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NLM Citation: Toro C, Shirvan L, Tifft C. *HEXA* Disorders. 1999 Mar 11 [Updated 2020 Oct 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

HEXA Disorders

Synonyms: Beta-Hexosaminidase A Deficiency; GM2 Gangliosidosis, Type I; Tay-Sachs Disease

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Created: March 11, 1999; Updated: October 1, 2020.

Summary

Clinical characteristics

HEXA disorders are best considered as a disease continuum based on the amount of residual beta-hexosaminidase A (HEX A) enzyme activity. This, in turn, depends on the molecular characteristics and biological impact of the *HEXA* pathogenic variants. HEX A is necessary for degradation of GM2 ganglioside; without well-functioning enzymes, GM2 ganglioside builds up in the lysosomes of brain and nerve cells.

The classic clinical phenotype is known as Tay-Sachs disease (TSD), characterized by progressive weakness, loss of motor skills beginning between ages three and six months, decreased visual attentiveness, and increased or exaggerated startle response with a cherry-red spot observable on the retina followed by developmental plateau and loss of skills after eight to ten months. Seizures are common by 12 months with further deterioration in the second year of life and death occurring between ages two and three years with some survival to five to seven years.

Subacute juvenile TSD is associated with normal developmental milestones until age two years, when the emergence of abnormal gait or dysarthria is noted followed by loss of previously acquired skills and cognitive decline. Spasticity, dysphagia, and seizures are present by the end of the first decade of life, with death within the second decade of life, usually by aspiration.

Late-onset TSD presents in older teens or young adults with a slowly progressive spectrum of neurologic symptoms including lower-extremity weakness with muscle atrophy, dysarthria, incoordination, tremor, mild spasticity and/or dystonia, and psychiatric manifestations including acute psychosis. Clinical variability even among affected members of the same family is observed in both the subacute juvenile and the late-onset TSD phenotypes.

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Diagnosis/testing

The diagnosis of a *HEXA* disorder is established in a proband with abnormally low HEX A activity on enzyme testing and biallelic pathogenic variants in *HEXA* identified by molecular genetic testing. Targeted analysis for certain pathogenic variants can be performed first in individuals of specific ethnicity (e.g., French Canadian, Ashkenazi Jewish). Enzyme testing of affected individuals identifies absent to near-absent HEX A enzymatic activity in the serum, white blood cells, or other tissues in the presence of normal or elevated activity of the beta-hexosaminidase B enzyme. Pseudodeficiency refers to an in vitro phenomenon caused by specific *HEXA* variants that renders the enzyme unable to process the synthetic (but not the natural) GM2 substrates, and leads to false positive enzyme testing results.

Management

Treatment of manifestations: Treatment is mostly supportive and directed to providing adequate nutrition and hydration, managing infectious disease, protecting the airway, and controlling seizures. The treatment for the subacute juvenile and late-onset Tay-Sachs phenotypes is directed to providing the services of a physiatrist and team of physical, occupational, and speech therapists for maximizing function and providing aids for activities of daily living.

Agents/circumstances to avoid: Positioning that increases aspiration risk during feedings and seizure medication dosages that result in excessive sedation for those with acute infantile TSD; situations that increase the likelihood of contractures or pressure sores, such as extended periods of immobility; circumstances that exacerbate the risk of falls (i.e., walking on uneven or unstable surfaces) in those with subacute juvenile TSD; psychiatric medications that have been associated with disease worsening, including haloperidol, risperidone, and chlorpromazine.

Genetic counseling

Acute infantile Tay-Sachs disease (TSD), subacute juvenile TSD, and late-onset TSD (comprising the clinical spectrum of *HEXA* disorders) are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (carriers) are asymptomatic. Once both *HEXA* 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. Molecular genetic testing and/or HEX A enzyme testing can be used for carrier detection in individuals who do not have a family history of TSD. If both members of a reproductive couple are known to be heterozygous for a *HEXA* pathogenic variant, molecular genetic prenatal testing and preimplantation genetic testing for the *HEXA* pathogenic variants identified in the parents are possible.

GeneReview Scope

HEXA Disorders: Included Phenotypes

Biochemical phenotype	Clinical phenotypes
Beta-hexosaminidase A deficiency [1]	• Acute infantile Tay-Sachs disease • Subacute juvenile Tay-Sachs disease • Late-onset Tay-Sachs disease

For synonyms and outdated names see Nomenclature.

1. Beta-hexosaminidase A (HEX A; often referred to in the shortened form, "hexosaminidase A") is a heterodimer comprising a single alpha chain and a single beta chain. The alpha chain is encoded by *HEXA*; the beta chain is encoded by *HEXB*. Deficiency of HEX A can therefore be the result of pathogenic variants in *HEXA* or *HEXB*. (HEX A deficiency caused by pathogenic variants in *HEXB* is referred to as Sandhoff disease; see Differential Diagnosis.)

