Journal of Genetic Mutation Disorders
Volume 3 | Issue 1

Case Report Open Access

Spinal Muscular Atrophy-Type1, Unraveling the tapestry from highly inbred region of North India

Rukhsana Hassan[1], Gh Rasool Bhat[1*], Hilal Ahmad Ganie[2*], Feroze Ahmad Mir[2], Mushtaq Ahmad Bhat[3] Ravouf Parvez Asimi[2] and Dil Afroze[1*]

[1]Advanced Centre for Human Genetics, Sher.i. Kashmir Institute of Medical Sciences, Soura, Jammu and Kashmir, India
[2]Department of Neurology, Sher.i. Kashmir Institute of Medical Sciences, Soura, Jammu and Kashmir, India
[3]Department of Pediatrics, Sher.i. Kashmir Institute of Medical Sciences, Soura, Jammu and Kashmir, India

***Corresponding Author:** Dil-Afroze, Advanced Centre for Human Genetics, Sher.i. Kashmir Institute of Medical Sciences, Soura, Jammu and Kashmir, India, Tel: +91 194240 1013, Ext 2477, Fax: +91 194 2403470, E-mail: afrozedil@gmail.com

Citation: Rukhsana Hassan, Gh Rasool Bhat, Hilal Ahmad Ganie, Feroze Ahmad Mir, Mushtaq Ahmad Bhat et al. (2023) Spinal Muscular Atrophy-Type1, Unraveling the tapestry from highly inbred region of North India. J Gene Mutat 3(1): 101

Received Date: October 08, 2023 **Accepted Date:** November 08, 2023 **Published Date:** November 15, 2023

Abstract

Spinal muscular atrophy is an autosomal recessive disorder characterized by degeneration of alpha motor in anterior horn cells of brain and spinal cord, which results in muscular atrophy, hypotonia, fasciculations, areflexia, paralysis and even death in most severe cases. The underlying cause of this disease is biallelic loss of survival motor neuron 1 (SMN1) gene. Depending upon the clinical features & patient's age, SMA is classified into different distinctive sub types.

In this study, we presented a case of one-year-old male floppy infant born of consanguineous marriage presented with history of recurrent chest infection, generalized hypotonia and inability to crawl, and delay in developmental milestones. Apart from routine clinical assessment, genetic analysis of the patient confirmed the homozygous deletion of the SMN1 gene. Moreover, the Multiplex Ligation Probe Assay (MLPA) analysis of proband also revealed the heterozygous duplication with MLPA ratio of 1.43 & 1.41 respectively. MLPA analysis of the parents also presented that the mother of the proband have heterozygous duplication of exons 7 and 8 of SMN1 gene, with MLPA ratio of 1.44 & 1.42 and the father of the proband have heterozygous deletion of exons 7 and 8 in the SMN1gene, with MLPA ratio of 0.49 & 1.48 respectively.

The main aim of the study is to highlight the genetic landscape of the SMA in the highly inbred region of North India as the most frequent mutation is homozygous disruption of SMN1, and the genes that cause SMA are thought to affect the mechanism of how RNA is processed as well as how proteins are transported and degraded. Over the past 20 years, significant advancements in patient care, genetic concepts and biology of SMA have shown potential in therapeutics and have paved a successful approach in diagnosis and providing the genetic counselling to the affected families.

Keywords: Spinal Muscular Atrophy; Multiplex Ligation Probe Assay

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive, neuromuscular single gene disorder. SMA is a characterized by the deterioration of alpha motor neurons (α-MNs) in the anterior horn cells of brain and the spinal cord resulting in muscle weakness, atrophy, paralysis and even death in most severe cases [1-3]. SMA is the second most fatal disorder after cystic fibrosis and one of the main cause of infant mortality worldwide[4, 5]. The incidence of SMA varies among various ethnic groups, overall estimated incidence is 1in 10,000 to 11,000 births live birth with carriers frequency of (heterozygotes) 1 in 40 to 60 [6, 7] in general population. SMA is caused by homozygous deletion of the survival motor neuron gene (SMN1), located on the telomeric region of chromosome 5q13.1 [8]. Clinically SMA is classified into five variants based on age of onset and achieved motor milestones [9, 10]. Among all of them, type 1 is the most common form of SMA and contributes about 45% cases. Type 1 SMA is also known as Werdnig–Hoffmann disease, with a severe muscle weakness evident within the first few months of birth (~ six months at most). Most of the type 1 patients have two or three copies of the SMN2 gene with generalized muscle weakness, often no head control, not able to sit independently. Such patients also have respiratory insufficiency, difficulty in breathing, coughing and swallowing. Due to weakness of the respiratory muscles, they have breathing issues and increased risk of aspirations [11-14] which may lead to difficulty with feeding and a failure to thrive. Preferential diagnosis is based on molecular genetic analysis, CPK (Creatine Phosphokinase), EMG (Electromyography) and NCS (Nerve Conduction Studies). Medical follow up and palliative care are the two aspects of patients with SMA. Genetic counseling is an essential and integral component for the families of these patients.[15]

