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Carrier frequency of spinal muscular atrophy in Turkish population

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Abstract

Objective: The aim of this retrospective cohort study is to evaluate the carrier frequency of spinal muscular atrophy (SMA) among pregnant women and their partners admitted to our clinic for routine pregnancy follow-up.

Methods: The study included pregnant women and their partners who were informed about SMA disease and screening at first trimester and who accepted to undergo screening for SMA. Carrier screening for SMA was carried out using DNA extracted from peripheral blood with a quantitative real-time polymerase chain reaction (qPCR) assay targeting the recurrent SMN1 exon 7-8 gene deletion. The data of the study were analyzed by SPPS version 15.0 statistical software package. Descriptive statistical analyses were carried out. Fisher's exact test was used for intergroup comparisons.

Results: The study included a total of 250 subjects, of whom 182 were female and 68 were male. The carrier frequency of SMN1 deletion was 3.6% (9/250) (95% CI: 1.66–5.54) in the entire study population, with a carrier frequency of SMN1 deletion of 1/27.8. Of 182 female participants, 6 had SMN1 deletion, with a carrier frequency of SMN1 deletion of 3.3% (95% CI: 1.3–6.2). Of 68 male participants, 3 had SMN1 deletion, with a carrier frequency of SMN1 deletion of 4.4% (95% CI: 0.35–9.4). There was no significant difference between female and male participants in terms of SMN 1 deletion frequencies (p=0.712). SMN1 duplication frequency was 8% (95% CI: 5.18–10.8) in all gender.

Conclusion: The results of this study demonstrated a carrier frequency of SMN1 deletion of 1/27.7 in the Turkish population, which is higher than in many other countries. The results of the study will be useful for genetic counseling for SMA.

Keywords: Spinal muscular atrophy, SMA, SMN-1, carrier frequency.

Introduction

Spinal muscular atrophy (SMA) is the most common neurodegenerative disease in childhood, characterized by progressive muscle weakness and muscle atrophy.[1] SMA is an autosomal recessive single gene disorder caused by homozygous or compound heterozygous mutations in the SMN-1 gene located on the 5q.13.2 region of chromosome 5. Approximately 95% of SMA patients, irrespective of their clinical type, have a homozygous deletion of the SMN1 gene (exon 7 and 8).[2]

The SMN gene has a genomic length of 20 Kb and has 9 exons. It encodes a 32 kD protein consisting of 294 amino acids. This gene has something unique called the survival motor neuron (SMN) gene, which is a copy of this gene located in the telomeric region of the same chromosome (5q11.2-13.3) SMN1 (or SMNt), a pathogenic gene. The other copy of this gene, called SMN2, is located in the centromeric region of the chromosome 5q13.2, and a single nucleotide substitution (840C>T) in SMN2 gene results in different splicing on exon7 and

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the production of a less functional protein. The only difference of the SMN2 gene from SMN1 is that thymine replaces cytosine at a single point. Because of this slight difference, the gene produces a transcript that does not contain exon 7. As a result, synthesized protein that is short and unstable breaks down quickly and does not function normally. The low rate (about 10%) of complete protein synthesis from the same gene also plays a role in SMN2 being a determinant of the severity of the disease. Naturally, as the number of SMN2 increases, the amount of normal protein that can be produced will also increase. It has been observed that the more SMN2 copies patient has, the milder disease becomes. For example, SMA type 1 is observed in patients with two SMN2 copies, while SMA type 3 patients have 3 or 4 copies of SMN2. In other words, the severity of the disease is modulated by SMN2, though the SMN1 is the pathogenic one.[3–7] Adult form of SMA type 4, while less frequent, has also been reported. This group includes patients who are able to walk in adulthood and have no respiratory and nutritional problems.[8] The remaining 5% of the affected individuals may have compound heterozygote for a deleted gene and an intragenic mutation on the other SMN1 gene.[6,9]

The aim of this study was to determine the carrier frequency of SMA among pregnant women and their partners admitted to our clinic for routine pregnancy follow-up.

Methods

The study included pregnant women and their partners who presented to the department of Obstetrics and Gynecology for pregnancy follow-up between May 1, 2012 and December 30, 2021 and who were informed about SMA disease and carrier screening, and offered SMA carrier screening at first trimester. Informed consent was obtained from all families. Pregnant women and/or their partners who accepted carrier screening test for SMA were included in the study.

Carrier screening test for SMA was carried out using DNA extracted from peripheral blood with a quantitative real-time polymerase chain reaction (qPCR) assay targeting the recurrent SMN1 exon 7-8 gene deletion. All families were informed in detail about the carrier screening results by the Department of Medical Genetics. The approval for the study was obtained from the local Ethics Committee (24.12.2021/008).

SPSS version 15.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used to analyze the statistical data. Descriptive statistical analyses were carried out. Fisher's exact test was used for intergroup comparisons (male and females). A p-value <0.05 was considered statistically significant.

