Spinal Muscular Atrophies in Pakistan: A Complex Genetic Disease

Sabiya Azam[1*], Fatima Batool[2]

Abstract

Spinal Muscular Atrophy (SMA) is a severe hereditary neuromuscular disorder, most commonly manifesting in childhood, characterized by the degeneration of spinal motor neurons and progressive muscle atrophy, paralysis, and respiratory complications that often lead to early mortality1. This study employed a comprehensive literature review methodology, synthesizing genetic, clinical, and epidemiological data with a focus on the Pakistani population. The review analyzed the roles of SMN1 and SMN2 genes on chromosome 5q13, as well as other genetic contributors such as HSPB1, GARS1, and VAPB, to understand the molecular mechanisms and inheritance patterns underlying both distal and proximal SMA variants. The Key findings reveal that approximately 68% of Pakistani SMA Patients have SMN gene deletions, a prevalence influenced by high rates of consanguinity and birth rates in the region1. The study highlights the genetic heterogeneity of SMA, with various genes affecting pathways like RNA metabolism, axonal transport, and protein folding. Recent therapeutic advances, particularly antisense oligonucleotide treatments targeting SMN2 splicing, have shown promise in increasing functional SMN protein levels, though long-term efficacy remains uncertain1. The findings underscore the importance of early diagnosis, genetic counseling, and targeted public health interventions to reduce the burden of SMA in high-risk populations, while also emphasizing the need for continued research into novel therapies and comprehensive care strategies.

Keywords: *Androgen Receptor, ATPase Copper Transporting Alpha, Bicaudal D Homolog 2, Barkor (LC3-Associated) Autophagy Regulator 2, Dynactin Subunit 1, DnaJ Heat Shock Protein Family (Hsp40) Member B2, Immunoglobulin Heavy Chain Binding Protein 2.*

Introduction

Degeneration of spinal motor neurons is a hallmark of the potentially fatal hereditary illnesses known as Spinal Muscular Atrophies (SMA). Primarily affecting

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the motor neurons in the spinal cords frontal horns, this degeneration causes gradual muscle atrophy, paralysis, breathing issues, and frequently results in infant death (Farrar & Kiernan, 2015b). The survival motor neuron (SMN) protein, which is vital for the health of motor neurons, is primarily blamed for the illness. Mutations in the same genes are associated with different kinds of SMA. Severe and widespread muscle weakness is the usual symptom of SMA in children, which can appear at confinement or during the first three months of life expectancy (Finkel et al., 2017). Most infant deaths happen in the first two months of life (Fink). Approximately 68% of SMA patients in Pakistan, who are mostly youngsters, have SMN gene deletions. Particularly high rates of consanguinity and birth rates have contributed to the increased occurrence of this neuromuscular illness, which affects a sizable section of the juvenile population, in Pakistan, Iran, and Saudi Arabia (Laddhani et al., 2020)

Table 1(A): *Pertaining Mutations for Distal Spinal Muscular Atrophy*

Gene	Location	Mutation	Inheritance	Protein	Function	Reference
HSPB1	7q11.23	404C-T	Autosomal Dominant	Heat Shock Protein Beta-1	prevent aggregation	(Evgrafov et al., 2004)
HSPB3	*12q24.23*	423G→C 421A→G	Autosomal Dominant	Heat Shock Protein Family B Member 3	protecting cells from stressors	(Kolb et al., 2010)
HSPB8	*5q11.2*	21G-T	Autosomal Dominant	Heat Shock Protein Beta-8	folding and refolding of misfolded proteins	(Irobi et al., 2004)
FBXO38	5q32	616T>C	Autosomal Dominant	F-box only protein 38	ubiquitination of target proteins	(Sumner et al., 2013)
SMAR	11q13	Het 1178G>A Het 1284+5G>A	Autosomal Recessive	BRG1 protein	Regulation of gene expression by modifying chromatin structure	(Viollet et al., 2004)
GARS	7p14.3	815T>G	Autosomal Dominant	glycyl-tRNA synthetase	incorporation of glycine into proteins, maintaining integrity of protein synthesis process	(Chung et al., 2018)
BSCL2	11q12.3	263A→G 269C→T	Autosomal Dominant	Seipin	lipid homeostasis	(Windpassinger et al., 2004)
REEP1	2p11.2	303+1 7GTAATAT>AC	Autosomal Dominant	Receptor Expression-Enhancing Protein 1	Expression, trafficking of membrane receptors	(Schottmann et al., 2015)
IGHMBP2	11q13.3	(c.138T>A) c.2911-12 R-971Glufs	Autosomal Recessive	immunoglobulin mu-binding protein 2	RNA metabolism and immune function	(Cottenie et al., 2014)