Index Case, Ethical Statement & Pedigree

The current study was approved by the Institutional ethics committee of the Sher-i-Kashmir Institute of Medical Sciences (SKIMS) under notification no. #RP 250/2022. All the information was carried in predesigned consent form. All the experiments were carried under standard guidelines.

One year old, floppy male child was referred to Department of Advanced Centre for Human Genetics, SKIMS J&K India with chief complaints of recurrent chest infection, hypotonia, inability to crawl, and delay in developmental milestones. He was born with a birth weight 2.7 kg at gestational age of 40 weeks. He was the first child born of consanguineous parents as shown in figure 1. There was no history of any other neuromuscular disorder from either side of patient's family. There was also no history of sucking or swallowing difficulty and no fasciculation. However, deep tendon reflexes were absent and Power was also decreased.

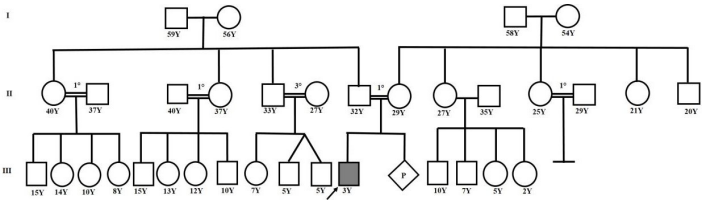

Figure 1: Showing the Pedigree of the Proband Along With the Degree of Consanguinity in the Family from Maternal (Right) and Paternal Side (Left).

Clinical Investigations & Results

Various laboratory investigations like blood tests including complete blood cell count (CBC), Creatine phosphokinase (CPK), lactate dehydrogenase (LDH), Thyroid profile, Tendem Mass Spectrometry (TMS) were all within normal ranges. MRI brain didn't reveal any substantial pathological features. However, the sleep study showed some slow & lagging wave discharges & EEG (Electroencephalogram) recorded also showed mild abnormality. NCS study also showed, mild to moderate motor axonal neuropathy and no sensory abnormality was detected thus pointing towards the case of motor neuron disease. To confirm the diagnosis, genetic analysis for deletion of exon7 of SMN 1 gene was performed, the results revealed that proband is confirmed case of type 1 SMA.

To further check the disease severity, copy number analysis of proband and his parents were performed by MLPA (Multiplex Ligation Dependent Probe Amplification Assay) which showed that proband has heterozygous duplication of exon 7 and 8 of SMN1 gene with SMN1/SMN2copy number ratio of 3:2. Copy number analysis of proband's mother revealed heterozygous duplication of SMN1/SMN1 gene with copy number ratio of 3:2 (SMN1/SMN2) and heterozygous deletion of exons 7 and 8 was found in proband's father with a copy number of 1:2 (SMN1/SMN2) which indicates that patient's father is a carrier of SMA. All these findings suggest that proband is a confirmed case of type 1 SMA.

Clinical Correlation and Variant Interpretation in the Proband

Heterozygous duplication of exons 7 and 8 of SMN1 gene, with MLPA ratio of 1.43 & 1.41 was detected in the proband (Reference range 0.80 to 1.20). Although, no other deletions or duplications were detected in the exons 7 and 8 of the SMN2 gene as shown in table 1 & figure 2. Proband thus has an SMN1:SMN2 gene copy number ratio of 3:2. As there is no deletion detected in SMN1 gene.

