which also involve GM2 ganglioside accumulation due to a shared biochemical pathway for the enzymes involved – Sandhoff disease is also referred to as "GM2 gangliosidosis type II" or "GM2 gangliosidosis variant 0."

Prevalence

The prevalence of Sandhoff disease in the general population is not known. The estimated prevalence is around 1:500,000 to 1:1,500,000 depending on the population studied [Tim-Aroon et al 2021].

Populations reported to have an increased prevalence of acute infantile Sandhoff disease include the following (see Table 14 for possible founder variants in these populations):

- Maronite community in Cypress [Drousiotou et al 2000]
- Individuals of Métis ancestry in northern Saskatchewan [Fitterer et al 2014]
- Creole population in northern Argentina [Kleiman et al 1994]

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Acute Infantile Sandhoff Disease

Table 2. Genetic Disorders of Interest in the Differential Diagnosis of Acute Infantile Sandhoff Disease

Gene	DiffDx Disorder [1]	Clinical Features of DiffDx Disorder			
		Cherry-red macula (≤12 mos)	Onset of neurologic regression	Other features / Comments	Not observed in acute infantile SD
ASPA	Canavan disease		≤6 mos	Macrocephaly, head lag, hypotonia, seizures	Leukoencephalopathy
CLN5 *CLN6* *CLN8* *CTSD* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid lipofuscinoses, infantile & late infantile (OMIM PS256730)		≤6 mos	Visual deficits, seizures	Abnormal ERG
CTSA	Galactosialidosis (OMIM 256540)	+	<6 mos	Seizures	Coarse features & skeletal disease
GALC	Krabbe disease		≤6 mos	Seizures	Leukodystrophy, peripheral neuropathy, & irritability

Table 2. continued from previous page.

Gene	DiffDx Disorder [1]	Clinical Features of DiffDx Disorder			
		Cherry-red macula (≤12 mos)	Onset of neurologic regression	Other features / Comments	Not observed in acute infantile SD
GBA1 (*GBA*)	Gaucher disease type 2		≤6 mos	Seizures in some persons	Oculomotor abnormalities, hypertonia, & opisthotonos
GFAP	Alexander disease, infantile form		≤6 mos	Macrocephaly, seizures	Leukodystrophy
GLB1	GM1 gangliosidosis type 1 (See *GLB1* Disorders.)	+	≤12 mos	Seizures	Coarse facies & skeletal disease
GM2A	Activator-deficient TSD [2] (See GM2 Activator Deficiency.)	+	≤6 mos	Phenotype identical to acute infantile SD; [3] extremely rare disorder	No distinguishing features
GNPTAB	Mucolipidosis II (I-cell disease) (See *GNPTAB* Disorders.)		≤12 mos		Coarse facies, hyperplastic gums, skeletal disease; absence of seizures
HEXA	Tay-Sachs disease (See *HEXA* Disorders.)	+	≤6 mos	Clinical course nearly identical to acute infantile SD	No HSM (See Molecular Pathogenesis for comparison of enzymatic basis of SD & TSD.)
NEU1	Sialidosis type II (OMIM 256550)	+	≤12 mos	Seizures	Coarse facies & skeletal abnormalities
SMPD1	Niemann-Pick disease type A (See Acid Sphingomyelinase Deficiency.)	+	≤12 mos		Poor growth, xanthomas, & absence of seizures

DiffDx = differential diagnosis; ERG = electroretinogram; HSM = hepatosplenomegaly; SD = Sandhoff disease; TSD = Tay-Sachs disease

1. The disorders included in Table 2 are inherited in an autosomal recessive manner, with the exception of Alexander disease, which is inherited in an autosomal dominant manner.

2. In activator-deficient TSD, enzymatic activity of both beta-hexosaminidase A and beta-hexosaminidase B is normal, but GM2 ganglioside accumulation occurs because of a deficit of the intralysosomal glycoprotein ("GM2 activator") that is required for the degradation of GM2 ganglioside.

