Current Trends in Biotechnology and Pharmacy
Vol. 18(4) 2062-2070, October 2024, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2024.4.51

Advances in SMA: Genetic Insights, Prevalence in GCC, and Emerging Therapeutic Approaches

Mohamed A Salama[1,2], Mohamed H. Zani[1], Mohamed Morsi Ahmed[1,3], Omran Rashidi[4], Reham H Baaqeel[5], Lujain Alsini[6], Noor Ahmad Shaikh[5*]

[1]Department of Biology, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia.
[2]Eurofins Clinical, Riyadh, Saudi Arabia.
[3]Nucleic Acids Research Department, Genetic Engineering and Biotechnology Research Institute (GEBRI), City for Scientific Research and Technological Applications. Alexandria, Egypt.
[4]Genalive Medical Co, Riyadh, Saudi Arabia.
[5]Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
[6]Translational Pathology Department, National Guard Hospital, Riyadh, Saudi Arabia.

[*]Corresponding author: nshaik@kau.edu.sa

Abstract

SMA is a neurodegenerative autosomal recessive disorder characterized by progressive degeneration of motor neurons of the spinal cord, leading to muscle weakness and early mortality. SMA can be divided into four types, extending from severe infantile-onset type I to milder forms that appear later in life, such as types II, III, and IV. The GCC countries have an unusually high prevalence of SMA, largely due to the high rate of consanguineous marriages, a situation that increases the risk of inheritance of autosomal recessive conditions. Genetic predisposition to SMA is due to mutations in the Survival Motor Neuron gene occurring in two almost identical copies, SMN1 and SMN2. The severity of this disease is correlated with the number of functional copies of these genes; however, SMN2 is also capable of playing a very critical compensatory role. The more the number of copies of SMN2 one has, the milder the forms of the disease. Molecular screening techniques such as genetic testing and carrier screening are very essential in this regard for early diagnosis and management of SMA. This orphan disease has several FDA- and EMA-approved treatment options for SMA, including Nusinersen, Onasemnogene abeparvovec, and Risdiplam. Results with these treatments are very promising and show improved motor function and survival in the affected patients. The present review outlines current developments in research and treatment of the disease, drawing attention to the high prevalence of the condition in GCC countries and also to the contribution that genetic screening, combined with the emerging therapies, can have in managing this devastating disorder.

Keywords: SMA, SMN1, SMN2, Risdiplam, Onasemnogene Abeparvovec, Nusinersen

Introduction

Spinal muscular atrophy (SMA) includes a group of inherited neurodegenerative diseases of an autosomal recessive nature. Clinically, SMA is characterized by muscle weakness and atrophy associated with loss of spinal and sometimes bulbar motor neurons (1).

Since the disease's first clinical identification in 1891, we have learned more about its pathogenesis and anatomical features during the course of the following century (1, 2, 3, 4). This ailment was first linked to the 5q13.2 locus in 1990, and by 1995, the gene survival motor neuron (SMN) was implicated in the disorder's presentation (1, 4). The identification of the gene helped in the creation of animal models by the early 2000's, and this in turn enabled the identification of the role of *SMN2* in preserving the phenotype and providing new avenues of therapeutic interventions. Advances in SMA genetic testing and diagnosis have provided accurate epidemiological information; at least 1 in 10,000–20,000 live newborns have the condition, and over 90% of affected individuals are homozygous for SMN1 deletion (5; 4). In contrast, some studies report that SMA affects approximately 1 in 6,000 individuals and is the most common form of hereditary cause of childhood mortality (2).

This review gleans insights and evidence from published literature and aims to provide a comprehensive overview of the condition, mainly focusing on SMA's genetic predisposition, global and national frequencies in Saudi Arabia, and molecular screening and testing techniques.

