Dosage Analysis of SMN1 and SMN2 for Spinal Muscular Atrophy

GENE LIST: SMN1 & SMN2

CLINICAL FEATURES:

Spinal muscular atrophies (SMA) are a clinically and genetically heterogenous group of disorders characterized by the progressive degeneration of the anterior horn cells in the spinal cord and brain stem nuclei, leading to progressive muscle weakness and wasting.[1] Individuals typically present with symmetric proximal extremity weakness that may progress to distal, axial, intercostal, and bulbar muscles; however age-of-onset and disease severity vary.[2] Pathogenic variants in the *SMN1* gene cause autosomal recessive spinal muscular atrophy, which accounts for 95% of cases of SMA.[3]

SMN1-related SMA was originally classified into five clinical subtypes (SMA 0-4) prior to the utilization of genetic testing in the diagnosis of SMA. These subtypes include **SMA 0**, characterized by prenatal onset, neonatal hypotonia, severe weakness, early respiratory failure, and death within 6 months of life. **SMA I** has an onset prior to 6 months, mild joint contractures, minimal facial weakness, swallow difficulties, and an average lifespan of less than 2 years of age. **SMA II** has an onset between 6-18 months, independent sitting when placed, and a lifespan typically into adulthood. **SMA III** has an onset after 18 months, independent ambulation, and normal lifespan. **SMA IV**, the mildest form, is associated with muscle weakness in 2nd-3rd decade of life and a normal lifespan.[1] These subtypes are influenced by *SMN2* copy number and individuals with a greater number of *SMN2* copies typically have milder disease.[1]

GENETICS:

Ninety-five percent of individuals with SMA have a defect in the *SMN1* gene.[3] Individuals with *SMN1*-related SMA most commonly harbor a homozygous loss of exon 8 (aka exon 7), although 5% of *SMN1*-related SMA is due to the presence of a pathogenic sequencing-based change on one allele and loss of exon 8 on the other allele.[4] Loss of exon 8 occurs as a result of either a deletion including at least exon 8 of the *SMN1* gene or a conversion of the exon 8 *SMN1* sequence into the *SMN2* sequence. The *SMN2* gene sequence differs from the *SMN1* gene sequence by only 5 base pairs, with the most significant difference being a single C>T nucleotide change within the coding sequence of exon 8. This change in *SMN2* alters gene splicing, resulting in the skipping of exon 8 and the production of a truncated protein that is rapidly degraded. However, ~10% of *SMN2* transcripts undergo proper splicing, retaining exon 8, and producing full length protein.[3] The greater the number of *SMN2* copies present, the greater the amount of functional SMN protein is produced. Therefore the greater the number of *SMN2* copies an individual has, the less severe the disease will be.

TEST METHODS:

Using genomic DNA from the submitted specimen, multiplex ligation-dependent probe amplification (MLPA) is completed to determine the copy number of the *SMN1* and *SMN2* genes in the provided specimen, compared to control specimens.

The clinical sensitivity of dosage analysis of the genes included in this panel depends in part on the patient's clinical phenotype. The technical sensitivity of MLPA analysis for the dosage of *SMN1* and *SMN2* is estimated to be >99%. MLPA analysis is unable to determine whether two copies of *SMN1* are present on opposite chromosomes (92-97% of cases) or on the same chromosome (3-8% of cases) in an individual. MLPA analysis is also unable to detect sequence changes in the *SMN1* gene which occur in 3-5% of *SMN1*-related SMA cases.

REFERENCES:

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