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Case Series

Deciphering spinal muscular atrophy through pedigree and molecular genetic analysis

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ABSTRACT

Spinal muscular atrophy (SMA) is a severe autosomal recessive neuromuscular disorder characterized by degeneration of anterior horn cells of the spinal cord, leading to progressive muscle weakness and atrophy. It is primarily caused by mutation or deletion in the survival motor neuron-1 gene SMN1 gene on chromosome 5q13.2, resulting in reduced levels of SMN protein, while the SMN2 gene provides only partial compensation. The present study investigated the inheritance pattern and molecular characteristics of SMA in ten clinically diagnosed cases. Clinical histories were collected through patient, family and physician interactions and pedigree charts were constructed to assess inheritance patterns. Molecular diagnosis was performed using genomic DNA analysis, multiplex ligation-dependent probe amplification (MLPA), automated DNA sequencing and multiplex PCR to detect SMN1 gene deletions. The findings revealed that most patients exhibited deletions in exon regions of the SMN1 gene, with six cases showing homozygous deletion of exon 7, two cases showing deletion of both exons 7 and 8 and two cases showing homozygous deletion of exon 7 along with heterozygous deletion of exon 8. Additionally, two patients demonstrated overlapping clinical features of SMA and Duchenne muscular dystrophy (DMD). Pedigree analysis confirmed an autosomal recessive inheritance pattern, with affected individuals born to phenotypically normal carrier parents. The study highlights that homozygous deletion of exon 7 of the SMN1 gene is the most common molecular cause of SMA and emphasizes the importance of molecular genetic testing for accurate diagnosis, carrier detection, prenatal screening and effective genetic counseling.

Keywords: Homozygous, Neuromuscular, SMN1, 38kDa protein

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder which is characterized by degeneration of the anterior horn cells of the spinal cord that lead to symmetrical muscle weakness and atrophy. Mostly babies, infants and young children are affected. In this disorder, weakness tends to affect more severely at the proximal parts as compared to the distal parts of the body.[1] SMA is caused by mutation or deletion on chromosome (5q13.2) in the telomeric copy of the SMN1 gene.[2-4]

SMA results from an insufficient level of 38kDa protein, known as SMN and also due to mutation or homologous deletion of the SMN1, which is located in the telomeric region of the chromosome. At least one copy of a very similar gene i.e. SMN-2, is present in the centromeric part of the same chromosome which is retained in all the patients. SMN protein is completely synthesized due to SMN-1 gene and SMN-2 gene is only responsible for a part of its production. SMN-2 gene produces only 10-25 percent functional protein while other 75% protein is unstable, truncated and quickly degraded. Severity of the disease reduces as the number of copies of SMN2 increase. Average incidence of all types of SMA together is around 8 per 100,000 live births.[5]

On the basis of age of onset and motor functions, SMA is clinically diagnosed into four categories.[6] SMA type 1 (known as Werdnig Hoffmann disease) is diagnosed before 6 months of age and patients have onset of clinical signs such as failure in the ability to sit unsupported and have low muscle tone. They have a short life expectancy i.e. <2 years.[7-10] SMA type 2 (known as Chronic SMA) is diagnosed between the ages of 7 to 18 months. Patients have the ability to sit unaided and some of them are able to achieve standing position, but they do not attain the ability to walk independently. Their life span is around 10 to 40 years.[1,11] SMA type 3 (known as Kugelberg-Welander disease) has patients who are capable to walk independently and their life expectancy is unspecified. They typically achieve all the major motor milestones.[12] SMA type 4 includes patients with adult onset (>18 years), having normal lifespan and are capable to walk normally.[1,11]

Diagnosis of SMA is done by electromyography, muscle biopsy and also by molecular analysis.[11] Patients need a range of particular treatments or care such as supportive therapies, respiratory, nutritional and orthopedic care that can stop the progress of the disease and extend their lives. The significance of the present study was to achieve deeper insights into the inheritance pattern of autosomal recessive disorder i.e. SMA. The present study retrieved those patients who suffered from SMA as well as from DMD/BMD and it can be elaborated that homozygous deletion of exon 7 of SMN1 gene was observed in 98% of SMA patients along with exon 7 and 8 of SMN1 gene and heterozygous deletion of exon 8 of SMN1 gene was also analyzed. The main objective of the present study is to investigate the inheritance pattern of the disease.

The cases considered in the present study were already identified cases of SMA taken from the hospitals. One of the subjects was suffering from SMA and the subject's sibling was aborted due to the same problem. The history of other cases was collected by discussing with doctors and interacting personally with the subjects and their families. Progeny online pedigree tool was further used to generate pedigrees.