SLC5A7	2q12.3	1497delG	Autosomal Dominant	high-affinity choline transporter 1 (CHT1)	synthesis of acetylcholine, supporting neurotransmission	(Barwick et al., 2012)
DCTN1	2p13.1	175G>A	Autosomal Dominant	dynein cytoplasmic 1	intracellular transport	(Hwang et al., 2016)
DNAJB 2	*2q35*	(352+1G>A)	Autosomal recessive	DnaJ homolog subfamily B member 2	maintaining protein homeostasis	(Sanchez et al., 2016)
WARS	14q32.2	c.770A>G	Autosomal dominant	tryptophanyl -tRNA synthetase	protein synthesis, gene regulation and cellular signaling	(Tsai et al.,2017)
ATP7	*Xq21.1*	4156C >T (Family A) 2981C>T (Family B)	X-Linked lymphocyte regulated	copper-transporting ATPase 1	regulating copper levels	(Kenner son et al., 2010)

Mode of Inheritance of Spinal Muscular Atrophy

Distal spinal muscular atrophy and proximal spinal muscular atrophy are the two primary kinds of spinal muscular atrophy (SMA) that are distinguished by inheritance patterns. Distal spinal muscular atrophy is further subdivided into dominant forms (distant spinal muscular atrophy, or dHMN) and recessive forms (DSMA), or distal spinal muscular atrophy. The latter condition rarely impairs bulbar function and progresses slowly (Rossor et al., 2012). While mutations in the GARS gene alter the tRNA sequence that is important for amino acylation, mutations in chaperone proteins including HSPB1, HSPB3, and HSPB8 impair appropriate protein folding (Bansagi et al., 2017).

Protein Family Related to Spinal Muscular Atrophy

Heat shock proteins (HSPs) are the leading genealogy of proteins found in organisms. The human genome has ten distinct types of HSPs, designated HSPB1 through HSPB10. While some of these proteins HSPB2, HSPB3, HSPB4, HSPB7, HSPB9, and HSPB10 have tissue specific expressions, others—HSPB1, HSPB5, HSPB6, and HSPB8 have broad expressions (Nefedova et al., 2015). Three key domains make up the HspB family: the extremely sealed α-crystallin domain, the N-terminal domain, and the C-terminal domain. Many functions are associated with genes connected to distal hereditary motor neuropathy: RNA metabolism (IGHMBP2, GARS), protein folding (HSPB1, HSPB8, BSCL2), axonal transport (HSPB1, DYNC1H1, DCTN1), and cation-channel dysfunction (ATP7A and TRPV4) (Penttilä, 2018) as mentioned in table 1.