3. Progressive weakness and loss of motor skills between ages six and 12 months, associated with an increased startle response, a cherry-red spot of the macula of the retina, and normal-size liver and spleen

Subacute Juvenile Sandhoff Disease

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of Subacute Juvenile Sandhoff Disease

Gene	DiffDx Disorder [1]	Clinical Features of DiffDx Disorder			
		Cherry-red macula (≤12 mos)	Onset of neurologic regression	Other features / Comment	Not observed in subacute juvenile SD
ASPA	Canavan disease		≤6 mos	Macrocephaly, head lag, hypotonia, seizures	Leukoencephalopathy

Table 3. continued from previous page.

Gene	DiffDx Disorder [1]	Clinical Features of DiffDx Disorder			
		Cherry-red macula (≤12 mos)	Onset of neurologic regression	Other features / Comment	Not observed in subacute juvenile SD
CLN3	CLN3 disease (Batten disease; OMIM 204200)		9-18 yrs	Seizures	Progressive visual loss (onset age 4-5 yrs), retinitis pigmentosa, cataracts, myoclonus, parkinsonism, & abnormal ERG
CTSA	Galactosialidosis (OMIM 256540)	+	>12 mos	Seizures	HSM w/coarse features & skeletal disease
GBA1 (*GBA*)	Gaucher disease type 3		≥12 mos	Seizures	Characteristic looping of saccadic eye movements
GLB1	GM1 gangliosidosis type II (See *GLB1* Disorders.)		1-5 yrs	Seizures	Skeletal disease
HEXA	Tay-Sachs disease (See *HEXA* Disorders.)	+	3-5 yrs	Clinical course nearly identical	See Molecular Pathogenesis for comparison of enzymatic basis of SD & TSD.
SMN1	Spinal muscular atrophy (SMA types II & III)		6 mos to childhood	Progressive hypotonia, fatigue, fasciculations, muscle atrophy	Lack of seizures & brain atrophy; prominent hypotonia

DiffDx = differential diagnosis; ERG = electroretinogram; HEX A = beta-hexosaminidase A; HEX B = beta-hexosaminidase B; HSM = hepatosplenomegaly; SD = Sandhoff disease

1. The disorders included in Table 3 are inherited in an autosomal recessive manner.

Spinocerebellar ataxia (SCA). Some SCA syndromes (e.g., ataxia caused by pathogenic variants of *FGF14*, *MTCL1*, or *TXN2* or SCA7 with extreme anticipation) may be associated with early onset and can be considered in the differential diagnosis of subacute juvenile Sandhoff disease (see Hereditary Ataxia Overview).

Late-Onset Sandhoff Disease

Table 4. Genetic Disorders in the Differential Diagnosis of Late-Onset Sandhoff Disease

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/late-onset SD	Distinguishing from late-onset SD
AR	Spinal & bulbar muscular atrophy	XL	Neurogenic weakness/atrophy (proximal > distal), tremor, cramps & fasciculations, slow progression	Tongue atrophy, facial weakness, androgen insensitivity, gynecomastia, & glucose intolerance
C9orf72 *FUS* *SOD1* *TARDBP* (>30 genes) [1]	Amyotrophic lateral sclerosis	AD AR XL	Progressive neurogenic atrophy, cramps & fasciculations, spasticity	Neurogenic atrophy often asymmetric; bulbar onset (in some persons); absence of cerebellar deficits
CLN6 *CTSF* *DNAJC5*	Adult-onset neuronal ceroid lipofuscinosis (OMIM 204300, 615362, 162350)	AR AD	Ataxia	Seizures, myoclonus, & early intellectual deterioration

Table 4. continued from previous page.

