Spinal Muscular Atrophy

Indications for Ordering

- Diagnostic testing to confirm a suspected diagnosis of spinal muscular atrophy (SMA)
- Prenatal or preconception carrier screening for SMA in the general population
- Carrier screening for reproductive partner of known SMA carrier
- Carrier screening for parents of a child with a deletion of the *SMN1* gene or other family history of SMA

Test Description

Multiplex ligation-dependent probe amplification (MLPA) to determine copy number for the *SMN1* and *SMN2* genes

Tests to Consider

Primary tests

Spinal Muscular Atrophy (SMA) Copy Number Analysis 2013436

- Diagnostic or carrier testing for SMA
  - *SMN2* copy number will be reported only for patients with zero copies of *SMN1* detected, or for symptomatic individuals with one *SMN1* copy
  - Test also includes 2 *SMN1* variants that are part of a haplotype associated with *SMN1* duplication in silent carriers, especially in Ashkenazi Jewish and Asian populations
    - c.*3+80T>G (rs143838139)
    - c.*211_*212del (rs200800214)

Spinal Muscular Atrophy (SMA) Copy Number Analysis, Fetal 2013444

- Prenatal diagnostic testing for SMA when both parents carry a deletion of *SMN1* or have a previous child with SMA caused by a deletion of *SMN1*
  - *SMN2* copy number will be reported only if zero copies of *SMN1* are detected

Related tests

SMA carrier screening is included in the following panels, along with carrier screening for other disorders (tests performed at Counsyl)

- Prenatal Carrier Screening Targeted Mutation Panel, 85 Disorders 2007539
- Prenatal Carrier Screening Targeted Mutation Panel, 85 Disorders with Fragile X 2007541
- Prenatal Carrier Screening Next Generation Sequencing, 85 Disorders with Fragile X 2008704
- Expanded Carrier Screening Panel Targeted Mutation, 100-Plus Disorders 2007543
- Expanded Carrier Screening Panel Targeted Mutation, 100-Plus Disorders with Fragile X 2007531
- Expanded Carrier Screening Next Generation Sequencing, 100-Plus Disorders with Fragile X 2008701

Disease Overview

Incidence – ~1/10,000 live births in the U.S.

- Carrier rate ~1/50 overall in the U.S.; varies by ethnicity
  - Caucasians – 1/35
  - Ashkenazi Jews – 1/41
  - Asians – 1/53
  - African Americans – 1/66
  - Hispanics – 1/117

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
    - Difficulty swallowing
    - Difficulty 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
    - Severe muscle weakness
    - Survival is typically <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 copies of *SMN1* usually indicates patient is not a carrier
  - 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
  - If paired with *SMN1* loss (zero copies) on the opposite chromosome, these individuals are "silent carriers"
- ≥Two copies of *SMN1* on the same chromosome is rare but more frequent in certain populations
  - African Americans
  - Ashkenazi Jews
- Two variants part of a haplotype associated with *SMN1* duplication are tested
  - Presence of two *SMN1* copies plus the variants suggests increased risk that the individual is a silent carrier but is not definitive
  - Likely silent carrier if patient is Ashkenazi Jewish or Asian

Pathophysiology

- SMA is caused by low levels of survival motor neuron (SMN) protein essential for motor neurons
- Majority of SMN protein production comes from *SMN1* gene
- Some SMN protein production comes from *SMN2 gene*
  - *SMN2* differs very little from *SMN1*
    - Does not contain exon 7
      - Alters mRNA splicing and protein production
  - Usually multiple copies of *SMN2* per chromosome
    - Increased SMN protein production from *SMN2* may partially compensate for SMN protein production missing due to altered *SMN1* gene

Genetics

Genes – *SMN1*, *SMN2*

Inheritance – autosomal recessive

- 98% of SMA is caused by abnormality in both copies of *SMN1* gene

De novo rate – 2%, usually paternal in origin

Variants tested/reported

- *SMN1* copy number
  - Does not report mechanism (gene deletion vs gene conversion)
  - Variants tested for haplotype associated with *SMN1* duplication
    - c.*3+80T>G (rs143838139)
    - c.*211_*212del (rs200800214)
      - Associated with "silent carriers"
      - Will be reported only if detected during carrier screening in a patient with ≥two copies of *SMN1*
- *SMN2* copy number
  - Will be reported only for individuals with zero *SMN1* copies or for symptomatic individuals with one *SMN1* copy, for prognostic purposes

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity for diagnostic testing (Hendrickson, 2009; Luo, 2014; Prior, 2013)
  - 95-98% of individuals with SMA have zero copies of *SMN1*
  - 2-5% of individuals with SMA have one copy of *SMN1* plus a pathogenic sequence variant
- Detection rate for carrier screening
  - Caucasians – 95%
  - Ashkenazi Jews – 94%
  - Asians – 93%
  - Hispanics – 91%
  - African Americans – 71%
- Analytical sensitivity/specificity – 99%

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 *SMN1* detected
    - Not affected with SMA
- Carrier screening results
  - One copy of *SMN1* detected
    - Individual is a carrier for SMA
  - Two or more copies of *SMN1* detected
    - Carrier risk is reduced but not eliminated
  - Two copies of *SMN1* detected and positive for targeted variant(s)
    - Normal copy number but increased risk to be a silent carrier (may have both *SMN1* copies on same chromosome, zero copies on the other chromosome)
      - Not definitive

Limitations

- Test is unable to determine
  - Whether *SMN1* copies are on the same or opposite chromosomes
    - ≥One copy of *SMN1* on each chromosome (not a carrier) indistinguishable from ≥two copies of *SMN1* on one chromosome and zero copies on the opposite chromosome (silent carrier)
  - Whether *SMN1* and *SMN2* copies are on the same or opposite chromosomes
- Only copy number will be detected for *SMN1* and *SMN2*
- Sequence variants in *SMN1* or *SMN2* will not be detected
- Diagnostic errors can occur due to rare sequence variations

References

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- Muralidharan K, Wilson RB, et al. Population carrier screening for spinal muscular atrophy. J Mol Diagn. 2011;13:3-6
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- Prior TW, Russman BS. Spinal muscular atrophy. 2000 Feb 24 [Updated 2013 Nov 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1352/)