Diagnosis

HEXA disorders are best considered as a disease continuum based on the amount of residual beta-hexosaminidase A (HEX A) enzyme activity. This, in turn, depends on the molecular characteristics and biological impact of the *HEXA* pathogenic variants. HEX A is necessary for degradation of GM2 ganglioside; without well-functioning enzymes, GM2 ganglioside builds up in the lysosomes of brain and nerve cells. The classic clinical phenotype is known as Tay-Sachs disease (TSD), after ophthalmologist Warren Tay and neurologist Bernard Sachs, who originally described the disorder in the late 19th century. For convenience, the clinical phenotypes are often divided into acute infantile, subacute juvenile, and late-onset disorders, with unique phenotypes common to each subset.

Suggestive Findings

Acute infantile Tay-Sachs disease should be suspected in infants with the following clinical findings:

- Progressive weakness and loss of motor skills beginning between ages three and six months
- Decreased attentiveness
- An increased or exaggerated startle response
- A cherry-red spot of the fovea centralis of the macula of the retina
- A normal-sized liver and spleen
- Generalized muscular hypotonia with sustained ankle clonus and hyperreflexia
- Onset of seizures beginning around age 12 months
- Progressive macrocephaly with proportionate ventricular enlargement on neuroimaging beginning at age 18 months

Subacute juvenile Tay-Sachs disease should be suspected in individuals with the following clinical findings:

- A period of normal development until ages two to five years followed by a plateauing of skills and then loss of previously acquired developmental skills
- Progressive spasticity resulting in loss of independent ambulation
- Progressive dysarthria, drooling, and eventually absent speech
- Normal-sized liver and spleen
- Onset of seizures
- Progressive global brain atrophy on neuroimaging [Nestrasil et al 2018]

Late-onset Tay-Sachs disease should be suspected in individuals with the following clinical findings:

- Onset of symptoms in teens or adulthood
- Progressive neurogenic weakness of antigravity muscles in the lower extremities and frequent falls
- Dysarthria, tremor, and incoordination
- Acute psychiatric manifestations including psychosis (which can be the initial manifestation of disease)
- Isolated cerebellar atrophy on neuroimaging

Establishing the Diagnosis

The diagnosis of a *HEXA* disorder **is established** in a proband with abnormally low HEX A activity on enzyme testing and biallelic pathogenic (or likely pathogenic) variants in *HEXA* 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 a heterozygous *HEXA* variant of uncertain significance does not establish or rule out the diagnosis.

HEX A enzymatic activity testing. Testing identifies absent to near-absent HEX A enzymatic activity in the serum, white blood cells, or other tissues in the presence of normal or elevated activity of the beta-hexosaminidase B (HEX B) enzyme [Hall et al 2014].

- Individuals with acute infantile TSD have no or extremely low HEX A enzymatic activity.
- Individuals with subacute juvenile or late-onset TSD have some minimal residual HEX A enzymatic activity.

Note: The enzyme HEX A is a heterodimer of one alpha subunit and one beta subunit (encoded by the genes *HEXA* and *HEXB*, respectively); the enzyme HEX B, on the other hand, is a homodimer composed of two beta subunits. Only HEX A is able to degrade GM2 ganglioside.

Note: Pseudodeficiency refers to an in vitro phenomenon caused by specific *HEXA* variants that renders the enzyme unable to process the synthetic (but not the natural) GM2 substrates, and leads to false positive enzyme testing results.

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 *HEXA* disorders is broad, infants with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those (especially older individuals) with a phenotype indistinguishable from many other disorders presenting later in life with neurodegeneration or developmental regression 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 a *HEXA* disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *HEXA* is performed first followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

  Targeted analysis for pathogenic variants can be performed first in individuals of specific ethnicity:

  - **French Canadian descent.** A 7.6-kb genomic deletion of the *HEXA* promoter and exon 1
  - **Ashkenazi Jewish populations.** p.Tyr427IlefsTer5, c.1421+1G>C, c.1073+1G>A, p.Gly269Ser, and two pseudodeficiency alleles: p.Arg247Trp and p.Arg249Trp (See Table 12.)

    Note: (1) The presence of one pseudodeficiency allele reduces the in vitro HEX A enzymatic activity toward synthetic substrates but does not reduce enzymatic activity with the natural substrate, GM2 ganglioside. All enzymatic assays use the artificial substrate because the naturally occurring GM2 ganglioside is not a stable reagent and is not available. Thus, a problem emerges in interpreting enzymatic deficiency. Molecular genetic testing provides the basis to differentiate a pathogenic allele from a pseudodeficiency allele. (2) About 35% of non-Jewish individuals identified as heterozygotes by HEX A enzyme-based testing are carriers of a pseudodeficiency allele. (3) About 2% of Ashkenazi Jewish individuals identified as heterozygotes by HEX A enzyme-based testing in carrier screening programs are actually heterozygous for a pseudodeficiency allele (see Table 12).

