Spinal muscular atrophy (SMA) is a motor neuron disease characterized by degeneration of spinal cord anterior horn cells and muscular atrophy. Based on the age of onset and severity of the clinical course, 3 types of childhood-onset SMA (SMA I, II, III) and 1 type of adult-onset SMA (SMA IV) have been defined. All 3 types of childhood-onset SMA have been shown to be caused by mutations in the survival motor neuron (SMN) gene on chromosome 5q13.

Testing of the SMN gene is complicated by the presence of 2 homologous sequences, a telomeric copy (SMN-T or SMN1) and a centromeric copy (SMN-C or SMN2), that differ by just 5 nucleotide differences (1 in intron 6, 1 in exon 7, 2 in intron 7, and 1 in exon 8).

Approximately 96% of childhood-onset SMA patients have mutations in the SMN-T gene, while 4% are not linked to the SMN-T gene on chromosome 5q13. Of the 5q13 linked SMA patients, approximately 96% show a homozygous deletion of exon 7 and 8 or exon 7 only within the SMN-T gene, while the remaining cases have a more subtle mutation on 1 of the chromosomes and a deletion/gene conversion on the other.

Detection of SMN-T exons 7 and 8 deletions by DNA analysis is possible because of the base pair differences noted between SMN-T and SMN-C (one in exon 7 and another in exon 8, both of which alter restriction enzyme digestion sites).

Although the percentage of cases of adult-onset SMA with homozygous deletions of the SMN-T gene is not well established, homozygous deletions within this gene have been described.

**Clinical**

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**Useful For**

- Confirmation of clinical diagnosis of spinal muscular atrophy
- Prenatal diagnosis of SMA

**Interpretation**

The report will include specimen information, pedigree (when appropriate), assay information, background information, and estimate of carrier risk based on test results.

**Cautions**

- This method can detect homozygous deletions in affected individuals but, due to technical limitations, it cannot detect heterozygous deletions in carriers of SMA.
- A negative result does not rule out the diagnosis of SMA. Approximately 5-10% of patients affected with SMA do not have homozygous SMN-T gene deletions, but have other types of alteration not identified by this assay.
- Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given to us is inaccurate or incomplete.
- Medical genetic consultation is available for all cases and is particularly indicated in complex cases or in situations in which the diagnosis is atypical or uncertain.
- Prenatal diagnosis can only be performed if homozygous deletions were previously identified in a previously affected child.
Method

A polymerase chain reaction-based assay is utilized to identify microdeletions within the telomeric survival motor neuron gene (SMN-T). This assay includes DraI and Ddel digestions to distinguish between SMN-T and the highly homologous centromeric gene (SMN-C). This method is useful for detection of homozygous deletions in affected individuals, but cannot be used for detection of heterozygous deletions in carriers of SMA. (Van der Steege G, Grootscholten PM, Van der Draaijers TG, et al: PCR-based DNA test to confirm clinical diagnosis of autosomal recessive spinal muscular atrophy. Lancet 1995;345:985-986)

Specimen Required: Specimen should include a “Molecular Genetics Congenital Disorders Request Form” (Supply T245) or a “MayoConnect Additional Test Information Form” (Supply T357) with information including relevant clinical and family history information. Specimen must arrive within 96 hours of collection.

SUBMIT 1 OF THE FOLLOWING SPECIMENS:

Blood

Draw blood in a lavender-top (EDTA) tube(s) or a yellow-top (ACD) tube(s) and send 3.0 mL of whole blood in the original VACUTAINER(S). Invert several times to mix blood. Forward unprocessed whole blood promptly at ambient temperature.

Prenatal Specimens

All prenatal specimens must be accompanied by a maternal blood specimen.

Amniotic Fluid

Obtain 20 mL of amniotic fluid. Transfer specimen to 2 screw-capped, sterile centrifuge tubes. Send specimen refrigerated. SPECIMEN CANNOT BE FROZEN. A separate culture charge will be assessed under test #80334 “Amniotic Fluid Culture for Genetic Testing” unless a chromosome analysis on the specimen is also being performed at Mayo. Alternatively, we will accept 2 T-25 flasks of confluent cultured cells from another laboratory sent at ambient temperature.

