


ORIGINAL ARTICLE

Spinal muscular atrophy carrier frequency in Saudi Arabia

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Abstract

Background: Spinal Muscular Dystrophy (SMA) is one of the leading causes of death in infants and young children from heritable diseases. Although no large-scale population-based studies have been done in Saudi Arabia, it is reported that the incidence of SMA is higher in the Saudi population partly because of the high degree of consanguineous marriages.

Methods: The final analysis included 4198 normal volunteers aged between 18 and 25 years old, 54.7% males, and 45.3% females. Whole blood was spotted directly from finger pricks onto IsoCode Stix™ and genomic DNA was isolated using one triangle from the machine. To discern the *SMN1* copy number independently from *SMN2*, Multiplex PCR with Dral restriction fragment analysis was completed. We used the carrier frequency and population-level data to estimate the prevalence of SMA in the population using the life-table method.

Results: This data analysis showed the presence of one copy of the *SMN1* gene in 108 samples and two copies in 4090 samples, which resulted from a carrier frequency of 2.6%. The carrier frequency was twofold in females reaching 3.7% compared to 1.6% in males. 27% of participants were children of first-cousin marriages. We estimated the birth incidence of SMA to be 32 per 100,000 birth and the total number of people living with SMA in the Kingdom of Saudi Arabia to be 2265 of which 188 are type I, 1213 are type II, and 8,64 are type III.

Conclusion: The SMA carrier rate of 2.6% in Saudi control subjects is slightly higher than the reported global frequency of 1.25 to 2% with links to the high degree of consanguinity.

KEYWORDS

consanguineous marriages, epidemiology, mass screening, Saudi Arabia, spinal muscular atrophy

1 | INTRODUCTION

Spinal muscular atrophies (SMAs) are a group of genetic disorders described by motor neuron loss in the spinal

cord and lower brainstem, muscle weakness, and atrophy (Farrar & Kiernan, 2015; Wan et al., 2020). Following cystic fibrosis, it is the second most common fatal autosomal recessive disorder (Verhaart et al., 2017). It is well proven

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that SMA is initiated by genetic deletion or mutation in the survival of motor neuron 1 *SMN1* (600354) gene on chromosome 5, which results in decreased levels of the survival of the motor neuron (*SMN*) protein. The *SMN1* gene is located on an inverted duplication on chromosome 5q13.2 next to the *SMN2* (601627) gene (Lefebvre et al., 1995). The deletion of exon 7 on chromosome 5 is the most common mutation of the *SMN1* gene (Ogino & Wilson, 2002). The *SMN2* gene, although 99% identical to the *SMN1* gene, is a modifying gene that regulates phenotypic expression. Disease severity in SMA is inversely proportional to the *SMN2* copy number. This number varies from 0 to 8 in the normal population (Butchbach, 2016; Kolb & Kissel, 2015) where the presence of three or more copies of *SMN2* is associated with a milder phenotype (Mailman et al., 2002). While the majority of SMA forms are related to 5q mutations; there are cases of non-5q spinal muscular atrophies (Darras, 2011; Peeters et al., 2014).

The *SMN* protein deficiency preferentially affects α -motor neurons, leading to their degeneration and subsequent atrophy of limb and trunk muscles resulting in death in severe forms of the disease (Darbà, 2020; Nash et al., 2016).

The severity of SMA is highly variable and the clinical features can be classified into four main phenotypes (SMA I, SMA II, SMA III, SMA IV) based on the age of onset and maximum motor function achieved (Bertoli et al., 2017; Munsat & Davies, 1992). The most common and severe forms are SMA type I (SMA I) and type II (SMA II) which are caused by mutations in the survival motor neuron 1 (*SMN1*, *SMN T*, *telomeres*) gene, located on chromosome five (Lefebvre et al., 1995). Patients with SMA I develop symptoms before six months of age and never achieve the milestone of sitting without assistance. Moreover, patients have trouble swallowing and breathing, and many die or require permanent ventilator support by age two (De Sanctis et al., 2016; Finkel et al., 2014; Howell et al., 2019). Patients with less severe forms of SMA, such as SMA II and III develop symptoms later in childhood and achieve motor milestones such as independent sitting and walking although they may lose these abilities over time (Howell et al., 2019). In rare cases (~4%) SMA is caused by a mutation in another gene (*non-5q SMA*).