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/late-onset SD	Distinguishing from late-onset SD
FXN	Friedreich ataxia	AR	Ataxia, abnormal eye movements, dysarthria, neurogenic weakness & long tract findings, slow progression	Cardiomyopathy, EKG conduction defects, diabetes, pes cavus, scoliosis, slow sensory nerve conduction velocity, optic atrophy, hearing loss, & neurogenic bladder
HEXA	Tay-Sachs disease (See *HEXA* Disorders.)	AR	Similar clinical course w/ prominent progressive motor neuronopathy starting in lower extremities	Dysarthria, ataxia tends to be more prominent with more severe cerebellar atrophy; more sensory symptoms & dysautonomia than in SD; psychosis may be presenting manifestation
PMP22 (>80 genes)	Charcot-Marie-Tooth hereditary neuropathy	AD AR XL	Progressive weakness, muscle atrophy, sensory ataxia	Dysarthria; ataxia is sensory rather than cerebellar; motor neuron involvement
SMN1	Later-onset spinal muscular atrophy (SMA types III & IV)	AR	Tremor, fasciculations, atrophy, cramps, proximal muscle involvement	Early scoliosis, tongue fasciculations, progressive ↓ in pulmonary function, & absence of ataxia
CHCHD10 *TFG* *VAPB*	Late-onset SMA (See *CHCHD10*-Related Disorders.) & SMA-like disorder (OMIM 604484, 182980)	AD	Neurogenic atrophy	In large kindreds, no cerebellar deficits

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; EKG = electrocardiogram; MOI = mode of inheritance; SD = Sandhoff disease; XL = X-linked

1. C9orf72, *FUS*, *SOD1*, and *TARDBP* are the most commonly involved genes; for other genes associated with amyotrophic lateral sclerosis, see OMIM Phenotypic Series: Amyotrophic lateral sclerosis.

Spinocerebellar ataxia (SCA). Similar to late-onset Sandhoff disease, SCA is associated with tremor, cerebellar atrophy, and dysarthria and can be considered in the differential diagnosis. In particular, SCA2, SCA3, and SCA6 can also be associated with weakness due to neuropathy or motor neuronopathy (see Hereditary Ataxia Overview).

Acquired Disorders

Lead and other heavy metal poisoning, infectious and postinfectious meningoencephalitis, subacute sclerosing panencephalitis, hydrocephalus, and neurologic manifestations of other systemic diseases may mimic the neurologic findings associated with Sandhoff disease.

Management

No clinical practice guidelines for Sandhoff disease have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Sandhoff disease, the evaluations summarized in Tables 5, 6, and 7 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Acute Infantile Sandhoff Disease

System/Concern	Evaluation	Comment
Neurologic	Neurology eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Musculoskeletal system	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Need for adaptive devices • Need for PT (to prevent deformities)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl swallow study for eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/ dysphagia &/or aspiration risk. • Assess for constipation.
Eyes	Ophthalmologic exam	Eval for macular degeneration, cherry-red macula, visual loss
Respiratory	Evaluate for aspiration risk.	Assess need for airway hygiene.
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of this disorder to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.
Ethics consultation	Clinical ethics services	• Assess health care decisions in the context of the best interest of the child & values & preferences of the family. • For difficult life-prolonging decisions or for clarification of treatment options, consider further consultation w/independent clinical teams. [2]

EEG = electroencephalogram; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse
2. Linney et al [2019]

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Subacute Juvenile Sandhoff Disease

System/Concern	Evaluation	Comment
Neurologic	Neurology eval	• To incl brain MRI • Consider EEG if seizures are a concern. • Evaluate for spasticity.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for IEP
Speech-language development / Dysarthria	Speech-language eval	By speech-language pathologist
Musculoskeletal system	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, independence in ADL, & need for adaptive devices • Need for PT (to prevent fixed deformities)

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl swallow study for eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/ dysphagia &/or aspiration risk. • Assess for constipation.
Eyes	Ophthalmologic exam	Assess visual acuity.
Respiratory	Eval for aspiration risk	Assess need for airway hygiene & percussion vest.
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of this disorder to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.

ADL = activities of daily living; EEG = electroencephalogram; IEP = individualized education program; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Table 7. Recommended Evaluations Following Initial Diagnosis in Individuals with Late-Onset Sandhoff Disease

System/Concern	Evaluation	Comment
Neurologic	Neurology eval	• Assess for weakness, tremor, ataxia, & neuropathy. • To incl brain MRI • To incl EMG/NCS
Dysarthria	Speech eval	By speech-language pathologist
Psychiatric	Neuropsychiatric & psychiatric eval	Assess for psychosis, anxiety, & depression.
Musculoskeletal system	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to prevent falls & pressure wounds) &/or OT to maximize independence in ADL
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of this disorder to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources; • Social work involvement for support.

