Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is the most common lethal genetic disease in children and is characterized by progressive muscle weakness due to degeneration of the lower motor neurons. Onset ranges from before birth to adulthood and severity is highly variable. Individuals with SMA have no functioning copies of the SMN1 gene. Most (95%) have a loss of both copies of the SMN1 gene due to deletion or gene conversion, while a minority (5%) have a deletion of SMN1 on one chromosome and a SMN1 sequence variant on the other. The SMN2 gene, adjacent and highly homologous to SMN1, produces lower levels of survival motor neuron protein compared to SMN1. Disease severity has been shown to be modified by the SMN2 gene copy number in some cases, though phenotype cannot be predicted with certainty. An SMN1 variant, c.*3+80T>G, that is part of a haplotype associated with SMN1 duplication in silent carriers (two copies of SMN1 on one chromosome and no copies on the other), particularly in individuals of Ashkenazi Jewish descent, increases the likelihood that two copies of SMN1 are on the same chromosome.

Disease Overview

Incidence

Approximately 1/12,000 live births in the United States:

- Carrier rate varies by ethnicity: approximately 1/54 overall in the U.S.
- See the SMA Carrier Risk table for ethnicity-specific posttest carrier risk.

Symptoms

- Progressive muscle weakness due to degeneration of lower motor neurons:
  - Clinical findings of affected individuals fall on a spectrum.
  - The most common symptoms are difficulty in breathing, swallowing, and walking.
- SMA subtypes are distinguished by age of onset and severity for purposes of prognosis and management:
  - SMA 0: prenatal onset
    - Most severe form
    - Survival is typically <6 months without treatment
  - SMA 1: onset at 0-6 months
    - Most common subtype
    - Severe muscle weakness
    - Survival is <2 years without treatment
  - SMA 2: onset at 6-12 months
    - Child usually cannot walk without assistance
    - Untreated life span is not currently known
  - SMA 3: onset after 12 months
    - Milder muscle weakness; child usually can walk and stand without assistance
    - Normal life span
  - SMA 4: adult onset
    - Mild muscle weakness
    - Normal life span

Diagnostic Testing

- Diagnosis is based on clinical findings and molecular genetic testing. Electromyography (EMG), nerve conduction velocities (NCV), and muscle/nerve histology may aid in diagnosis.
- 95-98% of individuals with SMA have a homozygous loss of SMN1 (zero copies of SMN1).
- 2-5% of individuals with SMA have loss of SMN1 on one chromosome and a pathogenic sequence variant in the remaining copy of SMN1 (not detected by this test).
- It is not possible to definitively predict clinical subtype based on genotype.
  - A higher SMN2 copy number may correlate with milder disease severity in affected individuals.

Carrier Testing

- The presence of two or more copies of SMN1 usually indicates patient is not a carrier, although residual carrier risk exists.
- Test is unable to determine if SMN1 copies are on the same or opposite chromosomes.
- 3-4% of the general population have two copies of SMN1 on the same chromosome (also known as SMN1 duplication).
  - If paired with SMN1 loss (zero copies) on the opposite chromosome, these individuals are "silent carriers" or "2+0 carriers."
- Two or more copies of SMN1 on the same chromosome is rare but more frequent in individuals of African American or Ashkenazi Jewish descent.

Tests to Consider

<table>
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<th>SMA Carrier Risk</th>
<th>Method</th>
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<tr>
<td>SMA 0: prenatal onset</td>
<td>Multiplex Ligation-dependent Probe Amplification</td>
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<td>SMA 1: onset at 0-6 months</td>
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Spinal Muscular Atrophy (SMA) Copy Number Analysis

Method: Multiplex Ligation-dependent Probe Amplification

- Order to confirm a suspected diagnosis of SMA or for carrier screening.
- SMN1 and SMN2 copy number and the linked variant c.*3+80T>G (rs143838139) will be reported.

Spinal Muscular Atrophy (SMA) Copy Number Analysis

Method: Multiplex Ligation-dependent Probe Amplification

- Order for prenatal diagnosis of SMA when both parents carry a known deletion of SMN1 or have a previous child with SMA caused by two SMN1 deletions.
- Rare pathogenic SMN1 sequence variants will not be detected.
- SMN1 and SMN2 copy number will be reported, but the linked variant will not be reported.

Related Test

Genetic Carrier Screen, (CF, FXS, and SMA) with Reflex to Methylatation 3000258


- Reproductive carrier screening for cystic fibrosis (CF), fragile X syndrome (FXS), and SMA
- Recommended for carrier screening in women who are pregnant or planning a pregnancy.
- Not recommended for men as FXS carrier screening is not indicated.
- Not recommended for diagnostic testing for CF, FXS, or SMA; do not use for diagnostic testing in patients with symptoms of CF, FXS, or SMA.
Testing includes analysis of a linked variant, c.*3+80T>G, often associated with SMN1 gene duplication on the same chromosome.

