Genetics of Spinal Muscular Atrophy and Splicing of Smn Gene

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Abstract

Spinal muscular atrophy is characterized by loss of motor neurons and muscle atrophy, largely in childhood. It is a devastating neuromuscular disorder. In humans, nearly two identical inverted SMN genes (SMN1, SMN2) are present on chromosome 5q13. Homologous deletion of SMN1 results in SMA.SMA is initiated by low levels of the survival motor neuron protein (SMN) because of inactivating mutations in the encoding gene SMN1. Another functional protein for survival is produced by second duplicate gene SMN2.It produces a shortened, unstable SMN messenger RNA. From alternative splicing it produces a small length fully functional SMN messenger RNA. For SMA clinical severity, SMN2 gene copy number is a good prognostic biomarker. Many therapeutical strategies for spinal muscular atrophy are in clinical trials. Recently, Antisense oligonucleotide (ASO) therapy has been licensed. Though, several factors recommend that complementary strategies may be desirable for the long-term maintenance of neuromuscular disorder. During the establishment of structural connections of neuromuscular system, SMN protein is required in highest amount. Besides, people receiving SMN-based treatments may be vulnerable to delayed symptoms if rescue of the neuromuscular system is incomplete. Hence, for the treatment of CNS and periphery, a comprehensive whole-lifespan approach to SMA therapy is required. This therapy includes both SMN-dependent and SMN-independent strategies for the enhancement of SMN expressions many current and planned clinical trials are designed.

Keywords: SMN gene; Atrophy; Spinal muscle; Motor neuron; Protein; Disorder

Introduction

Guido Werdnig documented spinal muscular atrophy in two newborn brothers in 1891, and Johan Ho mann characterized it in seven further instances from 1893 to 1900. Although the title Werdnig-Ho mann illness was subsequently used to the severe infantile form of SMA, their cases were really of intermediate intensity; Sylvestre described severe infantile SMA in 1899 and Beevor in 1903 [1]. Wohlfart, Fez, and Eliasson rst described a milder form of SMA in the 1950s, with patients retaining the ability to stand and walk and living longer [1]. Kugelberg and Welander went on to describe it in greater detail. All of these descriptions identi ed and underlined the primary pathology as anterior horn cell degeneration, as well as the relevant clinical symptoms of symmetrical, proximal predominate extremities weakness a ecting axial, intercostal, and bulbar muscles [1]. During the next half-century, the severity variability was further identi ed and classi ed, and debate developed about whether the infantile, juvenile, and adult forms of SMA re ected one or many disorders. e numerous phenotypes were subsequently codi ed into a categorization scheme at a Muscular Dystrophy Association-sponsored International Consortium on Spinal Muscular Atrophy in 1991 [2]. is categorization distinguished three forms of SMA based on the maximum degree of motor function and the age of onset. Subsequent changes separated the type 3 group according to age of onset, introduced a type 4 for adult-onset cases, and included a type 0 for patients with prenatal onset and death within weeks. Although there are degrees of severity even within a single type, and up to 25% of individuals evade accurate classi cation, this approach remains relevant in the genetic era and gives signi cant clinical and prognostic information.

Spinal muscular atrophies (SMA) are fatal inherited disorder characterized by the loss of spinal motor neurons. It is caused by the degeneration of motor neurons of the spinal cord anterior horns, leading to progressive atrophy of proximal muscles, paralysis, respira

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Received: 01-Jan-2022, Manuscript No. nctj-22-51515, **Editor assigned:** 03-Jan-2022, Pre QC No. nctj-22-51515 (PQ), **Reviewed:** 17-Jan-2022, QC No. nctj-22-51515, **Revised:** 22-Jan-2022, Manuscript No: nctj-22-51515 (R), **Published:** 31-Jan-2022, DOI: 10.4172/nctj.1000110

Citation: Sohail S, Asif F, Asif MA, Ashraf A, Nisar M, et al. (2022) Genetics of Spinal Muscular Atrophy and Splicing of Smn Gene. Neurol Clin Therapeut J 6: 110.

transcriptome of motor neurons. is concept on the pathogenic role of RNA processing abnormalities in motor neuron illnesses is getting popular. Fortunately, based on human genotype phenotype research and preclinical investigations in SMA animal models, a thorough knowledge of the disease's molecular pathophysiology may not be an absolute requirement for the creation of sensible therapy methods. Nonetheless, knowing the molecular pathogenesis of SMA may give a footing and lead to an understanding of related motor neuron illnesses such as non-SMN spinal muscular atrophies and amyotrophic lateral sclerosis. Many pathogenic mechanisms in SMA are concerned with a large variety of genes. RNA splicing, metabolism and protein synthesis is implicated by SMN, SETX, DCNT1, GARS, RARS2, and LASIL. HSPB1, HSPB8, BSCL2, UBE1, AR, VAPB, DCNT1, MAPT are involved in Protein-folding, aggregation and degradation pathways. Genes DCNT1, DYNC1H1, PLEKHG5, HSPB1, SMN, BICD2, FBX034 are responsible for Axonal guidance and transport (Figure 1).