- **A multigene panel** that includes *HEXA* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For 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 a slowly progressive neurodegeneration, **comprehensive genomic testing**, which does not require the clinician to determine which gene(s) are likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 exome 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 *HEXA* Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
HEXA	Sequence analysis [3]	99% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare

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 clinical phenotype of *HEXA* disorders comprises a continuum including acute infantile, subacute juvenile, and late-onset Tay-Sachs disease. Although classification into subtypes is somewhat arbitrary, it is helpful in understanding the variation observed in the timing of disease onset, presenting symptoms, rate of progression, and longevity.

While case reports of individuals abound, there is a paucity of prospective natural history studies for Tay-Sachs disease delineating the progression of disease subtypes over time.

Subtypes of *HEXA* disorders include the following phenotypes:

- Acute infantile Tay-Sachs disease with onset before six months, rapid progression, and death generally before age five years
- Subacute juvenile Tay-Sachs disease with later onset and survival into late childhood or adolescence
- Late-onset Tay-Sachs disease with long-term survival. Affected individuals may present with various phenotypes including lower motor neuronopathy with progressive lower-extremity weakness, atrophy and fasciculations, progressive dystonia, spinocerebellar deficits, dysarthria, and/or psychosis.

Acute Infantile Tay-Sachs Disease

Presentation. Affected infants generally appear to be completely normal at birth.

- Progressive weakness begins between ages three and six months, along with myoclonic jerks and an exaggerated startle reaction to sudden stimuli.
- Decreasing visual attentiveness and unusual eye movements at age three to six months may be the first sign prompting parents to seek medical attention, where subsequent ophthalmologic evaluation reveals the characteristic cherry-red macula seen in virtually all children with infantile disease.

Progression. By age six to ten months, acquisition of developmental milestones plateaus and eventually ceases across multiple domains. Finally, children begin to lose previously demonstrated skills.

- After age eight to ten months, progression of the disease is rapid. Spontaneous or purposeful voluntary movements diminish, and the infant becomes progressively less responsive. Vision deteriorates rapidly. Seizures are common by age 12 months. Subtle partial complex seizures or absence seizures typically become more frequent and severe.
- Progressive enlargement of the head typically begins by age 18 months resulting from reactive cerebral gliosis but eventually followed by ventriculomegaly [Nestrasil et al 2018].
- Further deterioration in the second year of life results in decerebrate posturing, difficulties in swallowing, worsening seizures, and finally an unresponsive, vegetative state. Death from respiratory complications usually occurs between ages two and three years, although the use of a gastrostomy tube to minimize aspiration events and improved pulmonary hygiene with the use of vibrating vests has extended the life span of individuals with acute infantile Tay-Sachs disease to between five and seven years [Bley et al 2011, Regier et al 2016].

Subacute Juvenile Tay-Sachs Disease

Presentation. Children attain normal developmental milestones up until around age two years. Between ages two and five years, gains in motor and speech parameters slow down and eventually plateau. Abnormal gait or dysarthria begins to emerge, followed by loss of previously acquired skills and cognitive decline.

Progression. Spasticity, dysphagia, and seizures are present by the end of the first decade of life [Maegawa et al 2006].

- A decrease in visual acuity occurs much later in subacute juvenile Tay-Sachs disease than in the acute infantile form of the disease and the cherry-red spot is rarely observed. Optic atrophy and retinal pigmentation may be seen late in the course of the disease.
- A vegetative state with decerebrate posturing begins to appear in many individuals by age ten to 15 years, followed within a few years by death, usually from aspiration. Newer measures in supportive care that

protect airways and improve pulmonary toilet may extend life span. In some individuals, the disease pursues a particularly aggressive course, culminating in death within two to four years of symptom onset.

Clinical variability is observed in the subacute juvenile form of TSD even among affected members of the same family.

Late-Onset Tay-Sachs Disease (LOTS)

Presentation. Affected individuals present with a slowly progressive spectrum of neurologic and psychiatric symptoms as older teenagers or young adults. In retrospect, many parents can describe nonspecific subtle clumsiness or developmental irregularities earlier in life. As most subjects achieve nearly normal milestones to adulthood and the disorder progresses slowly over decades, the presentation may resemble that of other "neurodegenerative" conditions of adults. The later development of symptoms compared to the acute infantile and subacute juvenile versions of Tay-Sachs disease is attributed to the presence of residual beta-hexosaminidase A (HEX A) enzyme activity, enough to forestall the onset of symptoms to adulthood. Early symptoms may range from neurogenic lower-extremity weakness with atrophy of the quadriceps muscles to dysarthria, incoordination, tremor, mild spasticity, and/or dystonia. Up to 40% of individuals with LOTS may experience psychiatric manifestations, including acute psychosis [Masingue et al 2020; Toro, personal observation].