Since SMA is a rare condition with a heterogeneous representation, studying its prevalence and incidence may be challenging. The heterogeneity of the condition can lead to delays and complications in diagnosis especially outside of specialist clinics, which contributes to the challenges in understanding the epidemiology of the disease. A systematic review study done in 2017 showed that the incidence and prevalence of SMA differ between available studies. Most of these studies relied on clinical rather than genetic diagnosis and were often small cohort

studies studying mainly European populations in limited geographical populations (Verhaart et al., 2017). Based on the available data, the incidence of SMA is often cited as being approximately 10 in 100,000 live births worldwide. Prevalence is estimated to be approximately 1 to 2 in 100,000 persons and is affected by the considerably shortened life expectancy in the most common type of SMA (Verhaart et al., 2017).

Although SMA type I accounts for the majority of all new SMA cases (Ogino et al., 2004), the studies that examined a SMA type I in Norway, China, and Estonia only showed a prevalence of 0.04 to 0.28 per 100,000 (Chung et al., 2003; Tangsrud & Halvorsen, 1988; Vaidla et al., 2006), which is greatly lower than the 1–2 per 100,000 persons noted for all SMA. It is important to note that patients with SMA type I have a short life expectancy, which could be a customary reason for this lower prevalence. Currently, a median life expectancy of around 1 year of age is estimated for type I patients, whereas in type II 75–93% of patients survive beyond 20 years of age, and life expectancy for type III is assumed to be close to the normal population (Al Rajeh et al., 1993; Finkel et al., 2014; Verhaart et al., 2017; Zerres et al., 1997). The prevalence of both SMA type II and III together has been estimated at around 1.5 per 100,000 (Verhaart et al., 2017). Of the three studies that examined type II and type III individually, two found a higher prevalence of type III compared to type II (Norwood et al., 2009). This may be explained by the longer life expectancy of type III patients compared to type II SMA patients (Verhaart et al., 2017). In the case of SMA, the high mortality rate and the presence of the genotype at birth make birth prevalence a more precise measure of the prevalence of the disease. Since newborn screening is not extensively performed, the number of patients expressing the phenotype is used instead to estimate the incidence. When evaluating the incidence of all types of SMA combined, on average an incidence of around 8 per 100,000 live births is found (~1 in 12,000). However, some studies show a somewhat lower or higher incidence (Verhaart et al., 2017).

There is no cure for SMA; however, an understanding of the molecular genetics of SMA has led to the development of pre-clinical models and various potential therapeutic approaches (Arnold & Burghes, 2013; Kolb & Kissel, 2015; Lorson et al., 2010). Recent advances in the molecular genetics of SMA have led to the discovery of numerous therapies, and therapeutic strategies have been developed according to the exclusive genomic structure of the *SMN* genes. However, the clinical care of these patients continues to differ, for reasons like the geographical variation in the availability of medical expertise, large clinical phenotypic variation, multiorgan system involvement, differing value systems of clinicians and families, and variations

in financial resources (Wang & Lunn, 2008). The present study aimed to study the prevalence of SMA carriers in a representative sample of Saudi volunteers in Riyadh.

2 | METHODS

2.1 | Estimating SMA carrier frequency

Carrier status was examined in 4257 normal volunteers, 59 subjects were excluded due to age (more than 25 years). The final analysis included 4198 normal volunteers aged between 18 and 25 years old university and military college students, 54.7% males and 45.3% females all subjects answered questionnaires about health status, presence or absence of a family history of neurological disease, and especially neuromuscular ones, and consanguinity of their parents.

