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Carrier Frequency of Spinal Muscular Atrophy in India

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***Abstract*: Title: Carrier Frequency of Spinal Muscular Atrophy in India: A Systematic Review. Objective: This narrative review aims to summarize and analyze existing studies on the carrier frequency of spinal muscular atrophy (SMA) in the Indian population, providing insights into the prevalence of SMA carriers in India. Methods: A comprehensive search of electronic databases was conducted to identify relevant studies published in last past 5 years and only full text articles were included. Data were extracted, analyzed, and synthesized to provide an overview of the carrier frequency of SMA in India. Results: The review identified five studies investigating the carrier frequency of SMA in India. The studies reported carrier frequencies of 5620 live births among the Indian population. Variations in carrier frequencies were observed across different regions of India, with some studies reporting higher frequencies in certain ethnic or geographical groups. Discussion: The review highlights the variability in carrier frequency of SMA across India, indicating a need for further research to assess the genetic diversity within different regions and ethnic groups. The identified studies provide valuable insights into the prevalence of SMA carriers in India, contributing to the understanding of the disease burden and implications for genetic counseling and carrier screening programs. Conclusion: This systematic review reveals that the carrier frequency of spinal muscular atrophy in India varies across different regions and ethnic groups. The findings underscore the importance of continued research and implementation of genetic screening programs to facilitate early detection, counseling, and appropriate management of SMA carriers in India.**

***Keywords*: spinal muscular atrophy, carrier frequency, India, narrative review, genetic screening, genetic.**

1. Introduction

Spinal muscular atrophy (SMA) is recognised as a diverse genetic neuromuscular condition that causes increasing weakness in the skeletal and respiratory muscles, muscle atrophy, and severe impairment [1].

A. Pathophysiology

mRNA transportation plays a vital role in gene mutations in the human body and SMN protein helps in mRNA transport by vesicle release, actin dynamics and axon which process neuronal functions [2]. Homozygous deletion at 5q13 is identified as one of the major contributors in the SMA cases and accounted for about 95%.

B. Types of Spinal Muscular Atrophy

There are mainly five major types of SMA according to the severity of the disease and age of the patient including type 0 to type 4. Treatment of the patient is also decided with the identification of the stage of the disease.

1) Type 0

The lifespan of a patient with type 0 SMA is considerably shorter than patients with other types of SMA. According to several studies, this form of SMA is the deadliest one which can cause patients to die within the first week of their birth [3]. Apart from hypotonia, weakness, a patient with this condition may also face deformity in joints which can cause them to face failure while reaching motor milestones.

2) Type 1

Type 1 SMA can be observed among the infants of six months of age. In this type of situation, it is common for babies to face difficulties while sucking or swallowing. Lack of effective medical measurements can cause children with this condition to face severe issues in the respiratory system that can complicate their livelihood. This type is also known as “Werdnig-Hoffman disease” [4]. In other words the overall symptom of this stage is hypotonia and general muscle weakness within the first six months of the baby. Several articles have suggested that babies with this condition tend to live no more than 2 years which can be reasoned with the higher rate of respiratory issues due to presence of this condition. A rare case can often be used as an example where a patient with this condition lived near six years, who further demonstrated issues such as block in atrioventricular, episodes of tachycardia and atrial fibrillations.

3) Type 2

Type 2 SMA can be identified among the children between six months and 18 months of age. In this type of condition, they can affect lower areas of the limb, which can forbid them to walk in a normal manner [5]. This type of SMA is also known as Dubowitz disease that can allow individuals to sit up but not indulge in walking. The death rate in this type of SMA is considerably lower than the type 1, due to the differences in affected area. It is common for patients with this type of MSA to become an adult. The severity in these types of cases also plays a crucial role in the amount of lifespan of a patient. In other words, patients with severe conditions may survive less

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than patients with low severity. Patients with type 2 SMA may require the usage of a wheelchair for fulfilling their mobility purposes on a regular basis.

4) Type 3

Type 3 SMA is known for occurring within the first 18 months of the lifespan. It is also common for patients with this type to identify symptoms until the phases of adulthood. Type 3 SMA is often known as "juvenile-onset" or "Kugelbert-Welander" SMA [6]. In this type of SMA, it is usual for patients to face mild issues while walking or performing respiratory acts. In other words, it can influence the ability of one's to stand for a long period or walk in a continuous manner. The severity of Type 3 SMA is considerably lower than other types, which can also be observed in the impact level of it. Type 3 SMA is also known for not causing harmful impact on the life expectancy rate of a patient, but the daily livelihood can get impacted due to the presence of these medical conditions. In other words, it is ideal for a patient with type 3 SMA to adjust his daily routine that can cause less complications.

