

Feature

Carrier Testing for Tay-Sachs Disease and Other G_{M2} Gangliosidosis Variants: Supplementing Traditional Biochemical Testing with Molecular Methods

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Carrier Testing for Tay-Sachs Disease and Other G_{M2} Gangliosidosis Variants: Supplementing Traditional Biochemical Testing with Molecular Methods

Tay-Sachs disease (TSD) is a lysosomal storage disorder characterized by the accumulation of G_{M2} ganglioside in neurons due to deficient hexosaminidase A (Hex A) enzyme activity. Clinical manifestations involve a rapidly progressive and ultimately fatal neurodegenerative course. Certain ethnic populations, particularly individuals of Ashkenazi Jewish ancestry, show increased incidence of TSD. This, along with the tragic prognosis for individuals with TSD, prompted the development of laboratory-based methods for carrier detection in the early 1970s. TSD was the first disease for which population-based carrier screening was implemented and is now recognized as the prototype for heterozygote screening. Advances in laboratory methods over the last 20-30 years have improved the way that carrier detection is accomplished; molecular methods now supplement well-established biochemical screening techniques. To optimize test utilization, Mayo developed a testing protocol for evaluating carrier status that includes molecular testing when appropriate (see Figure 1, page 2).

Historical Information

Clinical features of TSD were first described in 1881 by Dr. Warren Tay, a British ophthalmologist, who reported a cherry-red spot in the retina of a 1-year-old patient with delayed development (see Figure 2). Dr. Bernard Sachs, an American neurologist, recognized the characteristic swollen neurons associated with TSD and noted the high prevalence of disease in the Ashkenazi Jewish population. Further investigation identified the storage material in the lysosomes of neurons as a new group of acidic glycosphingolipids. The newly described

glycolipid was called a ganglioside because of its high concentration in the plasma membranes of normal ganglion cells.

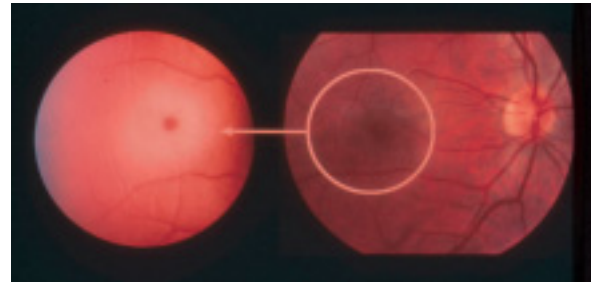


Figure 2. Cherry-red spot

The Accumulating Analyte— G_{M2} Ganglioside

Gangliosides contain a polar oligosaccharide chain (multiple sugar residues) attached to a lipid-soluble moiety called ceramide, which is capable of inserting into neuronal plasma membranes. The gangliosides, along with other cellular constituents, are systematically broken down (autophagy) in the lysosome (a specialized organelle that contains an array of degradative enzymes) during the course of normal cell turnover. Hexosaminidase is one member of this family of hydrolytic enzymes capable of catalyzing the sequential removal of terminal nonreducing sugars from the oligosaccharide structures of large macromolecules. This enzyme cleaves the terminal hexosamine residue from its preferred substrate, G_{M2} ganglioside (see Figure 3, page 3). The resulting product is a G_{M3} ganglioside that is subsequently acted on by other hydrolytic enzymes in this degradative pathway.