Serial No.	Gene Exons	Deletions/ Duplications	MLPA probe ratio (dosagequotient)	Copy Number	Disease OMIM	Inheritance
1	SMN1exons 7 & 8	Heterozygousduplication	Exon 7(1.43) Exon 8 (1.41)	3	Spinal MuscularAtrophy	Autosomalrecessive
2	SMN2exons 7 & 8	-	Exon 7(0.94) Exon 8(1.00)	2		

Table 1: Showing the MLPA data of SMN1 & SMN2 gene (exon 7 & 8) with heterozygous duplications along with the dosage quotient and copy number in the Proband.

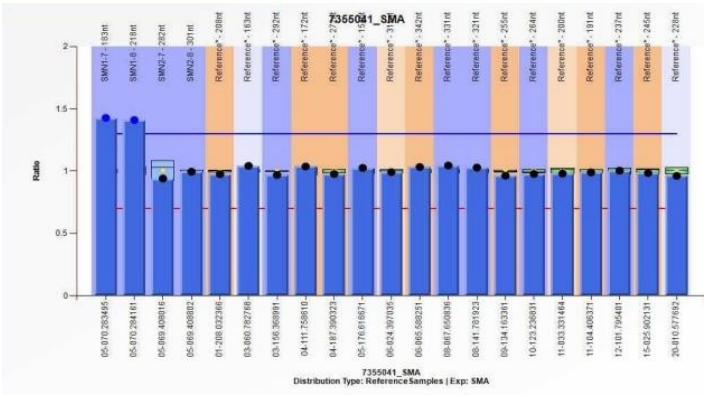

Figure 2: Showing the MLPA analysis of SMN1 & SMN2 genes with quotient ratio of 1.43 & 1.41 indicating that proband has heterozygous duplication of exons 7 & 8 of SMN1 gene.

Clinical Correlation and Variant Interpretation in the Mother of Proband

Heterozygous duplication of exons 7 and 8 of SMN1 gene, with MLPA ratio of 1.44 & 1.42 (Reference range 0.80 to 1.20) was observed in mother of proband. However, no deletions or duplications were detected in the exons 7 and 8 of the SMN2 gene as shown in table 2 and figure3. The mother of proband thus had an SMN1:SMN2 gene copy number ratio of 3:2. As no deletion was found in SMN1 gene.

Serial No.	GeneExons	Deletions/Duplications	MLPA probe ratio (Dosage Quotient)	Copy Number	Disease OMIM	Inheritance
1	SMN1exons 7 & 8	Heterozygous duplication	Exon 7(1.44)Exon 8 (1.42)	3	SpinalMuscular Atrophy	Autosomal Recessive
2	SMN2exons 7 & 8	-	Exon 7(0.94)Exon 8(1.01)	2		

Table 2: Showing the MLPA data of SMN1 & SMN2 gene (exon 7 & 8) with heterozygous deletions/duplications along with the dosage quotient and copy number in mother of the Proband.

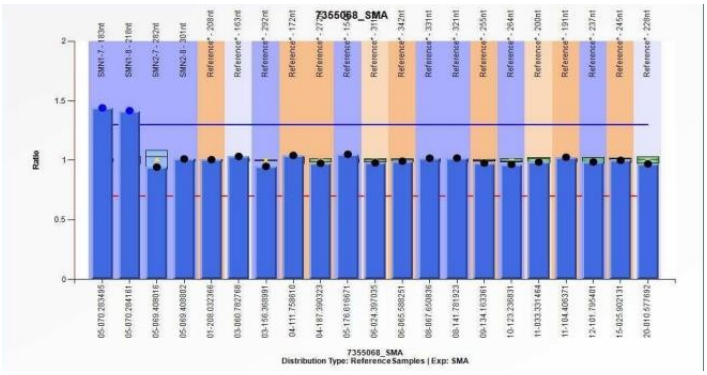

Figure 3: Demonstrating the MLPA analysis of SMN1 & SMN2 genes with quotient ratio of 1.44 & 1.42 indicating that mother of proband has heterozygous duplication of exons 7 & 8 of SMN1 gene.

Clinical Correlation and Variant Interpretation in the Father of Proband

Heterozygous deletion of exons 7 and 8 in the SMN1 gene, with MLPA ratio of 0.49 & 1.48 respectively was found in the father of Proband. (Reference range 0.80 to 1.20). However, no deletions or duplications were detected in the exons 7 and 8 of the SMN2 gene with ratio of 0.89& 0.97 respectively as shown in table 3 and figure 4.The father of proband thus has an SMN1:SMN2 ratio of 1:2, which indicates that the father of proband is an SMA carrier.

