U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Kaback MM, Desnick RJ. Hexosaminidase A Deficiency. 1999 Mar 11 [Updated 2011 Aug 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Hexosaminidase A Deficiency

Synonyms: HEX A Deficiency, GM2 Gangliosidosis

Michael M Kaback, MD, FACMG[1] and Robert J Desnick, PhD, MD, FACMG[2]

Created: March 11, 1999; Updated: August 11, 2011.

Summary

Clinical characteristics

Hexosaminidase A deficiency results in a group of neurodegenerative disorders caused by intralysosomal storage of the specific glycosphingolipid, GM2 ganglioside. The prototype hexosaminidase A deficiency is Tay-Sachs disease, also known as the acute infantile variant. Tay-Sachs disease is characterized by progressive weakness, loss of motor skills, decreased attentiveness, and increased startle response beginning between ages three and six months with progressive evidence of neurodegeneration including: seizures, blindness, spasticity, eventual total incapacitation, and death, usually before age four years. The juvenile (subacute), chronic, and adult-onset variants of hexosaminidase A deficiency have later onsets, slower progression, and more variable neurologic findings, including: progressive dystonia, spinocerebellar degeneration, motor neuron disease, and, in some individuals with adult-onset disease, a bipolar form of psychosis.

Diagnosis/testing

The diagnosis of hexosaminidase A deficiency relies on the demonstration of absent to near-absent beta-hexosaminidase A (HEX A) enzymatic activity in the serum or white blood cells of a symptomatic individual in the presence of normal or elevated activity of the beta-hexosaminidase B (HEX B) isoenzyme. Molecular genetic testing of *HEXA*, the only gene in which pathogenic variants cause hexosaminidase A deficiency, is used primarily to: (1) distinguish pseudodeficiency alleles from pathogenic variants in healthy individuals with apparent deficiency of HEX A enzymatic activity identified in population screening programs; and to (2) identify the specific pathogenic variants in an affected individual to allow for genetic counseling of at-risk family members.

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. Seizure control can

Author Affiliations: 1 Professor (Emeritus), Departments of Pediatrics and Reproductive Medicine, University of California, San Diego, San Diego, California; Email: mkaback@ucsd.edu. 2 Dean for Genetics and Genomics, Professor and Chair, Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, New York; Email: robert.desnick@mssm.edu.

usually be achieved using conventional antiepileptic drugs such as benzodiazepines, phenytoins, and/or barbiturates; but seizures are progressive and can change in type and severity. For individuals with adult-onset hexosaminidase A deficiency who have psychiatric manifestations, conventional antipsychotic or antidepressant therapy may be used.

Prevention of secondary complications: Good bowel management to avoid severe constipation.

Genetic counseling

Hexosaminidase A deficiency is 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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygotes (carriers) are asymptomatic. Heterozygotes are identified through testing of individuals with a positive family history or through population screening programs directed to people of Ashkenazi Jewish heritage. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible once the pathogenic variants have been identified in the family; prenatal testing is also possible by assay of HEX A enzymatic activity.

GeneReview Scope

Hexosaminidase A Deficiency: Included Disorders
• Tay-Sachs disease (TSD) • Juvenile (subacute) hexosaminidase A deficiency • Chronic and adult-onset hexosaminidase A deficiency

For synonyms and outdated names see Nomenclature.

Diagnosis

Clinical Diagnosis

The common clinical findings in individuals with Tay-Sachs disease (TSD), the prototype hexosaminidase A deficiency, are:

- Progressive weakness and loss of motor skills beginning between ages three and six months
- Decreased attentiveness
- An increased startle response

The typical findings on physical examination are:

- 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

The findings above are followed by signs of progressive neurodegeneration, seizures, blindness, and spasticity, usually leading to death before age four years.

Individuals with the juvenile, chronic, and adult-onset forms have later onset, slower progression, and more variable neurologic findings.

Testing

Beta-hexosaminidase A (HEX A) enzymatic activity

Affected individuals. The diagnosis of hexosaminidase A deficiency relies on the demonstration of absent to near-absent HEX A enzymatic activity in the serum, white blood cells, or other tissues from a symptomatic individual in the presence of normal or elevated activity of the beta-hexosaminidase B (HEX B) isoenzyme [Okada & O'Brien 1969].

- Individuals with the acute infantile form (TSD) have no or extremely low (0%-5%) HEX A enzymatic activity.
- Individuals with juvenile or chronic and adult-onset forms of hexosaminidase A deficiency have residual but low (<15%) HEX A enzymatic activity of HEX A activity.

Note: HEX A is composed of one alpha subunit and one beta subunit; HEX B is a homodimer composed of two beta subunits.

Carrier detection. In population screening, assay of HEX A enzymatic activity in serum or leukocytes using synthetic substrates provides a simple, inexpensive, and highly accurate method for heterozygote identification:

- **Serum** may be used to test all males and those women who are not pregnant and not using oral contraceptives.
- **Leukocytes** are used to test: (1) women who are pregnant; (2) women who are using oral contraceptives; and (3) any individual whose serum HEX A enzymatic activity is in an inconclusive range.