CASE SERIES

Genomic DNA sample proved that the cases were suffering from SMA due to deletion in their exon sequence. The medical reports of the subjects concluded that in most of the cases, SMA was caused by the homozygous deletion of exon 7 of SMN1 gene. Out of a total of 10 subjects of SMA, 6 subjects were having homozygous deletion of exon 7, two subjects were those who had deletion of exon 7 and exon 8 and two subjects had homozygous deletion of exon 7 and heterozygous deletion of exon 8 and two subjects were suffering from SMA as well as from DMD (Table 1).

Table 1: Diagnostic data representing the disorder among the cases.

Subject identity (Sex)	Age at diagnosis (Year when diagnosed)	Age at examination (in years)	Genetic disorder/ condition	Genetic tests for confirmation	Results	Interpretation
Case 1 (female)	10 (2012)	18	SMA	Genomic DNA was tested	Homozygous deletion in exon 7 of SMN1 gene	The diagnosis of SMA was confirmed in child
Case 2 Aborted fetus of unknown sex (sibling of case 1)	(2018)	Aborted	SMA	Automated DNA sequencing	Deletion of exon 7 and exon 8 of SMN1 gene. No deletion of exon 7 and exon 8 of SMN2 gene detected.	Exons 7 and 8 of SMN1 gene were deleted.
Case 3 (female)	1 (2019)	3	SMA	MLPA probe mix p060 B2 from MRC Holland	Homozygous deletion of exon 7 of SMN1 gene	Confirmed the diagnosis of SMA in the proband.
Case 4 (male)	10 (2018)	13	SMA and DMD	For SMA: MLPA analysis for exons 7 and 8 in SMN1 gene. For DMD: Multiplex PCR analysis for 20 exons of dystrophin gene	For SMA: Deletion of exon 7 and 8 of SMN1 gene For DMD: no deletion was present	For SMA: Confirmed the diagnosis of SMA in proband For DMD: Absence of deletion did not negate the diagnosis of DMD/BMD
Case 5 (male)	9	16	SMA and DMD	For SMA: Genomic DNA was tested For DMD: DNA was tested for dosage analysis of 79 exons of dystrophin gene.	For SMA: Homozygous deletion in exon 7 of SMN1 gene For DMD: No deletion or duplication in 79 exons was detected	For SMA: Confirmed the diagnosis of SMA in proband For DMD: Absence of deletion or duplication did not negate the diagnosis of DMD/BMD.

Continued.

Subject identity (Sex)	Age at diagnosis (Year when diagnosed)	Age at examination	Genetic disorder/ condition	Genetic tests for confirmation	Results	Interpretation
Case 6 (female)	4.5 (2004)	Death	SMA	Genomic DNA was tested	Homozygous deletion in exon 7 of SMN1 gene	Confirmed the diagnosis of SMA
Case 7 (male)	9 (2019)	Death	SMA	Genomic DNA was tested	Homozygous deletion in exon 7 of SMN1 gene	Confirmed the diagnosis of SMA
Case 8 (female)			SMA	Maternal DNA contamination test	Homozygous deletion in exon 7 of SMN1 gene	Confirmed the diagnosis of SMA in fetus
Case 9 (female)	4 (2019)	6	SMA	MLPA	Homozygous deletion in exon 7 of SMN1 gene and heterozygous deletion of exon 8	Confirmed the diagnosis of SMA in the subject
Case 10 (female)	1 and 3 months (2019)	3.5	SMA	MLPA	Homozygous deletion in exon 7 of SMN1 gene and heterozygous deletion of exon 8	Confirmed the diagnosis of SMA in the child

Case 1 was the proband who was suffering from SMA. The subject faced breathing problems with cough lasting forever and accumulation of mucus in the throat, incorrect neck and body posture and overall weakness. From the family interaction, it was illustrated that the disease showed linkup with the paternal family (Figure 1). The parents observed imbalanced walking style leading to crawling and getting restricted to wheel chair, as the motor limbs did not function properly and at the age of 18 years (during the course of this study), the subject expired. The diagnostic reports, physical features and body symptoms confirmed that the condition was SMA. Case 2 was an aborted fetus of unknown sex who was the sibling of case 1.

