GENEReviews

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Hexosaminidase A Deficiency

[*HEX A Deficiency, GM2 Gangliosidoses (Hexosaminidase A-Deficient). Includes: Chronic and Adult-Onset Hexosaminidase A Deficiency, Juvenile (Subacute) Hexosaminidase A Deficiency, Tay-Sachs Disease*]

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Summary

Disease characteristics. Hexosaminidase A deficiency results in a group of neurodegenerative disorders caused by intralysosomal storage of the specific glycosphingolipid GM2 ganglioside. Tay-Sachs disease (acute infantile), the prototype hexosaminidase A deficiency, is characterized by progressive weakness, loss of motor skills, decreased attentiveness, and increased startle response beginning between three and six months of age 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 the hexosaminidase A deficiencies 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 upon 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. Mutation analysis of the *HEXA* gene is used primarily for genetic counseling purposes 1) to distinguish pseudodeficiency alleles from disease-causing alleles in individuals with apparent deficiency of HEX A enzymatic activity identified in population screening programs and 2) to identify specific disease-causing alleles in affected individuals. Such testing is clinically available.

Management. Treatment is mostly supportive and directed to provide adequate nutrition and hydration, to manage infectious disease, to protect the airway, and to control seizures. Seizure control can usually be achieved using conventional anticonvulsant medications 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. 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.

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 is clinically available. Prenatal testing is available for at-risk pregnancies by molecular genetic testing when both parental mutations are known and/or by assay of HEX A enzymatic activity.

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 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

Affected Individuals —The diagnosis of hexosaminidase A deficiency relies upon 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]. For laboratories offering biochemical testing, see Testing.

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

Molecular Genetic Testing —Gene. *HEXA*, the gene encoding the alpha subunit of the HEX A enzyme, is the only gene associated with hexosaminidase A deficiency.

Molecular genetic testing: Clinical uses

- **Confirmatory diagnosis** in symptomatic individuals with borderline enzyme activity
- **Carrier testing**
  - To screen Ashkenazi Jewish individuals for the three common disease-associated mutations which account for between 92% and 94% of heterozygotes in this population
  - To distinguish pseudodeficiency alleles from disease-causing alleles in individuals with apparent deficiency of HEX A enzymatic activity identified in population screening programs
  - To identify the specific disease-causing alleles in an affected individual so that molecular genetic testing of *HEXA* can be used for carrier detection in at-risk family members.
- **Prenatal diagnosis** when both parental mutations are known

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** The panel of the six most common mutations comprises:
  - **Three null alleles,** (+TATC1278, +1IVC12, +1IVS9), which in the homozygous state or in compound heterozygosity are associated with TSD
  - **The G269S 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** (R247W and R249W), which are not associated with neurologic disease but are associated with reduced degradation of 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 substrate, and a pseudodeficiency allele, which reduces HEX A enzymatic activity to 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 disease-causing allele or 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 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 mutations that are specific to certain populations. In Quebec, a 7.6-kb deletion is the most common allele associated with TSD.

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

- **Sequence analysis/mutation scanning.** More than 100 *HEXA* mutations have been detected to date by sequence analysis or mutation scanning [McGinniss et al 2002].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Hexosaminidase A Deficiency

Test Method	Mutations Detected	Allele Status	Heterozygotes				Test Availability
			Obligate [1]		Screening [2]		
			Jewish	Non-Jewish	Jewish	Non-Jewish	
Targeted mutation analysis	+TATC1278	Null	81%	32%	80%	8%	Clinical Testing
	+1 IVS 12	Null	15%	0	9%	0	
	+1 IVS 9	Null	0	14%	0	10% [3]	
	G269S	Adult onset	2%	0	3%	5%	
	R247W	Pseudo-deficiency	0	0	2%	32%	
	R249W	Pseudo-deficiency	0	0	0	4%	
	All of the above	Not applicable	98%	46%	94%	59% [4]	

From Kaback et al 1993

1. Obligate heterozygotes (i.e., parents of a child with hexosaminidase A deficiency)
2. Individuals identified in screening programs as having levels of HEX A enzymatic activity in the heterozygous range
3. Primarily persons of Celtic, French, Cajun, Pennsylvania Dutch background
4. 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.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

Assay of HEX A enzymatic activity is the primary method of diagnosis for symptomatic individuals and of population screening for carrier detection given its greater sensitivity compared to targeted mutation analysis. However, in the Ashkenazi Jewish population, some have gone directly to targeted mutation analysis even though the sensitivity of this approach is lower; therefore, some carriers will not be identified.