Clinical manifestations

Classically, SMA presents with progressive muscle weakness and atrophy leading to irreversible loss of anterior horn cells in the spinal cord and the brain stem nuclei. The weakness associated with the condition ranges, with the weakness being progressive, symmetric, and greater in the proximal region than in the distal. Since its identification, attempts have been made to classify SMA into discrete and identifiable phenotypic subtypes, but with the advent of diagnostic technologies, it has become clear that SMA has varied phenotypes (6). Advances in next-generation technologies have now identified as many as 33 genes that have been implicated in the manifestation of the SMA phenotype. This technology has enabled researchers to identify the mechanisms that include defects in RNA metabolism and splicing, axonal transport, and motor neuron development and connectivity (6). This unraveling of mechanisms has helped progress from the disease being referred to as SMA5q (the most common form of the condition) to a multitude of phenotypes that can be attributed to the genetic heterogeneity (6). The location of the gene (*SMN1*) responsible for SMA is a complex locus, as it contains a 500-kb duplication and loss of a telomeric region, which is what leads to SMA, while the *SMN2* gene is a centromeric gene. Both genes differ by one exon, i.e., exon 7, that is spliced out in the *SMN2* gene because of a C>T transition at c840. Though most of the mRNA transcripts produced do not contain exon 7, there still are some transcripts that escape this predicament, and these transcripts are responsible for the 5-10% of full-length transcripts that rescue the SMN1 phenotype (7). A multitude of patients (approximately 96%) present with a *SMN1* homozygous deletion for the exons seven and eight or exon seven only, whereas the other four percent are compound heterozygotes for the *SMN1* locus with a deletion of one allele and a point mutation at the other (8).

The most common form of the condition manifests due to the homozygous disrupted *SMN1,* which results in a reduction in the SMN levels in the motor neurons, and is an autosomal recessive condition with a frequency of 1 in 6000 to 10,000 and a carrier frequency of 1 in 40 to 60 adults (6). The latest technological innovations have now been able to classify SMA into four types according to their symptom severity and genotypes, though this might change based on the advancements that have been achieved in the treatment of the condition (9). The below-given table classifies the different types of SMA (Table 1) (6).

Table 1: Spinal muscular atrophies (SMA) with known gene abnormalities/loci (adopted from Farrar & Kiernan, 2015)

Type of SMA	Inheritance	Age of onset	Clinical Phenotype	Gene/ Locus	Gene identified in
Proximal SMA SMA5q or SMN-related SMA	Autosomal recessive	By six months	Proximal greater than distal limb weakness; diaphragm and facial muscles relatively spread	SMN1	1995
SMA Type A (infantile SMA, Werdnig- Hoffman disease)					
SMA Type 2					
SMA Type 3 (Kugelberg-Welander disease)		6-18 months			
		18 months			
SMA Type 4		Adult			
X-linked infantile SMA Type 2	X-linked	Infantile	Similar to SMA Type 1. Severe congenital hypotonia, arthrogryposis	UBE1	2008
SMA phenotype due to mitochondrial dysfunction	Autosomal recessive	Infantile	Similar to SMA Type 1 with dilated cardiomyopathy, ptosis, impaired extraocular movements.	SCO2	1999
SMA with pontocerebellar hypoplasia type 1	Autosomal recessive	Congenital or infantile	Diffuse weakness, microcephaly with/without arthrogryposis	EXOSC3 TSEN54 RARS2 VRK1	2012 2011 2011 2009
SMALED1	Autosomal dominant	Congenital to adult	Proximal greater than distal leg weakness, arms normal	DYNC1H1	2012
SMALED2	Autosomal dominant	Congenital to adult	Proximal and distal muscle weakness of the lower limbs with or without mild upper limb weakness, mild upper motor signs	BICD2	2013
DSMA4	Autosomal recessive	By three years	Proximal weakness, difficulty walking and climbing stairs, progressing to nonambulant and respiratory weakness.	PLEKHG5	2007

