SickKids | Genome Diagnostics

Spinal Muscular Atrophy (Type 1, 2 & 3)

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

Reason for referral	*SMN1* Gene Dosage	Explanation
Diagnosis	0 copies (homozygous deletion)	This result supports a diagnosis of SMA
Diagnosis	1 copy	In symptomatic individuals, this result may be consistent with a diagnosis of SMA (deletion/point mutation)
Diagnosis	2 or more copies	This result does not support a diagnosis of SMA
Carrier testing	1 copy	This individual is a carrier of SMA and may transmit the mutation to offspring
Carrier testing	2 or more copies	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

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/

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

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=sma#sma

Families of SMA registry
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 or the National Society of Genetic Counsellors website at www.nsgc.org

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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 SMN_{tel} 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.