Molecular genetic testing using targeted mutation analysis for a panel of common *HEXA* mutations can be used when assay of HEX A enzymatic activity is abnormal:

- In a symptomatic individual in order to identify the disease-causing mutations;
- In an asymptomatic individual to evaluate for the presence of a pseudodeficiency allele.

Molecular genetic testing using sequence analysis or mutation scanning would be required to identify *HEXA* mutations in an individual who:

- Is affected but had only one or neither mutation identified using a panel of standard mutations

OR

- Has carrier-level enzymatic results but did not have a mutation identified using a panel of standard mutations.

Genetically Related (Allelic) Disorders

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

Clinical Description

Natural History

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 at three to six months of age, along with myoclonic jerks and an exaggerated startle reaction to sharp noise.

By six to ten months of age, 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 individuals.

After eight to ten months of age, 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 12 months of age. Subtle partial complex seizures or absence attacks typically become more frequent and more severe.

Progressive enlargement of the head typically begins by 18 months of age; 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 usually occurs between two and four years of age from bronchopneumonia.

Juvenile (subacute) hexosaminidase A deficiency. Juvenile hexosaminidase A deficiency often begins with ataxia and incoordination between two and ten years of age. 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 two and ten years of age; however, mentation and verbal skills tend to be involved later in the course [Rapin et al 1976]. The clinical presentation of the chronic form of hexosamindase 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]. More recently, impairment of executive functioning and memory has 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. Individuals with the acute infantile form (TSD) have excessive and ubiquitous neuronal glycolipid storage (up to 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 brainstem 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.

***HEXA*mutations associated with acute infantile hexosaminidase A deficiency (TSD).** Of the more than 100 specific mutations in the alpha subunit of the *HEXA* gene that have been described, the great majority (more than 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 mutation R178H, 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 mutation causing a B1 variant has twice the enzymatic activity of a compound heterozygote and has the milder chronic phenotype.

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

- The G269S mutation 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 G250D mutation occurs in exon 7 of the alpha subunit. Typically, either of these two mutations, 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 mutation, 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." Most individuals with pseudodeficiency 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.

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 about one in 3600 Ashkenazi Jewish births. At that birth rate, the carrier rate for TSD is about one in 30 among Jewish Americans of Ashkenazi extraction (i.e., from Central and Eastern Europe).

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 less common, 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, such as French Canadians of the eastern St. Lawrence River Valley area of Quebec, Cajuns from Louisiana and the Old Order Amish in

Pennsylvania, have been found to carry *HEXA* mutations with frequencies comparable to or even greater than those observed in Ashkenazi Jews.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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 as well.

Progressive weakness and loss of motor skills between ages six and twelve 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 suggests a diagnosis of acute infantile hexosaminidase A deficiency (Tay-Sachs disease). 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, I-cell disease, sialidosis, and Niemann-Pick A disease.

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, oligosaccharidurıa, 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; 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 at Initial Diagnosis to Establish the Extent of Disease

- 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 TSD is supportive and directed to provide adequate nutrition and hydration, to manage infectious disease, to protect the airway, and to control seizures.

Seizure control can usually be achieved using conventional anticonvulsant medications such as benzodiazepines, phenytoins, and/or barbiturates, but seizures are progressive and change in type and severity. Over time, changes in the dose or type of anti-epileptic drugs (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 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.

Therapies Under Investigation

Central nervous system enzyme replacement or neuronal-corrective gene therapy are experimental considerations at present, but are only at the theoretical stage clinically.

A genetically engineered mouse model of infantile hexosaminidase A deficiency has been constructed and is now being used to evaluate innovative treatment modalities.

Most recently, clinical trials have been initiated, utilizing enzymatic inhibitors which block (reduce) the biosynthesis of glycoshingolipids such as GM2 ganglioside. One such agent, N-deoxynigiromycin, has shown some efficacy with the non-CNS neuronal storage disorder, type I Gaucher disease [Pastores et al 2005]. Currently, trials are underway with individuals afflicted with adult-onset GM2 gangliosidosis. No results have as yet been reported.

Search ClinicalTrials.gov 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.

Although 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.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 disease-causing mutation in the *HEXA* gene.
- 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 *HEX A* 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 Detection

Both HEX A enzymatic and *HEXA* DNA mutation analysis can be used to identify carriers among at-risk family members.