ADL = activities of daily living; EMG = electromyogram; MOI = mode of inheritance; NCS = nerve conduction studies; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations – Acute Infantile Sandhoff Disease

For the most part, treatment for acute infantile Sandhoff disease is supportive and directed toward providing adequate nutrition and hydration, managing infectious disease, protecting the airway, and controlling seizures (see Table 8).

Table 8. Treatment of Manifestations in Individuals with Acute Infantile Sandhoff Disease

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Seizures are often progressive & refractory. • Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Complete seizure control is seldom achieved & requires balancing w/sedative side effects of ASMs. • Education of parents/caregivers [1]
Abnormal tone / Impaired mobility	PT/OT	For prevention of deformities
Feeding difficulties	Gastrostomy tube	Will ↑ longevity but not preserve developmental function
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Aspiration risks / Excess secretion	Gastrostomy tube, vibrator vest, improved pulmonary toilet, suppression of saliva production	Will ↓ aspiration & improve longevity but not developmental function
Family support	In-home nursing & respite care	Support for health & quality of life of caregivers & sibs
Ethics consultation	Clinical ethics services	• Assess health care decisions in the context of the best interest of the child & values & preferences of the family. • For difficult life-prolonging decisions or for clarification of treatment options, consider further consultation w/ independent clinical teams. [2]

ASM = anti-seizure medication; 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.
2. Linney et al [2019]

Treatment of Manifestations – Subacute Juvenile and Late-Onset Sandhoff Disease

Treatment for the subacute juvenile and late-onset Sandhoff disease phenotypes involves the supportive services of a physiatrist and team of physical therapists, occupational therapists, and speech-language pathologists in maximizing function and providing aids for activities of daily living (see Tables 9 and 10).

Table 9. Treatment of Manifestations in Individuals with Subacute Juvenile Sandhoff Disease

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Seizures are often progressive & refractory. • Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Complete seizure control is seldom achieved & requires balancing w/sedative side effects of ASMs. • Education of parents/caregivers [1]
Spasticity	Stretching, splints, pharmacologic treatment	
Developmental plateau / Cognitive decline	See Developmental Delay / Intellectual Disability Management Issues.	
Feeding difficulties	Gastrostomy tube	Will ↑ longevity but not preserve developmental function

Table 9. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Saliva pooling / Drooling	Botulinum toxin to salivary glands, topical anticholinergic agents (drops)	Botox may spread to adjacent bulbar muscles, worsening dysphagia.
Family support	In-home nursing & respite care as needed w/progression of disease	Support for health & quality of life of caregivers & sibs

ASM = anti-seizure medication; IEP = individualized education program
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.

Table 10. Treatment of Manifestations in Individuals with Late-Onset of Sandhoff Disease

Manifestation/Concern	Treatment	Considerations/Other
Weakness / Impaired mobility	PT/OT	• Adaptive equipment & mobility assists • Knee braces may be of particular help for locking knees.
Spasticity/Tremor	Symptom-targeted pharmacotherapy by experienced neurologist	
Dysarthria / Communication needs	By speech-language pathologist	• Focus on strategies to slow speech rate. • Consider eval for alternative means of communication (e.g., AAC) for those w/ expressive language difficulties.
Occupational counseling	Vocational rehab	
Psychiatric issues	• Antidepressant or antipsychotic medications may be used, but clinical response is variable & can be poor. • Cognitive behavioral therapy can ↑ coping skills.	Treatment needs to be individualized.
Family support	In-home nursing & respite care	Could be indicated for persons w/advanced disease

AAC = augmentative and alternative communication; OT = occupational therapy; PT = physical therapy

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 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

There are no formal guidelines for surveillance for individuals with Sandhoff disease. Tables 11, 12, and 13 provide suggestions for periodic evaluations to monitor existing disease manifestations and to identify new manifestations requiring modification of supportive care.