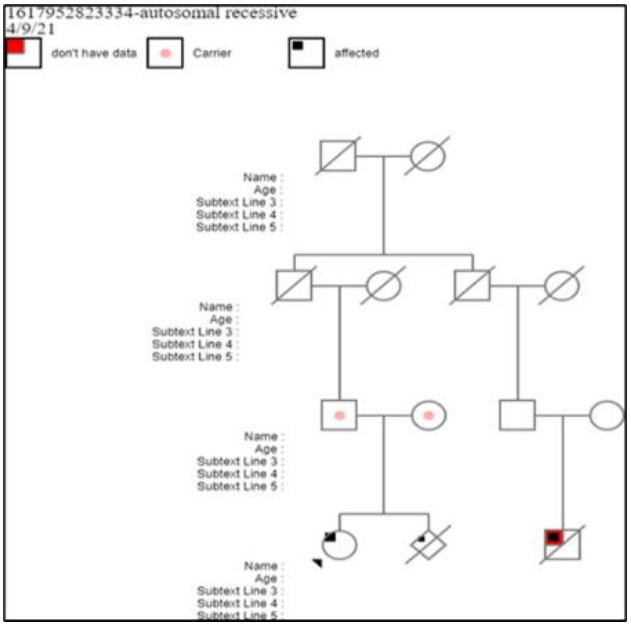

Figure 1: Pedigree of case 1.

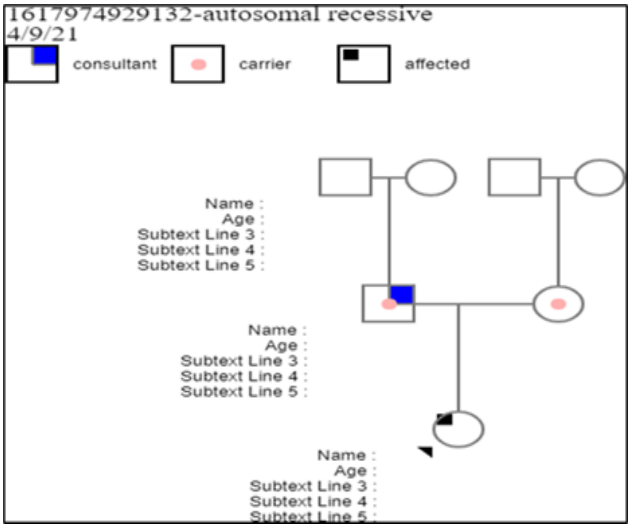

Figure 2: Pedigree of case 3.

Case 3 was a subject suffering from SMA. In the interview session, it was observed that there was breathing problem, inability to move the neck and the cough lasted forever. The proband had weakness and trouble passing the food through the mouth and throat and the disease had no linkup with paternal or maternal family (Figure 2).

Case 4 was suffering from SMA as well as DMD and studied in 8th grade. In the interactive session, the parents shared that muscle weakness started 3 years back and at the time of evaluation, the subject faced problems during walking, breathing and swallowing. The patient's younger sibling was normal. It was further found that the condition was not associated with paternal or maternal family (Figure 3).

Case 5 suffered from SMA as well as DMD. During the interview, it came out that the subject started facing problem in the spinal cord affecting the ability to walk, sit and control head movements while studying in the fifth class. The subject's older sibling was normal. The disorder was not reported in any members of the paternal as well as maternal family (Figure 4).

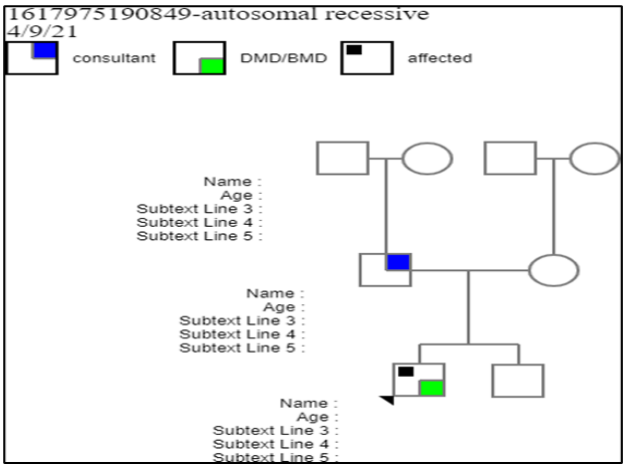

Figure 3: Pedigree of case 4.

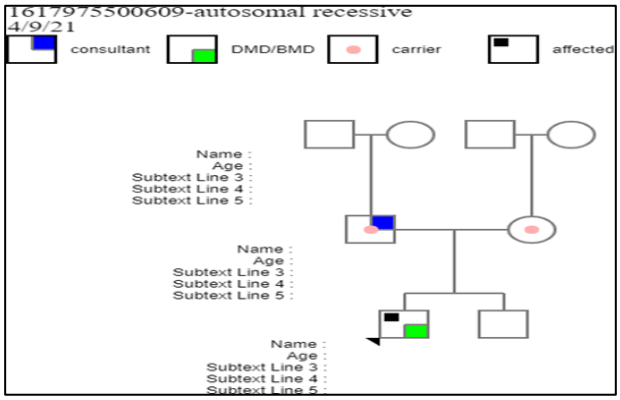

Figure 4: Pedigree of case 5.

