Test Definition: NAGS

Hexosaminidase A and Total Hexosaminidase, Serum

Overview

Useful For

Carrier detection and diagnosis of Tay-Sachs disease and Sandhoff disease

Ruling out I-cell disease

This test is **not useful for** pregnant females or those treated with hormonal contraception.

Testing Algorithm

For more information see Tay-Sachs and Related Disorders Diagnostic Testing Algorithm

Special Instructions

- Informed Consent for Genetic Testing
- Biochemical Genetics Patient Information
- Tay-Sachs and Related Disorders Diagnostic Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Heat Inactivation, Fluorometric, Automated

NY State Available

Yes

Specimen

Specimen Type

Serum

Ordering Guidance

Testing for Tay-Sachs Disease and Sandhoff Disease
The following tests are available for diagnostic and carrier testing for Tay-Sachs and Sandhoff diseases.

NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood:
-This is the recommended test for carrier testing for Tay-Sachs disease and Sandhoff disease.
-Testing begins with hexosaminidase A and total enzyme analysis. If the results are consistent with an affected or carrier for Tay-Sachs disease or Sandhoff disease, next generation sequencing to detect single nucleotide and copy number variants for *HEXA* or *HEXB*, respectively, will automatically be performed on the original specimen.
-This test is appropriate for males and pregnant or nonpregnant females.

NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes:
-This test can be used for diagnosis and carrier testing for Tay-Sachs disease or Sandhoff disease.
-Results for hexosaminidase A and total enzyme analysis are reported with recommendations for additional testing when appropriate. All follow-up testing must be ordered separately on new specimens.
-This test is appropriate for males and pregnant or nonpregnant females.

NAGS / Hexosaminidase A and Total Hexosaminidase, Serum:
-This test can be used for diagnosis and carrier testing for Tay-Sachs disease or Sandhoff disease.
-Results for hexosaminidase A and total enzyme analysis are reported with recommendations for additional testing when appropriate.
-If results indicate normal, indeterminate, or carrier status and the suspicion of Tay-Sachs disease remains high, MUGS / Hexosaminidase A, Serum for Tay-Sachs disease (B1 variant) can typically be added and performed on the same specimen.
-With the exception of MUGS, all follow-up testing must be ordered separately on new specimens.
-This test is **not appropriate for pregnant females** or women receiving hormonal contraception. This test is appropriate for males and nonpregnant females.
-This test is particularly useful when it is difficult to obtain enough blood to perform leukocyte testing (NAGR or NAGW), as may be the case with infants.

MUGS / Hexosaminidase A, Serum:
-This is the recommended test for diagnosis and carrier testing for the B1 variant of Tay-Sachs disease. This test will not detect Sandhoff disease.
-**This test should not be ordered as a first-line test**. Rather, this test should be ordered when the NAGR, NAGW, NAGS indicate normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. In most cases, this test can be performed on the original specimen collected for NAGS.

Specimen Required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 1 mL
Collection Instructions: Centrifuge and aliquot serum into plastic vial.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Biochemical Genetics Patient Information (T602)
3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Frozen (preferred)	30 days	
	Refrigerated	7 days	

Clinical & Interpretive

Clinical Information

Tay-Sachs and Sandhoff diseases, also referred to as GM2 gangliosidoses, are lysosomal storage disorders caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids result in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases.

Tay-Sachs and Sandhoff diseases are autosomal recessive conditions. Tay-Sachs disease results from 2 variants in *HEXA,* which encodes for the alpha subunit of hexosaminidase and causes a deficiency of hexosaminidase A enzyme. An increased carrier frequency for Tay-Sachs disease is observed in individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. Patients with Sandhoff disease have 2 variants in *HEXB*, which encodes for the beta subunit of hexosaminidase and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes. Sandhoff disease does not exhibit an increased carrier frequency in any specific population.

Clinical Phenotypes:
Phenotypically, patients with Tay-Sachs and Sandhoff diseases are virtually indistinguishable. Variability is observed with respect to age of onset and clinical symptoms. Enzyme analysis is generally required to distinguish between the 2 disorders.

The acute infantile forms of Tay-Sachs and Sandhoff diseases typically present with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age.

The juvenile or subacute forms often present between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death typically occurs 2 to 4 years later.

Disease progression is slower in patients with chronic or adult-onset Tay-Sachs and Sandhoff diseases. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families.

Testing Options:
Several tests are available for the detection of carriers of, and individuals affected with, Tay-Sachs and Sandhoff diseases (see Table, Ordering Guidance, and Testing Algorithm). The recommended test for both diagnostic and carrier testing is NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood. Testing begins with enzyme analysis and when indicated reflexes to the appropriate molecular analysis (either *HEXA* or *HEXB* gene), which includes sequencing and deletion/duplication analysis.

Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier, possible carrier, or affected ranges. This differentiates between nondisease causing pseudodeficiency alleles and disease-causing variants. In addition, molecular analysis allows for the facilitation of carrier testing and prenatal diagnosis for at-risk individuals.