Table 11. Recommended Surveillance for Individuals with Acute Infantile Sandhoff Disease

System/Concern	Evaluation	Frequency
Neurologic decline	By pediatric neurologist w/attention to seizure severity & response to ASM	Every 3-6 mos
Abnormal tone / Impaired mobility	• OT/PT assessment of ADL; need for splinting for contractures/scoliosis • Durable medical equipment for mobility	At each visit
Nutrition/feeding	By feeding team re aspiration risk / nutrition needs	
Respiratory	Assess need for airway hygiene.	
Family support & resources	Assess need for: • Social work involvement for parental support; • Palliative care referral; • Home nursing referral.	As needed

ADL = activities of daily living; ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy

Table 12. Recommended Surveillance for Individuals with Subacute Juvenile Sandhoff Disease

System/Concern	Evaluation	Frequency
Neurologic decline	Neurology eval for tone, cognition, seizure onset/control	Annually or as needed for seizures
Development	Developmental/educational needs	Annually
Speech-language development / Dysarthria	By speech-language pathologist	Per treating clinician
Musculoskeletal system	• OT/PT assessment of ADL; need for splinting for contractures/ scoliosis • Durable medical equipment for mobility	At each visit
Nutrition/Feeding	By feeding team re aspiration risk / nutrition needs	
Visual acuity	• Ophthalmologic exam • Assess need for low vision services.	Annually
Respiratory	Assess need for airway hygiene.	At each visit
Family support & resources	Assess need for: • Social work involvement for parental support; • Palliative care referral; • Home nursing referral.	As needed

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

Table 13. Recommended Surveillance for Individuals with Late-Onset Sandhoff Disease

System/Concern	Evaluation	Frequency
Neurologic	Neurology eval for emergence of new neurologic manifestations &/or progression of existing manifestations	Every 1-3 yrs
Dysarthria	• By speech-language pathologist • Consider eval for alternative means of communication (e.g., AAC).	As needed
Psychiatric issues	Assess for psychosis, anxiety, & depression.	At each visit
Musculoskeletal system	• OT/PT assessment of ADL; need for splinting for contractures/scoliosis • Durable medical equipment for mobility	
Family support		As needed

AAC = augmentative and alternative communication; ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

For individuals with **acute infantile** Sandhoff disease, avoid:

- Positioning that increases aspiration risk during feedings;
- Seizure medication dosages that result in excessive sedation.

For individuals with **subacute juvenile** Sandhoff disease, avoid:

- Situations that increase the likelihood of contractures or pressure sores, such as extended periods of immobility;
- Circumstances that exacerbate the risk of falls.

For individuals with **late-onset** Sandhoff disease, avoid:

- Situations that exacerbate fall risk (i.e., walking on uneven or unstable surfaces);

- Psychiatric medications that have been associated with disease worsening in late-onset Tay-Sachs disease, a similar disorder (e.g., haloperidol, risperidone, chlorpromazine) [Shapiro et al 2006].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

In-progress or recently concluded studies:

- A Phase II study (NCT03759665) assessing the safety and efficacy of N-acetyl-L-leucine for the treatment of GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease)
- A multicenter study (NCT04221451) assessing the efficacy and pharmacodynamics of daily oral dosing of venglustat when administered over a 104-week period in late-onset and subacute juvenile GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease)
- A Phase I/II (NCT04669535) dose-escalation and safety and efficacy study of AXO-AAV-GM2 in Tay-Sachs or Sandhoff disease
- A combination therapy (NCT02030015) using miglustat and the ketogenic diet for infantile and juvenile forms of GM1 and GM2 gangliosidoses (the latter refers to Tay-Sachs disease and Sandhoff disease)
- A survey (NCT03822013) of miglustat therapeutic effects on neurologic and systemic manifestations of infantile phenotypes of Tay-Sachs disease and Sandhoff disease

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

Acute infantile Sandhoff disease, subacute juvenile Sandhoff disease, and late-onset Sandhoff disease (comprising the clinical spectrum of Sandhoff disease) are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *HEXB* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *HEXB* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;

- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *HEXB* 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 inheriting neither of the familial pathogenic variants.
- Sibs who inherit biallelic *HEXB* pathogenic variants will have the same phenotype (i.e., acute infantile, subacute juvenile, or late-onset Sandhoff disease) as the proband (see Genotype-Phenotype Correlations). However, the subacute juvenile and late-onset phenotypes are associated with significant intrafamilial clinical variability.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with late-onset Sandhoff disease has children with an affected individual or a carrier,* offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *HEXB*; it is appropriate to offer carrier testing to the reproductive partners of individuals with late-onset Sandhoff disease.