Molecular Genetic Testing

Gene. *HEXA*, the gene encoding the alpha subunit of the HEX A enzyme, is the only gene in which pathogenic variants cause hexosaminidase A deficiency.

Targeted analysis for pathogenic variants. The panel of the six most common pathogenic variants comprises:

- **Three null alleles**, (p.Tyr427IlefsTer5, c.1421+1G>C, and c.1073+G>A), which in the homozygous state or in compound heterozygosity are associated with TSD
- **The p.Gly269Ser allele,** which is associated with the adult-onset form of hexosaminidase A deficiency in the homozygous state or in compound heterozygosity with a null allele
- **Two pseudodeficiency alleles** (p.Arg247Trp and p.Arg249Trp), which are not associated with neurologic disease but are associated with reduced degradation of the synthetic substrate when HEX A enzymatic activity is determined

  Note: (1) The presence of one pseudodeficiency allele reduces 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 potential problem exists in distinguishing between a disease-causing allele, which reduces HEX A enzymatic activity to both artificial and natural substrates, and a pseudodeficiency allele, which reduces HEX A enzymatic activity to the artificial substrate only. The potential problem is avoided by using molecular genetic testing when the enzymatic activity is abnormal, to determine if the reduced HEX A enzymatic activity is caused by a pathogenic variant or a pseudodeficiency variant. (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 Jewish individuals identified as heterozygotes by HEX A enzyme-based testing in carrier screening programs are actually heterozygous for a pseudodeficiency allele (Table 1).
- **Other.** Some laboratories offer extended panels or testing for selected pathogenic variants that are specific to certain populations. In Quebec, a 7.6-kb genomic deletion that involves the *HEXA* promoter and exon 1 is the most common allele associated with TSD [Myerowitz & Hogikyan 1987].

Note: When testing individuals from the French Canadian population or other populations with founder variants, care should be taken to identify a laboratory performing analyses for the appropriate pathogenic variants.

Sequence analysis/scanning for pathogenic variants. More than 130 *HEXA* pathogenic variants have been detected to date by sequence analysis or scanning [McGinniss et al 2002, Stenson et al 2009, www.hgmd.cf.ac.uk]

Table 1. Molecular Genetic Testing Used in Hexosaminidase A Deficiency

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Method [3]
HEXA	Sequence analysis	Sequence variants [4]	99%
	Targeted analysis for pathogenic variants	c.1274_1277dupTATC c.1421+1G>C c.1073+1G>A p.Gly269Ser p.Arg247Trp (pseudodeficiency) p.Arg249Trp (pseudodeficiency) 7.6-kb del including exon 1 [5]	Depends on ethnicity; see Table 2
	Deletion/duplication analysis [6]	Exon or whole-gene deletions	Rare

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Variant panels may vary by laboratory
6. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

Table 2. Molecular Genetic Testing Used in Carrier Detection for Hexosaminidase A Deficiency

Gene [1]	Method	Pathogenic Variants Detected [2]	Allele Status	Heterozygote Frequency			
				Obligate [3]		Screening [4]	
				Jewish	Non-Jewish	Jewish	Non-Jewish
HEXA	Targeted analysis for pathogenic variants [5]	c.1274_1277dupTATC	Null	81%	32%	80%	8%
		c.1421+1G>C	Null	15%	0	9%	0
		c.1073+1G>A	Null	0	14%	0	10% [6]
		p.Gly269Ser	Adult onset	2%	0	3%	5%
		p.Arg247Trp	Pseudodeficiency	0	0	2%	32%
		p.Arg249Trp	Pseudodeficiency	0	0	0	4%
		All of the above	Not applicable	98%	46%	94%	59% [7]

From Kaback et al [1993], Scott et al [2010]
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Obligate heterozygotes (i.e., parents of a child with hexosaminidase A deficiency)
4. Individuals identified in screening programs as having levels of HEX A enzymatic activity in the heterozygous range
5. Variant panels may vary by laboratory.
6. Primarily persons of Celtic, French, Cajun, and Pennsylvania Dutch background
7. Note: In non-Jewish individuals identified in screening programs as having levels of HEX A enzymatic activity in the heterozygous range: (1) the majority of identified alleles (36%/59%) are pseudodeficiency alleles; and (2) the minority of identified alleles (23%/59%) are disease related.

Testing Strategy

To establish the diagnosis in a symptomatic infant proband

- Assay of HEX A enzymatic activity is the primary method of diagnosis for symptomatic individuals.
- Molecular genetic testing can be used to identify the two pathogenic variants when assay of HEX A enzymatic activity is abnormal. The options are:
  - Targeted analysis for a panel of common *HEXA* pathogenic variants, followed by sequence analysis if only one or neither *HEXA* pathogenic variant was identified; OR
  - Sequence analysis.