Mayo Tay-Sachs Disease Carrier Testing Protocol

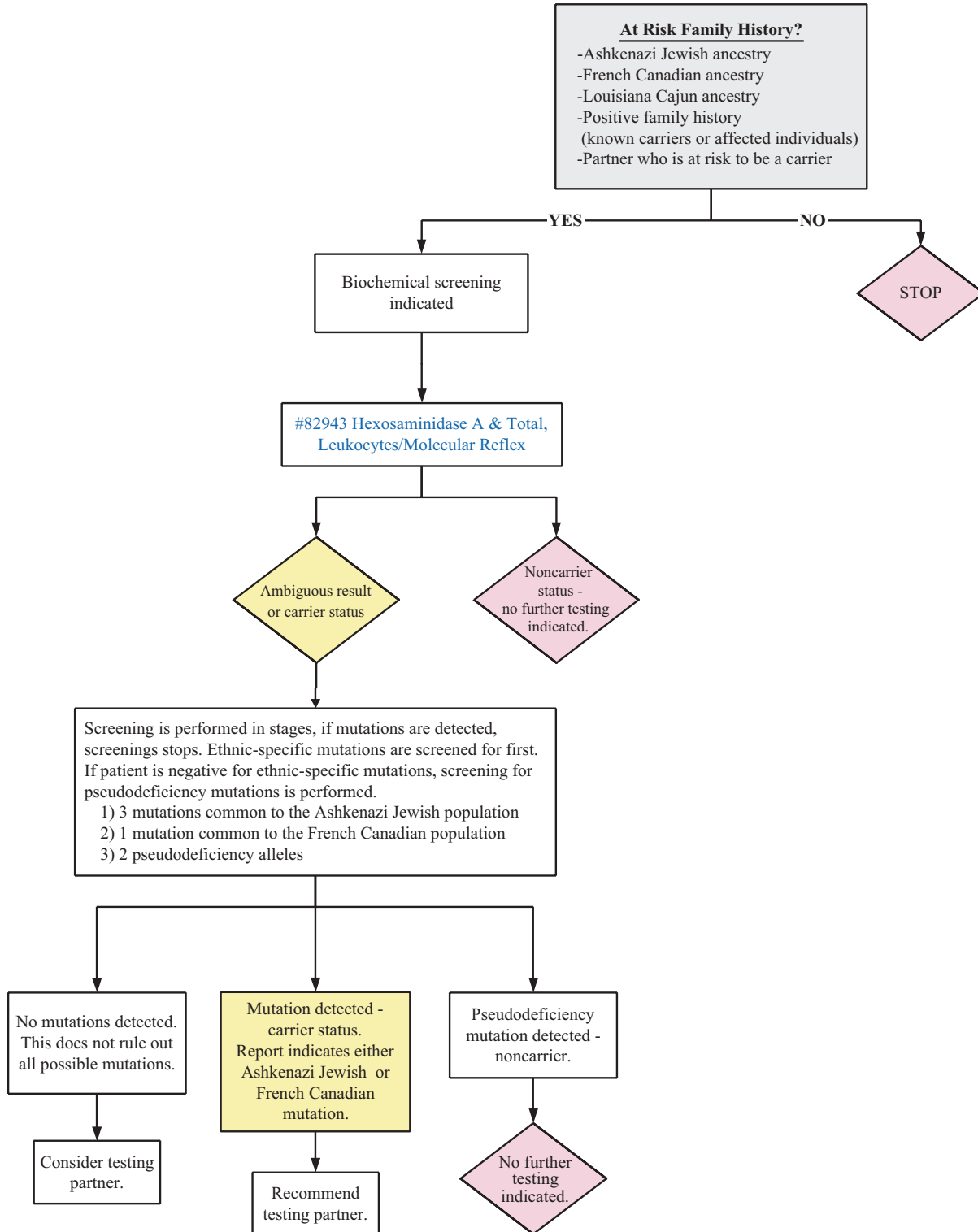


Figure 1. Mayo Tay-Sachs Disease Carrier Testing Protocol

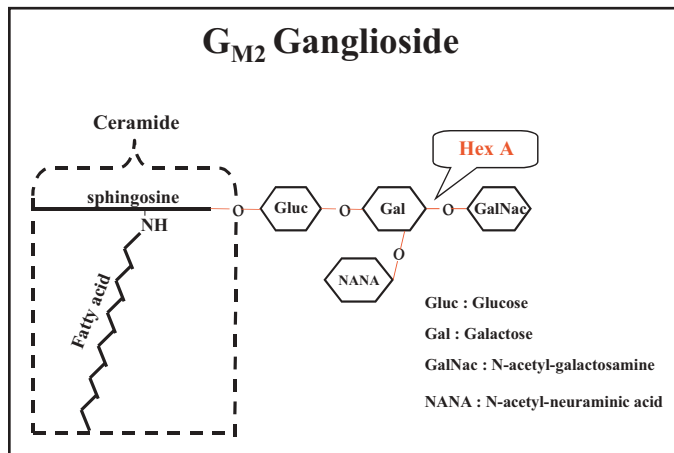


Figure 3. G_{M2} Ganglioside

The Enzymology and Molecular Basis of G_{M2} Gangliosidosis Variants

The Hexosaminidases

There are 2 major isozymes of hexosaminidase. Hexosaminidase A (Hex A) is a heterodimer with a subunit structure of $\alpha\beta$ and hexosaminidase B (Hex B) is a homodimer of structure $\beta\beta$. Only Hex A is capable of hydrolyzing G_{M2} ganglioside and it requires the presence of a cofactor called G_{M2} activator (GM2A) to facilitate the reaction. GM2A functions to bind membranous G_{M2} ganglioside and presents it to the α subunit of Hex A to start its sequential degradation. Therefore, the requirements for functional Hex A activity are the proper synthesis and assembly of the α and β subunits into the Hex A heterodimer and the presence of G_{M2} activator. The *HEXA* and *HEXB* genes encode the α and β subunits, respectively. The *GM2A* gene encodes the G_{M2} activator protein.