- The presence of two SMN1 copies and a linked variant increases risk of being silent carrier, especially in Ashkenazi Jewish individuals.
- Test is unable to identify pathogenic sequence variants in the SMN1 gene(s) that are present.
- SMN2 copy number is relevant only for affected individuals.

Pathophysiology

- SMA is caused by low levels of survival motor neuron (SMN) protein, which is essential for motor neurons.
- The majority of functional SMN protein is produced by the SMN1 gene.
- Only about 10% of functional SMN protein is produced by the SMN2 gene.
  - There may be multiple copies of SMN2 on each chromosome.
  - In affected individuals, higher SMN2 copy numbers may correlate with milder disease because more functional SMN protein is produced.
- FDA-approved drugs (eg, Spinraza [nusinersen], Zolgensma [onasemnogene abeparvovec-xioi], Evrysdi [risdiplam]) are used to treat SMA.

Genetics

Genes

SMN1, SMN2

Inheritance

Autosomal recessive

De novo Mutation Rate

2% of affected alleles

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity for diagnostic testing:
  - 95-98% of individuals with SMA have no copies of SMN1.
  - 2-5% of affected individuals have one copy of SMN1 plus a pathogenic sequence variant.
- Detection rate for carrier screening varies by ethnicity

Results

<table>
<thead>
<tr>
<th>Results Interpretation</th>
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<tbody>
<tr>
<td><strong>Diagnostic Test</strong></td>
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<tr>
<td>0 copies of SMN1</td>
<td>Consistent with diagnosis of SMA</td>
<td></td>
</tr>
<tr>
<td>1 copy of SMN1</td>
<td>Individual is at least a carrier of SMA</td>
<td>Individual may be affected if a pathogenic sequence variant is also present in the other SMN1 gene</td>
</tr>
<tr>
<td>2 or more copies of SMN1</td>
<td>Greatly reduced risk of being affected with SMA</td>
<td></td>
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<tr>
<td><strong>Carrier Screening Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 copy of SMN1</td>
<td>Individual is a carrier of SMA</td>
<td></td>
</tr>
<tr>
<td>2 copies of SMN1 with absence of linked variant</td>
<td>Carrier risk is reduced, but not eliminated</td>
<td></td>
</tr>
<tr>
<td>2 copies of SMN1 with presence of linked variant</td>
<td>Increased risk of being a silent carrier</td>
<td></td>
</tr>
<tr>
<td>3 or more copies of SMN1</td>
<td>Carrier risk is significantly reduced, but not eliminated</td>
<td></td>
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</table>

1 SMN2 copy number will be reported but cannot be used to predict disease severity with certainty.
2 Both SMN1 copies may be on the same chromosome, or a pathogenic sequence variant may be present on one chromosome.
3 Both SMN1 copies may be on the same chromosome with no copies on the other chromosome.
4 Linked variant is not clinically relevant.
Residual carrier risk for SMA depends on an individual’s genetic admixture.

### SMA Carrier Risk Based on Ethnicity and Test Result

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Carrier Frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Detection Rate Using SMN1 Copy No. and Linked Variant&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Posttest (Residual) Carrier Risk if 2 Copies of SMN1 and Linked Variant Absent&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Posttest Carrier Risk if 2 Copies of SMN1 and Linked Variant Present&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Posttest Carrier Risk if 3 or more SMN1 Copies are Detected&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>1 in 72</td>
<td>90%</td>
<td>1 in 375</td>
<td>1 in 39</td>
<td>1 in 4,200</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>1 in 67</td>
<td>93%</td>
<td>1 in 918</td>
<td>Likely carrier</td>
<td>1 in 5,400</td>
</tr>
<tr>
<td>Asian</td>
<td>1 in 59</td>
<td>93%</td>
<td>1 in 907</td>
<td>1 in 61</td>
<td>1 in 5,600</td>
</tr>
<tr>
<td>White</td>
<td>1 in 47</td>
<td>95%</td>
<td>1 in 921</td>
<td>1 in 69</td>
<td>1 in 5,600</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 in 68</td>
<td>93%</td>
<td>1 in 906</td>
<td>1 in 99</td>
<td>1 in 5,400</td>
</tr>
</tbody>
</table>

<sup>a</sup> Linked variant is SMN1 c.*3+80T>G.

<sup>b</sup> Posttest carrier risk if 3 or more SMN1 copies are detected.

Sources: Feng, 2017<sup>1</sup>; Sugarman, 2012<sup>2</sup>

### Limitations
- Diagnostic errors can occur due to rare sequence variations.
- Single base pair substitutions, small deletions/duplications, and regulatory region and deep intronic variants will not be detected.
- Test is unable to determine:
  - Whether SMN1 copies are on the same or opposite chromosomes
  - Whether SMN1 and SMN2 copies are on the same or opposite chromosomes

### References


### Additional Resources