    If proband is of French Canadian descent, deletion/duplication analysis for the 7.6-kb genomic deletion that involves the *HEXA* promoter and exon 1 should be performed before sequence analysis.

Carrier testing – population screening

- Assay of HEX A enzymatic activity is the primary method of population screening for carrier detection, as it has greater sensitivity than targeted analysis for pathogenic variants.

  Note: When individuals are identified with apparent deficiency of HEX A enzymatic activity, targeted analysis for pathogenic variants can then be used to distinguish pseudodeficiency alleles from disease-causing alleles.

- Targeted analysis for a panel of common *HEXA* pathogenic variants can be used to screen Ashkenazi Jewish individuals for the three common disease-associated variants that account for between 92% and 94% of heterozygotes in this population.

  Note: In the Ashkenazi Jewish population, the sensitivity of targeted analysis for pathogenic variants is lower than assay of HEX A enzymatic activity; therefore, some carriers are not identified using targeted analysis.

Carrier testing of at-risk relatives requires prior identification of the pathogenic variants in an affected family member either through use of targeted analysis for a panel of common *HEXA* pathogenic variants or by sequence analysis of *HEXA*.

Prenatal testing and preimplantation genetic testing (PGT) for at-risk pregnancies require prior identification of the pathogenic variants in the family.

Clinical Characteristics

Clinical Description

The phenotypes of hexosaminidase A deficiency include the following:

- **Acute infantile (Tay-Sachs disease)** with rapid progression and death before age four years
- **Juvenile (subacute)** with later onset and survival into late childhood or adolescence
- **Chronic and adult-onset** with long-term survival. Affected individuals have several different phenotypes, including: progressive dystonia, spinocerebellar degeneration, motor neuron disease with muscle weakness and fasciculations, and/or psychosis.

Acute infantile hexosaminidase A deficiency (Tay-Sachs disease, TSD). Affected infants generally appear to be completely normal at birth. Mild motor weakness begins between age three and six months, along with myoclonic jerks and an exaggerated startle reaction to sharp noise.

By age six to ten months, the infant fails to achieve new motor skills or even loses previously demonstrated skills. Decreasing visual attentiveness and unusual eye movements are associated with pallor of the perifoveal macula of the retina with prominence of the fovea centralis, the so-called cherry-red spot, which is seen in virtually all affected children.

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 attacks typically become more frequent and more severe.

Progressive enlargement of the head typically begins by age 18 months; it results from reactive cerebral gliosis, not hydrocephalus.

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 bronchopneumonia usually occurs between age two and four years.

Juvenile (subacute) hexosaminidase A deficiency. Juvenile hexosaminidase A deficiency often begins with ataxia and incoordination between age two and ten years. Speech, life skills, and cognition decline. Spasticity and seizures are present by the end of the first decade of life. Loss of vision occurs much later than in the acute infantile form of the disease, and a cherry-red spot is not consistently observed. Instead, optic atrophy and retinitis pigmentosa may be seen late in the course. A vegetative state with decerebrate rigidity develops by age

ten to 15 years, followed within a few years by death, usually from infection. In some cases, the disease pursues a particularly aggressive course, culminating in death in two to four years.

Chronic and adult-onset hexosaminidase A deficiency. These conditions represent a spectrum of later-onset, more slowly progressive neurodegenerative disorders, associated with low levels of residual HEX A enzyme activity. Early symptoms may range from muscle weakness to extrapyramidal findings to altered cerebellar manifestations.

In the **chronic form,** central nervous system involvement is widespread, although certain neurologic findings may predominate over others. Psychomotor regression may be less prominent. The age of onset ranges from early childhood to the end of the first decade. In some individuals, extrapyramidal signs of dystonia, choreoathetosis, and ataxia may be evident. In others, cerebellar signs of dysarthria, ataxia, incoordination, and abnormalities of posture develop between age two and ten years; mentation and verbal skills tend to be involved later in the course [Rapin et al 1976]. The clinical presentation of the chronic form of hexosaminidase A deficiency may suggest possible diagnosis of spinocerebellar degeneration, Friedreich ataxia, or amyotrophic lateral sclerosis (ALS).

Individuals with **adult-onset disease** tend to show progressive muscle wasting, weakness, fasciculations, and dysarthria, indistinguishable from progressive adolescent-onset spinal muscular atrophy (Kugelberg-Welander disease) or early-onset ALS. Upper motor neuron signs, nonspecific cerebellar atrophy [Neudorfer et al 2005], and abnormalities of saccades [Rucker et al 2004] may be present.

Cognitive dysfunction and dementia can be observed [Frey et al 2005]. As many as 40% of individuals have psychiatric manifestations (without dementia) including: recurrent psychotic depression, bipolar symptoms, and acute hebephrenic schizophrenia with disorganization of thought, agitation, delusions, hallucinations, and paranoia [Navon et al 1986]. Impairment of executive functioning and memory has also been observed [Zaroff et al 2004].

