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)

- Expanded Carrier Screen, Genotyping 2014674
- Expanded Carrier Screen, Genotyping with Fragile X 2014671
- Expanded Carrier Screen by Next Generation Sequencing 2014680
- Expanded Carrier Screen by Next Generation Sequencing with Fragile X 2014677

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
  o 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
  o 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
  o 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
  o 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
  o African Americans
  o Ashkenazi Jews
- Two variants part of a haplotype associated with SMN1 duplication are tested
  o Presence of two SMN1 copies plus the variants suggests increased risk that the individual is a silent carrier but is not definitive
  o 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
  o SMN2 differs very little from SMN1
    ▪ Does not contain exon 7
    ▪ Alters mRNA splicing and protein production
  o 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
  o Does not report mechanism (gene deletion vs gene conversion)
  o 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
  o 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)
  o 95-98% of individuals with SMA have zero copies of SMN1
  o 2-5% of individuals with SMA have one copy of SMN1
  ▪ plus a pathogenic sequence variant
- Detection rate for carrier screening
  o Caucasians – 95%
  o Ashkenazi Jews – 94%
  o Asians – 93%
  o Hispanics – 91%
  o African Americans – 71%
- Analytical sensitivity/specificity – 99%

Results
- Diagnostic test results
  o Zero copies of SMN1 detected
    ▪ Consistent with diagnosis of SMA
  o One copy of SMN1 detected
    ▪ May have SMA if an undetected pathogenic sequence variant is present
    ▪ At least a carrier for SMA
  o Two copies of SMN1 detected
    ▪ Not affected with SMA
- Carrier screening results
  o One copy of SMN1 detected
    ▪ Individual is a carrier for SMA
  o Two or more copies of SMN1 detected
    ▪ Carrier risk is reduced but not eliminated
  o 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