Serial No.	GeneExons	Deletions/Duplications	MLPA probe ratio(dosage quotient)	CopyNumber	DiseaseOMIM	Inheritance
1	SMN1exons 7 & 8	Heterozygous deletion	Exon 7(0.49)Exon 8 (1.48)	1	SpinalMuscular atrophy	Autosomal recessive
2	SMN2exons 7 & 8	-	Exon 7(0.89)Exon 8(0.97)	2		

Table 3: Showing the MLPA data of SMN1 & SMN2 gene (exon 7 & 8) with heterozygous deletions/duplications along with the dosage quotient and copy number in father of the Proband.

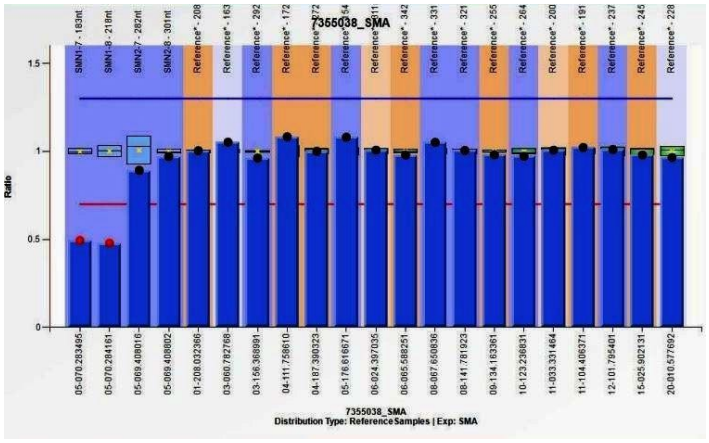

Figure 4: Exhibits theMLPA analysis of SMN1 & SMN2 genes with quotient ratio of 0.49& 1.48 indicating that father of proband has heterozygous deletion of exons 7 & 8 of SMN1 gene & suggest that father of proband is carrier of SMA disease.

Discussion

Spinal muscular atrophy is a neuromuscular disorder characterized by deterioration of anterior horn cells in lower motor neurons of brain and spinal cord resulting in muscle weakness and atrophy[16]. Based on the age of onset and severity of symptoms, SMA is classified into five phenotypes. Type 0, the rare and most severe form with prenatal onset. Type 1 (Werdnig- Hoffman), the most common form of SMA, with onset between 0 to 6 months. An intermediate form, Type 2 (Dubowitz disease), with onset before 18 months & type 3 (Kugelberg-Welander disease) with onset after 18 months of age [17] and type 4 form, mild and adult onset form of SMA. More than 95% of SMA patients have homozygous loss of SMN1 gene (Survival Motor Neuron1) and rest other patients are compound heterozygotes having intragenic mutation within SMN1 gene [18]. The highly homologous copy of SMN1 gene i.e. SMN2 is retained in almost all patient but due to splicing error this SMN2 is not able to compensate the loss caused due deletion of SMN1 to produce adequate amount of SMN protein, key protein for normal functioning and survival of motor neurons. The severity of SMA phenotype is related to SMN2 copy number, more the copy number, less severe is type of SMA [19]. Type 1 patients have 2 copies of SMN2 genes, represents about 45% of total SMA cases. So, it is the most common and severe form of SMA. SMA type 1 is also called as Werdnig-Hoffman is characterized by muscle weakness, hypotonia, respiratory distress and tongue fasciculations caused by degeneration of lower motor neurons in the spinal cord and brainstem nuclei. In normal individuals, SMN gene is translated and produces SMN protein, which is required for survival of lower motor neurons. These lower motor neurons transmit signals to skeletal muscles via brain and spinal cord that instructs skeletal muscles to contract which allows the body to move. In case of SMA patients, SMN gene is deleted which results in degeneration of lower motor neurons, these degenerated motors are not able to transmit signals to skeletal muscles which ultimately results in muscle atrophy or weakness as in figure 5.