Marked clinical variability is seen even within the same family; for example, psychosis may be severe by age 20 years in one individual, whereas another affected family member may function into the sixth or seventh decade with only neuromuscular findings.

Neuropathology

Children with the acute infantile form (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 chronic and adult-onset forms have less accumulation of glycolipid; it may even be restricted to specific brain regions. For example, in the adult-onset form, the cortex is almost unimpaired, whereas the hippocampus, the brain stem nuclei, and the spinal cord are markedly affected [Gravel et al 2001].

Genotype-Phenotype Correlations

HEX A enzymatic activity. The level of the residual activity of the HEX A enzyme correlates inversely with the severity of the disease; i.e., the lower the level of the enzymatic activity, the more severe the phenotype is likely to be:

- Individuals with the acute infantile form (TSD) have two null (non-expressing) alleles with no HEX A enzymatic activity.
- Individuals with juvenile or chronic and adult-onset forms of hexosaminidase A deficiency are usually compound heterozygotes for a null allele and an allele that results in residual but low activity of the HEX A enzyme toward GM2 ganglioside, or two alleles that result in low residual HEX A activity.

***HEXA* pathogenic variants associated with acute infantile hexosaminidase A deficiency (TSD).** Of the more than 100 specific pathogenic variants in the alpha subunit of *HEXA* that have been described, the great majority (>90) are associated with the acute infantile form [Gravel et al 2001].

B1 variant associated with juvenile and chronic hexosaminidase A deficiency. The B1 variant is a defective HEX A enzyme that has some activity toward GM2 ganglioside. The cause of the most common B1 variant is the pathogenic variant p.Arg178His, predominantly found in individuals of Portuguese background:

- An individual who is a compound heterozygote for a null allele and an allele causing a B1 variant has the juvenile phenotype.
- An individual who is homozygous for a pathogenic variant causing a B1 variant has twice the enzymatic activity of a compound heterozygote and has the milder chronic phenotype.

***HEXA* pathogenic variants associated with adult-onset hexosaminidase A deficiency.** While several private variants have been identified with later-onset forms of hexosaminidase A deficiencies, two pathogenic variants are primarily associated with the adult-onset hexosaminidase A deficiency:

- The p.Gly269Ser pathogenic variant occurs with significant frequency in the Ashkenazi Jewish population and results in an unstable alpha subunit precursor, which fails to associate with the beta subunit.
- The p.Gly250Asp pathogenic variant occurs in exon 7 of the alpha subunit.

Typically, either of these two pathogenic variants, when homozygous or combined with a null allele, results in the adult-onset phenotype.

***HEXA* pseudodeficiency alleles**

- Individuals heterozygous for a pseudodeficiency allele have an apparent deficiency of HEX A enzymatic activity, as seen in heterozygotes for TSD.
- Individuals with two altered *HEXA* alleles, one a pseudodeficiency allele and the second a disease-related variant, have extremely low or absent HEX A enzymatic activity with synthetic substrates but have no evidence of neurologic abnormality even into the seventh decade of life (the longest that any of these individuals has been followed). Such individuals have been called "pseudodeficient" or "HEX A minus, normal." Individuals with a pseudodeficiency allele are identified through carrier screening programs when a healthy individual appears to have HEX A enzymatic activity levels similar to those of a child with Tay-Sachs disease, or in carrier screening programs that specifically test for the pseudodeficiency variants by DNA-based methods.

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 "infantile ganglioside lipidosis," "type 1 GM2 gangliosidosis," and "acute infantile GM2 gangliosidosis."

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

When the juvenile and later-onset variants 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 to be approximately 1:3600 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).

Recent carrier screening studies indicated that the frequency of the Ashkenazi Jewish founder variants in individuals whose parents and four grandparents were Ashkenazi Jewish was 1:27.4, with the 1278insTATC insertion (c.1274_1277dupTATC) accounting for about 80% of the mutated alleles [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 of virtually all ethnic, racial, and religious groups.

Certain populations that are relatively isolated genetically have been found to carry *HEXA* pathogenic variants with frequencies comparable to or even greater than those observed in Ashkenazi Jews. These include:

- French Canadians of the eastern St. Lawrence River Valley area of Quebec
- Cajuns from Louisiana
- The Old Order Amish in Pennsylvania

Genetically Related (Allelic) Disorders

No other phenotypes are associated with pathogenic variants in *HEXA*. (See Differential Diagnosis for discussions of Sandhoff disease and GM2 activator disease)

Differential Diagnosis

The neurologic symptoms observed in individuals with hexosaminidase A deficiency are not pathognomonic and could be caused by a wide array of other conditions including toxic or infectious agents.

Progressive weakness and loss of motor skills between age 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, particularly in a child of Ashkenazi Jewish parents, strongly suggest a diagnosis of acute infantile hexosaminidase A deficiency (Tay-Sachs disease; TSD). Another extremely rare form of infantile GM2 ganglioside storage is called activator-deficient TSD. In this disorder, the 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. The phenotype of this condition is identical to classic TSD.