Mutations in 1 or more of these 3 genes (*HEXA*, *HEXB*, and *GM2A*), lead to alterations in the activity of the Hex A enzyme. The effect of the various mutations on the enzyme activity corresponds to 4 biochemically distinguishable G_{M2} gangliosidosis variants: B, B1, O, and AB. In clinical practice the G_{M2} gangliosidosis variants are commonly referred to by their disease names, Tay-Sachs disease (TSD), TSD variant B1, Sandhoff disease, and TSD variant AB, respectively. Since mutations in the 3 genes noted above all affect the function of Hex A, there is significant overlap in clinical features between the variants. Thus, determining the biochemical variant is important for confirmatory diagnosis. The 4 G_{M2} gangliosidosis variants are summarized in Figure 4.

Tay-Sachs Disease (G_{M2} Gangliosidosis Variant B)

TSD is caused by mutations in the *HEXA* gene that result in reduced, absent, or nonfunctional Hex A enzyme. Though difficult to establish using the artificial substrates commonly employed for enzyme testing, the amount of residual enzyme activity correlates inversely with clinical severity. Mutations in the *HEXA* gene affect only the α subunit of the Hex A enzyme; assembly of the Hex B ($\beta\beta$) enzyme is unaffected by *HEXA* mutations. In fact, the Hex B enzyme shows normal activity when *HEXA* mutations are present. TSD presents in 3 clinical variants: infantile (classic), late-onset subacute, late-onset chronic. TSD is an autosomal recessive disease, thus all clinical variants are caused by inheriting 2 copies of disease-causing mutations in the *HEXA* gene, 1 from each parent.

The *HEXA* gene is located on chromosome 15. Over 100 distinct mutations have been identified in the *HEXA* gene, 3 of which are common in the Ashkenazi Jewish population. The most frequent of these is a 4 base-pair insertion in exon 11 (1278ins4) causing a frameshift and premature termination codon. Another mutation occurs in a splice donor site of intron 12. Both the 1278ins4 and the splice donor site mutation result in null (absent) Hex A activity. Thus, when inherited in a homozygous or compound heterozygous fashion, they result in the severe infantile (classic) form of TSD.

A third mutation common to the Ashkenazi Jewish is more panethnic than the previous 2. It is a missense substitution of serine for glycine at codon 279 in exon 7 (G269S). This mutation allows for residual enzyme activity. When inherited homozygously or in combination with a null allele, it is associated with the adult onset form of TSD.

With 2 exceptions, there are no TSD mutations common in the non-Ashkenazi Jewish population. A 7.6-kb deletion of the *HEXA* gene is found most commonly in individuals of French Canadian ancestry. The carrier frequency in this population is approximately 1 in 30. The splice site mutation IVS-9(+1) is considered a relatively common (15-50%) TSD mutation in persons of Celtic descent.

Two nondisease-causing alleles, termed pseudodeficiency alleles, also have been identified. These pseudodeficiency alleles confer reduced Hex A enzymatic activity toward the synthetic substrates used by laboratories for biochemical carrier detection, but do not reduce enzymatic activity with the natural G_{M2} ganglioside substrate. Since the naturally occurring G_{M2}