Progression. Central nervous system involvement in LOTS is widespread, however, certain central nervous system structures appear to be more vulnerable to the disease than others, leading to particular clinical findings:

- Most, if not all, individuals with LOTS develop progressive neurogenic muscle weakness and wasting.

  Early in the disease course, weakness involves the lower extremities, particularly the knee extensors and hip flexors. Atrophy, cramps, and fasciculations are common. Affected individuals relate progressive difficulty in climbing steps or bleachers, eventually requiring the aid of handrails. As knee extensor muscle weakness progresses, individuals hyperextend ("lock") their knees to support their weight, producing a characteristic gait. Failure to maintain knees locked results in collapse and injury.

  Upper-extremity strength may become affected years later with a predilection for elbow extension (triceps) weakness. Long tract findings including spasticity, upgoing toes, and brisk reflexes can be present but may be obscured by lower motor neuron weakness.

- Dysarthria is common; the speech rate is fast and almost "pressured," which, together with poor articulation, affects speech intelligibility. The poor articulation emerges primarily from cerebellar dysfunction; however, individuals may demonstrate associated features of focal laryngeal dystonia (spasmodic dysphonia), leading to a "strangled" voice and overflow activation of neck and facial muscles. Despite prominent dysarthria, dysphagia and aspiration events are not common early in LOTS.

- Decreased balance requiring a wide base of support, decreased dexterity, and tremor are frequent findings in LOTS. These – along with the presence of 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 atrophy is evident even early in the disease, at times out of proportion to the extent of cerebellar deficits, and is almost universal in LOTS.

- Psychiatric manifestations including comorbid anxiety and depression are common. Acute psychosis and mania can occur, representing the initial manifestation of disease in some individuals.

- Deficits in executive function and memory are reported in some individuals and can be associated with progressive brain volume loss. Contrary to the acute infantile and subacute juvenile phenotypes, however, declines in higher cortical functioning develop slowly, often over decades after the onset of disease symptoms.

Clinical variability is significant for LOTS, even within a single family with more than one affected individual. Psychosis may be severe by age 20 years in one individual, whereas another older affected sib may function well into adulthood with mainly neuromuscular complaints [Author, personal observation].

Neuropathology

Children with the acute infantile form of TSD have excessive and ubiquitous neuronal glycolipid storage (≤12% of the brain dry weight), of which the enormous predominance is the specific glycolipid GM2 ganglioside. Individuals with the adult-onset forms have less accumulation of glycolipid; it may even be restricted to specific brain regions. For example, in LOTS the neocortex may be spared, while the hippocampus, brain stem nuclei, and the spinal cord are markedly affected [Gravel et al 2001].

Genotype-Phenotype Correlations

In general, individuals with two null (nonexpressing) alleles have the infantile form, individuals with one null allele and one missense allele have the subacute juvenile-onset phenotype, and individuals with two missense alleles have the milder late-onset phenotype. This reflects the inverse correlation of the level of the residual activity of the HEX A enzyme with the severity of the disease: the lower the level of the enzymatic activity, the more severe the phenotype is likely to be.

Nomenclature

Tay-Sachs disease was originally described as "infantile amaurotic idiocy" and "amaurotic familial infantile idiocy" by Tay and Sachs, respectively.

When GM2 ganglioside was identified as the major accumulating substrate, the nomenclature included the terms "infantile ganglioside lipidosis," "type 1 GM2 gangliosidosis," and "acute infantile GM2 gangliosidosis."

When deficient HEX A enzymatic activity was identified, the disease was then referred to as "hexosaminidase A deficiency," "HEX A deficiency," or "type 1 hexosaminidase A deficiency."

When the subacute juvenile and late-onset phenotypes were identified, they were referred to as the "B1 variant of GM2 gangliosidoses" or "juvenile (subacute) hexosaminidase deficiency" and "chronic or adult-onset hexosaminidase A deficiency," respectively.

Prevalence

Before the advent of population-based carrier screening, education, and counseling programs for the prevention of TSD in Jewish communities, the incidence of TSD was estimated at 1:3,600 Ashkenazi Jewish births. At that birth rate, the carrier rate for TSD is approximately 1:30 among Jewish Americans of Ashkenazi extraction (i.e., from Central and Eastern Europe).

Carrier screening studies have indicated that the frequency of the Ashkenazi Jewish founder variants in individuals whose parents and respective grandparents were of Ashkenazi Jewish descent is 1:27.4 [Scott et al 2010].

