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 homozygous loss of SMN1 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 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.

Incidence

~1/12,000 live births in the U.S.
- Carrier rate ~1/54 overall in the U.S.; varies by ethnicity
- See 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
  - Most common symptoms: difficulty 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
  - SMA 1: onset at 0-6 months
    - Most common subtype; severe muscle weakness, survival <2 years
  - SMA 2: onset at 6-12 months
    - Child usually cannot walk without assistance
  - SMA 3: onset after 12 months
    - Milder muscle weakness, child usually can walk and stand without assistance
  - 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)
- Not possible to definitively predict clinical subtype based on genotype
  - Higher SMN2 copy number may correlate with milder disease severity in affected individuals
  - SMN1 variant, c.*3+80T>G, often linked with SMN1 gene duplication in silent carriers is relevant only for carrier screening

Carrier Testing
- 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 chromosome
- 3-4% of general population has both 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 certain populations such as African American and Ashkenazi Jewish
  - A linked variant, c.*3+80T>G, often associated with SMN1 gene duplication on the same chromosome, is tested
    - Presence of two SMN1 copies and linked variant increases risk of being silent carrier, especially in Ashkenazi Jewish individuals
- SMN2 copy number is relevant only for affected individuals

Pathophysiology
- SMA is caused by low levels of survival motor neuron (SMN) protein essential for motor neurons
- Majority of full-length SMN protein production comes from SMN1 gene
- Some full-length SMN protein production comes from SMN2 gene
  - SMN2 differs very little from SMN1
    - Does not contain exon 7 which alters mRNA splicing and protein production
  - Usually multiple copies of SMN2 per chromosome
    - Increased full-length SMN protein production from SMN2 may partially compensate for SMN protein production missing due to altered SMN1 gene
- Spinraza (nusinersen) is an FDA-approved drug that can be used to treat SMA by increasing the amount of full-length SMN protein produced from SMN2

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
- See SMA Carrier Risk table for ethnicity-specific carrier risk

Results
- Diagnostic test results
  - Zero copies of SMN1 detected
    - Consistent with diagnosis of SMA
  - One copy of SMN1 detected
    - May have SMA if an undetected pathogenic sequence variant is present
    - At least a carrier for SMA
Two copies of \textit{SMN1} detected
- Greatly reduced risk to be affected with SMA

\textit{SMN2} copy number will be reported but cannot be used to predict the severity of SMA with certainty

Carrier screening results
- One copy of \textit{SMN1} detected
  - Individual is carrier of SMA
- Two or more copies of \textit{SMN1} detected
  - Carrier risk is reduced but not eliminated
- Two copies of \textit{SMN1} detected and linked variant present
  - Increased risk to be a silent carrier (may have both \textit{SMN1} copies on same chromosome, no copies on the other chromosome)

See SMA Carrier Risk table for ethnicity-specific residual carrier risk

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

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Carrier Frequency</th>
<th>Detection Rate for Carrier Screening</th>
<th>Posttest (Residual) Carrier Risk for 2 Copies \textit{SMN1}, Linked Variant Present</th>
<th>Posttest (Residual) Carrier Risk for 2 Copies \textit{SMN1}, Linked Variant Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>1 in 72</td>
<td>90%</td>
<td>1 in 39</td>
<td>1 in 375</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>1 in 67</td>
<td>93%</td>
<td>Likely carrier</td>
<td>1 in 918</td>
</tr>
<tr>
<td>Asian American</td>
<td>1 in 59</td>
<td>93%</td>
<td>1 in 61</td>
<td>1 in 907</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1 in 47</td>
<td>95%</td>
<td>1 in 69</td>
<td>1 in 921</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>1 in 67</td>
<td>93%</td>
<td>1 in 99</td>
<td>1 in 906</td>
</tr>
</tbody>
</table>

#### Limitations
- Diagnostic errors can occur due to rare sequence variations
- Single base pair substitutions, small deletions/duplications, regulatory region and deep intronic variants will not be detected
- Test is unable to determine:
  - Whether \textit{SMN1} copies are on the same or opposite chromosomes
  - One or more copies of \textit{SMN1} on each chromosome (not a carrier) indistinguishable from two or more copies of \textit{SMN1} on one chromosome and zero copies on the opposite chromosome (silent carrier)
  - Whether \textit{SMN1} and \textit{SMN2} copies are on the same or opposite chromosomes

#### REFERENCES