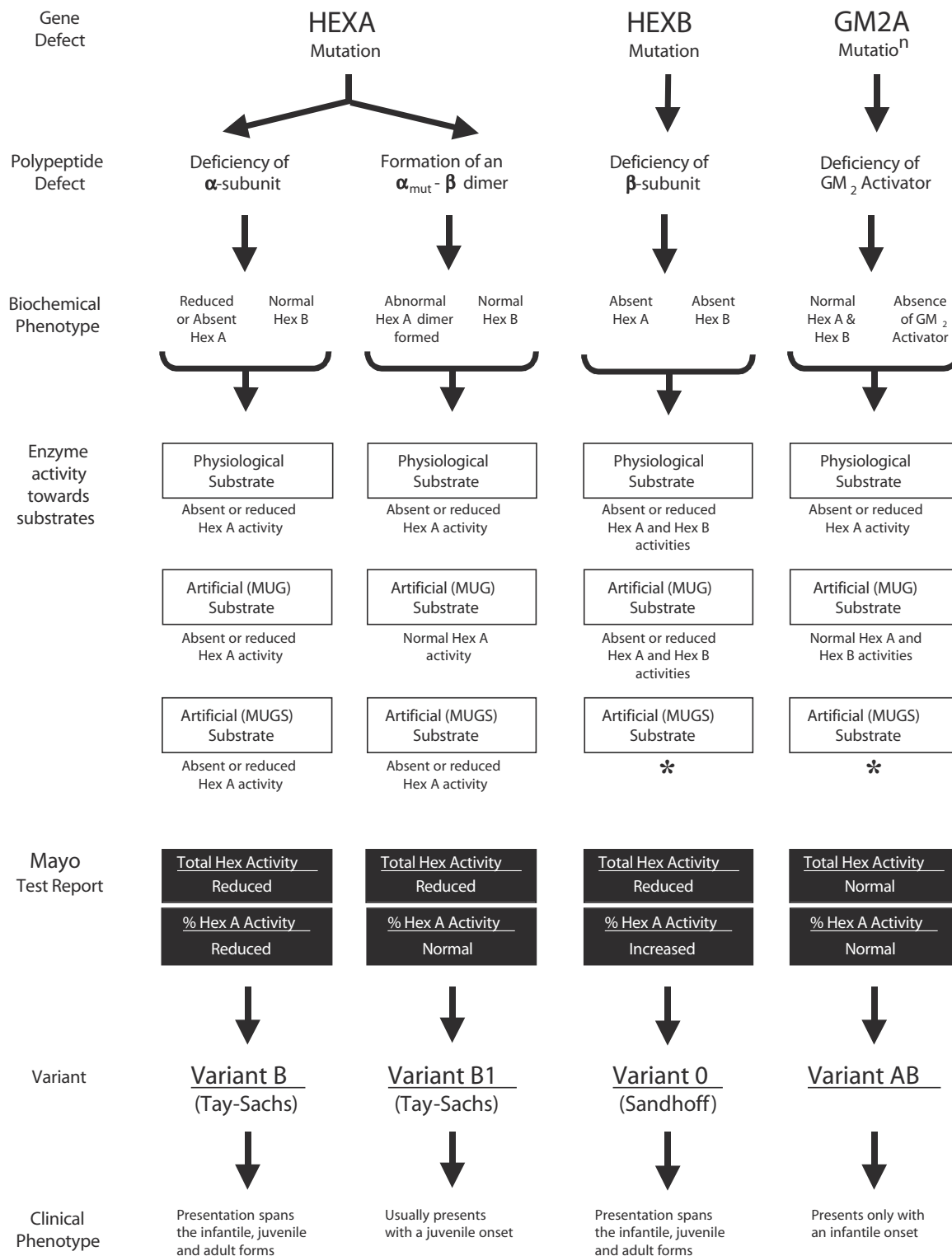


Figure 4. Biochemical and clinical phenotypes of the G_{M2} gangliosidosis variants.

*MUGS substrate relevant only for differentiating between variants B and B1.

ganglioside is not available as a stable reagent, laboratories must use synthetic substrates such as (4-methylumbelliferyl *N*-acetylglucosamine or MUG). MUG is commonly used for diagnosis and/or carrier identification of the usual Hex A deficiencies. Molecular studies allow the differentiation of individuals who carry pseudodeficient mutations from those who carry disease-causing mutations. Approximately 2% of Jewish individuals and 36% of non-Jewish individuals have carrier levels of enzyme as a result of having nondisease-causing pseudodeficiency alleles. Therefore, molecular analysis for pseudodeficiency alleles should be performed when enzymatic studies are ambiguous or positive for carrier status, but no ethnic specific mutations are identified.

Tay-Sachs Disease Variant B1 (G_{M2} Gangliosidosis Variant B1)

TSD variant B1 is a rare, subvariant of gangliosidosis variant B found most commonly in individuals of Portuguese descent. The B1 variant represents a class of specific mutations in the *HEXA* gene that result in the synthesis and assembly of a heterodimer that has several biochemical similarities with the normal Hex A enzyme. The α subunit produced in this case, α_{B1} is unable to hydrolyze its physiological substrate (G_{M2} ganglioside). The resulting heterodimer ($\alpha_{B1}\beta$) is, however, capable of hydrolyzing some synthetic substrates such as MUG. Using the MUG substrate, the Hex A activity of individuals with B1 variant mutation(s) appears to be within or near the normal range. Therefore, distinguishing the B1 variant from the B variant form of G_{M2} gangliosidosis requires the use of a sulfated substrate, (4-methylumbelliferyl *N*-acetylglucosamine 6-sulphate or MUGS), which is not hydrolyzed by $\alpha_{B1}\beta$.