As the result of extensive genetic counseling of carriers identified through carrier screening programs and monitoring of at-risk pregnancies, the incidence of TSD in the Ashkenazi Jewish population of North America has been reduced by greater than 90% [Kaback et al 1993, Kaback 2000].

Among Sephardic Jews and all non-Jews, the disease incidence has been observed to be about 100 times lower, corresponding to a tenfold lower carrier frequency (between 1:250 and 1:300).

TSD has been reported in children in virtually all population groups studied.

Other genetically isolated populations have been found to carry founder *HEXA* pathogenic variants at frequencies comparable to or even greater than those observed in Ashkenazi Jews. These include:

- French Canadians of the eastern St Lawrence Valley, Quebec;
- Cajuns from Louisiana.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The neurologic symptoms that develop in the course of *HEXA* disorders are not unique and can be caused by a wide array of hereditary and acquired conditions, including toxic and infectious/post-infectious disorders.

Hereditary Disorders

Infantile Onset

Table 2. Genetic Disorders of Interest in the Differential Diagnosis of Acute Infantile Tay-Sachs Disease

Gene	Disorder	Cherry-Red Spot (≤12 mos)	Onset of Neurologic Regression	Other Features / Comment	Features Distinguishing the Disorder from Acute Infantile TSD
ASPA	Canavan disease	–	≤6 mos	Macrocephaly, head lag, hypotonia, seizures	Leukoencephalopathy, ↑ N-acetyl aspartate in CSF
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	Hepatosplenomegaly w/coarse features & skeletal disease
GALC	Krabbe disease	–	≤6 mos	Seizures	Leukodystrophy, peripheral neuropathy, irritability
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	Hepatosplenomegaly w/coarse facies, skeletal disease
GM2A	Activator-deficient TSD [1] (GM2 gangliosidosis, AB variant) (See GM2 Activator Deficiency.)	+	≤6 mos	Phenotype identical to classic TSD; [2] extremely rare disorder	No distinguishing features

Table 2. continued from previous page.

Gene	Disorder	Cherry-Red Spot (≤12 mos)	Onset of Neurologic Regression	Other Features / Comment	Features Distinguishing the Disorder from Acute Infantile TSD
GNPTAB	Mucolipidosis II (I-cell disease) (See *GNPTAB* Disorders.)	–	≤12 mos		Hepatosplenomegaly w/coarse facies, hyperplastic gums, skeletal disease; absence of seizures
HEXB	Sandhoff disease [3]	+	≤6 mos	Seizures	Hepatosplenomegaly, skeletal abnormalities, deficiency of both HEX A & HEX B enzyme activity
NEU1	Sialidosis type II (OMIM 256550)	+	≤12 mos	Seizures	Hepatosplenomegaly w/coarse facies, skeletal abnormalities
SMPD1	Niemann-Pick disease type A (See Acid Sphingomyelinase Deficiency.)	+	≤12 mos		Hepatosplenomegaly, feeding difficulties, severe failure to thrive, xanthomas; absence of seizures

The disorders included in Table 2 are inherited in an autosomal recessive manner, with the exception of Alexander disease, which is an autosomal dominant disorder.
CSF = cerebrospinal fluid; ERG = electroretinogram; HEX A = beta-hexosaminidase A; HEX B = hexosaminidase B; TSD = Tay-Sachs disease
1. In activator-deficient TSD, enzymatic activity of both HEX A and HEX 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.
2. 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
3. In Sandhoff disease, the activity of HEX A is deficient, as is the activity of HEX B, since both enzymes lack the common beta subunit.

Subacute Juvenile Onset

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of Subacute Juvenile Tay-Sachs disease

Gene	Disorder	Cherry-Red Spot (≤12 mos)	Onset of Neurologic Regression	Other Features / Comment	Features Distinguishing the Disorder from Subacute Juvenile TSD
ASPA	Canavan disease	–	≤6 mos	Macrocephaly, head lag, hypotonia, seizures	Leukoencephalopathy & ↑ *N*-acetyl aspartate in CSF
CLN3	CLN3 disease (OMIM 204200) (Batten disease)	–	9-18 yrs	Seizures	Progressive visual loss (onset age 4-5 yrs), retinitis pigmentosa, cataracts, myoclonus, parkinsonism, abnormal ERG, ultrastructural abnormalities in lymphocytes, skin & other tissues
CTSA	Galactosialidosis (OMIM 256540)	+	>12 mos	Seizures	Hepatosplenomegaly 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

Table 3. continued from previous page.

