



Autosomal Recessive Spinal Muscular Atrophy (SMA) Types I, II and III

Childhood-onset spinal muscular atrophy (SMA), also known as Werdnig-Hoffman Disease, is a common autosomal recessive disorder, affecting ~1 in 6000 live births, the second most common severe childhood disorder after cystic fibrosis. The disease is characterized by symmetrical weakness, atrophy of limb muscles, and degeneration of anterior horn cells leading to progressive limb and trunk paralysis associated with muscular atrophy.

SMA also exhibits intermediate (type II) and less severe (type III) forms; Werdnig-Hoffman disease is type I. All three forms of SMA have been mapped to chromosome 5q13 and a candidate gene, *SMN*, has been found to be homozygously deleted or mutated in >95% of affected individuals by several large research groups. The *SMN* gene, like other genes in the critical region is duplicated and it is homozygous deletion of the telomeric copy (*SMN-t*) that is associated with disease. Occasional point mutations may also cause disease, and up to 5% of patients may contain one chromosome carrying a deleted *SMN-t* and a point mutation on the other - or rarely two point mutations.

The test employs PCR amplification of genomic DNA isolated from patient white blood cells for exons 7 and 8 of the *SMN* gene followed by restriction endonuclease digestion and gel electrophoresis to identify normal or homozygously deleted individuals at each locus. The centromeric (*SMN-c*) and telomeric *SMN* (*SMN-t*) copies differ in exons 7 and 8 by only two base pairs, one in exon 7 and one in exon 8, thus allowing distinction of the centromeric and telomeric *SMN* gene copies by RFLP analysis. A customized report is generated which takes into account family history (if provided) and the inheritance pattern of this disorder.

Homozygous deletion of telomeric *SMN* confirms a diagnosis of autosomal recessive spinal muscular atrophy, permitting therapeutic decisions to be made shortly after birth or later in life. In families where both parents are known to carry a deleted *SMN-t* allele by virtue of prior birth of SMA-affected children or genetic testing which has established them as heterozygous carriers, prenatal diagnosis may also be performed. Non-deletion SMA carriers with point mutations in the *SMN-t* gene have been described but are uncommon; linkage analysis (not offered in our laboratory) using polymorphic genetic markers flanking the SMA gene locus may permit assessment of prenatal and carrier status in such families in the absence of recombination.

Note: The assay performed in our laboratory detects only affected individuals carrying two copies of chromosome 5 on which the telomeric *SMN* (*SMN-t*) genes have been partially or fully deleted. It will not detect heterozygous carriers (one chromosome with a deletion + one normal chromosome) or rare affected individuals bearing one *SMN-t* deletion and one point mutation, or very rare affected individuals carrying two point mutations in the *SMN* gene. Carrier screening for heterozygous *SMN-t* deletion carriers is available in several laboratories, but must be interpreted cautiously because of limitations by which rare SMA deletion carriers may exhibit normal *SMN-t* copy numbers.

Turnaround Time: 4-5 weeks. When possible, samples are grouped so a small 'batch' can be run. However, it is common because of clinical circumstances after consultation with referring healthcare professionals to perform this test more rapidly.

Specimen Requirements: See Oncology/Genetics Specimen Handling Protocol or Molecular Diagnostics Genetics Requisition Form.

Informed Consent: It is the responsibility of the referring health care professional to obtain proper informed consent from the patient for genetic testing. Test results are released only to the primary referring physician and/or genetic counselor. The laboratory report contains information that may be useful for genetic counseling of the patient and/or family members, although adjunct use of an experienced genetic counselor or medical geneticist may be beneficial for this genetic disorder.