The B1 mutation is designated R178H in the *HEXA* gene. The severity of clinical phenotype associated with the B1 variant is dependent upon whether the B1 variant mutation is inherited in a homozygous fashion or if it is inherited with a different disease-causing mutation within the *HEXA* gene. Results within the carrier level of Hex A when using MUG (with an affected child) suggest a genetic compound of B1 with a more usual *HEXA* mutation. Since the hallmark of the B1 variant of Tay-Sachs is the very specific substrate preference described above, the implication is that the mutation causes active site dysfunction. The rarity of this mutation precludes its inclusion into the algorithm. However, the B1 variant can be implied when activity towards MUGS is partially or totally absent. Sandhoff disease (G_{M2} gangliosidosis variant O)

Sandhoff disease is caused by mutations within the *HEXB* gene. Individuals with mutations in the *HEXB* gene fail to produce adequate levels of both Hex A ($\alpha\beta$) and Hex B ($\beta\beta$) isoenzymes. Residual hexosaminidase activity may be due to the presence of small quantities of the Hex S isoenzyme ($\alpha\alpha$). This disease is called Sandhoff disease, acknowledging the biochemical differentiation from classical TSD. Numerous deletions and point mutations in the *HEXB* gene have been found to cause Sandhoff disease. However, detection of Sandhoff disease currently remains in the province of enzymology.

Tay-Sachs Variant AB (G_{M2} Gangliosidosis Variant AB)

TSD variant AB is caused by mutations within the *GM2A* gene. Individuals with mutations in the *GM2A* gene show normal activity of both Hex A and Hex B isoenzymes using artificial substrates. Few patients have been identified with G_{M2} activator deficiency. A limited number of mutations have been associated with activator deficiency, but as with Sandhoff disease, they are not yet used routinely to detect this rare condition.

Clinical Presentation of G_{M2} Gangliosidoses

TSD, Sandhoff disease, and TSD variant AB are difficult to distinguish by clinical presentation. Further, there is a wide spectrum of clinical phenotypes associated with each of these G_{M2} variants. The initial symptoms become apparent anywhere from infancy to adulthood. Except for the rare adult form of Sandhoff disease, neurological deterioration is the most notable clinical manifestation, but this varies greatly with age of onset.

Neuropathology may be severe, leading to death within the first few years of life, or may have a milder course that is compatible with longer survival, which is seen in adult-onset Tay-Sachs presenting as ataxia from 20 years of age onward. Clinical severity correlates inversely with residual enzyme activity. If the clinical phenotype and enzyme activity are not consistent, we recommend consulting a genetic counselor.

Infantile Onset

The most severe and common form of TSD, Sandhoff disease, and G_{M2} activator deficiency occur with infantile onset. Affected infants appear normal at birth, but within the first 6 months of life weakness associated with movement, involuntary shock like muscle contractions (myoclonic jerks), and exaggerated responses to sharp noises becomes evident. Eventually,

affected infants either lose, or fail to acquire, mental and motor skills appropriate for their age. Visual inattentiveness and unusual eye movements often prompt ophthalmologic investigation, and the identification of a “cherry-red spot” of the macula is a characteristic finding (see Figure 2, page 1). As the infants approach their first birthday, progressive deterioration results in a lack of responsiveness to their environment. Death usually occurs before the age of 5.

Juvenile Onset

The clinical presentation associated with juvenile-onset G_{M2} gangliosidosis is variable. Symptoms usually develop between 2 and 10 years of age and disease course (poor muscle coordination, visual difficulties, and loss of acquired mental and motor skills) is similar to that of the infantile onset. As neurodegeneration progresses, affected children eventually fall into a vegetative state between the ages of 10 and 15 years. Death usually follows within the next few years. A milder form of juvenile onset parallels adult-onset G_{M2} gangliosidosis, and is associated with a more chronic than progressive clinical course.

Adult Onset

The adult-onset presentation is more common in TSD than in Sandhoff disease, and has not been described in patients with G_{M2} activator deficiency. Individuals with adult-onset G_{M2} gangliosidosis have a milder, chronic clinical course and survive for decades after their diagnosis. The age at diagnosis may be anywhere from 20 to 50+ years of age and clinical severity correlates with genotype. Symptoms include involuntary movements, muscle weakness, and a milder neurological involvement that can include psychiatric abnormalities such as schizophrenia and paranoia.

Clinical Presentation of the B1 Variant

Special mention needs to be made of the relationship between disease-causing mutations and the clinical presentation of patients diagnosed with the B1 variant. Typically, B1 mutations result in a higher level of “residual” Hex A enzyme activity than other disease-causing *HEXA* mutations. Thus, homozygous inheritance of B1 variant mutations often results in a less severe, slower-progressing juvenile-onset phenotype. In contrast, when B1 mutations are inherited with another disease-causing *HEXA* mutation that confers significantly reduced or absent Hex A enzyme activity, a severe juvenile onset results. Infantile onset is rare, with only a few cases of the infantile presentation described in the literature.