Whole blood was spotted directly from finger pricks onto IsoCode Stix™. Genomic DNA was isolated using one triangle from the IsoCode Stix. The eluted DNA was quantified and then used for multiplex-PCR. To facilitate the detection of SMA carriers harboring a heterozygous *SMN1* deletion, a multiplex PCR assay followed by fragment analysis was developed. Internal standards *BRCA1* (113705) and *MLH1* (120436) genes were used. Multiplex PCR with Dral restriction fragment analysis was conducted to identify *SMN1* NG_008691.1 and *SMN2* NG_008728.1 separately. The patterns generated from two control samples (each having either 1 or 2 *SMN1* copies) were used to distinguish between 2 copies and 1 copy of *SMN1* in carriers. Peak areas were used to calculate the *SMN1* copy number. The assay also detected *SMN2* copied which controlled the phenotype.

We have developed a protocol that optimizes the detection of *SMN1* copy numbers in the human genome producing a specific and sensitive assay using DNA from dried blood spots as well as from the QIAGEN extracted DNA. The use of fluorescent-labeled primers for specific fragment amplification (in our case *SMN1* exon 7 and *MLH1* exon 18) and subsequent application of genomic ratio (ratio of Area Under Peak of *MLH1* and *SMN1* peaks) are compatible with the copy number of the *SMN1* gene in each genome. *SMN1* copy number was interpreted by visual impression of peaks compared to controls. Thus, all healthy individuals without a family history of SMA have shown the presence of 2 *SMN1* copies per genome, and there is no overlapping in the *MLH1/SMN1* ratio between the two groups, at least in this small number of samples. Only *SMN1* and not *SMN2* was quantified in the normal participants because the focus of the study was *SMN1* carrier status. The current method, similarly to other methods reported to date (Feldkötter et al., 2002; Martín

et al., 2002; Scheffer et al., 2000), does not distinguish between individuals with two *SMN1* copies in both chromosomes (genotype 1:1, non-SMA carrier) and individuals with 2 *SMN1* copies in single chromosomes (genotype 0:2, SMA carrier) (Majumdar et al., 2005). The methodology was verified using known positive cases. Samples from a clinical genetics laboratory that were confirmed affected for *SMN1* exon 7 deletion by CAP-approved protocol were