The cherry-red spot of the fovea centralis of the macula of the retina, which is seen in virtually all individuals with TSD, can also be seen in the first 12 months of life in other disorders, including: infantile Gaucher disease, GM1 gangliosidosis, galactosialidosis, Niemann-Pick disease type A, and Sandhoff disease.

Neurologic regression is seen in the first six months of life in many conditions, including: Krabbe disease, Canavan disease, Alexander disease, infantile Gaucher disease, and the infantile form (Santavuori-Haltia disease) and late-infantile form (Bielschowsky-Jansky) of neuronal ceroid-lipofuscinosis.

Neurologic regression in the first year of life and hepatosplenomegaly with coarse facies may suggest GM1 gangliosidosis, mucolipidosis II (I-cell disease), sialidosis, and Niemann-Pick disease type A.

Sandhoff disease and its variants are associated with deficiencies of both HEX A and HEX B enzymatic activity. Sandhoff disease presents with the same neurologic findings as TSD; however, Sandhoff disease is rarely seen in Jewish infants. In Sandhoff disease, involvement outside of the nervous system is evidenced by organomegaly, skeletal abnormalities, oligosaccharidiuria, and storage cells, as seen on histologic examination of a bone marrow aspirate. The enzymatic activity of HEX A is deficient, as is that of HEX B, since both enzymes lack the common beta subunit.

In the child presenting with symptoms of juvenile hexosaminidase A deficiency, the two TSD variants, combined HEX A and HEX B deficiency (Sandhoff disease variants), juvenile neuronal ceroid-lipofuscinosis (Batten disease), and other neurodegenerative disorders need to be considered.

Hexosaminidase A deficiency of late onset may mimic other conditions. Adolescent-onset spinal muscular atrophy (SMA3) as well as Friedreich ataxia (FRDA), amyotrophic lateral sclerosis (ALS), adult-onset neuronal ceroid-lipofuscinosis (Kuf's disease), and other lysosomal storage diseases need to be considered in individuals with the chronic or adult-onset forms of hexosaminidase A deficiency. As noted, these individuals often present with muscle wasting and weakness, fasciculations, and diverse other neurologic findings.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hexosaminidase A deficiency, the following are recommended:

- Complete history and physical examination, including ophthalmologic examination
- Family history, including ethnicity
- Referral to a pediatric neurologist and/or ophthalmologist

Treatment of Manifestations

For the most part, treatment for Tay-Sachs disease is supportive and directed to providing adequate nutrition and hydration, managing infectious disease, protecting the airway, and controlling seizures.

Seizure control can usually be achieved using conventional antiepileptic drugs (AEDs) such as benzodiazepines, phenytoins, and/or barbiturates. However, seizures are progressive and change in type and severity; thus, over time changes in the dose or type of AEDs may be necessary for optimal seizure control.

For older individuals with adult-onset hexosaminidase A deficiency who have psychiatric manifestations, conventional antipsychotic or antidepressant therapy may be used; but the clinical response is unpredictable and generally poor.

Treatment with lithium salts and electroconvulsive therapy has been reported to be beneficial, at least in ameliorating for a period the episodes of psychotic depression.

Prevention of Secondary Complications

As the child with the acute infantile form (Tay-Sachs disease) becomes more debilitated and disabled, good bowel management becomes essential. Good hydration, food additives, stool softeners, laxatives, and other measures should be employed to avoid severe constipation.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Early experimental intravenous enzyme replacement trials were unsuccessful, as the large molecular weight enzyme did not cross the blood-brain barrier [reviewed in Desnick & Kaback 2001].

Central nervous system enzyme replacement or neuronal-corrective gene therapy are experimental considerations [Matsuoka et al 2011, Tsuji et al 2011].

A clinical trial used HEX A inhibitors to reduce the biosynthesis of glycosphingolipid precursors to GM2 ganglioside. Although one such agent, *N*-deoxynojirimycin, showed some efficacy with the non-CNS neuronal storage disorder, type I Gaucher disease [Pastores et al 2005], no improvement was observed in a trial of substrate reduction therapy for individuals with adult-onset GM2 gangliosidosis [Shapiro et al 2009].

Preclinical studies for individuals with later-onset Tay-Sachs disease are underway to evaluate pharmacologic chaperone therapy using an immuno sugar that is an active site inhibitor of HEX A activity [Clarke et al 2011]. Since residual enzyme activity is very low (but detectable), chaperone therapy is designed to rescue newly synthesized mutated enzymes in the endoplasmic reticulum before they are removed for degradation and to deliver them to the lysosome where they may function [Rountree et al 2009].

For studies of pathogenesis and preclinical evaluation of various therapeutic strategies, animal models are available. A genetically engineered mouse model of infantile hexosaminidase A deficiency (TSD) has been constructed and can be used to evaluate innovative treatment modalities. Recently, a sheep model of TSD with HEX A deficiency was identified in which affected animals progressively accumulate GM2 ganglioside, have neurologic pathology, and experience a neurodegenerative clinical course [Torres et al 2010].

