



Spinal Muscular Atrophy (SMA): Molecular Diagnostic Testing

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SMA is the second most common fatal autosomal recessive disorder after cystic fibrosis, affecting approximately 1:6,000 newborns. The disease is characterized by progressive limb and trunk muscle weakness due to degeneration of lower motor neurons and muscular atrophy. In 1991 the international SMA consortium subdivided the disease into three major clinical phenotypes: type I or acute form (Werdnig-Hoffmann disease), type II or intermediate form, and type III or juvenile form (Kugelberg-Welander disease). Although clinical severity displays a continuous range from severe to mild forms, this classification is useful for prognosis and management of the patients. A generalized muscle weakness and areflexia characterize the severe type I form. These patients generally die by 2 years of age. In type II SMA, patients have a slower progression of the disease, being able to sit unsupported but unable to stand or walk unaided. Finally, in type III SMA, symptoms appear from 18 months to adult life. These patients have typical proximal muscle weakness with a progressive waddling gait and difficulties climbing stairs. No evidence of sensory or upper motor involvement is recognized in SMA patients. In addition to the clinical parameters, additional studies used for diagnosis of SMA are electromyography (EMG) and determination of serum creatine phosphokinase (CK) activity. Although a typical muscle biopsy pattern of “denervation” is highly supportive for the diagnosis of SMA, this invasive study is not longer required if the clinical diagnosis of SMA is confirmed using readily available molecular testing.

In 1995, the Survival of Motor Neuron (*SMN1*) gene on 5q13 was identified as the causative gene in the three types of SMA. About 95% of individuals with SMA are homozygous for absence of exon 7 or exons 7 and 8 of *SMN1*. Less than 5% of patients are compound heterozygous for absence of exon 7 or exons 7 and 8 in one *SMN1* allele and a point mutation in the other. No correlation exists between the type of mutation found in *SMN1* and the severity of the disease. The presence of three or more copies of a near identical copy of the *SMN1* gene – called *SMN2* – is correlated with a milder clinical phenotype.

SMN, the protein product of *SMN1*, appears to have a role in the biogenesis and function of the small nuclear ribonucleoproteins (snRNPs), which participate in RNA splicing. The SMN protein localizes to small dot-shaped nuclear structures – called “gems” – interacting with coiled bodies and, eventually, participating in the metabolism of small nuclear RNAs. Decreased levels of SMN protein and/or mutant forms of the protein are present in individuals with SMA.

Polymerase chain reaction (PCR) and restriction fragment length polymorphism analyses (RFLPs) are used to determine the presence of a homozygous deletion in *SMN1*. In a first step, PCR is used to amplify two different DNA fragments spanning the regions of exons 7 and 8 of *SMN1* and *SMN2*. In a second step, specific restriction enzymes are used to determine whether the amplified exons 7 and 8 come from the *SMN1* and/or *SMN2* genes. Detection of a homozygous deletion of exon 7 or exons 7 and 8 of *SMN1* confirms the clinical diagnosis of SMA. The <5% of SMA patients who are compound heterozygous for a deletion of one *SMN1* allele and a point mutation in the other allele cannot be identified with this molecular test.

Quick Facts

- ▶ SMA is an autosomal recessive inherited neuromuscular disease.
- ▶ SMA is a common cause of muscle weakness in childhood.
- ▶ Muscle weakness, areflexia, tongue fasciculations, mild elevated serum CK, and normal cognitive functions are clinical characteristics of SMA.
- ▶ SMN analysis should be considered for “floppy” newborns as well as children or young people with proximal muscle weakness and areflexia.
- ▶ SMA is caused by either homozygous or compound heterozygous mutations in the *SMN1* gene on 5q13.
- ▶ PCR and RFLP analyses are used to detect homozygous deletions of the *SMN1* gene.

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Test Information

DESCRIPTION **SMA ANALYSIS**

METHOD PCR, RFLP

ORDER CODE SMAPCR

This test must be ordered on a paper requisition that accompanies the specimen. It is not an orderable test using PAML computer system.

CPT CODE 83891, 83901×2, 83892×2, 83894×4, 83912

SPECIMEN 3-5 mL EDTA whole blood (lavender-top tube). Submit original and unopened tube only. Store and transport at room temperature. If delayed more than 72 hours, store and transport refrigerated. Do not freeze specimen. Note clinical indication.

COMMENTS *Minimum amount:* 1 mL

Unacceptable conditions: Heparinized whole blood, serum, grossly hemolyzed specimens, frozen specimens, specimens over 5 days old, and specimens in leaky containers. Also, specimens not received in the original collection tubes.

Alternate Specimen: Sodium citrate or ACD whole blood (blue- or yellow-top tube).

Stability: 72 hours at room temperature, 5 days refrigerated, unstable frozen.

SCHEDULE Weekly

TURNAROUND 1-2 weeks

RANGES "See separate report."

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