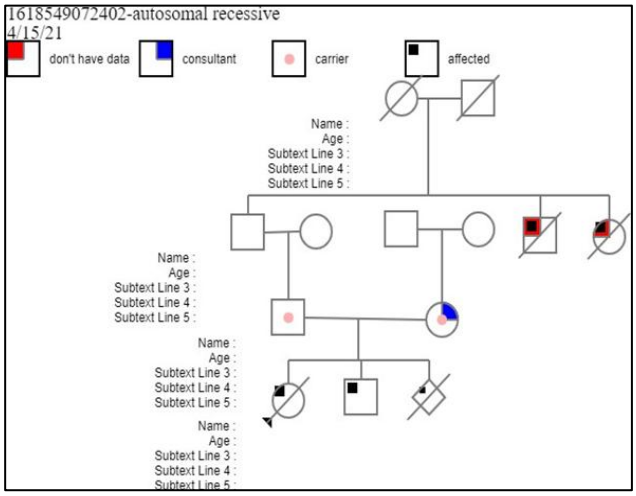

Figure 5: Pedigree of cases 6-8.

Case 6, also a SMA patient, had no neck control and faced problems during swallowing. Further investigation showed that the condition was linked up with paternal family (Figure 5). The subject's younger sibling (Case 7) also suffered from SMA and similar symptoms to those of case 6 were observed, thereby proving association within the paternal family (Figure 5). Case 8 was also related with case 6 and 7.

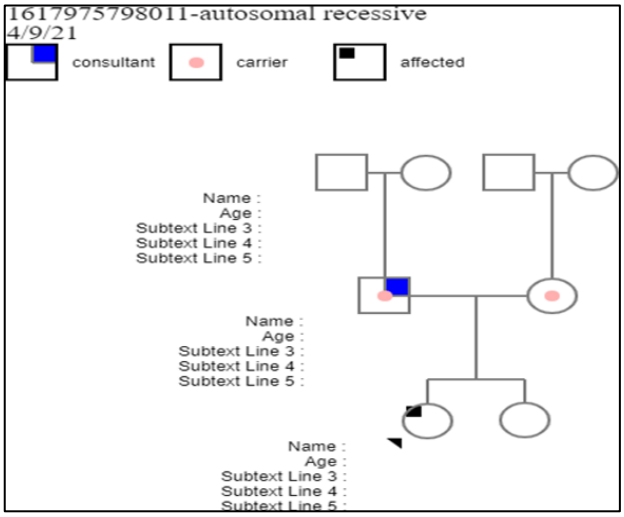

Figure 6: Pedigree of case 9.

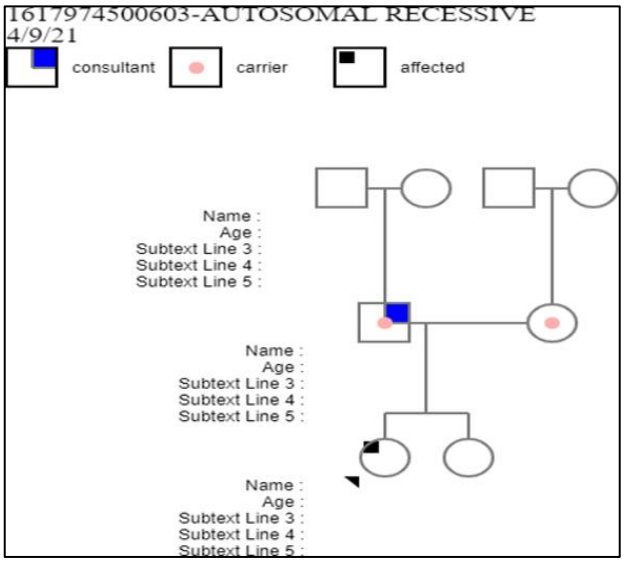

Figure 7: Pedigree of case 10.

Case 9 was a SMA patient. Investigation showed that by the age of 8-9 months, the subject was chubby and healthy but within a month, the weight was lost and muscle movements as well as limb movements gradually slowed down. There was no relationship with paternal or maternal family (Figure 6). The subject faced problems quite similar to the ones faced by case 1. The patient's older sibling was normal and healthy.

