Genetic Profile of Spinal Muscular Atrophy: A Case Series from Bangladesh

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Abstract

Background: Spinal muscular atrophy is an autosomal recessive neuromuscular disorder caused primarily by homozygous deletions of the survival motor neuron 1 (SMN1) gene. Disease severity is influenced by the number of SMN2 gene copies and other modifiers such as neuronal apoptosis inhibitory protein (NAIP). Molecular confirmation is essential for diagnosis, family counseling, and therapeutic planning.

Objective: To describe the molecular findings of clinically suspected spinal muscular atrophy patients referred for genetic testing in Bangladesh.

Methods: Eight patients were evaluated in the Department of Pathology, National Institute of Laboratory Medicine and Referral Center, Dhaka-1207, between September 2024 and January 2025. Multiplex ligation-dependent probe amplification (MLPA) was performed to assess deletions or duplications in SMN1, SMN2, and NAIP. Variants were classified according to international standards.

Results: Five of the eight patients demonstrated homozygous deletions of SMN1 exons 7 and/or 8, confirming the diagnosis of spinal muscular atrophy. Most of these patients carried three copies of SMN2, which is associated with relatively milder phenotypes. All of them also showed heterozygous deletions of NAIP, which may contribute to disease severity. One patient exhibited multiple heterozygous duplications involving SMN1 and SMN2; this was classified as a variant of uncertain clinical significance. Another child had a normal copy number profile despite clinical suspicion. In one additional child, homozygous deletions of SMN2 exons 7 and 8 were found along with multiple heterozygous deletions across SMN1; this was interpreted as carrier status with uncertain clinical impact.

Conclusion: This case series confirms the predominance of SMN1 exon 7 and 8 deletions in Bangladeshi spinal muscular atrophy patients, with SMN2 copy number and NAIP status acting as important modifiers. Genetic testing using MLPA is a valuable diagnostic tool in the local context. Broader access to molecular diagnostics and counseling services is essential.

[Journal of Histopathology and Cytopathology, 2026 Jan; 10 (1):49-52]
DOI: https://www.doi.org/10.69950/jhc.2026.10.1.6

Keywords: Spinal muscular atrophy, SMN1, SMN2, MLPA, NAIP

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Introduction

Spinal muscular atrophy (SMA) is a leading genetic cause of infant morbidity and mortality, with an estimated incidence of 1 in 6,000 to 10,000 live births worldwide.[1] It is inherited as an autosomal recessive disorder, with a carrier frequency reported as approximately 1 in 38 individuals.[2] The disorder is characterized by progressive degeneration of the anterior horn cells of the spinal cord, leading to muscular weakness, hypotonia, and atrophy.[3]

Molecularly, SMA results from homozygous deletions or mutations in the survival motor neuron 1 (SMN1) gene, located on chromosome 5q13. More than 95% of patients carry homozygous deletions of exon 7 of SMN1, while a minority harbor compound heterozygous mutations.[4] A nearly identical gene, SMN2, produces limited amounts of functional SMN protein and acts as a critical disease modifier. The number of SMN2 copies strongly correlates with disease severity: patients with one or two copies usually present with severe SMA type I, whereas those with three or more copies may develop type II or III phenotypes with relatively slower progression.[5,6] Other genetic factors, including deletions in neuronal apoptosis inhibitory protein (NAIP), may further modify the clinical spectrum. NAIP loss has been associated with earlier onset and greater disease severity.[7] The phenotypic heterogeneity of SMA thus results from a complex interplay between SMN1 deletion, SMN2 copy number, and additional modifiers. Recent therapeutic advances—including antisense oligonucleotides (nusinersen), small molecules (risdiplam), and gene therapy (onasemnogene abeparvovec)—have revolutionized the management of SMA.[8,9] However, access to these therapies remains limited in low- and middle-income countries, underscoring the importance of early molecular confirmation for appropriate counseling and clinical planning.

Despite the global burden of SMA, molecular data from Bangladesh are sparse. This study presents a case series of eight patients evaluated in a national referral center, highlighting the genetic spectrum of SMA and the significance of copy number variation in SMN1, SMN2, and NAIP genes.