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.

Other

The poor response to tricyclic antidepressants and phenothiazines has been attributed to the observation that these drugs inhibit HEX A enzymatic activity in vitro and induce lysosomal lipidosis in fibroblasts and accumulation of lipids in experimental animals in vivo.

Several attempts have been made at purified enzyme replacement therapy for children with acute infantile hexosaminidase A deficiency; none has been successful.

Cellular infusions and even bone marrow transplantation have been attempted, with no evidence of benefit.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hexosaminidase A deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry a single copy of a pathogenic variant in *HEXA*.
- Heterozygotes are asymptomatic.

Sibs of a proband and offspring of two carriers

- 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- Individuals with chronic or adult-onset hexosaminidase A deficiency may reproduce.
- Each child will inherit one *HEXA* disease-causing allele from the affected parent. It is appropriate to offer carrier detection to the reproductive partners of such individuals, to provide optimal counseling.

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

Carrier (Heterozygote) Detection

Both analysis of HEX A enzymatic activity and *HEXA* molecular genetic testing can be used to identify carriers among at-risk family members.

Carrier testing is appropriate for:

- The identification of the specific *HEXA* pathogenic variants of the carrier parents or proband for purposes of future prenatal testing and for identification of carriers in other family members;
- The reproductive partners of individuals with chronic or adult-onset hexosaminidase A deficiency;
- The reproductive partners of known carriers.

Population Screening

People of Ashkenazi Jewish heritage. Because of the relatively increased frequency of pathogenic variants in Ashkenazi Jews and the availability of genetic counseling and prenatal diagnosis, population screening was initiated for Jewish individuals of reproductive age in 1970 and is recommended in published guidelines of the American College of Obstetrics and Gynecology and the American College of Medical Genetics [Kaback et al 1993, ACOG Committee on Genetics 2009]. Through this type of screening program, couples in which both partners are carriers can be made aware of their status and risks before having affected children. Then, through genetic counseling and the option of prenatal testing, such families can, if they choose, bring to term only those pregnancies in which the fetus is unaffected.

In population screening, assay of HEX A enzymatic activity in serum or leukocytes using synthetic substrates provides a simple, inexpensive, and highly accurate method for heterozygote identification:

- **Serum** is used for testing males and for testing women who are not pregnant and who are not using oral contraceptives.
- **Leukocytes** are used for testing women who are pregnant, for women who are using oral contraceptives, and for any individual who has a tissue-destructive disorder (e.g., diabetes mellitus, hepatitis, rheumatoid

arthritis) or who is taking unusual medications, whose serum HEX A enzymatic activity is in an inconclusive range.

When the enzymatic testing is abnormal in any individual, molecular genetic testing of *HEXA* is performed in order to identify the pathogenic variant if possible and/or to rule out the presence of a pseudodeficiency allele. Of note, individuals who are heterozygotes for a pseudodeficiency allele are not at increased risk of having a child with TSD or any of the other types of hexosaminidase A deficiency because individuals who are compound heterozygotes for a disease-causing allele and a pseudodeficiency allele who have been followed into the seventh decade do not manifest related neurologic symptoms.

People of non-Jewish heritage. The American College of Obstetrics and Gynecology recommends offering testing of HEX A enzymatic activity to both members of a couple if one member is of Ashkenazi Jewish heritage.

Because individuals of French Canadian (specifically from the eastern St. Lawrence River Valley of Quebec), Cajun, and Old Order Amish ancestry may be at risk of being heterozygous for *HEXA* null variants, screening may be offered to such individuals as well.

Related Genetic Counseling Issues

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 or ethnic background should be offered carrier testing. If the gamete recipient is a carrier, any potential gamete donor must be screened to rule out heterozygosity.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Prenatal testing on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15 to 18 weeks' gestation is possible when:

- Assay of HEX A enzyme activity has shown both parents to be heterozygous **and** molecular genetic testing has ruled out the presence of a pseudodeficiency allele in either parent. Prenatal testing can use either of the following:
  - Assay of HEX A enzymatic activity
  - Molecular genetic testing of *HEXA* if the pathogenic variants have been identified in both parents
- One parent is a known heterozygote and the other parent has inconclusive HEX A enzymatic activity and no *HEXA* pathogenic variant identified on molecular genetic testing. Options for testing can be explored in the context of formal genetic counseling.
- The mother is a known heterozygote and the father is unknown or unavailable for testing. Options for testing can be explored in the context of formal genetic counseling.

Note: Gestational age is expressed either as menstrual weeks calculated from the first day of the last normal menstrual period or as menstrual weeks calculated by ultrasound measurements.

Preimplantation genetic testing (PGT) may be an option for some families in which the pathogenic variants have been identified.

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.