Results

The study included a total of 250 subjects, of whom 182 were female and 68 were male. The carrier frequency of SMN1 deletion was 9/250 in the entire study population, with a carrier frequency of SMN1 deletion of 1/27.8. The frequency of SMN1 duplication was calculated as 20/250 for all participants.

There was no significant difference between female and male participants in terms of SMN 1 deletion (p=0.712) and duplication (p=0.602) frequencies. Of 182 female participants, 6 had SMN1 deletion and 16 had SMN1 duplication, with a carrier frequency of SMN1 deletion of 3.3% (95% CI: 1.3–6.2). Of 68 male participants, 3 had SMN1 deletion and 4 had SMN1 duplication, with a carrier frequency of SMN1 deletion of 4.4% (95% CI: 0.35–9.4). In other words, the carrier frequency of SMN1 deletion was 1/30.3 in female participants and 1/22.7 in male participants (**Table 1**). There was no couple with both partners identified to be carriers. Considering the diversity of mutations,

Table 1. Analysis of SMN1 Exon7&8 deletion/duplication.

	Female	Male	Total
SMN1 deletion	6 (3.3%) (95% CI: 1.3–6.2)	3 (4.4%) (95% CI: 0.35–9.4)	9 (3.6%) (95% CI: 1.66–5.54)
SMN1 duplication	16 (8.8%) (95% CI: 6.1–13.9)	4 (5.9%) (95% CI: 1.37–11.8)	20 (8%) (95% CI: 5.18–10.8)
Normal	160 (87.9%)	61 (89.7%)	221 (88.4%)
Total	182	68	250

exon 7 deletion was noted in 2/6 and exon 7&8 deletion in 4/6 of female mutations. Exon 7 deletion was detected in 1/3 of men and exon 7&8 deletion in 2/3 of male mutations (**Table 2**).

Table 2. Distribution of SMN1 carriers by gender and exon.

	Del exon 7	Del exon 7&8	Total
Female	2	4	6
Male	1	2	3
Total	3	6	9

Discussion

SMA is the most common monogenic cause of infant mortality and is characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy.[10] However, to date, there is a limited number of published studies evaluating the carrier frequency of SMA. The reported incidence of SMA ranges from 4 to 10 in 100,000 live births[5,6] and the carrier frequency of disease-causing SMN1 mutations ranges from 1/200 to 1/20 among different ethnicities.[11–20] Since the rate of consanguineous marriage increases from the west to the east of Turkey, the frequency of SMA carriers also increases.[21]

The present study demonstrated a carrier frequency of SMN1 deletion of 3.6% (9/250) in our population, with a carrier frequency of SMN1 deletion of 1/28. Moreover, there was no significant difference between female and male participants in terms of SMN 1 deletion frequencies. A study by Prior et al.[4] performed carrier testing on 500 pre-conceptual or pregnant women in the USA and reported a carrier frequency of SMA of approximately 1/31 (95% CI: 1.19–1.54). Zhang et al.[7] performed the largest-scale carrier screening for SMA carriers in 13,069 pregnant women in China. They found that a total of 231 women were carriers (1.77%; 95% CI: 1.56–2.01%), indicating a carrier frequency of approximately 1/56 in the population. In the present study, the carrier frequency of SMA was found to be 1/30.3 in female participants.

Given the carrier frequency studies conducted in various societies, the SMA carrier frequency was reported 1/27 in the Morocco population,[12] 1/49 in the Australian population,[13] 1/56 in the Thai population,[14] 1/38 in the Indian population,[15] 1/34 in the Italian population,[16] 1/48 in the French population and 1/57 in the Swedish population.[17] In a meta-analysis of 10 different publications conducted between 2005 and 2016 in China, random effects models showed an overall carrier frequency of SMA of 2.0% (95% CI: 1.7–2.3%).[18] Sangaré et al.[19] reported that the carrier frequency of SMA was 1/209 in Malians, 1/120 in Kenyans, and 1/60 in Nigerians. They stated that the carrier frequency of SMA was much lower in sub-Saharan Africans than in Eurasians. Hasanzad et al.[20] showed a higher carrier frequency of SMA in Iran (1/20) than in the European population.

Due to the high prevalence of SMA carriers in the United States, the American College of Medical Genetics recommends offering carrier testing to all couples regardless of race or ethnicity.[5] The American College of Obstetricians and Gynecologists (ACOG) recommends that screening for SMA should be offered to all women who are considering pregnancy or are currently pregnant.[6]

Conclusion

This study is the first report addressing the estimation of SMA carrier frequency in Turkish population. Based on the results of the study, the carrier frequency of SMN1 deletion in Turkish population was 1/27.7, which is higher than in many other societies. The limitation of this study is the relatively small number of participants in the study. However, our work will be an inspiration and guide for future studies. Study findings may be useful for genetic counseling about SMA. Moreover, considering the high rate of consanguineous marriage in Turkish population, it will be beneficial for couples to have carrier screening before pregnancy or during pregnancy to prevent SMA disease.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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