Table 1(B): *Pertaining Mutations for Distal Spinal Muscular Atrophy*

Gene	Location	Mutation	Inheritance	Protein	Function	Reference
HSPB1	7q11.23	404C-T	Autosomal Dominant	Heat Shock Protein Beta-1	prevent aggregation	(Evgrafov et al., 2004)
HSPB3	*12q24.23*	423G→C 421A→G	Autosomal Dominant	Heat Shock Protein Family B Member 3	protecting cells from stressors	(Kolb et al., 2010)
HSPB8	*5q11.2*	21G-T	Autosomal Dominant	Heat Shock Protein Beta-8	folding and refolding of misfolded proteins	(Irobi et al., 2004)
FBXO 38	5q32	616T>C	Autosomal Dominant	F-box only protein 38	ubiquitination of target proteins	(Sumner et al., 2013)
SMAR	11q13	Het 1178G>A Het 1284+5G>A	Autosomal Recessive	BRG1 protein	Regulation of gene expression by modifying chromatin structure	(Viollet et al., 2004)
GARS	7p14.3	815T>G	Autosomal Dominant	glycyl-tRNA synthetase	incorporation of glycine into proteins, maintaining integrity of protein synthesis process	(Chung et al., 2018)
BSCL2	11q12.3	263A→G 269C→T	Autosomal Dominant	Seipin	lipid homeostasis	(Windpassinger et al., 2004)
REEP1	2p11.2	303+1 7GTAATA T>AC	Autosomal Dominant	Receptor Expression-Enhancing Protein 1	Expression, trafficking of membrane receptors	(Schottmann et al., 2015)
IGHM BP2	11q13.3	(c.138T>A) c.2911-12 R-971Glufs	Autosomal Recessive	immunoglobulin mu-binding protein 2	RNA metabolism and immune function	(Cottenie et al., 2014)
SLC5 A7	2q12.3	1497delG	Autosomal Dominant	high-affinity choline transporter 1 (CHT1)	synthesis of acetylcholine, supporting neurotransmission	(Barwick et al., 2012)
DCTN 1	2p13.1	175G>A	Autosomal Dominant	dynein cytoplasmic 1	intracellular transport	(Hwang et al., 2016)

DNAJ B2	*2q35*	(352+1G>A)	Autosomal recessive	DnaJ homolog subfamily B member 2	maintaining protein homeostasis	(Sanchez et al., 2016)
WARS	14q32.2	c.770A>G	Autosomal dominant	tryptophanyl-tRNA synthetase	protein synthesis, gene regulation and cellular signaling	(Tsai et al.,2017)
ATP7	*Xq21.1*	4156C >T (Family A) 2981C>T (Family B)	X-Linked lymphocyte regulated	copper-transporting ATPase 1	regulating copper levels	(Kennerson et al., 2010)

Proximal Spinal Muscular Atrophy

Relapse of alpha motor neurons in the brainstem and vertebral column is the result of proximal spinal muscular atrophy, an autosomal recessive hereditary situation. There are three main categories for this condition (Farrar & Kiernan, 2015) as shown in table 2.

Table 2: *Genes Related with Proximal Spinal Muscular Atrophy*

Gene	Position	Mutation	Disease	Proteins	References
TRPV4	12q24.11	805C>T 806G>A Messene 946C-T Transition	Scapuloperoneal SMA	Transient Receptor Potential Vanilloid 4	(Auer-Grumbach et al.,2010)
DYNC1H1	14q32.31	heterozygous 1750A-C	Lower extremity predominant SMA type 1	Dynamin Cytoplasmic 1 Heavy Chain	(Harms et al., 2012)
BICD2	9q22.31	320C>T c.2108C>T 563A>C	Lower extremity predominant SMA type 2	Bicaudal D homolog 2	(Neveling et al., 2013)
VAPB	20q13.32	heterozygous 166C-T Transition	Finkel-type lateonset SMA	Vesicle-Associated Membrane Protein-Associated Protein B	(Nishimura et al., 2004)
LMNA	1q22	exon 3 codon208, delAAG	Adult-onset proximal SMA, followed by cardiac involvement	lamin A/C	(Muchir, 2000)
TFG	3q12.2	854C>T	Hereditary motor and sensory neuropathy, Okinawa type	Tumor Protein p53-Inducible Protein 1	(Ishiura et al., 2012)

AR	Xq12	CAG repeat (Exon 1 AR gene)	Spinal and bulbar muscular atrophy	Androgen Receptor (AR)	(Spada et al., 1991)

The utmost severe pattern of SMA, type 1, identified as Werdnig-Hoffmann affects about 50% of people who are diagnosed. Babies suffering from this ailment frequently do not make it past their second birthday and are unable of sitting up without assistance. The inability to control head motions, flaccid paralysis, and extreme muscle weakness (hypotonia) are among the symptoms (Raposo et al., 2019). There's evident limb rigidity and restricted natural movement. Reduced fetal movements in severe circumstances may be a sign of prenatal onset, which is linked to severe muscular weakness and joint contractures (D'Amico et al., 2011).