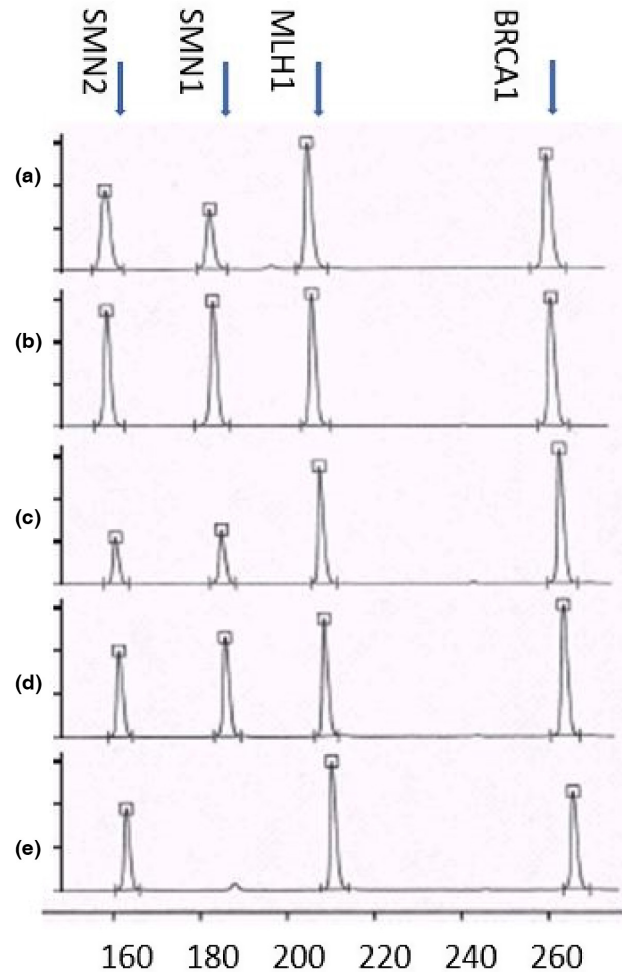


FIGURE 1 The pattern of multiplex-PCR of individual DNA samples. Migration of peaks corresponding to fragments of the genes (*SMN2*, *SMN1*, *MLH1*, and *BRCA1*) is shown by arrows. Relative fluorescence intensity of each peak is shown in Y-axis and base pair size scale is shown at the bottom. Lanes a and B indicate the DNA from an SMA carrier (a) and a healthy volunteer (b), and lanes C and D indicate the DNA from an individual having 1 *SMN1* copy (c) and an individual having 2 *SMN1* copies per genome (d); latter samples were received as a gift from France. Lane E indicates the DNA from an SMA patient (known to have homozygous deletion of *SMN1*). Each multiplex-PCR (IsoCode extracted DNAs, lanes A [parent of a patient] and B [a healthy volunteer]; and QIAGEN extracted DNAs, gift from Dr. Saugier-veber, lanes C [contains only 1 *SMN1* copy] and D [contains 2 *SMN1* copies]) yielded a pattern composed of four fluorescent peaks, corresponding to exon fragments of *SMN2*, *SMN1*, *MLH1*, and *BRCA1*

included as a positive control in each run for SMA carrier screening (known positive CAP survey samples were also included). Both maternal and paternal DNA from these affected patients were also included as controls.

2.2 | Estimating the number of people living with SMA

We used the life-table method (Lally et al., 2017), to combine different epidemiological parameters to estimate the total number of people living with SMA in KSA as well as by type. The model input included the total number of population living in KSA for each one year of age, the population background mortality rate for each year of age, the estimated birth at incidence per 100,000 live birth, the distribution of SMA types at birth, the probability of survival for each SMA type at any given age. The total number of population living in KSA for each 1 year of age as well as the background mortality rate was obtained from the Saudi National Statistics Authority for the year of 2018. We used data published by WHO on the relationship between the carrier frequency and affected birth per 1000 to derive the incidence of SMA at birth using our estimated carrier rate (WHO. Hereditary Diseases Programme, 1985). The distribution of the SMA type was obtained from Ogino (Ogino et al., 2004). We obtained the probability of SMA survival by type at each age from Brian (Chung et al., 2004). We finally obtained the earliest Age at SMA onset from Kaufmann et al. (Kaufmann et al., 2014).

3 | RESULTS

A representative analysis of the determination of *SMN1* exon 7 copy by multiplex-PCR is given in Figure 1.

TABLE 1 Total number of a screened carrier for the *SMN1*^a gene defect among Saudi population

1 T (carrier individual)	2 T (Normal individual)	Problematic samples	Total no.
108	4090	143	4343

^aNG_008691.1.

As expected, the peak representing the *SMN1* fragment is missing in the SMA patient's sample (lane E, DNA extracted by the IsoCode method). The simultaneous amplification of *MLH1* and *BRCA1* fragments allowed a reasonable comparison of electropherograms generated from different samples. In addition, the completeness of Dra1 digestion was monitored by the absence of an undigested *MLH1* product (conversion of 244 bp to 209 bp), a feature that is essential to distinguish between *SMN1* and *SMN2*. The results in parents of SMA patients and the initial 186 controls used in the pilot study are shown in Table 1. A total of 2297 (54.7%) were male, among the male population 38 (1.6%) were carrier individual and among the female 70 (3.7%) were carrier individual.

The total number of carriers screened for the *SMN1* gene defect among Saudi contributors is shown in Table 1. One hundred and seventy samples were done twice. Technical problems or the DNA did not amplify were noted in around 3% of the sample (145 samples). This was due to either high hemoglobin contamination from the IsoCode sample resulting in no PCR products or due to a manufacturer problem caused by labeled PCR primers originating from the primer provider. The analysis showed the presence of one copy of the *SMN1* gene in 108 samples and two copies (normal) in 4090 samples resulted in a carrier frequency of 2.6%. Despite the low proportion of female participation in this practice compared to male participation, and the population distribution which was almost (51% male and 49% female) the carrier frequency was twofold in females reaching 3.7% compared to 1.6% in males (Table 2).