Carrier testing is appropriate for:

- The identification of the specific *HEXA* mutations of the carrier parents or proband for purposes of future prenatal testing and for identification of carriers in other family members (see Molecular Genetic Testing);
- The reproductive partners of individuals with chronic or adult-onset hexosaminidase A deficiency.

Population Screening

People of Ashkenazi Jewish heritage. Because of the relatively increased gene frequency 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]. 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, DNA analysis of the *HEXA* gene is performed in order to identify the disease-causing mutation 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, since 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 in which one member is of Ashkenazi Jewish heritage.

Since 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 mutations, 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* mutation because of family history or ethnic background should be offered carrier testing. If the gamete recipient is a carrier, then any potential gamete donor must be screened to rule out heterozygosity.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the specific disease-causing mutations have not yet been elucidated in a particular family or when interpretation of results is difficult. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing is available when:

- HEX A enzyme assay has shown both parents to be heterozygous **and** molecular genetic testing has ruled out the presence of a pseudodeficiency allele in either parent. For such couples, prenatal testing can be performed by assay of HEX A enzymatic activity of fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the disease-causing mutations have been identified in both parents, prenatal testing can be performed by mutation analysis of the *HEXA* gene in fetal DNA extracted from cells obtained by CVS or amniocentesis.

  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.

- One parent is a known heterozygote and the other parent has inconclusive enzymatic activity and no disease-causing mutation has been found on DNA analysis. 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.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hexosaminidase A Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
HEXA	15q23-q24	Beta-hexosaminidase alpha chain

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hexosaminidase A Deficiency

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

Table C. Genomic Databases for Hexosaminidase A Deficiency

Gene Symbol	Locus Specific	Entrez Gene	HGMD
HEXA	HEXA	3073 (MIM No. 606869)	HEXA

For a description of the genomic databases listed, click here.

Normal allelic variants: The *HEXA* gene spans approximately 35,000 base pairs, contains 14 exons, and has both 5' regulatory elements (TATA) and 3' untranslated regions.

Pathologic allelic variants: Of the more than 100 *HEXA* mutations 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 producing stop codons result in this clinical phenotype. In general, these mutations are immunologically CRM-negative. Most splice mutations fall into this category, but important exceptions exist (see following section). Among Ashkenazi Jewish people in North America and Israel, the two mutations associated with the acute infantile form account for 90-95% of all alleles; the mutation G269S associated with the chronic form accounts for 3%, and the two pseudodeficiency alleles (R247W) account for 2%. In the non-Jewish general population, about 35% of alleles are accounted for by two mutations associated with the acute infantile phenotype, and about 5% are accounted for by mutations 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 (R247W or R249W).

The mutations 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, +TATC1278, which creates a frameshift and downstream stop codon in the coding sequence. Although the *HEXA* gene is transcribed normally, the mRNA is undetectable by Northern blotting. The second major allele is a donor splice-junction mutation in intron 12, +1 IVS- 12G>C, which results in the production of several aberrantly spliced mRNAs. The most common mutation in the French-Canadian population is a 7.6-kb deletion at the 5' end of the *HEXA* gene from which no mRNA is produced.

Several mutations have been described that affect subunit assembly or processing of the newly synthesized alpha precursor polypeptide. 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.

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

Abnormal gene product: The mutations result in a variety of effects, ranging from defective processing or subunit assembly to defective catalytic activity.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

March of Dimes
Tay-Sachs disease

Medline Plus
Tay-Sachs Disease

National Library of Medicine Genetics Home Reference
Tay-Sachs disease

National Tay-Sachs and Allied Diseases Association, Inc
2001 Beacon Street Suite 204
Brighton MA 02135
Phone: 800-906-8723; 617-277-4463
Fax: 617-277-0134
Email: info@ntsad.org
www.ntsad.org

NCBI Genes and Disease
Tay-Sachs disease

Canadian MPS Society
PO Box 30034
RPO Parkgate North Vancouver
British Columbia
Canada V7H 2Y8
Phone: 800-667-1846; 604-924-5130
www.mpssociety.ca

Chicago Center for Jewish Genetic Disorders
Ben Gurion Way
One South Franklin Street Fourth Floor
Chicago IL 60606
Phone: 312-357-4718
Fax: 312-855-3295
Email: jewishgeneticsctr@juf.org
www.jewishgeneticscenter.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

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Suggested Readings

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Chapter Notes

Revision History

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