Case 10 was a SMA patient who had hypotonia in her whole body at the age of 15 months, which is termed as "flobby baby syndrome" during infancy and was not able to hold the neck. The disorder did not show any linkup with paternal as well as maternal family (Figure 7). The individual was suffering from cough and cold after an interval of every 4 to 5 days. The subject's older sibling was normal.

DISCUSSION

The present study highlighted the clinical and molecular aspects of SMA. Molecular analysis of the cohort demonstrated that majority of SMA cases arose from homozygous deletions in exon 7 of the SMN1 gene located on chromosome 5q13.2. The present findings were consistent with previous literature reporting that 95-98% of SMA patients exhibited loss of exon 7 in the SMN1 gene, often accompanied by variable deletion of exon 8.[13,14] In the present study population, 6 of the 10 subjects exhibited homozygous deletion of exon 7, while 2 individuals presented dual deletion of exon 7 and exon 8 and 2 subjects were diagnosed with homozygous deletion of exon 7 and heterozygous deletion of exon 8. The detection pattern reinforced the notion that exon 7 deletion plays a central pathogenic role in SMA, whereas deletion of exon 8 may modify phenotype but is not universally present.

An important clinical observation emerging from the study is the co-occurrence of SMA with DMD in two male patients. Although rare, reports of dual neuromuscular pathologies highlight the need for broader genetic assessment in children presenting atypical or overlapping neuromuscular phenotypes. In the present cases, no deletions or duplications in dystrophin exons were detected through PCR and dosage analysis; however, the absence of deletion did not rule out DMD/BMD entirely, as point mutations, small rearrangements, and deep intronic variants could contribute to pathogenesis. This underscores the diagnostic limitations of exon-based deletion/duplication testing and supports the use of more comprehensive sequencing strategies when clinically indicated.

The findings also reaffirmed the autosomal recessive inheritance pattern, where affected individuals typically inherit the two nonfunctional SMN1 alleles from phenotypically normal carrier parents. This pattern was evident in case 1, where recurrence of the disorder in a subsequent pregnancy resulted in fetal termination following prenatal diagnosis. Such outcomes emphasize the value of genetic counseling, carrier screening and prenatal or preimplantation genetic testing, particularly in families with known SMA history. The presence of at least one functional copy of SMN2 in all patients is noteworthy, as SMN2 copy number is known to modify disease severity by partially compensating SMN protein production. While the current study did not quantify SMN2 copies, the observed variability in clinical presentation among cases suggests differential SMN2 copy contribution, particularly in patients who survived into adolescence.

The documented clinical course also reflected mortality in two children diagnosed during early childhood, consistent with natural history of early-onset SMA types 1 and 2, which carry significant respiratory and nutritional complications. However, advances in supportive care and advanced molecular therapies, including SMN-enhancing treatments (such as nusinersen, onasemnogene abeparvovec, and risdiplam) have shown potential to alter the disease outcomes. Although these therapies were not part of the current study, the results underscore the need for early diagnosis to maximize therapeutic benefit. The scenario of the COVID-19 pandemic further highlighted the vulnerability of children with underlying neuromuscular disorders to respiratory compromise, reinforcing the importance of multidisciplinary supportive management in SMA.

Overall, the study illustrated that homozygous deletion of SMN1 exon 7 remained the most reliable molecular marker for SMA diagnosis and molecular testing was indispensable for confirmation, carrier evaluation and prenatal decision-making. The coexistence of SMA with DMD/BMD in a subset of patients underscores phenotypic complexities and genetic heterogeneity requiring comprehensive diagnostic approaches. Larger population studies combined with SMN2 copy analysis may provide deeper insight into genotype-phenotype correlations and disease severity modulation.

Limitations

The major problem was that some patients had same clinical symptoms, but parents did not get genetic analysis conducted, but they accepted them as a handicap individual. There is lack of awareness and consciousness among parents and society for accepting the condition as a genetic disorder and create ways for management of life in such conditions.

CONCLUSION

The present study confirms that SMA is predominantly associated with homozygous deletion of exon 7 of the SMN1 gene, reinforcing its role as a key molecular marker for diagnosis. The findings support an autosomal recessive inheritance pattern, with most affected individuals born to carrier parents. The occasional coexistence of SMA with DMD highlights the need for comprehensive genetic evaluation in neuromuscular disorders. Molecular diagnostic techniques proved essential for accurate detection, carrier screening and prenatal diagnosis. Overall, the study emphasizes the importance of early genetic testing and counseling to improve disease management and enable informed reproductive decisions in affected families.

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