Gene	Disorder	Cherry-Red Spot (≤12 mos)	Onset of Neurologic Regression	Other Features / Comment	Features Distinguishing the Disorder from Subacute Juvenile TSD
HEXB	Sandhoff disease	+	3-5 yrs	Clinical course nearly the same as subacute juvenile TSD	Deficiency of both HEX A & HEX B enzyme activity

The disorders included in Table 3 are inherited in an autosomal recessive manner.
CSF = cerebrospinal fluid; ERG = electroretinogram; HEX A = beta-hexosaminidase A; HEX B = hexosaminidase B; TSD = Tay-Sachs disease

Spinocerebellar ataxia (SCA). Some spinocerebellar ataxia syndromes (e.g., ataxia caused by mutation 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 TSD (see Hereditary Ataxia Overview).

Late Onset

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

Gene	Disorder	MOI	Overlapping Features	Distinguishing Features
AR	Spinal & bulbar muscular atrophy (SBMA)	XL	Neurogenic weakness/atrophy (proximal > distal), tremor, cramps & fasciculations, slow progression	In SBMA: tongue atrophy, facial weakness, androgen insensitivity, gynecomastia, & glucose intolerance
C9orf72 *FUS* *SOD1* *TARDBP* (>30 genes) [1]	Amyotrophic lateral sclerosis (ALS)	AD AR XL	Progressive neurogenic atrophy, cramps fasciculations, spasticity	In ALS: neurogenic atrophy is often asymmetrical, bulbar onset (in some persons); absence of cerebellar deficits
CLN6 *CTSF* *DNAJC5*	Adult-onset neuronal ceroid-lipofuscinosis (CLN) (OMIM 204300, 615362, 162350)	AR AD	Ataxia	In adult-onset CLN: seizures, myoclonus, early intellectual deterioration
FXN	Friedreich ataxia (FRDA)	AR	Ataxia, abnormal eye movements, dysarthria, neurogenic weakness & long tract findings, slow progression	In FRDA: cardiomyopathy, EKG conduction defects, diabetes, *pes cavus,* scoliosis, slow sensory nerve conduction velocity, optic atrophy, hearing loss, neurogenic bladder
HEXB	Sandhoff disease	AR	Progressive motor weakness beginning in lower extremities	In Sandhoff disease: sensory neuropathy, less dysarthria than in LOTS
SMN1	Later-onset spinal muscular atrophy (SMA types III & IV)	AR	Tremor, fasciculations, atrophy, cramps, proximal muscle involvement	In SMA: 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	Large kindreds, no cerebellar deficits, ↑ CPK in some affected persons

AD = autosomal dominant; AR = autosomal recessive; CPK = creatine phosphokinase; EKG = electrocardiogram; LOTS = late-onset Tay-Sachs disease; MOI = mode of inheritance; 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 Amyotrophic Lateral Sclerosis Phenotypic Series.

Spinocerebellar ataxia (SCA). Similar to late-onset TSD, SCA is associated with tremor, cerebellar atrophy, and dysarthria and can be considered in the differential diagnosis (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 *HEXA* disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *HEXA* disorder, 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 Tay-Sachs 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 spot, visual loss
Respiratory	Evaluate aspiration risk.	Assess need for airway toileting.
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.

EEG = electroencephalogram; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Subacute Juvenile Tay-Sachs 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

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
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)
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	Evaluate aspiration risk.	Assess need for airway toileting & 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 Tay-Sachs Disease

System/Concern	Evaluation	Comment
Neurologic	Neurology eval	Assess for weakness & tremor.
Dysarthria	Speech eval	
Psychiatric	Neuropsychiatric 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; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

For the most part, treatment for acute infantile Tay-Sachs disease (TSD) is supportive and directed to providing adequate nutrition and hydration, managing infectious disease, protecting the airway, and controlling seizures. The treatment for the subacute juvenile and late-onset TSD phenotypes is directed to providing the services of a

physiatrist and team of physical, occupational, and speech therapists for maximizing function and providing aids for activities of daily living.

Table 8. Treatment of Manifestations in Individuals with Acute Infantile Tay-Sachs 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 ASM. • 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

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.

Table 9. Treatment of Manifestations in Individuals with Subacute Juvenile Tay-Sachs 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 ASM. • Education of parents/caregivers [1]
Spasticity	Stretching, splints, pharmacologic treatment	
Developmental plateau / Cognitive decline	IEP	
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
Saliva pooling / Drooling	Botulinum toxin to salivary glands, topical (drops) anticholinergic agents	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 Tay-Sachs Disease

Manifestation/Concern	Treatment	Considerations/Other
Weakness / Impaired mobility	PT/OT	Adaptive equipment & mobility assists
Spasticity/Tremor	Symptom-targeted pharmacotherapy by experienced neurologist	
Communication needs	Voice therapy	Focus on strategies to slow speech rate.
Occupational counseling	Vocational rehab	
Psychiatric issues	• Antidepressant or antipsychotic medications may be used, but clinical response is variable & can be poor. • Cognitive behavioral therapy ↑ coping skills. • Electroconvulsive therapy reported beneficial in some cases	Treatment needs to be individualized.
Family support	In-home nursing & respite care	Could be indicated for individuals w/ advanced disease

OT = occupational therapy; PT = physical therapy

Surveillance

There are no formal guidelines for surveillance for those affected with *HEXA* disorders.