5) Type 4

It is common for this type of SMA to not occur until the adulthood of a person. Studies have also suggested type 4 SMA as the mildest type of SMA [7]. Several studies have addressed the complications of type 4 SMA with tremors in muscle or moderate amount of weakness in muscle [8]. Studies have also illustrated that these type of SMS can be considered as rare. Weakness in the muscle is one of the most common symptoms in this context. However, issues regarding swallowing and breathing are also common in SMA development.

Carrier frequency can be considered as a measurement aspect by which the determination of changes in genes can be done. A blood sample test is the main process involved in carrier screening [9]. Understanding the carrier frequency of SMA in India is crucial for genetic counseling, carrier screening programs, and raising awareness about the condition. Identifying carriers can help in providing appropriate information and support to families and individuals at risk of passing on the condition.

The carrier frequency of SMA in India has been an area of interest for researchers studying the prevalence of this condition in the population. SMA is the most frequent cause of death in the infantile age range, occurring in one in 10,000 live births. The SMA's carrier frequency in the West is one in fifty. However, the SMA carrier frequency was 1 in 38 in a recent Indian study [10]. Estimates from global studies suggest that the carrier frequency of SMA ranges from approximately 1 in 25 to 1 in 50 individuals. However, it's important to note that carrier frequencies can vary across different populations due to genetic and ethnic factors.

In India, a country known for its diverse population, the carrier frequency of SMA may vary among different ethnic groups and regions. Studies conducted in specific Indian populations have reported carrier frequencies ranging from 1 in 39 to 1 in 74 individuals. These numbers indicate that the carrier frequency of SMA in India might be comparable to or slightly higher than the global estimates.

Advancements in genetic testing techniques, such as carrier screening programs and preconception genetic counseling, can help identify individuals who carry the SMN1 mutation. These approaches enable couples to make informed reproductive decisions and take appropriate measures to manage the risk of having a child with SMA.

Additionally, initiatives focused on raising awareness about SMA and its carrier frequency can play a vital role in identifying at-risk individuals and promoting early diagnosis and intervention. Collaborative efforts involving healthcare professionals, researchers, advocacy groups, and policymakers are crucial in addressing the challenges posed by SMA and ensuring access to genetic testing and counseling services across India.

C. Objectives

The objective of this systematic review is to summarize and analyze existing studies to provide an overview of the prevalence and distribution of SMA carriers in the Indian population. This review aims to explore the available evidence on the carrier frequency of SMA, assess variations across different regions and ethnic groups in India, and provide insights into the implications for genetic counseling, carrier screening programs, and overall disease burden. By examining the existing literature, the objective is to contribute to the understanding of SMA carrier frequency in India and identify areas for further research or intervention.

2. Methodology

A. Inclusion Criteria

- Studies conducted in India about the carrier frequency of SMA and its determination process has been prioritised in this research.
- "Carrier screening" and "carrier frequency" is the keyword typically followed in terms of searching articles and selecting those for this specific research.
- Only the articles published in last past 5 years have been included in this narrative review.

B. Exclusion Criteria

The exclusion criteria display which data sources were eliminated, such as duplicate articles, as depicted in the provided flow chart.

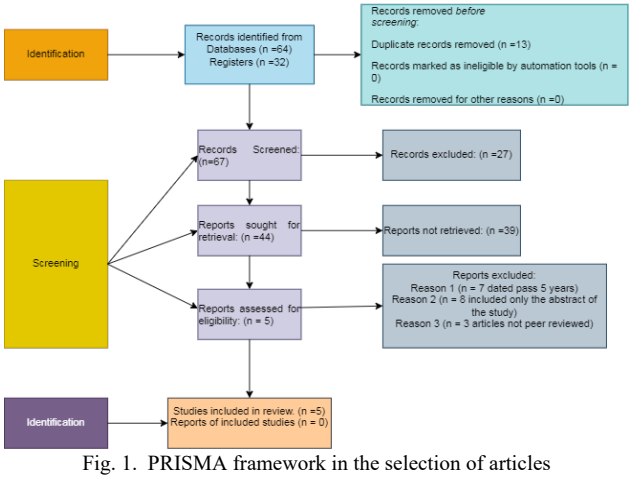

Fig. 1. PRISMA framework in the selection of articles

C. Information Sources

The literature reviewed in this research is the main source of information which is mainly collected from Google scholar, Pubmed, research gate and medline. Valid and authentic sources have been prioritized in this research to collect information. The selection of the articles was made according to their relevance to the topic at hand.