Adult-onset proximal SMA	Autosomal dominant	Adult	Proximal greater than distal weakness	VAPB	2004
Adult-onset proximal SMA followed by cardiac involvement	Autosomal dominant	Adult	Proximal greater than distal weakness	LMNA	2007
Adult-onset proximal SMA with respiratory failure	Autosomal dominant	Adult	Proximal weakness of upper limbs followed by prominent respiratory failure	MAPT	2014
Spinal and bulbar muscular atrophy (Kennedy Syndrome)	X-linked recessive	Adult	Widespread and prominent fasciculations, Progressive proximal and distal limb and bulbar muscle weakness and atrophy, dysphagia, gynaecomastia, and androgen resistance	AR	1991
Distal SMA/HMN					
HMN1	Autosomal dominant	Child to young adult	Distal leg then arm weakness	HSPB1, HSPB8, GARS, DYNC1H1, 7q34	
HMN2	Autosomal dominant	Adult	Distal leg then arm weakness		
HMN2A				HSPB8	2004
HMN2B				HSPB1	2004
HMN2C				HSPN3	2010
HMN2D				FBXO38	2013
HMN3 (DSMA3)	Autosomal recessive	Childhood	Mild distal leg then arm weakness	11q13	
HMN4 (DSMA3)	Autosomal recessive	Infancy to young adult	Severe proximal and distal weakness, diaphragmatic palsy	11q13	
HMN5	Autosomal dominant	Child to adult	Upper limb predominance with onset in thenar and first dorsal interosseus muscles and subsequent weakness of legs		
HMN5A				GARS	2003
HMN5B				REEP1	2012
HMN5C				BSCL2	2004
HMN6 (DSMA1 or SMARD1)	Autosomal recessive	Infancy	Early diaphragm weakness, distal greater than proximal limb weakness	IGHMBP2	2001

HMN7 HMN7A HMN7B	Autosomal dominant	Juvenile/ young adult	Vocal cord paresis, hand weakness and subsequent distal leg weakness	SLC5A7; CHT DCTN1	2012 2003
DSMA5	Autosomal recessive	Young adult	Progressive distal greater than proximal lower limb muscle weakness and atrophy	DNAJB2; HSJ1	2012
HMN with upper motor neuron signs	Autosomal dominant	Juvenile	Distal leg then arm weakness with pyramidal signs	SETX	2004
HMNJ (DSMA2)	Autosomal recessive	Juvenile	Distal leg then arm weakness with pyramidal signs originating from the Jerash region of Jordan	9p21	2000
X-linked dHMN (SMAX3)	X-linked recessive	Child to adult	Distal leg then arm weakness	ATP7A	2010
SMARD2	X-linked recessive	Neonatal	Distal weakness, early onset diaphragmatic weakness and respiratory failure	LASIL	2014
		Young adult	Distal and scapuloperoneal weakness with or without congenital absence of muscles or laryngeal palsy	TRPV4	2010
Congenital DSMA	Autosomal dominant	Congenital	Proximal and distal non-progressive lower limb weakness with or without vocal cord paralysis or arthrogryposis	TRPV4	2010
DSMA with mitochondrial dysfunction	Mitochondrial	Childhood to adult	Episodic weakness associated with a later-onset distal lower limb weakness and atrophy Episodic weakness associated with a later-onset distal motor neuropathy	mtATP6 mtATP8	2012 2013

*Distal HMN is based on the original classification by Harding

SMN: survival motor neuron; SMALED: spinal muscular atrophy with lower extremity predominance; DSMA: distal spinal muscular atrophy; HMN: distal hereditary motor neuropathy, SMARD: spinal muscular atrophy with respiratory distress, HMNJ: distal hereditary motor meuropathy, Jerash type; dHMN: distal HMN

Most 5q SMA patients present with a homozygous deletion of the seventh exon of *SMN1,* with the remaining presenting with a deletion and a heterozygous point mutation. De novo mutations have been reported in two percent of the cases, indicating that this particular region on the fifth chromosome is unstable due to the presence of a high number of copy number repeats causing problems during the crossing over, thus leading to de novo mutations. Patients who present with mild symptoms might undergo gene conversion of the *SMN1* and *SMN2* genes (10). The number of copies of SMN2 varies in the general population, with 15% of individuals not having even a single copy of the gene, 33% having a single copy, and 50% of the general population having two copies of the gene (10).

