Test Specific Guidelines

Tay-Sachs Disease Testing

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
HEXA Known Familial Mutation Analysis	81403
HEXA Targeted Mutation Analysis	81255
HEXA Full Gene Sequencing	81406
Beta-Hexosaminidase A Enzyme Analysis	83080

What Is Tay-Sachs Disease?

Definition

Tay-Sachs disease (TSD) is a neurodegenerative genetic disorder.[1]

Prevalence

Before widespread carrier screening, TSD affected about 1 in 3,600 Ashkenazi Jewish births.[1] Approximately 1 in 30 Ashkenazi Jewish individuals are carriers for Tay-Sachs disease.[1-3]

Symptoms

Affected individuals typically present in infancy with progressive weakness, loss of motor skills, decreased attentiveness, and increased startle response between 3-6 months of age. Eventually they develop seizures and blindness, with death in early childhood.[1,2]

Rare, less severe, Tay-Sachs variants exist that are associated with later onset, and less progressive symptoms, and cause more variable neurological problems. These variants include juvenile, chronic, and adult-onset forms.[1]

Cause

TSD is caused by pathogenic mutations in the HEX A gene. HEX A gene mutations lead to reduced activity of the β-hexosaminidase A enzyme, allowing toxic substances to build up in the cells of the brain and spinal cord. Eventually, neurons are destroyed, causing the signs and symptoms of Tay-Sachs disease.[1]

Inheritance

TSD is inherited in an autosomal recessive fashion.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Carrier Screening

Individuals at increased risk to have a child with Tay-Sachs should routinely be offered carrier screening. This includes those with:[1-5]

Ashkenazi Jewish, French Canadian, or Cajun ancestry,

A family history of Tay-Sachs disease (regardless of ethnicity), or

A partner who is a known carrier of Tay-Sachs (or affected with a late-onset variant).

Carrier screening for TSD is widely available as part of an "Ashkenazi Jewish Panel" that includes several other genetic diseases that are more common in this population. For information on carrier screening panels for individuals with Ashkenazi Jewish ancestry, please refer to the guideline *Ashkenazi Jewish Carrier Screening*.

The HEXA gene is also included on pan-ethnic expanded carrier screening panels.

Diagnosis

The diagnosis of TSD is made on the basis of clinical suspicion with low HEX A activity on enzyme analysis, and/or finding two pathogenic mutations in HEXA by molecular analysis.[1]

Management

There is no cure for TSD and treatment is supportive.[1,2]

Survival

In classic TSD, death is commonly between ages 2 and 3 years, with some individuals surviving from 5 to 7 years.[1] In later onset variants of TSD, survival into adolescence or adulthood is expected.[1]

Test Information

Introduction

Testing for TSD may include known family mutation analysis, targeted mutation analysis, sequencing, or enzyme analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon patient ethnicity, phenotypic presentation, or other case-specific characteristics.

Targeted mutation analysis test looks for the most common HEXA gene mutations (such as +TATC1278, +1 IVS 12, +1 IVS 9, G269S, R247W, and R249W), which account for up to 92% of all Ashkenazi Jewish Tay-Sachs mutations.[1,6] The detection rate of standard HEXA common mutation panels is much lower in other ethnicities. Some panels include mutations more common in other at-risk ethnic groups (e.g., a 7.6kb deletion more common in French Canadians).[1] If using common mutation panels in non-Ashkenazi Jewish individuals, providers should confirm the panel includes any ethnicity-specific mutations.Paragraph

Sequencing

HEXA sequencing analyzes the entire coding region of the HEXA gene and finds the vast majority of HEXA variants that cause TSD. Sequence analysis of HEXA is performed first followed by gene-targeted deletion/duplication analysis if only

one or no pathogenic variant is found. HEXA common variant panels can be performed first in individuals of high-risk ethnicity.[1] However, new data provides evidence and support for NGS-based screening as the optimal method to identify TSD carriers, irrespective of ethnicity.[7]

Enzyme Analysis

Hexosaminidase A (HEX A) enzyme analysis measures the activity of HEXA in the serum or white blood cells. This test is used both for diagnostic testing of symptomatic individuals, and carrier screening.

Individuals with classic TSD have little to no HEX A enzyme activity in the presence of normal or elevated activity of the beta-hexosaminidase B (HEX B) isoenzyme. HEX A enzyme activity levels correctly diagnose the vast majority of people with all forms of TSD.

