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 *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

~1/12,000 live births in the U.S.

- Carrier rate varies by ethnicity: ~1/54 overall in the U.S.
- 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

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 chromosomes
- Test is unable to identify pathogenic sequence variants in the *SMN1* gene(s) that are present
- 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

Tests to Consider

Spinal Muscular Atrophy (SMA) Copy Number Analysis 2013436

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, Fetal 2013444

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

Related Tests

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

Method: Polymerase Chain Reaction/Fluorescence Monitoring, Polymerase Chain Reaction/Capillary Electrophoresis, Multiplex Ligation-dependent Probe Amplification

- 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
- Do not use for diagnostic testing in patients with symptoms of CF, FXS, or SMA
- Not recommended for diagnostic testing for CF, FXS, or SMA

Pathophysiology

- SMA is caused by low levels of survival motor neuron (SMN) protein essential for motor neurons
- Majority of functional SMN protein is produced by *SMN1* gene
- Only about 10% of functional SMN protein is produced by *SMN2 gene*
  - May be multiple copies of *SMN2* per chromosome
    - In affected individuals with two missing or mutated copies of the *SMN1* gene, SMN protein produced by *SMN2* may reduce the severity of symptoms
- Spinraza (nusinersen) is an FDA-approved drug that can be used to treat SMA by increasing the amount of functional 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[1,2]
  - 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
    - Individual is at least a carrier of SMA and may be affected if a pathogenic sequence variant is present
  - Two copies of *SMN1* detected
    - Greatly reduced risk to be affected with SMA
  - *SMN2* copy number will be reported but cannot be used to predict disease severity with certainty
- Carrier screening results
  - One copy of *SMN1* detected
    - Individual is carrier of SMA
  - Two or more copies of *SMN1* detected
    - Carrier risk is reduced but not eliminated (both *SMN1* copies may be on same chromosome or may have a pathogenic sequence variant in one chromosome)
  - Two copies of *SMN1* detected and linked variant present
    - Increased risk to be a silent carrier (both *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

Ethnicity	Carrier Frequency[3]	Detection Rate Using *SMN1* Copy No. and Linked Variant[a] [1]	Posttest (Residual) Carrier Risk If 2 Copies of *SMN1* and Absence of Linked Variant[a] [1]	Posttest Carrier Risk If 2 Copies of *SMN1* and Linked Variant Present[a] [1]
African American	1 in 72	90%	1 in 375	1 in 39
Ashkenazi Jewish	1 in 67	93%	1 in 918	Likely carrier
Asian	1 in 59	93%	1 in 907	1 in 61

Ethnicity	Carrier Frequency[3]	Detection Rate Using *SMN1* Copy No. and Linked Variant[a] [1]	Posttest (Residual) Carrier Risk If 2 Copies of *SMN1* and Absence of Linked Variant[a] [1]	Posttest Carrier Risk If 2 Copies of *SMN1* and Linked Variant Present[a] [1]
White	1 in 47	95%	1 in 921	1 in 69
Hispanic	1 in 68	93%	1 in 906	1 in 99

[a]Linked variant is *SMN1* c.*3+80T>G.

Sources: Feng, 2017[1]; Sugarman, 2012[3]

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 *SMN1* copies are on the same or opposite chromosomes
  - Whether *SMN1* and *SMN2* copies are on the same or opposite chromosomes

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3. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27-32. PubMed

Additional Resources

ACOG Committee on Genetics. ACOG Committee Opinion No. 691: carrier screening for genetic conditions. Obstet Gynecol. 2017;129(3):e41-e55. PubMed

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Content Review September 2020 | Last Update September 2020