Chorionic Villus

Obtain 20 mg of chorionic villus specimen. Send specimen refrigerated in transport media in 15-mL centrifuge tube. SPECIMEN CANNOT BE FROZEN. A separate culture charge will be assessed under test #80333 “Fibroblast Culture for Genetic Testing” unless a chromosome analysis on the specimen is also being performed at Mayo. Alternatively, we will accept 2 T-25 flasks of confluent cultured cells from another laboratory sent at ambient temperature.

Reference Values: An interpretive report will indicate whether or not results are consistent with a diagnosis of Spinal Muscular Atrophy.

Analytic Time: 8 days

Days Set Up: Tuesday

Fee: $280.60

CPT Code: 83890/Molecular isolation or extraction
83892/Enzymatic digestion
83894/Separation by gel electrophoresis
83898/Amplification of nucleic acid, each primer pair
83912/Interpretation and report
Tay-Sachs disease is an autosomal recessive condition caused by an absence of enzyme activity, which results in the accumulation of the sphingolipid GM2 ganglioside. Mutations within the lysosomal enzyme N-acetyl-hexosaminidase A (Hex A) cause the clinical manifestations of Tay-Sachs disease. Storage of GM2 occurs in the brain and results in ballooning of the neurons such that most of their intracellular space becomes occupied with lipid-engorged lysosomes. The most common form (infantile) becomes apparent at about 6 months, when mild motor weakness is noted along with impaired visual acuity and the presence of a “startle response.” Further aspects of this condition include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death.

Hexosaminidase A was shown to be absent in Tay-Sachs in 1969. Since that time analysis of this enzyme activity has been used to both diagnose the disease (absence of Hex A activity) and determine carrier status (half the normal level of this enzyme’s activity). Hex A is a dimeric protein with nonidentical subunits denoted alpha and beta. Biochemical testing for carrier status can result in equivocal levels of Hex A in which carriers and noncarriers cannot be adequately distinguished. In such cases, molecular analysis can assist in clarifying the status of these patients.

The causal mutations in Tay-Sachs disease are found within the gene encoding the alpha subunit (HEXA), located on chromosome 15. Because of a founder effect, Tay-Sachs occurs more commonly in persons of Ashkenazi Jewish descent. Molecular analysis has identified different causative mutations within the HEXA gene, but 3 mutations common in the Ashkenazi Jewish population account for approximately 98% of these mutations. Detection of the 3 common mutations for Tay-Sachs disease is particularly helpful in confirming or clarifying carrier status in Ashkenazi Jewish patients in whom biochemical test results are within the equivocal range. Additionally, the identification of the causative mutations can allow for accurate prenatal diagnosis for at-risk families.

Useful For
- Identifying carriers of Tay-Sachs disease
- Confirming a diagnosis of Tay-Sachs disease
- Determining carrier status for individuals with enzyme activity within the carrier or equivocal ranges
- Prenatal diagnosis for at-risk families

Interpretation
An interpretive report is provided based on laboratory results, clinical presentation, ethnic background, and family history, if provided.

Cautions
- Interpretation may not be possible when the ethnic background and family history are not provided.
- Mutations detected are common within the Ashkenazi Jewish population. Residual risks for individuals with other ethnic backgrounds may not be available.
- For diagnostic purposes, results should be interpreted in the context of biochemical test results.
Tay-Sachs Diagnosis and Carrier Detection

#82588

References

Method
A polymerase chain reaction-based assay is used to test for the Exon 11 [1278insTATC], intron 12 [IVS12(+1)G>C], and Exon 7 [G269S] mutations within the alpha-chain of the lysosomal enzyme beta-hexosaminidase A gene. (Ririe KM, Rasmussen RP, Wittwer CT. Product differentiation by analysis of DNA melting curves during the polymerase chain reaction. Anal Biochem 1997 Feb 15;245[2]:154-60)

Specimen Required: Specimen should include a “Molecular Genetics Congenital Disorders Request Form” (Supply T245) or a “MayoConnect Additional Test Information Form” (Supply T357) with information including relevant clinical and family history information. Specimen must arrive within 96 hours of collection.

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Reference Values: An interpretive report will be issued, which will include a risk analysis (probability of being a carrier).

Analytic Time: 5 days
Days Set Up: Monday, Wednesday, Friday
Fee: $260.20
CPT Code: 83890/Molecular isolation or extraction
83898x3/Amplification of nucleic acid, each primer pair
83912/Interpretation and report