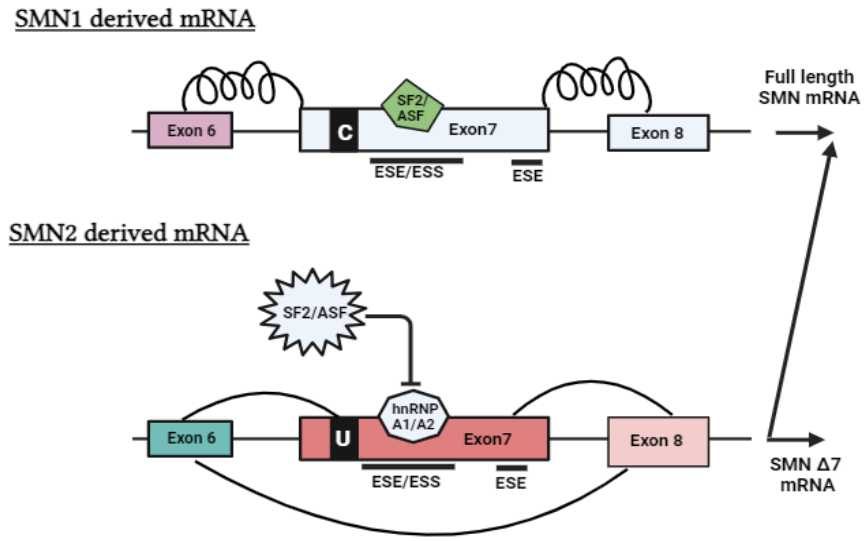
Usually in children, SMA type 2, sometimes referred to as Dubowitz syndrome, is an uncommon genetic condition. It is distinguished by a delay in growth, a tiny head size (nanocephaly), short height, unique facial traits, skin anomalies, and mild to severe cognitive impairment. Individuals diagnosed with SMA type 2 are unable to walk on their own, but they may frequently sit unassisted and, in certain situations, stand with help. In severe cases, kyphoscoliosis and joint contractures are common consequences (Messina et al., 2008).

Early childhood muscle weakness is a symptom of SMA type 3, usually referred to as Kugelberg-Welander illness. In spite of this, most people with this illness are able to stand and walk on their own. But ultimately issues including osteoporosis, reduced mobility, scoliosis, and obesity could ensue. When motor skills deteriorate, breathing problems arise because once respiratory muscle strength is lost, it cannot be recovered, resulting in persistent breathing difficulties (Mushtaq et al., 2016).

Molecular Mechanism

The splicing process depends on the spliceosome, a highly complex piece of molecular machinery whose function is regulated by a variety of variables. The regulation of the splicing of the SMN1 and SMN2 genes is largely dependent on both trans- and cis-acting elements (Ahmad et al., 2016). This complex mechanism is disrupted by a single nucleotide alteration, namely a C-to-T transition at position 6 of exon 7 in the SMN2 gene. This mutation disrupts an exonic splice enhancer (ESE), which is normally identified by SF2/ASF and results in the presence of exon 7 in the concluding record. Moreover, the alteration may result in the development of an exonic splice suppressor (ESS), which enlists the proteins hnRNP A1/A2 and excludes exon 7 (Sun et al., 2005).

Figure 1: *Splicing Defect in Spinal Muscular Atrophy*



Functions of SMN protein

The SMN protein has a mass of about 38 kilo dalton and 294 amino acids. It is widely distributed in motor neuron growth cones and is essential for ribonucleoprotein biosynthesis (Govoni et al., 2018). SMN forms a compound with Gemins, spliceosomal U-snRNPs, SMA proteins, and profilins, and is essential to the splicing mechanism. This SMN complex's gemin-8 component assembles spliceosomal snRNPs in the cytoplasm, but the nucleus is where pre-mRNA splicing really takes place (Sun et al., 2010).