Neurology evaluations should commence at the time of diagnosis for all subtypes of TSD if not previously established, and follow up should be dictated by emergent clinical concerns.

Agents/Circumstances to Avoid

For individuals with **acute infantile TSD**, avoid:

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

For individuals with **subacute juvenile TSD**, 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 TSD**, avoid:

- Situations that exacerbate fall risk (i.e., walking on uneven or unstable surfaces);
- Psychiatric medications that have been associated with disease worsening (e.g., haloperidol, risperidone, and 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

Current studies include:

- A Phase II study to assess the safety and efficacy of N-acetyl-L-leucine for the treatment of GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease);

- A multicenter study to assess 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 combination therapy using miglustat and the ketogenic diet for infantile and juvenile individuals with gangliosidoses;
- A survey of miglustat therapeutic effects on neurologic and systemic symptoms of infantile types of Tay-Sachs and Sandhoff disease.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on other clinical studies.

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 Tay-Sachs disease (TSD), subacute juvenile TSD, and late-onset TSD (comprising the clinical spectrum of *HEXA* disorders) are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *HEXA* 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 *HEXA* 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 a *HEXA* 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.
- Sibs who inherit biallelic *HEXA* pathogenic variants will have the same *HEXA* disorder phenotype (i.e., acute infantile, subacute juvenile, or late-onset TSD) as the proband (see Genotype-Phenotype Correlations). However, the subacute juvenile and late-onset phenotypes are associated with significant intrafamilial clinical variability (see Clinical Description).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with late-onset TSD has children with an affected individual or a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *HEXA*; it is appropriate to offer carrier testing to the reproductive partners of individuals with late-onset TSD (see Related Genetic Counseling Issues, **Population screening**).

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

Carrier Detection

Molecular genetic testing. Once both *HEXA* 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. Assay of beta-hexosaminidase A activity is a highly sensitive method for the identification of carriers; however, follow-up molecular testing is required if a carrier couple wishes to pursue prenatal/preimplantation genetic testing. Note: Leukocyte testing (rather than serum testing) should be ordered for TSD carrier detection in women who are pregnant or using oral contraceptive medication. Additional limitations of enzyme testing are addressed in Related Genetic Counseling Issues, **Population screening**.

Carrier testing recommendations for the reproductive partners of known carriers (or the reproductive partners of individuals with late-onset TSD) who do not have a family history of TSD are addressed in **Population screening**.

Related Genetic Counseling Issues

Population screening. Recent studies suggest that full-exon *HEXA* next-generation sequencing (NGS) is equally or more sensitive for the detection of carriers than targeted testing for specific variants and HEX A enzyme testing [Hoffman et al 2013, Cecchi et al 2019]. These findings are reflected in the 2019 position statement of the National Tay-Sachs and Allied Disorders Association (NTSAD Position Statement); see Table 11 for a summary of the NTSAD recommendations.

Table 11. Population Screening for *HEXA* Disorders Based on Recommendations from the 2019 Update of the NTSAD Position Statement on Standards for Tay-Sachs Carrier Screening

Method	Advantages	Disadvantages/Limitations	Comment
Full-exon *HEXA* NGS (detects coding sequence changes throughout *HEXA*)	Highly sensitive in all populations	• Does not detect some noncoding pathogenic variants. • Detection of VUS	There is an evolving trend toward routine use of full-exon *HEXA* NGS for carrier screening in persons of all backgrounds.
Ethnicity-based (e.g., Ashkenazi Jewish) [1] or comprehensive [2] targeted analysis for specific *HEXA* pathogenic variants	VUS are not detected.	• Limited sensitivity • As marriage outside of the ethnic group becomes more common, ethnicity-based targeted screening loses predictive value.	Generally not recommended for population screening

Table 11. continued from previous page.

Method	Advantages	Disadvantages/Limitations	Comment
HEX A enzyme activity testing	Highly sensitive in all populations	• Serum enzyme assay results may be w/in "inconclusive" range. [3] • False positives resulting from pseudodeficiency alleles [4] • False negatives resulting from B1 variant allele [5]	• Follow-up molecular testing required if a carrier couple wants to pursue prenatal testing / PGT • Leukocyte testing (rather than serum testing) should be ordered in women who are pregnant or using oral contraception.

HEX A = beta-hexosaminidase A; NGS = next-generation sequencing; PGT = preimplantation genetic testing; VUS = variants of uncertain significance

Based on the NTSAD Position Statement

1. See Prevalence for other genetically isolated populations known to carry founder *HEXA* pathogenic variants.

2. More than 150 *HEXA* variants have been reported (see ClinVar).

3. In individuals with an inconclusive result on serum enzyme assay (as well as pregnant women and women taking oral contraceptives), white blood cells rather than serum must be assayed.