Spinal muscular atrophy in gulf cooperation council countries

Data specific to SMA in GCC is limited, but there is an increase in it. Research shows that globally, the occurrence of SMA is different, with estimates ranging from 1 case per 6,000 live births. Caused by genetic factors and consanguinity, there are high

levels of this illness within some populations that could be higher than others. The number of cases of genetic abnormalities such as SMA could be on the rise in GCC countries than in non-consanguineous communities, as consanguineous marriages are more common.

"In the GCC states the distribution and prevalence of SMA genotypes are influenced by a number of factors, consisting of consanguinity rates inclusive of genetic diversity within populations of Saudi Arabia, Kuwait, Qatar, Bahrain, and Oman, along with the United Arab Emirates." According to this quotation from Alkuraya et al. (2004), approximately 20% of loci known so far exhibit no polymorphisms, while most others depict variability along their DNA sequence, such as insertion/deletions, frameshifts, etc. Among them, it was found that ~42% came within a 100-bp region near one neighboring coding gene (11)."

Saudi Arabia has a very high prevalence of SMA, estimated at 13.26 per 100,000 people (12; 13). The incidence rate is equally high, estimated at 40 times the rate in Western countries at 10-193 for every 100,000 births (14). Verhaart et al. (2017) attribute the high prevalence to parental consanguinity (i.e., intra-familial unions involving first/second cousins or other familial ties). Studies estimate that 1 billion people reside in communities that practice consanguineous marriages, especially in the Middle East, North Africa, and West Asia (15). An estimated 20% to 50% of marriages worldwide are considered to be such marriages. As a result, children born in these areas have a high incidence of genetic and congenital illnesses. The closer the familial relation, the higher the risk of the offspring inheriting identical copies of genes (including faulty ones) from both parents. A recent study in Saudi Arabia reported an SMA carrier frequency of 2.6%, which is higher than the reported global frequency of 1.25–2% (16). Valuable insights into the genetic landscape of SMA have been provided by research undertaken in Saudi Arabia. In the study carried out by Alfadhel et al. (2017), they investigated the molecular genetics of SMA in a group of patients from this country. The prevalent type of SMA among all affected individuals participating in their research turned out to be possession of one copy only of one gene called SMN1 exon 7, which resulted in its complete deletion on both chromosomes, resulting in what is known as homozygous deletions. Thereafter signs emerged as those of classical nerve degeneration, which involved early age onset while leaving individuals fully restrained or even dead (17). Studies that have explored Kuwait's genetic epidemiology of SMA have provided insight into its prevalence and the specific genetic variants that are present in this population. The disorder is seen among different ethnic and cultural groups across Kuwait, although there has been no mention of particular incidences of SMA in the literature (18).

Diagnosis of spinal muscular atrophy

Diagnosing SMA primarily depends on the deletion of the SMN1 gene and the number of SMN2 gene copies, which are prognostic indicators and modifiers of the disease. Early onset of SMA is linked to fewer SMN2 copies, resulting in shorter survival, whereas more copies correlate with later onset and longer survival (19). Phosphorylated neurofilament chains also serve as biomarkers, with elevated levels observed in presymptomatic individuals with two SMN2 copies and in SMA patients (20; 21). Non-molecular biomarkers like compound muscle action potential (CMAP) amplitude, motor unit number estimation (MUNE), and electrical impedance myography (EIM) are crucial for understanding SMA's etiopathogenesis and differentiating between symptomatic and presymptomatic patients (20). Imaging tools such as MRI, muscle ultrasound, and multispectral optoacoustic tomography help detect the symptomatic phase of SMA (19).

Genetic counselling in spinal muscular atrophy

Genetic counseling plays a vital role

in identifying individuals at risk of inheriting diseases or passing on the risk alleles to the future generation. Generally, prenatal testing is requested by would-be parents who have had prior history of the condition in their family or have a child who is positive for SMA. Newborn screening should be made compulsory in those families that have a history of SMA within their family. Because most cases arise from consanguineous marriages, it is critical that the couple undertake genetic testing to avoid complications.

Treatment for spinal muscular atrophy

Treatment options for spinal muscular atrophy (SMA) are under continuous exploration due to the rarity of the condition. This scarcity has led to limited interest from drug manufacturers in developing SMA therapies. Currently, the available treatments are orphan drugs, which are specifically developed for rare diseases. Three orphan drugs have been authorized for SMA treatment: nusinersen, onasemnogene abeparvovec, and risdiplam (22).