Diagnosis

The G_{M2} gangliosidoses are clinically indistinguishable. However, the usual clinical forms of G_{M2} gangliosidosis are readily detected by enzymatic testing that evaluates Hex A activity using 4-methylumbelliferyl *N*-acetylglucosamine (MUG). Special testing for the B1 variant using the sulfated substrate (MUGS) is only done if the ordering physician provides evidence that this mutation may be possible (eg, the patient has Portuguese ancestry). Though the algorithm presented in Figure 1 is primarily a carrier detection sequence, it is equally as useful in detection of affected individuals. This is important for future diagnosis in a pedigree, particularly for prenatal diagnosis.

Management and Prognosis

There is no cure for TSD and its associated variants. Treatment is supportive and seeks to maintain proper nutrition and manage symptoms of affected individuals. Current research is focusing on treatment modalities such as enzyme replacement therapy, bone marrow transplant, and substrate deprivation. The effectiveness of each remains controversial and may be limited to milder phenotypes.

Carrier Testing

The goal of carrier screening is to identify individuals who are healthy, but at risk for having children affected with severe disease. In the United States, approximately 1 in 283 individuals is a heterozygous unaffected carrier of a *HEXA* mutation. Heterozygosity is much more common (1 in 30) for individuals of Ashkenazi Jewish descent.¹ Carrier testing for TSD should be offered to couples when at least 1 individual is of Ashkenazi Jewish, French Canadian, Louisiana Cajun, or Pennsylvania Dutch ancestry. Additionally, carrier testing should be offered to individuals who have a family history of TSD or have biological relatives who are known carriers.

If possible, carrier testing should be performed prior to conception. When an at-risk individual is identified as a noncarrier, testing of his/her partner is unnecessary, as negative results in the at-risk individual impart extremely low risk for the couple to have an affected child. Should carrier testing reveal that both members of a couple are carriers, their risk to have a child affected with TSD is 1 in 4 or 25%. When identified prior to conception, these couples have the option of

exploring alternatives such as prenatal testing, sperm or ovum donation, preimplantation genetic diagnosis, or adoption. If the woman is pregnant, it may be prudent to test both partners concurrently. This approach can save time if 1 of the partners is determined to be ambiguous or a carrier.

Since most of the G_{M2} gangliosidoses are difficult to distinguish clinically, and carriers are totally asymptomatic, a stepwise approach to laboratory carrier detection is recommended (see Figure 1, page 2). Due to the rarity and panethnic nature of the occurrence of mutations other than those specific to the *HEXA* gene, the systematic approach presented here (which includes molecular testing) is limited to Tay-Sachs variant B. Enzyme analysis remains the preferred first-tier testing method for carrier detection as it is simple, inexpensive, highly accurate, and carrier detection is not dependent on ethnic background. Molecular testing is indicated if 1 or both members of a couple have ambiguous or carrier results.

Molecular testing available through Mayo Medical Laboratories (MML) includes investigation for the 3 alleles common to Ashkenazi Jewish individuals, the mutation prevalent in persons with French Canadian ancestry, the Celtic mutation, and the 2 identified pseudodeficiency alleles. Enzymatic detection remains the method to detect Sandhoff disease ([#8775 Hexosaminidase A and Total Hexosaminidase, Leukocytes](#)) and the B1 variant ([#80350 Hexosaminidase A \(MUGS\), Serum](#)), with the need for the special substrate when the latter is suspected.

MML's [#82943 Hexosaminidase A & Total, Leukocytes/ Molecular Reflex](#) is the most comprehensive carrier/ diagnostic testing available from MML. Molecular testing will automatically be performed when biochemical results are within the ambiguous or carrier range (see Figure 1, page 2). With this test, no additional specimen collection is needed and charges for molecular analysis only incur if results of enzyme analysis prompt the additional testing. To ensure accurate interpretation of results, a TSD Questionnaire (MC 1235-70) must accompany the patient specimen. A supply of TSD Questionnaires can be obtained by contacting Mayo Medical Laboratories at 1-800-533-1710.

In those cases where biochemical testing has already been performed and additional testing is necessary, a sample can be submitted to Mayo for further analysis.

In this instance, [#82588 Tay-Sachs Diagnosis and Carrier Detection](#) is available and utilizes direct mutation analysis by polymerase chain reaction (PCR) to identify the specific mutation present.

If biochemical testing is ordered separately from molecular analysis, the following should be considered:

- Pregnancy and oral contraceptives elevate Hex A enzyme levels in serum. Thus, carrier detection for women who are pregnant or taking oral contraceptives is only accurate when performed on leukocytes (order [#82943 Tay-Sachs Enzyme Testing With Molecular Reflex](#)).
- Molecular testing cannot be performed on serum specimens. Therefore, molecular testing cannot be performed on specimens originally ordered as [#8774 Hexosaminidase A and Total Hexosaminidase, Serum](#).