Table.

Test ID	Test Name	Tay-Sachs disease		Sandhoff disease		Reflexes to molecular genetic testing	Use during pregnancy or hormonal contraception	Preferred use
		Carrier	Affected	Carrier	Affected			
NAGR	Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood	Yes	Yes	Yes	Yes	Yes	Yes	Diagnostic or carrier testing
NAGW	Hexosaminidase A and Total Hexosaminidase, Leukocytes	Yes	Yes	Yes	Yes	No	Yes	Diagnostic or carrier testing
NAGS	Hexosaminidase A and Total Hexosaminidase, Serum	Yes	Yes	Yes	Yes	No	No	Diagnostic
MUGS*	Hexosaminidase A, Serum	Yes	Yes	No	No	No	No	Diagnostic, secondary only

*MUGS testing should be utilized only when one of the other assays indicates normal, indeterminate, or carrier results and the clinical suspicion of Tay-Sachs disease remains high.

Reference Values

Hexosaminidase total
< or =15 years: > or =20 nmol/min/mL
> or =16 years: 10.4-23.8 nmol/min/mL

Hexosaminidase percent A
< or =15 years: 20-90%
> or =16 years: 56-80%

Interpretation

Interpretation is provided with report.

Cautions

GM2 activator deficiency (AB variant, *GM2A*) is a rare disorder with clinical features similar to Tay-Sachs and Sandhoff diseases; however, levels of both hexosaminidase A and B are normal. GM2 activator deficiency is not detected with this assay. Molecular genetic analysis of *GM2A* is available; see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Clinical Reference

1. Delnooz CCS, Lefeber DJ, Langemeijer SMC, et al. New cases of adult-onset Sandhoff disease with a cerebellar or lower motor neuron phenotype. J Neurol Neurosurg Psychiatry. 2010;81(9):968-972
2. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K: The GM2 gangliosidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed September 10, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225547784
3. Toro C, Shirvan L, Tifft C. *HEXA* Disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1218/
4. Hall P, Minnich S, Teigen C, Raymond K. Diagnosing lysosomal storage disorders: the GM2 gangliosidoses. Curr Protoc Hum Genet. 2014;83:17.16.1-8. doi:10.1002/0471142905.hg1716s83
5. Leal AF, Benincore-Florez E, Solano-Galarza D, et al. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. Int J Mol Sci. 2020;21(17):6213. Published 2020 Aug 27. doi:10.3390/ijms21176213

Performance

Method Description

The hexosaminidases are among the more active of the lysosomal enzymes, which hydrolyze derivatives of beta-D-*N*-acetylglucosamine and beta-D-*N*-acetylgalactosamine. Natural substrates are certain sphingolipids (ie, GM2) in which acetylgalactosamine is the terminal monosaccharide. The 2 hexosaminidase isoenzymes, A and B, differ in their electrophoretic mobility and heat stability. Hexosaminidase A moves toward the anode and is heat labile, while

hexosaminidase B moves toward the cathode and is heat stable.

The procedure is performed using an automated pipetting station and a spectrophotometer. The substrate used is 4-methylumbelliferyl-*N*-acetyl-beta-D-glucopyranoside (4-MUF-acetamido-2-deoxy-beta-D-glucopyranoside) from which the fluorescent compound, 4-methylumbelliferone, is liberated by both hexosaminidases.

The sample is mixed with citrate phosphate buffer and mixture is separated into 2 tubes. One tube stays at ambient temperature and the other is heated at 51.5 degrees C for 15 minutes. On the automated pipetting station, sample and substrate are pipetted into a microtiter test tube located in a 37 degree C waterbath. The hexosaminidase A fraction is destroyed in the heated sample, leaving only hexosaminidase B to react with the substrate. The unheated sample provides the total hexosaminidase (A and B). The reaction is stopped with glycine after the 30-minute incubation. Sample intensities are compared to that of a 4-methylumbelliferone standard curve to quantitate both the total and the B fraction. The percentage of the A fraction that was inactivated by heating is calculated based on these results. The difference in heat inactivation is used to fractionate hexosaminidase activities.(O'Brien JF, Burtis CA, Ashwood ER: Lysosomal storage diseases. In: Tietz Textbook of Clinical Chemistry. 2nd ed. WB Saunders Company; 1994:2149-2160; Cowan T, Pasquali M: Laboratory investigations of inborn errors of metabolism. In: Sarafoglou K, Hoffman GF, Roth KD, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill; 2017:1139-1158)

PDF Report
No

Day(s) Performed
Wednesday

Report Available
2 to 6 days

Specimen Retention Time
30 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

83080 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NAGS	Hexosaminidase A and Total, S	87545-0

Result ID	Test Result Name	Result LOINC® Value
27612	Hexosaminidase Total, S	1956-2
27613	Hexosaminidase Percent A, S	12914-8
27216	Interpretation (NAGS)	59462-2
27218	Reviewed By	18771-6