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Mini Review

Genotype-Phenotype Correlation in Spinal Muscular Atrophy

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative lower motor neuron disease with an incidence of 1/6000-1/10000 world-wide and characterised by symmetrical muscle weakness. Based on the age at onset and clinical severity, SMA classified clinically into the following types: 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). All types of SMA are the result of mutations in survival motor neuron (*SMN1*) gene and infantile type is the second leading genetic cause of death in infants. Although, mutations in *SMN1* gene are essential for pathogenesis of the SMA, copy number variation in *SMN2* gene and modification by some are genes such as *NAIP, SERF1A* and *PLS3* determine the age of onset and the severity of disease in its phenotypic continuum.

Keywords: SMA; SMN; NAIP; Spinal Muscular Atrophy; Werdnig-Hoffmann; Kugelberg-Welander

Introduction

Spinal muscular atrophy (SMA), with an incidence of 1/6000-1/10000 world-wide [1] is the most common childhood genetic lower motor neuron disease characterized by symmetrical muscle weakness with significant phenotype variability. Based on the age at onset and clinical severity, SMA classified clinically into the following types: 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). All types of SMAs are the result of mutation in the survival motor neuron 1 (*SMN1*) gene and the severity of SMAs related to the copy number of *SMN2* gene and modification with some other genes. SMN gene located on 5q11.2-q13.3 chromosomal region [2,3], and this region is a duplicated area of approximately 500 kb, where, at least four genes (SMN, NAIP, SERF1 and GTF2H2) are duplicated. Each of these duplicated genes has a telomeric and a centromeric copy.

SMN gene has two homologue copies, *SMN1* (telomeric copy) and *SMN2* (centromeric copy), which differ by only eight nucleotides (five are intronic and three are exonic, located within exons 6, 7, and 8) [4-7].

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 [5], which consequently leads to reduced amount of full length transcripts [3], which is insufficient to counteract the development of SMA. So, SMA is caused by low levels of SMN protein rather than the complete absence of SMN [8,9]. Although, mutations in *SMN1* gene are essential for pathogenesis of the SMA, copy number variation in *SMN2* gene and modification by some are genes such as *NAIP, SERF1A* and *PLS3* determine the age of onset and the severity of disease in its phenotypic continuum.

SMN1 gene:

SMN1 gene was introduced as a candidate gene for SMA in 1995 [4,10,11]. Reduced levels of SMN result in degeneration of α motor neurons in the spinal cord, leading to muscle atrophy and weakness in SMA patients [12]. SMN is a housekeeping protein involved in small nuclear ribonucleoprotein biogenesis, neuromuscular junction formation, axonal growth, and transport of RNA along axons [13-15].

Approximately, 95% - 98% of all types of SMA patients show homozygous deletion of SMN1 exon 7 [16,17]. Only 2 - 5% of SMA patients are compound heterozygous with a deletion of exon 7 and a point mutation [18-22]. Homozygous subtle mutations are very rare in patients with SMA [23,24].

SMN2 gene:

Depending on the copy number of the gene, *SMN2* produces a reduced amount of full length transcripts [3], which is insufficient to prevent the development of SMA. So, the severity of SMA is related to the reduced levels of SMN protein rather than the complete absence of SMN [8,9]. Approximately 5% of normal individuals do not carry the *SMN2* gene [4].

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 [25,26]. Copy number variation or gene dosage can also be determined via MAPH technique [27]. The presence of three or more copies of *SMN2* is associated with a milder phenotype [28-31]. Even, unaffected patients with a homozygous deletion of the *SMN1* gene, with four or five *SMN2* copies, have been reported [32].

As, there is a significant relationship between the clinical phenotype and *SMN2* copy number, *SMN2* can be considered as an important SMA-modifying gene [33]. A nucleotide variation in exon 7 of the *SMN2* gene (c.859G > C) has been described as a positive phenotype modifier in SMA patients, that is, found in SMA patients with a lower SMN2 copy number than expected according to their phenotypes [34-36]. So, considering this nucleotide variation in the *SMN2* gene, it seems that all copies of the *SMN2* genes don't have a similar protective effect.

Other genes in the 5q13.2 region:

NAIP (neuronal apoptosis inhibitory protein) and *SERF1A* (small EDRK-rich factor 1A) genes have been suggested as possible SMA modifier genes. These genes are deleted in approximately 50% of the patients with severe SMA [10,33,37,38]. In a recent study, *NAIP* and *SERF1A* copy number showed a positive correlation with the SMA phenotype, where, *NAIP* genes was absent in nearly 73% of type I SMA and in only a few cases with type II and III disease, and *SERF1A* was absent in the 35% of type I SMA and in only one case with type II [39].

Higher frequency of homozygous deletion of *SMN1* gene in severe type I SMA suggests involvement of *NAIP* deletion in the SMA phenotype. Deletion in the *NAIP* gene can worsen the prognosis independent of the number of *SMN2* copy numbers [40-42]. *NAIP* gene is an apoptosis inhibitor, thus its deletion may result in the loss of spinal motor neurons.

Plastin 3 (*PLS3*) gene:

Recent documents revealed that PLS3, located on chromosome Xq23 and highly expressed in the spinal cord, can play a role as a positive modifier of SMA phenotype [43,44]. *PLS3* is a Ca^{2+} dependent F-actin-binding protein that plays an important role in axon development, cell polarity and migration [45,46].