SMN protein is required in all cells, including motor neurons, to assemble snRNPs in the cytoplasm and transport them into the nucleus for RNA splicing. It is also needed in sensory neurons, to maintain motor circuit activity and MN activity in motor neuron axons to transport actin mRNA to the neuromuscular junction (NMJ) and both pre- and post-synaptically at NMJs for their normal function and stability. e main molecular approach to treatment has been to try to increase SMN levels by increasing SMN production or stability. is may be required systemically, rather than in motor neurons alone and may be complemented by measures to stabilize NMJ stability or maintain sensory inputs to motor neurons. Sites of action of SMN protein are shown in the gure at lower case grayscale, and potential sites for therapeutic intervention in upper case grayscale.

Methodology

Protein families related to spinal muscular atrophy

On the basis of mode of inheritance spinal muscular atrophy is classi ed into two distinct forms i.e. Distal spinal muscular atrophy and the other one is proximal spinal muscular atrophy [5]. Distal spinal muscular atrophy is a slowly progressive disease with a rare bulbar involvement. It may be dominant, named as distal hereditary motor neuropathy (dHMN) and recessive, distal spinal muscular atrophy (DSMA), Mutation in the chaperones like HSPB1, HSPB3, HSPB8 resulting in the dysfunction of protein folding. Mutation in GARS gene alters the transfer RNA sequence which is responsible for amino acylation [6].

Heat shock proteins (HSP) is the most abundant protein family in organisms. In Human genome there are almost ten di erent types of HSPB named as HSPB1-HSPB10. Some of them are expressed ubiquitously like (HSPB1, HSPB5, HSPB6, HSPB8) while some of the family members are tissue speci c in nature like HSPB2, HSPB3, HSPB4, HSPB7, HSPB9, HSPB10 [7]. ere are three major domains of HspB family that i.e. C-terminal domain, N-terminal domain and highly conserved α-Crystallin domain [8]. e genes responsible for the distal hereditary motor neuropathy have diverse function such as (HSPB1, HSPB8, BSCL2) in the Protein folding, (IGHMBP2, GARS) in the RNA metabolism, (HSPB1, DYNC1H1, DCTN1) axonal transport and (ATP7A and TRPV4) in cation-channel dysfunction [9] (Table 1).

Types of Spinal muscular atrophy

Proximal spinal muscular Atrophy: Proximal spinal muscular atrophy is the autosomal recessive disorder causes the degeneration of the α-spinal motor neurons in brain stem and spinal cord. It is categorized into three types [4].

Gene	Location	Mutation	Inheritance
HSPB1	7q11.23	Transition404C-T	AD
HSPB8	12q24.23	423G→C, (Transversion) (Belgian, Czech) 421A→G, (transition) (Bulgarian and English)	AD
HSPB3	5q11.2	Transversion21G-T	AD
FBXO38	5q32	Transition616T>C	AD
SMAR	11q13	Het 1178G>A Het 1284+5G>A	AR
GARS1	7p14.3	815T>G	AD
BSCL2	11q12.3	263A→G Transition (Austrian, Italian, English) 269C→T missense (Brazilian family)	AD
REEP1	2p11.2	303+1 7GTAATAT>AC	AD
IGHMBP2	11q13.3	Nonsense 5'mutation (c.138T>A) 3Frame shifts c.2911_2912 delAG: p. Arg971Glufs	AR
SLC5A7	2q12.3	1497delG	AD
DCTN1	2p13.1	175G>A	AD
DNAJB2	2q35	Transition (352+1G>A)	AR
WARS	14q32.2	Heterozygous mutation c.770A>G	AD
ATP7A	Xq21.1	4156C>T (Family A) Transition 2981C>T (Family B) Transition	XLR
mtATP6	----------	9185T>C	Mitochondria
mtATP8	----------	(m.8403T>C)	Mitochondria

Table 1: Variants responsible for DSMA in populations.
AR: Autosomal Recessive; XLR: X-linked Recessive; AD: Autosomal Dominant; .6403 c.2m

Werdnig-Ho mann (SMA type 1): It is reported that about 50% patient were diagnosed with this severe type of SMA. Infants with SMA type-1don't have the ability to sit unsupported and, usually do not survive further than the rst 2 years. ese patients have intense hypotonia, accid paralysis, and no head control. Natural motility is generally poor and movements of limbs are typically not observed. In the most severe forms, decreased inside the womb movements suggest prenatal onset of the disease with severe weakness and joint contractures [10].

Dubowitz syndrome (SMA type2): Dubowitz syndrome is a rare autosomal recessive disorder and was rst identi ed in children. Its manifest growth retardation, microcephaly, short stature, facial features, skin eruptions, and mild to severe mental retardation. Patients are able to sit unsupported and some of them are able to attain standing position, but they do not have the ability to walk independently. Joint contractures and kyphoscoliosis are very common severe type II patients [10].

Kugelberg-Welander disease: SMA type3 (Kugelberg-Welander disease) causes muscle weakness in infancy. People with this condition will stand and walk independently; there are some genes responsible for the proximal spinal muscular atrophy. Scoliosis and some medical problems like poor mobility, obesity and osteoporosis arise in those patients who lose ambulation. Respiratory system requires most care as it became weakened it will never recover again and make breathing di culties (Table 2).

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