* See Prevalence for populations reported to have an increased prevalence of Sandhoff disease.

Carrier Detection

Molecular genetic testing. Once both *HEXB* pathogenic variants have been identified in an affected family member, targeted analysis for the specific familial variants can be used for carrier testing in at-risk relatives.

Biochemical testing to detect carriers of Sandhoff disease is not routinely done, and results would need to be confirmed with molecular genetic testing.

Related Genetic Counseling Issues

Family planning

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

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *HEXB* 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.

- **MedlinePlus**
  Sandhoff disease
- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  Phone: 617-277-4463
  Email: info@ntsad.org
  www.ntsad.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. Sandhoff Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HEXB	5q13.3	Beta-hexosaminidase subunit beta	HEXB database	HEXB	HEXB

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 Sandhoff Disease (View All in OMIM)

268800	SANDHOFF DISEASE
606873	HEXOSAMINIDASE B; HEXB

Molecular Pathogenesis

The enzyme beta-hexosaminidase comprises an alpha subunit and a beta subunit encoded by the genes *HEXA* and *HEXB*, respectively. The combination of the alpha and beta subunits forms the enzyme beta-hexosaminidase A (HEX A), whereas the combination of two beta subunits forms the enzyme beta-hexosaminidase B (HEX B). GM2 activator, a substrate-specific cofactor, together with HEX A catalyzes the degradation of GM2 gangliosides.

The two main forms of GM2 gangliosidosis are Tay-Sachs disease (resulting from biallelic pathogenic variants in *HEXA*) and Sandhoff disease (resulting from biallelic pathogenic variants in *HEXB*).

Since HEX A comprises both an alpha subunit and a beta subunit, HEX A activity will be decreased in both Tay-Sachs disease and Sandhoff disease.

- In Tay-Sachs disease, total hexosaminidase activity (i.e., HEX A plus HEX B) is decreased, whereas HEX B activity is normal.
- In Sandhoff disease, both HEX A activity and HEX B activity as well as total hexosaminidase activity (i.e., HEX A and HEX B) are decreased; however, the percent contribution from HEX A is increased, since the percent contribution from HEX B is disproportionately decreased by loss of the function of the beta subunit.

The molecular pathogenesis of these two GM2 gangliosidoses, Tay-Sachs disease and Sandhoff disease, is the following: gangliosides (normally present in neurons in very small quantities) are progressively stored in neurons leading to neuronal impairment and loss, causing the characteristic central nervous system and peripheral nervous system neurodegeneration.

Only HEX A (in the presence of the GM2 activator protein, GM2A) is responsible for the degradation of GM2 gangliosides.

HEX B is able to hydrolyze certain neutral oligosaccharides [Sandhoff 1969, Hepbildikler et al 2002]. HEX B is also thought to play a role in glycosphingolipid degradation.

Mechanism of disease causation. Loss-of-function *HEXB* variants cause decreased-to-absent activity of HEX B.

Table 14. Notable *HEXB* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000521.4 NP_000512.2	c.76delA	p.Met26CysfsTer5	Common variant in Maronite community in Cypress [Drousiotou et al 2000] [1]
	c.115delG	p.Val39TrpfsTer25	Common variant in persons of Métis ancestry in northern Saskatchewan [Fitterer et al 2014] [1]
NM_000521.4	c.445+1G>A	--	Common variant in Creole population in northern Argentina [Kleiman et al 1994] [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. See Genotype-Phenotype Correlations.

Chapter Notes

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