Nusinersen

This antisense oligonucleotide was the first drug approved for SMA by the FDA in 2016 and the EMA in 2017. Nusinersen targets the intronic splice silencing site (ISS-N1) in intron 7 of the SMN2 gene, preventing the binding of hnRNPA1 and hnRNPA2 to ISS-N1. This allows exon 7 to be included in the final transcript, producing a full-length SMN protein. However, nusinersen cannot cross the blood-brain barrier, requiring recurrent lumbar punctures for administration (22).

Onasemnogene abeparvovec

Approved in 2020 for patients under two years old with biallelic SMN1 mutations and either three or four copies of the SMN2 gene or infantile-onset SMA, this gene replacement therapy uses adeno-associated viral vector serotype 9 (scAAV9) for delivery. It works through recombinant self-complementation and has shown significantly improved lifespan in preclinical mouse studies, with the ability to cross the blood-brain barrier (22). This suggests potential effectiveness in humans diagnosed early in life.

Risdiplam

An oral medication approved in 2020 by the FDA and EMA, risdiplam is a coumarin-based pyrido-pyrimidinone derivative. It has excellent tissue distribution, as shown in pharmacokinetic analyses from preclinical studies (22). These advancements in SMA treatment highlight the ongoing efforts to manage this rare but debilitating condition.

Conclusion

Spinal muscular atrophy (SMA) is a genetic disability marked by progressive muscle degeneration and diminished strength due to the breakdown of nerve cells controlling muscle movement in the brainstem and spinal cord. This condition primarily results from SMN1 gene mutations, with varying severity levels from type 0 (detected before birth) to type IV (appearing in adulthood). The disorder severely impacts patients' mobility, affecting activities like walking and sitting, and can lead to breathing and swallowing difficulties in advanced stages. Early identification and management are crucial. Significant advancements in genetic research and therapeutics, including treatments like nusinersen (Spinraza), onasemnogene abeparvovec (Zolgensma), and risdiplam (Evrysdi), have improved the outlook for SMA patients by potentially halting or restoring neurological functions. Timely initiation of these treatments, supported by newborn screening programs, is essential. Thus, further efforts are still being made in relation to gene therapy, while other complementary treatments, such as physiotherapy/occupational therapy, ventilator use, and nutrition management, have led to better standards of living among patients with SMA. However, even with advancements, some problems still exist. High treatment costs, lifelong need for medical attention,

and their effect on the social and mental well-being of patients and their relatives require that management be all-inclusive. To address these demands, joint health workers must have multidisciplinary teams comprising neurologists, genetic counselors, and others. Continued research, early intervention, and holistic care approaches are key to improving outcomes and offering hope to individuals and families affected by this disorder.

Conflict of Interest

All the authors state that none of them have any conflict of interest.

Acknowledgements:

Authors would like to acknowledge the technical support received from King Abdulaziz University.

Funding Source

Authors did not receive any funding for this work

References

1. Sumner, C.J., Paushkin, S. and Ko, C.-P. (2017) *Spinal muscular atrophy: Disease mechanisms and therapy*. London: Academic Press, an imprint of Elsevier.

2. Ross, L.F. and Kwon, J.M. (2019) 'Spinal muscular atrophy: Past, present, and future', *NeoReviews*, 20(8). doi:10.1542/neo.20-8-e437.

3. Mercuri, E. *et al.* (2022) 'Spinal muscular atrophy', *Nature Reviews Disease Primers*, 8(1). doi:10.1038/s41572-022-00380-8.

4. Nishio, H. *et al.* (2023) 'Spinal muscular atrophy: The past, present, and future of diagnosis and treatment', *International Journal of Molecular Sciences*, 24(15), p. 11939. doi:10.3390/ijms241511939.

5. Kolb, S.J. and Kissel, J.T. (2015) 'Spinal muscular atrophy', *Neurologic Clinics*, 33(4), pp. 831–846. doi:10.1016/j.ncl.2015.07.004.

