Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is the second most common lethal, autosomal recessive disorder in Caucasians, with an incidence of approximately 1/10,000 and a carrier frequency of 1/50. SMA is characterized by anterior horn cell degeneration which causes a symmetrical muscle weakness and wasting. SMN1 is deleted in about 95% of individuals with SMA. This carrier assay tests for the common SMN1 deletion only; other pathogenic variants will not be detected.

Approximately 5-8% of carrier individuals will have a normal SMN1 copy number of two, but both copies will be on the same chromosome (in cis) with a deletion on the second chromosome. This assay will not detect these carrier individuals. This assay will not report SMN2 copy number.

Although a positive test result should not affect the health of the individual, she could be at a 25% risk for passing that condition on to her children depending on the carrier status of the partner. In addition to the specific pathogenic variants identified by the panel, EGL Genetics also offers single-gene, full gene sequencing for genes on the panel, which can be utilized to screen partners of positive carriers. Knowing about these risks ahead of time can help couples make decisions about testing options prior to and during pregnancy, and can help healthcare providers be more readily prepared to offer appropriate follow-up care at delivery.

Genes

ABC8, ASPA, BCKDHB, BLM, CFTR, CLRN1, DLD, ELP1, FANCC, FKTN, FMR1, G6PC, GBA, HEXA, MCOLN1, NEB, PCDH15, SMN1, SMPD1, TMEM216

Indications

Appropriate for:
- Carrier testing in individuals of Ashkenazi Jewish descent.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient’s gene sequences are then compared to a standard reference sequence. Only known pathogenic variants will be reported.

Fragile X Syndrome Repeat Analysis: Both normal CGG repeat tracts and expanded CGG repeat tracts are detected by PCR amplification, using a CGG repeat-specific probe, and capillary electrophoresis. Expanded CGG repeat tracts will be reflexed to a gene specific PCR and sized by agarose sequencing. The patient’s gene sequences are then compared to a standard reference sequence. Only known pathogenic variants will be reported.

Note that the quoted detection rates and residual carrier risks are directly applicable only to persons of Ashkenazi Jewish descent. The carrier detection rate in persons from other ethnic backgrounds is likely to be significantly lower.

For more information on individual diseases, please visit the Emory Jewish Genetic Disease Program website.

Click here for a complete list of conditions.

Individuals of Ashkenazi Jewish descent are at a higher risk than the general population to be carriers of certain genetic diseases. This carrier screening panel tests for 20 of these diseases. The panel meets the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) Ashkenazi Jewish ancestry carrier screening recommendations, and also includes additional diseases that occur more frequently in this population.

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Spinal Muscular Atrophy (SMA) Testing: SMN1 gene deletions were quantified by multiplex ligation polymerase chain reaction amplification (MLPA) of exons 7 and 8. Gene dosage ratios of SMN1 are calculated relative to the average of 16 reference loci and are expressed as gene dosage, and/or copy number. Diploid gene dose or 2 copies of SMN1 indicates normal (not affected) status, 1x gene dosage or 1 copy of the SMN1 gene most likely indicates carrier status and deletions (less than 0.1x) of SMN1 or 0 copies of the SMN1 gene designates affected status. This carrier assay tests for the common SMN1 deletion only; other pathogenic variants will not be detected. SMN2 copy number is not assessed.

Detection

Next Generation Sequencing: Next Generation Sequencing: Clinical Sensitivity: See results report. Pathogenic variants in regions other than the targeted area, including the promoter region, some mutations in the introns and other regulatory element mutations, cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

For Fragile X Syndrome Repeat Analysis: All cases of fragile X syndrome caused by CGG expansion will be detected by this assay. Rare cases of fragile X syndrome caused by other pathogenic variants in the FMR1 gene will not be detected by this assay.

For Spinal Muscular Atrophy (SMA) Testing: Deletions of the SMN1 gene are found in approximately 95% of individuals with SMA. This carrier assay tests for the common SMN1 deletion only; other pathogenic variants will not be detected. Approximately 5-8% of carrier individuals will have a normal SMN1 copy number of two, but both copies will be on the same chromosome (in cis) with a deletion on the second chromosome. This assay will not detect these carrier individuals. SMN2 copy number is not assessed.

Reference Range

For Fragile X Testing:
Normal: Approximately 5-44 CGG repeats.
Intermediate: Approximately 45-54 unmethylated CGG repeats.
Premutation: Approximately 55-200 CGG repeats and methylation of expanded allele.
Affected: Over 200 CGG repeats and methylation of expanded allele.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
20µg
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Related Tests

- Ashkenazi Jewish Carrier Screen: Targeted Mutation Panel
- Pan-Ethnic Carrier Screen: Gene Sequencing Panel
- ACOG/ACMG Carrier Screen: Gene Sequencing Panel