

Spinal Muscular Atrophy Copy Number Analysis

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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.

Featured ARUP Testing

[Spinal Muscular Atrophy \(SMA\) Copy Number Analysis 2013436](#)

Method: Multiplex Ligation-Dependent Probe Amplification (MLPA)

- 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 (MLPA)

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.

- 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.
- 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 (e.g., 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^{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 varies by ethnicity

Results

Results Interpretation	
Diagnostic Test ^a	
0 copies of <i>SMN1</i>	Consistent with diagnosis of SMA
1 copy of <i>SMN1</i>	Individual is at least a carrier of SMA

Individual may be affected if a pathogenic sequence variant is also present in the other *SMN1* gene

2 or more copies of <i>SMN1</i>	Greatly reduced risk of being affected with SMA
Carrier Screening Test	
1 copy of <i>SMN1</i>	Individual is a carrier of SMA
2 copies of <i>SMN1</i> with absence of linked variant	Carrier risk is reduced, but not eliminated ^b
2 copies of <i>SMN1</i> with presence of linked variant	Increased risk of being a silent carrier ^c
3 or more copies of <i>SMN1</i>	Carrier risk is significantly reduced, but not eliminated ^d

^a*SMN2* copy number will be reported but cannot be used to predict disease severity with certainty.

^bBoth *SMN1* copies may be on the same chromosome, or a pathogenic sequence variant may be present on one chromosome.

^cBoth *SMN1* copies may be on the same chromosome with no copies on the other chromosome.

^dLinked 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					
Ethnicity	Carrier Frequency ³	Detection Rate Using <i>SMN1</i> Copy No. and Linked Variant ^{a 1}	Posttest (Residual) Carrier Risk if 2 Copies of <i>SMN1</i> and Linked Variant Absent ^{a 1}	Posttest Carrier Risk if 2 Copies of <i>SMN1</i> and Linked Variant Present ^{a 1}	Posttest Carrier Risk if 3 or more <i>SMN1</i> Copies are Detected ³
African American	1 in 72	90%	1 in 375	1 in 39	1 in 4,200
Ashkenazi Jewish	1 in 67	93%	1 in 918	Likely carrier	1 in 5,400
Asian	1 in 59	93%	1 in 907	1 in 61	1 in 5,600
White	1 in 47	95%	1 in 921	1 in 69	1 in 5,600
Hispanic	1 in 68	93%	1 in 906	1 in 99	1 in 5,400

^aLinked variant is *SMN1* c.*3+80T>G.

Sources: Feng, 2017¹; Sugarman, 2012³

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

1. Feng Y, Ge X, Meng L, et al. [The next generation of population-based spinal muscular atrophy carrier screening: comprehensive pan-ethnic SMN1 copy-number and sequence variant analysis by massively parallel sequencing.](#) *Genet Med.* 2017;19(8):936-944.
2. Prior TW. [Carrier screening for spinal muscular atrophy.](#) *Genet Med.* 2008;10(11):840-842.
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.