Proposed Mechanisms Underlying Spinal Muscular Atrophies

A significant amount of SNPs are involved in many pathogenic pathways in SMA. Protein synthesis, metabolism, and RNA splicing are associated with genes including SMN, SETX, DCNT1, GARS, RARS2, and LASIL. Additional genes that are implicated in processes linked to molecular chaprones, accumulation, and deprivation include HSPB1, HSPB8, BSCL2, UBE1, AR, VAPB, DCNT1, and MAPT. Genes involved in axonal guidance and transport include DCNT1, DYNC1H1, PLEKHG5, HSPB1, SMN, BICD2, and FBX034.

Mutational Analysis

Following the mutational work performed in (Alayoubi et al., 2013) mutational studies have determined that SMA is an autosomal recessive neurological ailment that is predominantly brought on by mutations in the SMN1 gene, which is

found on chromosome 5. Lower motor neuron function is dependent on SMN1. Although complete SMN protein can be shaped with the assistance of multiple counterfeits of the SMN2 gene, this gene generally codes SMN protein with less efficiency. Modification in the VAPB gene on chromosome 20 is linked to Finkel style Spinal Muscular Atrophy (Craig et al., 2007). the research of (Govoni et al., 2018), VAPB protein is produced by this gene, which is involved in the endoplasmic reticulum's function in folding freshly generated proteins for cellular transport. This gene's mutation, which causes serine to replace proline at position 56, inhibits the misfolded protein, causes protein accumulation and rises the risk of motor neuron death (Nishio et al., 2023).

Discussion and Conclusion

A devastating neurological condition with high rates of morbidity and mortality, spinal muscular atrophy (SMA) primarily affects children (Crawford & Pardo, 1996). The survival gene, which is essential for generating the (SMN) protein and is found on chromosome 5q13, is removed or altered in the mainstream of SMA cases. It is well known that the condition has a hereditary foundation (Lefebvre et al., 1995). The SMN2 gene functions as a modulator of the condition and is now a major area of research for therapeutic development since it produces a shortened but partially functioning SMN protein.

Countless other genes, in addition to SMN1 and SMN2, add to the genetic complexity of the distal and proximal variants of SMA (Lorson et al., 1999). The disease's varied genetic landscape is reflected in the involvement of genes including HSPB1, GARS1, and VAPB. The intricate nature of SMA is further demonstrated by the important functions these genes play in RNA metabolism, axonal transport, protein folding, and other cellular processes (Deguise et al., 2021).

Significant revolutions in the treatment of (SMA) have been made recently with the introduction of antisense oligonucleotide (ASO) medicines. Some clinical symptoms of SMA are reduced by ASO treatment, which targets SMN2 splicing to raise the quantities of functional SMN protein. But given that patients may still experience delayed symptoms, especially if early neuromuscular development is compromised, concerns regarding the treatments' long-term efficacy persist (Mendell *et al*., 2017).

A deep and long-term strategy to SMA therapy is important, concentrating not only on the CNS but also on tissues in the marginal regions (Jablonka et al., 2022). Combining SMN-dependent and SMN-independent treatment techniques is probably necessary for effective care across various life stages. These might include larger strategies targeted at neuroprotection and muscular augmentation, gene therapy, and small compounds to modify SMN expression (Wirth et al., 2020).

In total approx. 68% of SMA patients in Pakistan have SMN gene deletions, highlighting the significance of population-specific genetic studies and the potential for targeted therapies in these regions. Research indicates that early diagnosis and public health programs emphasizing genetic counseling could show a vital part in reducing the burden of SMA in countries with high rates of consanguinity, such as Saudi Arabia, Pakistan, and Iran (Hui & Zumla, 2014).

In conclusion, despite significant advancements in knowledge and care, SMA remains a complex genetic disease with unresolved problems that require further research and innovative treatment strategies. Future efforts should focus on improving existing treatments, looking into novel therapeutic targets, and ensuring that patients have fair access to healthcare globally. Early intervention programs and genetic counseling may have a significant impact on the management and prevention of SMA in high-risk populations.

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