Consanguineous marriages play a key role in the scattering of the SMA among the population since virtually 27% of carriers are children of first-cousin marriages. Moreover, second and third-degree marriages were present in 19.3% of the total number of carriers detected in this investigation (Refer to Supplementary Table S1). We estimated the total number of people living with SMA in KSA to be 2265 of which 188 are type I, 1213 are type II, and 864 are type III. The prevalence per 1,000,000 population is estimated to be 9.1, 58.4, and 41.6 for SMA type I, type II, and type III, respectively. Finally, we estimated the average age for individuals living with SMA type I, type II, and type III to be 1.9, 16, and 17 years of age, respectively (Table 3).

Consanguinity status	Total no.	1 T (carrier individual)	2 T (Normal individual)
Not related	2253 (53.7%)	61 (2.7%)	2192 (97.3%)
1st cousin	1134 (27.0%)	27 (2.4%)	1107 (97.6%)
Other relatives	811 (19.3%)	20 (2.5%)	791 (97.5%)
Total	4198	108 (2.6%)	4090 (97.4)

TABLE 2 The incidence rate of *SMN1*^I carrier based on the relative marriages sculpture in Saudi population

TABLE 3 Estimated number of SMA by type and by age

Age	Type I	Type II	Type III	Total SMA
0	110	55	25	190
1	28	37	17	82
2	12	37	17	66
3	7	37	17	61
4	5	37	17	59
5	4	40	18	62
6	3	39	18	60
7	3	38	18	59
8	3	38	18	58
9	2	37	18	58
10	2	33	16	51
11	2	33	16	51
12	1	33	16	50
13	1	33	16	50
14	1	33	16	50
15	1	31	15	47
16	1	31	15	47
17	1	31	15	47
18	1	31	15	47
19	1	31	15	47
20	1	35	17	53
21	0	35	17	52
22	0	35	17	52
23	0	35	17	52
24	0	35	17	52
25	0	33	16	50
26	0	33	16	49
27	0	33	16	49
28	0	33	16	49
29	0	33	16	49
30	0	29	15	44
31	0	29	15	44
32	0	29	15	44
33	0	29	15	44
34	0	29	15	44
35	0	7	13	20
36	0	2	13	15
37	0	1	13	13
38	0	0	13	13
39	0	0	13	13
40	0	0	11	11
41	0	0	11	11
42	0	0	11	11
43	0	0	11	11
44	0	0	11	11

(Continues)

TABLE 3 (Continued)

Age	Type I	Type II	Type III	Total SMA
45	0	0	9	9
46	0	0	9	9
47	0	0	9	9
48	0	0	9	9
49	0	0	9	9
50	0	0	7	7
51	0	0	7	7
52	0	0	7	7
53	0	0	7	7
54	0	0	7	7
55	0	0	6	6
56	0	0	6	6
57	0	0	6	6
58	0	0	6	6
59	0	0	6	6
60	0	0	4	4
61	0	0	4	4
62	0	0	4	4
63	0	0	4	4
64	0	0	4	4
65	0	0	3	3
66	0	0	3	3
67	0	0	3	3
68	0	0	3	3
69	0	0	3	3
70	0	0	2	2
71	0	0	2	2
72	0	0	2	2
73	0	0	2	2
74	0	0	2	2
75	0	0	1	1
76	0	0	1	1
77	0	0	1	1
78	0	0	1	1
79	0	0	1	1
80	0	0	8	8
	188	1213	864	2265

4 | DISCUSSION

This data analysis showed the presence of one copy of the *SMN1* gene in 108 samples and no copies (normal) in 4090 samples. This would result in a carrier frequency of 2.6%. This data highlighted the importance of entering this genetics investigation as a pre-marriage genetic screening in Saudi Arabia. Also, despite the low proportion of

participation of females in this practice compared to males, the carrier frequency was twofold in females (3.7%) compared to males (1.6%).