Methods

This case series was conducted in the Department of Pathology, National Institute of Laboratory Medicine and Referral Center, Dhaka-1207, between September 2024 and January 2025. Peripheral blood DNA samples were analyzed using MLPA, targeting exons 7 and 8 of SMN1 and SMN2, as well as NAIP. Copy number variations were quantified through capillary electrophoresis. Peripheral blood samples (3–5 mL) were collected in EDTA tubes from clinically suspected spinal muscular atrophy (SMA) patients after obtaining informed consent. Genomic DNA was extracted from leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. DNA quality and concentration were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA) and confirmed by agarose gel electrophoresis. Multiplex Ligation-dependent Probe Amplification (MLPA) was performed to analyze copy number variations of SMN1, SMN2, and NAIP genes using the commercially available SALSA MLPA kit P060-B1 SMA (MRC-Holland, Amsterdam, Netherlands). The procedure involved denaturing the DNA and allowing the MLPA probes to hybridize to their target sequences, followed by ligation of the hybridized probes. The ligated probes were then amplified by PCR, and the resulting fragments were separated and detected. Finally, the data were analyzed to determine

the copy number variations of the target genes. All procedures were carried out under standardized laboratory conditions to ensure accuracy and reproducibility. Results were interpreted according to the standards of the American College of Medical Genetics and Genomics.[10]

Results

Five of the eight patients (62.5%) were confirmed with homozygous deletions of SMN1 exons 7 and/or 8. Most of them carried three SMN2 copies, which is typically associated with milder phenotypes. More than half of the patients had a heterozygous NAIP deletion. Two patients showed variants of uncertain clinical significance.

Table I. Genetic findings of SMA patients (n=8)

Case	Age Year(y)	Sex	SMN1 Status	SMN2 Status	NAIP Status	Interpretation
1.	19y	F	Exon 7 homozygous deletion, Exon 8 heterozygous deletion	3 copies	Heterozygous deletion	Pathogenic SMA
2.	11y	F	Exon 7 & 8 homozygous deletion	3 copies	Heterozygous deletion	Pathogenic SMA
3.	1y	M	Exon 7 & 8 homozygous deletion	3 copies	Heterozygous deletion	Pathogenic SMA
4.	2y	F	Exon 7 & 8 homozygous deletion	3 copies	Heterozygous deletion	Pathogenic SMA
5.	1y	F	Multiple heterozygous duplications	Multiple duplications	Heterozygous duplication	Variant of uncertain significance
6.	3y	M	Exon 7 & 8 homozygous deletion	3 copies	Heterozygous deletion	Pathogenic SMA
7.	5y	M	Normal copy number	Normal copy number	Normal	No SMA detected
8.	1y	F	Multiple heterozygous deletions (exons 1–6, introns)	Exon 7 & 8 homozygous deletion	Multiple heterozygous deletions	Carrier / uncertain clinical impact

Discussion

This case series demonstrates that the genetic landscape of spinal muscular atrophy in Bangladeshi patients is consistent with global data, where homozygous deletions of SMN1 exons 7 and 8 are found in the majority of cases.[1,2] The modifying role of SMN2 copy number was evident, as most affected patients carried three SMN2 copies, a finding that is typically associated with less severe clinical manifestations.[5,6] The relatively high frequency of heterozygous NAIP deletions in this cohort is consistent with earlier studies that link NAIP to disease severity.[3]

One case with multiple duplications in SMN1 and SMN2 underscores the limitations of MLPA in detecting complex rearrangements and highlights the need for more comprehensive genetic tools such as next-generation sequencing.[10]

The presence of one clinically suspected but genetically negative case emphasizes that a subset of patients may remain undiagnosed with standard deletion/duplication analysis alone. These patients may carry point mutations or subtle rearrangements that are missed by MLPA.[8]

Finally, the unusual case with SMN2 homozygous deletion illustrates the challenges of variant interpretation in clinical practice. Although SMN2 deletions are not

typically disease-causing, their coexistence with multiple heterozygous deletions across SMN1 raises questions regarding potential modifying roles. For such patients, careful follow-up and expanded genetic testing are warranted.[9,10]

Conclusion

In this Bangladeshi cohort, five of eight clinically suspected spinal muscular atrophy patients were confirmed to have homozygous deletions of SMN1 exon 7 and 8. Most had three SMN2 copies, consistent with milder phenotypes, and half exhibited heterozygous NAIP deletions. Variants of uncertain significance and atypical findings were also observed, reflecting both the complexity of spinal muscular atrophy genetics and the limitations of current testing methods. Molecular confirmation using MLPA remains an essential first-line diagnostic tool for SMA in the local setting. However, broader access to advanced genetic testing modalities and structured genetic counseling services is urgently needed in Bangladesh to improve diagnostic accuracy, patient management, and family counseling.

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