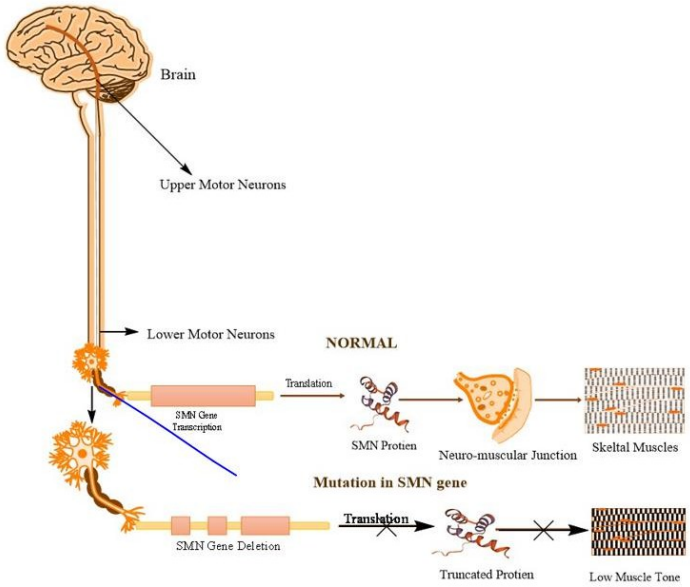

Figure 5: Showing the molecular pathway in the progression of spinal muscular atrophy both in normal state and mutated state.

In the above-mentioned peculiar case, no tongue fasciculation was observed, muscles enzymes were within the normal limits. EMG study was also found to be normal. Usually, NCS in SMA patients show the electrophysiological evidence of denervation with subsequent slowing of motor conduction velocity in motor nerves [20] which was also mild to moderately reported in our index patient. Genetic diagnosis is considered as standard technique to confirm the diagnosis in such patients. Until 2016 no treatment modality was available for SMA and management usually consisted of supportive measures. However, significant advancement in treatment strategies that are currently being used towards expedited therapeutics include antisense oligonucleotide to correct the SMN2 splicing error, gene therapies, small molecules like SMN enhancers &neuro protectants [21, 22]. Precise diagnosis and impeccable therapeutics are the two important aspects that may provide the maximum benefits to patients with SMA in genetically less explored population in Northern India.

Conclusion

The main aim of the study is to highlight the genetic landscape of the SMA in the highly inbred region of North India as the most frequent mutation is homozygous disruption of SMN1. The critical gene(s) that causes SMA are thought to affect the mechanism of how RNA is processed, proteins transported and degraded. Although number of therapeutic modalities are available for such patients, but main limitations of such treatment options include the cost of the therapy. Moreover, the delay in accurate diagnostics and therapeutics may increase the severity of disease. So, in future we are taking into quest to address the genetic architecture of this rare & fatal neuromuscular disorder in highly inbred & low resource regions of Jammu & Kashmir where most of the people practice consanguinity due to which burden of such rare genetic disorders are quite high which needs to overcome. Because most of the suspected cases of genetic disorders remain camouflaged due to paucity of appropriate clinical as well as diagnostic resources available in such unexplored regions, causing patients to face a huge psycho-socio-economic crisis and most of the time suffer life-long with such life threatening diseases. Therefore, precise clinical examination, genetic screening of patients carrying such pathogenic genetic variants is essential to provide the proper genetic counseling to the individuals / families & appropriate management of the disorder in a timely manner. Thus, proper counseling is of great importance especially for those families with history of such severe disorders.

Information Note Proband's mother is 13 weeks pregnant, so proper genetic counseling about disease, its prognosis, recurrence risk and prenatal diagnosis will help them in successful pregnancy and reproductive planning in future.

Authors Contribution

RH, GRB and DA planned the work, RH carried out work on SMN samples and RH wrote the manuscript and restructured it, HAG, MAB, FAM helped in sampling processes, GRB, RH performed data analysis, RH, GRB, HAG, FAM, MAG, DA finally refined the manuscript. All the authors meet the criteria for authorship. Every author is aware of, has agreed to this paper's content, and is listed as an author on the paper.

Authors Contributed Equally: Gh Rasool Bhat, Hilal Ahmad Ganie.

Acknowledgement

RH and DA acknowledge the family members and patient for their contribution in the study.

Conflict of Interest

The authors declare that they have no competing interests.

Key Clinical message

Genetic landscape of the SMA in the highly inbred region of North India as the most frequent mutation is homozygous disruption of SMN1.

Funding

This research was supported by Grant provided Institutional Intramural grant (SKIMS). Consent: Written informed consent was obtained from the patients to publish this report in accordance with the journal's patient consent policy.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

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