- **Medline Plus**
  Tay-Sachs Disease
- **My46 Trait Profile**
  Tay-Sachs disease
- **National Library of Medicine Genetics Home Reference**
  Tay-Sachs disease
- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  2001 Beacon Street
  Suite 204
  Boston MA 02135
  Phone: 800-906-8723 (toll-free)
  Fax: 617-277-0134
  Email: info@ntsad.org
  www.ntsad.org
- **NCBI Genes and Disease**
  Tay-Sachs disease
- **Center for Jewish Genetics**
  Ben Gurion Way
  30 South Wells Street
  Chicago IL 60606
  Phone: 312-357-4718
  Email: jewishgeneticsctr@juf.org
  www.jewishgenetics.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. Hexosaminidase A Deficiency: 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 Hexosaminidase A Deficiency (View All in OMIM)

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

Gene structure. *HEXA* spans approximately 35,000 base pairs and comprises 14 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Of the more than 100 *HEXA* pathogenic variants identified to date, the vast majority (>90) are associated with the acute infantile phenotype (Tay-Sachs disease) [Gravel et al 2001]. All the small insertions or deletions producing frameshifts and the nucleotide substitutions causing premature stop codons result in this clinical phenotype. In general, these pathogenic variants are immunologically negative for cross-reactive material. Most splice variants fall into this category, but important exceptions exist.

Among Ashkenazi Jews in North America and Israel, the two pathogenic variants associated with the acute infantile form account for 90%-95% of all alleles; the pathogenic variant p.Gly269Ser associated with the chronic form accounts for 3%, and the two pseudodeficiency alleles p.Arg247Trp and p.Arg249Trp account for 2%.

In the non-Jewish general population, about 35% of alleles are accounted for by two pathogenic variants associated with the acute infantile phenotype; and about 5% are accounted for by pathogenic variants associated with the juvenile, chronic, and adult-onset types. Of particular importance, approximately 35% of enzymatically defined, non-Jewish heterozygotes are carriers for one of the two pseudodeficiency alleles (p.Arg247Trp or p.Arg249Trp).

The pathogenic variants that account for most of the TSD occurring in Ashkenazi Jews are null alleles because they result in no protein product, although the gene is transcriptionally active in both cases.

- The most frequent allele is a 4-bp insertion in exon 11 (p.Tyr427IlefsTer5), c.1274_1277dupTATC, which creates a frameshift and downstream stop codon in the coding sequence. Although *HEXA* is transcribed normally, the mRNA is undetectable by Northern blotting.
- The second major allele is a donor splice-junction variant in intron 12 (c.1421+1G>C), which results in the production of several aberrantly spliced mRNAs.

The most common pathogenic variant in the French Canadian population is a 7.6-kb genomic deletion involving the *HEXA* promoter and exon 1; no mRNA is produced by this allele.

Several pathogenic variants that affect subunit assembly or processing of the newly synthesized alpha precursor polypeptide have been described. Most have been detected at the 3' end of the protein, although there is no direct evidence for a sequence or structure near the C terminus specifically involved in subcellular transport.

Table 3. Selected *HEXA* Variants

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
Pseudodeficiency	c.739C>T	p.Arg247Trp	NM_000520.4 NP_000511.2
	c.745C>T	p.Arg249Trp	
Pathogenic	c.533G>A	p.Arg178His	
	c.749G>A	p.Gly250Asp	
	c.805G>A	p.Gly269Ser	
	c.1073+1G>A (+1IVS9)	--	
	c.1274_1277dupTATC (+TATC1278) (1278dupTATC)	p.Tyr427IlefsTer5	
	c.1421+1G>C (+1IVS12)	--	
	(7.6-kb del) [2]	--	

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. Variant designation that does not conform to current naming conventions
2. See Molecular Genetic Testing and Molecular Genetics, **Pathogenic variants**.

Normal gene product. *HEXA* encodes the alpha chain of the heterodimeric protein, beta-hexosaminidase A (HEX A), also called GM2 gangliosidase. The HEX A protein comprises a single alpha chain and a single beta chain, which is encoded by *HEXB*. This isoenzyme cleaves the terminal beta-linked N-acetylgalactosamine from GM2 ganglioside.

Abnormal gene product. The pathogenic variants result in a variety of effects, ranging from defective processing or subunit assembly to defective catalytic activity (see Genotype-Phenotype Correlations).

References

Published Guidelines / Consensus Statements

Committee on Obstetricians. Screening for Tay-Sachs disease. American College of Obstetricians and Gynecologists, Chicago. American College of Obstetrics and Gynecologists Committee Opinion No.3. 1991.

Literature Cited

ACOG Committee on Genetics. ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstet Gynecol. 2009;114:950–3. PubMed PMID: 19888064.

Clarke JT, Mahuran DJ, Sathe S, Kolodny EH, Rigat BA, Raiman JA, Tropak MB. An open-label Phase I/II clinical trial of pyrimethamine for the treatment of patients affected with chronic GM2 gangliosidosis (Tay-Sachs or Sandhoff variants). Mol Genet Metab. 2011;102:6–12. PubMed PMID: 20926324.

Desnick RJ, Kaback MM. Advances in genetics: Tay-Sachs disease. *Advances in Genetics Series*. Vol 44. San Diego, CA: Academic Press; 2001.

