Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by the progressive degeneration of cells in the spinal cord and brainstem. The onset of weakness ranges from before birth to young adulthood, and progresses with age. SMA affects children with varying severity.

**GENETICS**

Spinal muscular atrophy is an autosomal recessive disorder caused by mutations in the survival motor neuron 1 (SMN1) gene, on chromosome 5. Affected patients inherit two non working copies of the SMN1 gene, one from each parent. An individual with one defective copy of the SMN1 gene and one normal copy will be a carrier. They will not develop SMA themselves, but they may pass the mutation on to their children.

Two carriers have a 25% chance of having an affected child. In 2% of SMA patients, only one parent is a carrier, and a new mutation (de novo mutation) in the offspring results in SMA. The presence of 3 or more copies of the related SMN2 pseudogene gene may result in a milder phenotype.

Molecular studies have shown that ~95% of SMA patients have homozygous deletions in both of the SMN1 genes. The remaining SMA patients do not have a homozygous deletion of SMN1, rather they carry a deletion of the SMN1 gene on one chromosome and a point mutation of the SMN1 gene on the other chromosome.

**WHO SHOULD BE TESTED?**

- Individuals clinically suspected of being affected with SMA
- Individuals with a family history of SMA, to determine carrier status
- Pregnancies at risk due to family history

**TEST METHODS**

Quantitative testing of exons 7 and 8 of both the SMN1 and adjacent SMN2 genes to identify the number of gene copies present, using MLPA (Multiplex Ligation-dependent Probe Amplification)

**TEST SENSITIVITY**

Deletion analysis will detect the 95% of individuals with SMA who have homozygous deletions of exon 7 of the SMN1 gene. Dosage analysis will detect the 95% of SMA carriers who have a deletion in one copy of the SMN1 gene.

Approximately 5% of affected individuals and 5% of SMA carriers have mutations other than deletions in the SMN1 gene. These cases will not be detected by the procedures used.

About 4% of the population have 2 SMN1 copies on one chromosome (cis) and may be misdiagnosed as a non-carrier. Analysis of affected individual and parent’s DNA will confirm results.

**POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS**

<table>
<thead>
<tr>
<th>Reason for referral</th>
<th>SMN1 Gene Dosage</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>0 copies (homozygous deletion)</td>
<td>This result supports a diagnosis of SMA</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>1 copy</td>
<td>In symptomatic individuals, this result may be consistent with a diagnosis of SMA (deletion/point mutation)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>2 or more copies</td>
<td>This result does not support a diagnosis of SMA</td>
</tr>
<tr>
<td>Carrier testing</td>
<td>1 copy</td>
<td>This individual is a carrier of SMA and may transmit the mutation to offspring</td>
</tr>
<tr>
<td>Carrier testing</td>
<td>2 or more copies</td>
<td>This result indicates that the individual is unlikely to be a carrier of SMA. It is also unlikely this individual will transmit a mutation to offspring</td>
</tr>
</tbody>
</table>

**For More Information**

- Type 1 # 253300
- Type 2 # 253550
- Type 3 # 253400
- Type 4 # 271150


Families of SMA registry [http://www.fsma.org](http://www.fsma.org)

1-800-886-1762 (toll-free)

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at [www.cagc-accg.ca](http://www.cagc-accg.ca) or the National Society of Genetic Counsellors website at [www.nsgc.org](http://www.nsgc.org)

1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility that the individual carries a rare SMN1 gene mutation not detected by this assay.

2. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

3. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.