6. Farrar, M.A. and Kiernan, M.C. (2015) 'The genetics of Spinal Muscular Atrophy: Progress and challenges', *Neurotherapeutics*, 12(2), pp. 290–302. doi:10.1007/s13311-014-0314-x.

7. Mailman, M.D. *et al.* (2002) 'Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2', *Genetics in Medicine*, 4(1), pp. 20–26. doi:10.1097/00125817-200201000-00004.

8. Alías, L. *et al.* (2008) 'Mutation update of spinal muscular atrophy in Spain: Molecular characterization of 745 unrelated patients and identification of four novel mutations in the SMN1 gene', *Human Genetics*, 125(1), pp. 29–39. doi:10.1007/s00439-008-0598-1.

9. Keinath, M.C., Prior, D.E. and Prior, T.W. (2021) 'Spinal muscular atrophy: Mutations, testing, and clinical relevance', *The Application of Clinical Genetics*, Volume 14, pp. 11–25. doi:10.2147/tacg.s239603.

10. Oskoui, M., Darras, B.T. and De Vivo, D.C. (2017) 'Spinal muscular atrophy', *Spinal Muscular Atrophy*, pp. 3–19. doi:10.1016/b978-0-12-803685-3.00001-x.

11. Rabea, F. *et al.* (2024) 'Spinal muscular atrophy genetic epidemiology and the case for premarital genomic screening in Arab populations', *Communications Medicine*, 4(1). doi:10.1038/s43856-024-00548-1.

12. Verhaart, I.E. *et al.* (2017) 'Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review', *Orphanet Journal of Rare Diseases*, 12(1). doi:10.1186/s13023-017-0671-8.

13. Al Jumah, M. *et al.* (2022) 'Spinal muscular atrophy carrier frequency in Saudi Arabia', *Molecular Genetics & Genomic Medicine*, 10(11). doi:10.1002/mgg3.2049.

14. Alghamdi, A. *et al.* (2023) 'Identifying clinical and genetic characteristics of spinal muscular atrophy patients and families in Saudi Arabia', *Cureus* [Preprint]. doi:10.7759/cureus.46452.

15. Hamamy, H. (2011) 'Consanguineous marriages', *Journal of Community Genetics*, 3(3), pp. 185–192. doi:10.1007/s12687-011-0072-y.

16. AlTawari, A. *et al.* (2024) 'Nusinersen treatment for spinal muscular atrophy: Retrospective multicenter study of pediatric and adult patients in Kuwait', *Neurology International*, 16(3), pp. 631–642. doi:10.3390/neurolint16030047.

17. Alfadhel, M. *et al.* (2017) 'Expanded newborn screening program in Saudi Arabia: Incidence of screened disorders', *Journal of Paediatrics and Child Health*, 53(6), pp. 585–591. doi:10.1111/jpc.13469.

18. Mendell, J.R. *et al.* (2017) 'Single-dose gene-replacement therapy for spinal muscular atrophy', *New England Journal of Medicine*, 377(18), pp. 1713–1722. doi:10.1056/nejmoa1706198.

19. Babić, M. *et al.* (2023) 'Molecular biomarkers for the diagnosis, prognosis, and pharmacodynamics of spinal muscular atrophy', *Journal of Clinical Medicine*, 12(15), p. 5060. doi:10.3390/jcm12155060.

20. Pino, M.G., Rich, K.A. and Kolb, S.J. (2021) 'Update on biomarkers in spinal muscular atrophy', *Biomarker Insights*, 16, p. 117727192110356. doi:10.1177/11772719211035643.

21. Schwartz, O. *et al.* (2022) 'Spinal muscular atrophy – is newborn screening too late for children with two SMN2 copies?', *Journal of Neuromuscular Diseases*, 9(3), pp. 389–396. doi:10.3233/jnd-220789.

22. Crisafulli, S. *et al.* (2023) 'Pharmacological therapies of spinal muscular atrophy: A narrative review of Preclinical, clinical–experimental, and real-world evidence', *Brain Sciences*, 13(10), p. 1446. doi:10.3390/brainsci13101446.