Frey LC, Ringel SP, Filley CM. The natural history of cognitive dysfunction in late-onset GM2 gangliosidosis. Arch Neurol. 2005;62:989–94. PubMed PMID: 15956171.

Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K. The GM2 gangliosidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Diseases*. 8 ed. Vol 3. New York, NY: McGraw-Hill; 2001:3827-77

Kaback M, Lim-Steele J, Dabholkar D, Brown D, Levy N, Zeiger K. Tay-Sachs disease--carrier screening, prenatal diagnosis, and the molecular era. An international perspective, 1970 to 1993. The International TSD Data Collection Network. JAMA. 1993;270:2307–15. PubMed PMID: 8230592.

Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. Eur J Pediatr. 2000;159 Suppl 3:S192–5. PubMed PMID: 11216898.

Matsuoka K, Tamura T, Tsuji D, Dohzono Y, Kitakaze K, Ohno K, Saito S, Sakuraba H, Itoh K. Therapeutic potential of intracerebroventricular replacement of modified human β-hexosaminidase B for GM2 gangliosidosis. Mol Ther. 2011;19:1017–24. PubMed PMID: 21487393.

McGinniss MJ, Brown DH, Fulwiler A, Marten M, Lim-Steele JS, Kaback MM. Eight novel mutations in the HEXA gene. Genet Med. 2002;4:158–61. PubMed PMID: 12180151.

Myerowitz R, Hogikyan ND. A deletion involving Alu sequences in the beta-hexosaminidase alpha-chain gene of French Canadians with Tay-Sachs disease. J Biol Chem. 1987;262:15396–9. PubMed PMID: 2824459.

Navon R, Argov Z, Frisch A. Hexosaminidase A deficiency in adults. Am J Med Genet. 1986;24:179–96. PubMed PMID: 2939718.

Neudorfer O, Pastores GM, Zeng BJ, Gianutsos J, Zaroff CM, Kolodny EH. Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. Genet Med. 2005;7:119–23. PubMed PMID: 15714079.

Okada S, O'Brien JS. Tay-Sachs disease: generalized absence of a beta-D-N- acetylhexosaminidase component. Science. 1969;165:698–700. PubMed PMID: 5793973.

Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment. Clin Ther. 2005;27:1215–27. PubMed PMID: 16199246.

Rapin I, Suzuki K, Suzuki K, Valsamis MP. Adult (chronic) GM2 gangliosidosis. Atypical spinocerebellar degeneration in a Jewish sibship. Arch Neurol. 1976;33:120–30. PubMed PMID: 175770.

Rountree JS, Butters TD, Wormald MR, Boomkamp SD, Dwek RA, Asano N, Ikeda K, Evinson EL, Nash RJ, Fleet GW. Design, synthesis, and biological evaluation of enantiomeric beta-N-acetylhexosaminidase inhibitors LABNAc and DABNAc as potential agents against Tay-Sachs and Sandhoff disease. ChemMedChem. 2009;4:378–92. PubMed PMID: 19145603.

Rucker JC, Shapiro BE, Han YH, Kumar AN, Garbutt S, Keller EL, Leigh RJ. Neuro-ophthalmology of late-onset Tay-Sachs disease (LOTS). Neurology. 2004;63:1918–26. PubMed PMID: 15557512.

Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with Carrier Screening and Prenatal Diagnosis for Sixteen Ashkenazi Jewish Genetic Diseases. Hum Mut. 2010;31:1240–50. PubMed PMID: 20672374.

Shapiro BE, Pastores GM, Gianutsos J, Luzy C, Kolodny EH. Miglustat in late-onset Tay-Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment. Genet Med. 2009;11:425–33. PubMed PMID: 19346952.

Stenson PD, Ball EV, Howells K, Phillips AD, Mort M, Cooper DN. The Human Gene Mutation Database: providing a comprehensive central mutation database for molecular diagnostics and personalized genomics. Hum Genomics. 2009;4:69–72. PubMed PMID: 20038494.

Torres PA, Zeng BJ, Porter BF, Alroy J, Horak F, Horak J, Kolodny EH. Tay-Sachs disease in Jacob sheep. Mol Genet Metab. 2010;101:357–63. PubMed PMID: 20817517.

Tsuji D, Akeboshi H, Matsuoka K, Yasuoka H, Miyasaki E, Kasahara Y, Kawashima I, Chiba Y, Jigami Y, Taki T, Sakuraba H, Itoh K. Highly phosphomannosylated enzyme replacement therapy for GM2 gangliosidosis. Ann Neurol. 2011;69:691–701. PubMed PMID: 21520232.

Zaroff CM, Neudorfer O, Morrison C, Pastores GM, Rubin H, Kolodny EH. Neuropsychological assessment of patients with late onset GM2 gangliosidosis. Neurology. 2004;62:2283–6. PubMed PMID: 15210895.

Chapter Notes

Revision History

- 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

License