

## Mutation Spectrum of Survival Motor Neuron Gene in Spinal Muscular Atrophy

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### Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive disease and characterized by symmetrical muscle weakness. All types of SMA are the result of mutations in survival motor neuron (*SMN1*) gene. Although, mutations in *SMN1* gene are essential for pathogenesis of the disease, copy number variation in *SMN2* are related to the age of onset and the severity of disease. The most common mutation on the *SMN1* is homozygous deletion of exon 7 that is seen in 95%-98% of patients, followed by compound heterozygous for a deletion of exon 7 and a point mutation in the another allele of *SMN1* which is seen in 2%-5% of cases. SMA patients with homozygous point mutation in *SMN1* gene reported very rarely.

**Keywords:** Spinal muscular atrophy; *SMN1* gene; Homozygous point mutation; Copy number

### Clinical Aspects of SMA

Spinal muscular atrophy (SMA), with an incidence of 1/10000 world-wide [1,2] is a lower motor neuron disease and characterized by symmetrical muscle weakness and atrophy resulting from progressive degeneration of alpha motor neurons and loss of the anterior horn cells in the spinal cord and the brain stem nuclei. The inheritance pattern of SMA is autosomal recessive and classified clinically into the following types, based on the age at onset and clinical severity: SMA 0 (prenatal onset), SMA I (Werdnig-Hoffmann disease with onset before age 6 months), SMA II (Dubowitz disease with onset between age 6 and 18 months), SMA III (Kugelberg-Welander disease with onset after age 18 months), and SMA IV (onset after age 18 years). After unraveling the genetic basis of SMA, all *SMN1*-associated clinical types can be considered as a continuum without a clear delineation.

### Survival Motor Neuron (*SMN*) Gene

Survival motor neuron (*SMN*) gene, the SMA determining gene, located on 5q12.2-q13.3 with two homologue copies, *SMN1* (survival motor neuron 1; telomeric copy) and *SMN2* (survival motor neuron 2; centromeric copy), which differ by only eight nucleotide (five are intronic and three are exonic, located within exons 6, 7, and 8) [3-6]. *SMN1* and *SMN2*, both containing nine exons with 99% nucleotide identity, are arranged in tandem on each chromosome encoding a 294-amino acid RNA-binding protein. One of the coding sequence of *SMN2* that differs from that of *SMN1* by a single nucleotide (840 C>T) results in alternative splicing of exon 7 [4]. Due to the alternative splicing of exon 7, *SMN2* genes produce a reduced amount of full length transcripts, and a variable amount of mRNA lacking exon 7, which give raise to a truncated and unstable protein [7], whereas *SMN1* produces full-length transcripts.

Full-length product of *SMN1* is necessary for lower motor neuron function and loss of *SMN1* is essential to the pathogenesis of SMA, while *SMN2* copy number modifies the severity of phenotype.

### Copy Number Variation of *SMN2* Gene

The number of *SMN2* copies (arranged in tandem in cis configuration on each chromosome) ranges from zero to five that can be detected using quantitative PCR and MLPA methods [8,9]. The presence of three or more copies of *SMN2* is associated with a milder

phenotype [10-13]. All SMA patients retain at least one copy of *SMN2*, so, SMA is caused by low levels of SMN protein rather than complete absence of the protein. Most SMA type I patients have two copies of *SMN2*, three *SMN2* copies are common in SMA type II, while type III and IV generally have three or four copies. On the other hand, no correlation exists between the loss of *SMN1* exon 7 and the severity of disease, that is, the homozygous exon 7 deletions is observed with the same frequency in all phenotypes.

### Mutation Spectrum of *SMN1* Gene

Approximately 95%-98% of all types of SMA patients show homozygous deletion of *SMN1* exon 7 (and exon 8 in the majority of cases) [14-16]. Approximately 6% of parents of a child with homozygous *SMN1* deletion have normal results of *SMN1* copy number testing because 4% of carriers have two copies of *SMN1* on a single chromosome and a deletion on the other chromosome [14,17] and also *de novo* deletion of exon 7 of one *SMN1* allele occurs in 2% of individuals with SMA [18].

Only 2-5% of SMA patients are compound heterozygous, that is, deletion of exon 7 (and exon 8) on one of their alleles and an intragenic point mutation of the *SMN1* gene on the another allele [19-23]. Point mutations are dispersed all over the *SMN1* gene; however, most of them are located in exons six and three that encode self-oligomerization and Tudor domains of SMN protein, respectively [24-26]. These subtle pathogenic mutations in *SMN1* include base substitutions resulting in amino acid changes, splice site alterations, termination codons, and small insertions or deletions resulting in frame-shift [20,27,28]. Although, more than 60 subtle mutations of *SMN1* gene have been reported worldwide [22], homozygous subtle mutations are very rarely

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reported in patients with SMA. Kirwin et al. reported homozygous double mutation in a SMA patient [29] and Rad et al. reported homozygous point mutation (c.549delC at exon 5) which resulted in frame-shift on *SMN1* gene in a SMA type I patient [30]. These reports imply that although DNA sequencing is routinely carried out on SMA patient with only one copy of *SMN1* gene, it should also be carried out in patients with clinical diagnosis of SMA who show even two copies of *SMN1* gene [31].

## Summary

One of the following mutation conditions can occur on the *SMN1* gene in the SMA patients:

1. Homozygous deletion of exon 7 (with or without deletion of exon 8) (95%-98% of cases)
2. Compound heterozygous for a deletion of exon 7 and a point mutation (2%-5% of cases)
3. Homozygous for a subtle or point mutation (very rare)

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