The frequency we recorded was higher than the number recorded in a Korean study conducted on 1581 DNA samples. In that study, samples were taken from an umbilical cord blood bank and tested for *SMN1* and *SMN2* gene copies using a multiplex ligation-dependent probe amplification assay which showed that only 29 of the 1581 newborns were SMA carriers with one copy of *SMN1*, and no homozygous *SMN1* deletion was detected. Based on these findings, the carrier frequency in the Korean population was estimated to be 1834 per 100,000 (Park et al., 2020).

However, our results were similar to those retrieved from SMA studies in China and Thailand. A meta-analysis conducted in China included a total sample of more than 120,000 reported the prevalence of SMA carriers in China as the pooled rate of 2.0% (Li et al., 2020). Similarly, a study from Thailand established the carrier frequency of SMA in the selected Thai population at 1.8% (Dejsuphong et al., 2019).

Moreover, our numbers are close to those of Middle Eastern countries (Lyahyai et al., 2012). Studies have shown that SMA is predominant in Middle Eastern countries, Iran, Egypt, Pakistan, and Saudi Arabia, where consanguineous marriages are common (Ibrahim et al., 2012; Oniya et al., 2019). In the present study, we found high parental consanguinity among the study population. 27% of individuals carrying one copy of the *SMN1* gene were children of 1st cousin family members while 19.3% of participants carrying one copy were children of second and third-degree cousins. This correlation between consanguineous marriages and SMA was further proved in a study from Pakistan where 68% of children with diagnosed SMA were children of consanguineous marriages (Ibrahim et al., 2012). Another study from Turkey determined that male patients who were born into families where consanguineous marriages were predominant mostly carry the homozygous loss of *SMN1* exon 7 and 8 and four copies of the *SMN2* gene without *NAIP* (600355) deletions (Bora-Tatar et al., 2015). These results are not surprising as SMA is an autosomal recessive disorder and consanguineous marriage increases the risk of the disease in the family.

With the development of drugs for the treatment of SMA, the requirement for newborn or carrier screening for the early diagnosis of SMA has become imperative. The US Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children recommends the addition of SMA screening to default newborn screening programs, and the American College of Medical Genetics and the American College of Obstetricians and Gynecologists both recommend

a routine SMA carrier screening (American College of Obstetricians and Gynecologists, 2017; Prior, 2008).

5 | CONCLUSION

In conclusion, there has been high-quality insight tackling of one of the widespread genetic diseases in our community in regards to the frequency of SMA carriers here in Saudi Arabia. However, this test should be instigated as a premarital test due to its high carrier rate in the community. It is noteworthy to mention that our data are leaning toward the role of consanguineous marriages in causing this mortal disease. Considering this observation, it is essential to develop a method for screening carriers of SMA in the Saudi population.

AUTHOR CONTRIBUTIONS

Mohammed Al Jumah: Conceptualization (lead); Funding Acquisition (lead); Methodology; Data Curation (lead); Formal Analysis (lead); Writing – Original Draft Preparation (lead). **Saad Al Rajeh:** Data Curation (equal); Funding Acquisition (equal). **Wafaa Eyaid:** Data Curation (equal); Funding Acquisition (equal). **Ahmed Al-Jedai:** Data Curation (equal); Funding Acquisition (equal). **Hajar Al Mudaiheem:** Data Curation (equal); Funding Acquisition (equal). **Mohammed Hussein:** Conceptualization (equal); Methodology (equal); Formal Analysis (equal); Writing – Original Draft Preparation (equal). **Ibrahim Al Abdulkareem:** Conceptualization (equal); Methodology (equal); Formal Analysis (equal).

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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 restrictions.

ETHICAL COMPLIANCE

The local ethics committee reviewed the study and informed consent was obtained from the study participants. To maintain privacy and confidentiality, no identifying data was used or presented in the written data analysis resulting from the study.

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