Carriers have about 50% of the normal level of HEX A activity.[1,2] HEX A enzyme analysis detects 97%-98% of carriers, regardless of ethnicity.[3,4]

A small percentage of individuals will get a false positive result by enzyme analysis. This means that they have enzyme activity that appears to be in the carrier range, but they are not actually carriers of a disease-causing mutation. These individuals carry a "pseudodeficiency allele." [1] Inconclusive enzyme analysis results are also possible where enzyme activity is in the overlap range between carrier and normal levels.[1] If HEXA enzyme analysis is abnormal or inconclusive, HEXA mutation analysis may be considered.[1,3]

Guidelines and Evidence

American College of Obstetricians and Gynecologists

Consensus Guidelines on Carrier Screening for Genetic Conditions from the American College of Obstetricians and Gynecologists (ACOG; Reaffirmed 2020) recommended:[3]

"Screening for TSD should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French–Canadian, or Cajun descent. Those with a family history consistent with TSD also should be offered screening."

"When one member of a couple is at high risk (i.e., of Ashkenazi Jewish, French–Canadian, or Cajun descent or has a family history consistent with TSD) but the other partner is not, the high-risk partner should be offered screening…If the high-risk partner is determined to be a carrier, the other partner also should be offered screening. If the woman is already pregnant, it may be necessary to offer screening to both partners simultaneously to ensure that results are obtained promptly and that all options are available to the couple."

"Enzyme testing in pregnant women and women taking oral contraceptives should be performed using leukocyte testing because serum testing is associated with an increased false-positive rate in these populations."

"If both partners are determined to be carriers of Tay-Sachs disease, genetic counseling and prenatal diagnosis should be offered."

"If Tay-Sachs disease screening is performed as part of pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay-Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel."

National Tay-Sachs and Allied Disorders Association

The National Tay-Sachs and Allied Disorders Association (NTSAD; 2019) Position Statement stated:[8]

"Full-exon gene sequencing via NGS is a highly sensitive molecular test that detects coding sequence changes throughout the HEXA gene for Tay-Sachs disease and has a high carrier detection rate across all ethnic groups. In rare cases, this technology is limited by the inability to detect some non-coding pathogenic variants or to properly classify some VUS."

"Genotyping is a molecular test that detects the presence of a select number of prespecified pathogenic variants within the HEXA gene. It is less sensitive than full exon gene sequencing by NGS, and in most instances, should not be the test of choice when screening for carrier status for TSD."

"Tay-Sachs Sachs disease carrier screening via Hex A enzyme activity testing is a sensitive assay for carrier detection. Of note, subsequent molecular testing may be needed to allow for utilization of reproductive options for carrier couples, and leukocyte testing (rather than serum testing) should be ordered for Tay-Sachs disease carrier screening in women who are pregnant or using oral contraceptive medication."

"Current data supports a shift toward the routine use of full-exon HEXA NGS for Tay-Sachs carrier screening in individuals of all ethnic backgrounds due to the benefits and few limitations of NGS, while continuing to regard Hex A enzyme activity testing as another reliable method for Tay-Sachs carrier status detection."

Selected Relevant Publications

A 2020 comprehensive literature review stated:[1]

"The diagnosis of a HEXA disorder is established in a proband with biallelic pathogenic variants in HEXA identified by molecular genetic testing. Targeted analysis for certain pathogenic variant scan be performed first in individuals of specific ethnicity (e.g., French Canadian, Ashkenazi Jewish). Enzyme testing of

affected individuals identifies absent to near-absent HEX A enzymatic activity in the serum, white blood cells, or other tissues in the presence of normal or elevated activity of the beta-hexosaminidase B enzyme."

Professional guidelines support population-based Tay-Sachs carrier screening for those at increased risk. They do not generally recommend a specific testing strategy (enzyme and/or mutation analysis) for Ashkenazi Jewish individuals, but do recommend enzyme analysis as a first-line test for non-Jewish individuals.[2,3] These organizations generally recommend prenatal testing for Tay-Sachs disease in any of the following situations:1-4

HEX A enzyme activity testing revealed both parents to be carriers of Tay-Sachs disease and pseudodeficiency alleles have been ruled out.

Disease-causing mutations in HEXA have been identified in both parents.

One parent is a known carrier and HEX A enzyme activity testing in the other parent was inconclusive.