PLS3 can fully protect against SMA in *SMN1*-deleted individuals carrying 3 - 4 *SMN2* copies, where, *SMN2* products is insufficient to counteract the development of SMA.

It has been revealed that in some rare families with unaffected homozygous *SMN1*-deleted females, the expression of *PLS3* was higher than in their affected counterparts. The protective modifier effect of *PLS3* may be due to its axon genesis role [47] that can rescue the axonal growth defects [48].

SMA type 0:

SMA Type 0 or congenital SMA (sometimes classified as SMA type Ia) is the most severe type with prenatal onset [49-51]. The presence of only one copy of *SMN2* has been described mostly in patients with congenital SMA or severe neonatal forms [52,53]. No patient has been reported with a homozygous deletion of both *SMN1* and *SMN2* genes, and this may be due to in utero lethality of this condition.

SMA type I (Werdnig-Hoffmann disease):

Type I SMA is a severe type which shows generalized muscle weakness and hypotonia with onset in the first six months of life. Patients with affected Type I SMA never sit without aid and generally die of respiratory failure before two years of age [54]. Type 0 or congenital SMA sometimes classified as SMA type Ia, where, the classical form of the disease with onset after the neonatal period considered as type Ib, and patients with head control as type Ic [49,55]. Approximately, all SMA type I patients have two copies of *SMN2* gene regardless of subtypes Ib and Ic [33,39].

SMA type II (Dubowitz disease):

The onset of symptoms in SMA type II occurs between 6 and 18 months. Patients can sit but unable to walk without aid [54]. Depending on the respiratory involvement and management of the complications they can reach adolescence and even adult age.

Most SMA type II patients have three copies of *SMN2* gene [33]; however, rarely SMA type II patient with only one copy of the *SMN2* gene has been reported [41].

SMA type III (Kugelberg-Welander):

Patients with Kugelberg-Welander disease or juvenile SMA are able to walk and the lifespan is generally not reduced [54]. SMA type III classified into two types of IIIa with onset before three years of age and IIIb with onset between three and 20 years of age. The probability of being able to walk after 10, 20 and 40 years of age is 73%, 44% and 34%, respectively, in SMA IIIa, and 97%, 89% and 67% in SMA IIIb [56,57].

SMA type III patients generally have three or four *SMN2* copies [33,39]. The presence of four copies of the *SMN2* gene is more frequent in type IIIb than in type IIIa SMA [58,39]. SMA type III patients with more than three *SMN2* copies show better motor function over time regardless of age at onset [30]. However, the influence of *SMN2* copy number is not strict, e.g., three *SMN2* copies have been detected in both SMA I and SMA III. One explanation may be that all *SMN2* copies are not functionally equivalent [59].

SMA type IV (Adult SMA):

SMA type IV is a less common form of the disease and its symptoms manifest between 20 and 30 years of age with a normal life expectancy [50,60,61]. The high copy number of *SMN2* in types IV SMA, generally more than three copies, can partially compensate for the absence of *SMN1* product [28], and more than four copies of *SMN2*, even 6 copies, are also reported in milder type or type IV SMA [25,58,62]. Since, general population has an average of one or two copies of *SMN2* gene, greater copy number in the mild form of SMA probably result from the conversion of *SMN1* into *SMN2* gene [63].

Phenotypic Discordances:

Usually, siblings affected with SMA are very similar in their clinical presentations, in terms of age at onset and the progression of disease. However, in rare cases, phenotypic discordances can be seen in the SMA patients, that is, individuals are asymptomatic or mildly affected despite carrying the same *SMN1* mutations as their affected siblings, which suggests the effect of genetic modifiers [47].

Phenotypic discordances have been reported between haploidentical siblings with milder forms in adulthood i.e. SMA type III. Patients with severe forms (type I and type II) tended to show fairly similar phenotypic presentation [32]. The Phenotypic discordances could be due to the presence of genetic phenotypic modifiers other than *SMN2* that may act in early life. For instance, *PLS3* has higher expression in unaffected *SMN1*-deleted individuals in comparison with their affected siblings [47]. *PLS3* is an important factor for the process of axonogenesis through increasing the level of F-actin, so defects in the axonogenesis may be the major cause in the pathogenesis of SMA [47].

Gender Effect:

The influence of gender on the phenotype of SMA remains unclear; however, it seems to play a role in the severity of disease. In a study on 1039 SMA patients, the overall ratio of females to males was F/M = 0.82, and the gender disproportion was higher for milder forms, that is, F/M ratio for SMA3b was 0.45 [41].

Milder forms of SMA, with the onset at the age of over 3 years, were seen approximately twice as frequently in males than females, and it is suggested that estrogens may play as a protective role in milder forms in females [41,64]. Also, asymptomatic cases with biallelic mutation of the *SMN1* gene have been reported more frequently in women than in men [41,65,66]. On the other hand, the more severe genotype, that is, *NAIP* gene deletion and the presence of two *SMN2* copies, was observed more frequently in female than males [41,67].

Summary

All types of SMA result from mutations in *SMN1* gene and its significant variations in the age of onset and the severity of clinical symptoms are due to modifier genes. 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. No correlation exists between the loss of *SMN1* exon 7 and the severity of disease, that is, the homozygous exon 7 deletion is observed with the same frequency in all phenotypes. It seemed that a large deletion including neighbouring genes such as *NAIP* and *SERF1A* cause the severe phenotypes of SMA. And also, *PLS3* gene, located on chromosome Xq23, can play a role as a positive modifier of SMA phenotype.

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