4. Alleles that code for an enzyme that does not metabolize the synthetic substrate for GM2 ganglioside in vitro, but does metabolize GM2 ganglioside in vivo

5. The protein encoded by the B1 allele metabolizes the synthetic substrate for GM2 ganglioside in vitro but does not metabolize GM2 ganglioside in vivo.

Assisted reproductive technologies. Individuals who are pursuing reproductive technologies that involve gamete (egg or sperm) donation and who are at increased risk of being heterozygous for a *HEXA* pathogenic variant because of family history (see Carrier Detection) or ethnic background (see Related Genetic Counseling Issues, **Population screening**; Prevalence) should be offered testing. If the gamete recipient is a known carrier, any potential gamete donor must undergo molecular testing to determine if the donor is also a carrier.

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 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

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

Population screening. If both members of a reproductive couple are known to be heterozygous for a *HEXA* pathogenic variant, prenatal and preimplantation genetic testing for the *HEXA* pathogenic variants identified in the parents 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**
  Tay-Sachs Disease
- **National Library of Medicine Genetics Home Reference**
  Tay-Sachs disease
- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  Phone: 617-277-4463
  Email: info@ntsad.org
  www.ntsad.org
- **NCBI Genes and Disease**
  Tay-Sachs disease
- **Norton & Elaine Sarnoff Center for Jewish Genetics**
  Phone: 312-357-4718
  Email: jewishgenetics@juf.org
  www.juf.org/cjg

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. HEXA Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HEXA	15q23	Beta-hexosaminidase subunit alpha	HEXA database	HEXA	HEXA

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 HEXA Disorders (View All in OMIM)

272800	TAY-SACHS DISEASE; TSD
606869	HEXOSAMINIDASE A; HEXA

Molecular Pathogenesis

Biallelic pathogenic variants in *HEXA* lead to absent or reduced activity in β-hexosaminidase A, a lysosomal hydrolytic enzyme required for the breakdown of ganglioside GM2 in neurons, where synthesis of complex gangliosides is the highest. The buildup of GM2 ganglioside, normally present in neurons in very small quantities, leads to impairment and subsequent progressive loss of neurons and resultant neurodegeneration.

Mechanism of disease causation. Loss-of-function variants cause decreased to absent β-hexosaminidase activity.

***HEXA*-specific laboratory technical considerations.** Pseudodeficiency refers to an in vitro phenomenon caused by specific *HEXA* alleles (see Table 12) that renders the β-hexosaminidase A enzyme unable to process the synthetic (but not the natural) GM2 substrates, and leads to false positive enzyme testing results.

In contrast, the so-called B1 variant allele results in a β-hexosaminidase A enzyme that is able to degrade the artificial substrate, but not the natural GM2 ganglioside, which leads to false negative enzyme testing results.

Table 12. Notable *HEXA* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000520.5 NP_000511.2	c.1274_1277dupTATC	p.Tyr427IlefsTer5	Most common Ashkenazi Jewish pathogenic variant [Kaback et al 1993]
NM_000520.5	c.1421+1G>C	--	Second-most frequent Ashkenazi Jewish pathogenic variant [Kaback et al 1993]
	c.-207-2357_253+5128delinsG (7.6-kb del)	--	Most common French Canadian pathogenic variant [Myerowitz & Hogikyan 1987]
NM_000520.5 NP_000511.2	c.805G>A	p.Gly269Ser	Most common in LOTS [Paw et al 1989]
	c.533G>A	p.Arg178His	B1 variant allele [Tanaka et al 1988]
	c.739C>T	p.Arg247Trp	Pseudodeficiency allele [Cao et al 1993]
	c.745C>T	p.Arg249Trp	Pseudodeficiency allele [Cao et al 1993]

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

Chapter Notes

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Acknowledgments

This work was supported by funds from the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA.

The authors wish to acknowledge all participants in the Neurodegeneration in Glycosphingolipid Storage Disorders' Natural History Study at the NIH (ClinicalTrials.gov Identifier: NCT00029965) and the longstanding contribution of the National Tay-Sachs and Allied Diseases Association (www.ntsad.org) to the support and education of patients and families with GM1 and GM2 gangliosidosis.

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Revision History

- 1 October 2020 (ha) Comprehensive update posted live
- 11 August 2011 (me) Comprehensive update posted live
- 19 May 2006 (me) Comprehensive update posted live
- 9 January 2004 (me) Comprehensive update posted live
- 30 October 2001 (me) Comprehensive update posted live
- 11 March 1999 (me) Review posted live
- April 1998 (mk) Original submission

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