The mother is a known carrier and the father's status is unknown or he is unavailable for testing.

Guidelines do not generally recommend a specific testing strategy (HEX A enzyme activity and/or mutation analysis). However, the clinical circumstances may deem one strategy more accurate than the other. For instance, mutation analysis is most accurate if both of the parental mutations are known.

Criteria

HEXA Known Familial Mutation Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous genetic testing that would detect the familial mutation, AND

Diagnostic Testing:

HEXA mutation identified in both biologic parents, or

Biallelic HEXA mutations identified in an affected sibling, OR

Carrier Screening:

Known family mutation in HEXA identified in 1st, 2nd, or 3rd degree biologic relative(s), OR

Prenatal Testing for At-Risk Pregnancies:

HEXA mutation identified in both biologic parents, and

Pseudodeficiency allele mutation has been ruled out, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Diagnostic Testing

- HEXA Targeted Mutation Analysis for Common Mutations and Pseudodeficiency Alleles

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic testing:

The requested testing has not been performed previously, and

No known HEXA mutation in family, AND

Member is Ashkenazi Jewish, French Canadian, Cajun from Louisiana, or other ethnicity with known HEXA founder mutations, AND

Requested targeted mutation analysis contains appropriate founder mutations for the individual's ethnicity, AND

The member is suspected of having Tay-Sachs Disease based on at least one of the following:

Abnormal or indeterminate HEX A enzymatic activity in serum, white blood cells, or other tissues, and clinical symptoms of TSD, but diagnosis remains uncertain, OR

Children under the age of 6 months suspected of having Tay-Sachs Disease based on the following:

Progressive weakness and loss of motor skills, or

Decreased attentiveness, or

Increased startle response, or

Macular cherry red spot, or

Seizures, or

Blindness, OR

Young children suspected of having Tay-Sachs Disease based on the following:

Ataxia and incoordination, or

Speech, life skills, and cognition decline, or

Spasticity and seizures, or

Loss of vision, sometimes with:

Cherry red spot, or

Optic atrophy, or

Retinitis pigmentosa, OR

Adolescent/adult (and SMA type Kugelberg-Welander disease or early onset ALS has been ruled out) suspected of having Tay-Sachs Disease based on the following:

Progressive dystonia, or

Spinocerebellar degeneration, or

Motor neuron disease, or

Cognitive dysfunction, dementia, recurrent psychotic depression or bipolar symptoms, OR

Asymptomatic individual with abnormal HEX A enzymatic activity in order to test for a pseudodeficiency allele, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HEXA Full Gene Sequencing

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Testing:

No previous full sequencing of HEXA, and

Member is Ashkenazi Jewish, French Canadian, Cajun from Louisiana, or other ethnicity with known founder mutations, and:

Biallelic disease causing HEXA mutations were not identified by targeted mutation analysis, or

Member is of another ethnicity, and:

Biallelic disease causing HEXA mutations were not identified by targeted mutation analysis, if performed, AND

Member meets clinical criteria for targeted mutation analysis in symptomatic individuals (see above), AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HEXA Deletion/Duplication Analysis

Genetic Counseling:

Pre and post genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous HEXA deletion/duplication analysis, and

Biallelic disease causing HEXA mutations were not identified by HEXA sequencing analysis, AND

Member meets clinical criteria for HEXA sequence analysis (see above), AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Carrier Screening

HEXA Targeted Mutation Analysis for Common Mutations and Pseudodeficiency Alleles

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

The requested testing has not been performed previously, and

No known HEXA mutation in family, AND

Member is Ashkenazi Jewish, French Canadian, Cajun from Louisiana, or other ethnicity with known HEXA founder mutations, and:

Requested targeted mutation analysis contains appropriate founder mutations for the individual's ethnicity, and

Member has the potential and intention to reproduce, OR

Member is an asymptomatic individual with abnormal HEX A enzymatic activity in order to test for a pseudodeficiency allele, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HEXA Full Gene Sequencing

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous full sequencing of HEXA, AND

Carrier testing for Individuals with Family History or Partners of Carriers:

Member has abnormal HEX A enzyme activity on carrier screen, or

Member has a 1st, 2nd, or 3rd degree biologic relative with Tay-Sachs clinical diagnosis, and familial mutation unknown, and affected relative unavailable for testing, or

Member's partner is monoallelic or biallelic for a HEXA mutation, AND

Member has the potential and intention to reproduce, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

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