Since the addition of the new molecular reflex test, [#82943 Tay-Sachs Enzyme Testing With Molecular Reflex](#), molecular reflex testing is no longer performed on leukocyte specimens ordered under MML [#8775 Hexosaminidase A and Total Hexosaminidase, Leukocytes](#).

Summary

The G_{M2} gangliosidoses are a group of clinically devastating disorders. While biochemical analysis remains the preferred first-tier testing method, recently developed molecular diagnostic techniques can aid in both carrier detection and diagnosis.

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Hepatitis B Surface Antigen Testing Changes

To more accurately reflect the components performed in the hepatitis B test profiles, components of the reflexes will be charged separately when performed. Previously, there was a single charge for the antigen and neutralization components when [#9013 Hepatitis B surface Antigen \(HBsAg\), Serum](#) was ordered. Clients ordering the hepatitis B profiles will need to add the neutralization test as a new code, 84396 Hepatitis Bs Neutralization (Confirmation), Serum, in the test file definitions. This neutralization test will not be separately orderable.

In addition to the component changes, MML will no longer contact clients when specimen volumes are insufficient to perform the neutralization test after obtaining a repeatedly reactive HBsAg screening test result. In cases of insufficient specimen volume, the test will be canceled and no charges will be generated. Test reports for these insufficient specimens will contain a comment requesting clients to submit additional specimen volume for repeat screening and neutralization testing.

This change affects [#9013 Hepatitis B surface Antigen \(HBsAg\), Serum](#) and the following profiles:

- [#9021 Previous Exposure Hepatitis Profile](#)
- [#9022 Acute Hepatitis Profile](#)
- [#9023 Chronic Hepatitis Profile \(Type B\)](#)
- [#9025 Chronic Hepatitis Profile \(Type Unknown\)](#)
- [#5566 Prenatal Hepatitis Profile](#)

Rubella Antibody Test Changes

A change in method for [#8172 Rubella Antibodies, IgG, Serum](#) has resulted in changes to the reference values. In addition, the word "only" was removed from the test title.

[New Method](#)

Enzyme-linked fluorescent immunoassay (ELFA)

[Previous Method](#)

Microparticle enzyme immunoassay (MEIA)

[New Reference Values](#)

Positive

[Previous Reference Values](#)

Immune or non-immune

Leukemia/Lymphoma Immunophenotyping by Flow Cytometry Specimen Requirements

In order to provide timely processing and accurate interpretation of results for [#3287 Leukemia/Lymphoma Immunophenotyping by Flow Cytometry](#), we require appropriate labeling and description of the specimen type. For this reason, please label both the specimen vial/tube and the accompanying paperwork with the appropriate specimen type: blood, bone marrow, or the specific fluid source. For blood and bone marrow specimens, please also include 5-10 unstained smears, if possible.

The following information is required when submitting a specimen for flow cytometric analysis:

1. A. Collection date
- B. Specimen source are required on request form for processing
- C. Pertinent clinical history
- D. Clinical or morphologic suspicion
- E. Specimen source
2. Label specimen appropriately (blood, bone marrow, or fluid type)
3. If ordering electronically, please complete and submit a "MayoConnect Additional Test Information Form" with the specimen. If not ordering electronically, please complete and submit "Hematopathology/Molecular Oncology/Cytogenetics Request Form" (Supply T241) with the specimen.

Note: Tissue specimens must be submitted for analysis by flow cytometry by ordering [#5439 Surgical Pathology Consultation](#) and [#9439 Leukemia/Lymphoma Immunophenotyping by Flow Cytometry, Tissue](#).

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Ask



US

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Q: Cytochrome P450 enzymes play a role in the metabolism of a variety of drugs. Why is this test, [#83180 Cytochrome P450 2D6 Genotyping](#), only available for patients receiving antidepressants? Will you accept specimens for assessment of other medications?

A: Our interpretive expertise is with the metabolism of drugs used for the treatment of depression and other psychiatric conditions. When specimens arrive for testing in conjunction with drugs used for other clinical purposes, we consult with the ordering physician to ensure that the drugs in question are indeed metabolized by CYP2D6 and that the results would have pertinence to the clinical situation presented. If that is the case, we will perform the test.

Q: I have noticed that there are no longer commas in the numerical results for [#81130 Hepatitis C Virus \(HCV\) Quantitation by bDNA, Serum](#) and [#82416 Hepatitis B Viral DNA Assay \(HBV-DNA\), Quantitative, Serum](#) (eg, 7692000 IU/mL vs 7,692,000 IU/mL). Why did this change?

A: The commas in the numerical results for these 2 assays no longer appear because the instrument that performs these tests has been interfaced to our laboratory information system (LIS). The interface eliminates human error in reporting results and reduces turnaround time, but does not allow the use of commas.

2004 Education Calendar

Interactive Satellite Programs . . .

Herbal Therapy 2004: Snakes in the Grass (Herb-Drug Interactions Clinicians Need to Know)

September 16, 2004

Presenter: Brent Bauer, MD

Moderator: Robert M. Kisabeth, MD

Markers of Inflammatory Bowel Disease

October 19, 2004

Presenter(s): Henry Homburger, MD and
Edward Loftus, MD

Moderator: Robert M. Kisabeth, MD

The Use of Diagnostic Tests in the Pediatric Age Group

November 2, 2004

Presenter: Robert Jacobson, MD

Moderator: Robert M. Kisabeth, MD

Thyroid Disease – Laboratory Support For Diagnosis and Management

December 7, 2004

Presenter: George Klee, MD, PhD

Moderator: Robert M. Kisabeth, MD

Upcoming Education Conferences . . .

Integration Through Community Laboratory Insourcing: Implementing a Successful Laboratory Outreach Program

June 17-19, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Bleeding and Thrombosing Diseases: The Basics and Beyond

Coagulation Conference and Wet Workshop
August 5-7, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Practical Surgical Pathology

September 16-18, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Practical Spirometry

November 2-3, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

Introductory Clinical Mycology

November 18-19, 2004

Mayo Clinic, Siebens Building
Rochester, Minnesota

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Appropriate Follow-up Testing of Specimens Reactive by Rapid HIV-1 Antibody Tests

The first CLIA-waived, point-of-care rapid HIV-1 antibody test was FDA licensed in January 2003. The sensitivity and specificity of the rapid HIV-1 antibody tests are comparable to those of enzyme immunoassay (EIA). However, when utilized in low-risk populations, the positive predictive value of the rapid tests is low, <30% (assuming a prevalence of 0.1% in a population). Therefore, false-positive results will be seen.

The US Centers for Disease Control and Prevention (CDC) recently issued a public notice (*Mortal Morbid Wkly Rpt* 2004; 53:221-222) advising healthcare providers and diagnostic laboratories on the appropriate follow-up serologic testing of serum specimens that are initially reactive by the FDA-approved rapid HIV-1 antibody tests. In the postmarketing surveillance to monitor the performance of these rapid tests (OraQuick® Rapid HIV-1 Antibody Test, Reveal™ HIV-1 Antibody Test, and Uni-Gold Recombigen™ HIV Test), CDC has noted that at least 5 HIV-infected persons were informed that their rapid HIV-1 antibody test results were false positive, which was incorrect. These individuals all had reactive rapid HIV-1 antibody test results, but their initial follow-up HIV-1 EIA results were nonreactive (or not done), and their subsequent Western blot (WB) results were positive or indeterminate. In response to these findings, CDC emphasizes that **serum specimens with reactive rapid HIV-1 antibody test results must be confirmed with either WB or immunofluorescent assay, even if the initial follow-up EIA results are nonreactive.** If such confirmatory test results are negative or indeterminate, follow-up testing (including EIA) should be done again at 4 weeks after the reactive rapid HIV-1 antibody test results.

The above CDC recommendation is a notable exception to the widely accepted laboratory practice of HIV serologic testing (such as MML #9333 [Human Immunodeficiency Virus 1/2 Antibody Evaluation](#)) in which HIV-1 testing by WB is done only on specimens that are repeatedly reactive by an FDA-licensed HIV-1/2 screening EIA.

Unless the EIA and WB tests are requested separately, MML does not perform the WB assay on serum specimens with nonreactive results on initial HIV-1 EIA. If you would like confirmation of a reactive rapid HIV test result, order:

- [#9190 Human Immunodeficiency Virus-1 \(HIV-1\) Antibody, Western Blot Assay, Serum](#) and [#9189 Human Immunodeficiency Virus 1/2 Antibody \(Combined Assay\), Serum](#) on separate accession numbers.
- If your laboratory requests only HIV-1 by WB (#9190) on repeatedly reactive (screening EIA) serum specimens, follow-up testing for HIV-2 by EIA (#86702) and by a HIV-2 confirmatory test (if necessary) also are recommended for specimens that are negative, indeterminate, or uninterpretable by HIV-1 WB. Sera from HIV-2-infected persons will yield repeated reactive results in HIV-1/2 screening EIA with negative or indeterminate results in HIV-1 by WB.

Due to the complexity of the ordering options for determining HIV 1/2 infection, an ordering algorithm defining the appropriate follow-up of a positive rapid HIV-1 antibody test is provided. We recommend follow-up testing with both EIA and WB to ensure that HIV-1 and HIV-2 have been ruled out.