D. Selection Sources

Selection of the sources mainly depends on the understanding of the researcher and relevancy has been maintained through determining the concept of the research. A computerized search of scientific literature was carried out on articles studying the carrier frequency of SMA in India. Only articles published within the last 5 years were considered in this review, and only studies conducted in India were included.

3. Discussion

The severity of SMA especially in the Indian landscape can be considered as one of the most effective reasons behind conducting the following research. According to several studies, the rate of survival in India from SMA is increasing. Carrier screening can be considered as an effective determination process which helps in understanding the level of severity among patients with SMA especially in the early stage. Selected articles have also described the robustness of the determination process regarding SMA especially in the earlier stage. The overall narrative review section of this research has also been considered as the source of information which indicates the development in the treatment process of SMA especially in earlier stages. However, insufficient productiveness of carrier screening can also be identified in the studies reviewed in this research. The carrier frequency of Spinal Muscular Atrophy (SMA) in India has been a topic of interest in the field of genetics and public health. Understanding the carrier frequency is important for several reasons, including genetic counseling, carrier screening programs, and raising awareness about the condition. One of the factors contributing to the higher carrier frequency of SMA in India is the prevalence of consanguineous marriages, particularly in certain communities. Consanguinity refers to marriages between close relatives, such as cousins. In such unions, there is an increased likelihood of inheriting autosomal recessive disorders like SMA. Both parents must carry the faulty gene for the condition to manifest in their child, and consanguineous marriages can increase the chances of this occurring.

Founder effects may also contribute to the carrier frequency of SMA in India. Founder effects occur when a small group of individuals with a particular genetic variation establishes a new population. Over time, certain genetic disorders can become more prevalent in these populations due to limited genetic diversity.

Table 1
Literature review

S.No.	Author(s) and Year	Objective	Sample(s) and Study Design	Methodology	Results
1.	Nilay *et al.* 2021 [11]	In this particular cohort study, the carrier frequency of spinal muscular atrophy was investigated in India.	The sample size in this cohort study consisted of 626 participants, with 20 individuals excluded due to having a family history of SMA. Out of the 606 tested subjects, 323 were male and 283 were female, and 16 were identified as carriers of SMA	Data was evaluated from a four-year period during which women who came for checkups were informed about SMA and were screened for it, especially those who had previously experienced some sort of termination or had a child with a history of a genetic disorder. This observational study used carrier testing with the MLPA technique, but excluded individuals who had a family history of SMA or childhood mortality with hypotonia.	The cohort happened to be 1:38 thus the prevalence of SMA according to this study was found to be one in 5620 live births according to the Hardy-Weinberg principle. Although this study emphasizes the significance of SMA's prevalence in India and can serve as essential data for future genetic counseling and diagnostic purposes. However, it is important to note that the study may have limitations due to the imposition of a biased selection, as it relies on a group of individuals who have previous history of disorders.
2.	Kaur *et al.* 2022 [12]	To estimate the carrier frequency of SMA among individuals of a reproductive age group in a North Indian cohort.	The screening was offered to individuals of reproductive age in this cohort study who were visiting tertiary care facility with their ill relatives. A group of 198 people underwent a screening process, consisting of equal numbers of males and females (99 each). The median age for males was 29 years, while for females it was 29.5 years. The majority of those surveyed, around 67.66%, hailed from the states of Punjab, Haryana, and Himachal Pradesh.	Blood samples were collected from the participants that signed the written consent form and the blood sample was contained in an “EDTA vacutainer at -20 degrees. In this research, MLPA was utilized as the carrier screening test to identify the SMN1 copy number status. The cost of screening a sample through this method was approximately 2500 rupees. However, the alternative method of quantitative RT-PCR was also used as a validation test and was able to identify the positive carrier status of all individuals detected using MLPA testing.	The cohort was found to have a carrier frequency of 1:30 for spinal muscular atrophy (SMA). Among the seven individuals who tested positive for the condition, three had only exon 7 deleted while the remaining four had deletion of both exons 7 and 8. By applying Hardy-Weinberg principle to this carrier frequency, the incidence of SMA is approximately 1 in 3333 live births.The cost per sample of RT-PCR was significantly less than MLPA and may be a more effective testing method for screening a large number of samples based on trial. The research thus revealed a carrier frequency of 1 in 30, demonstrating comparability to thalassemia.

S.No.	Author(s) and Year	Objective	Sample(s) and Study Design	Methodology	Results
3.	Ijpp.in, 2019 [13]	To examine and categorize genetic disorders as chromosomal disorders, single gene disorders, or multifactorial disorders, and to determine the pattern of inheritance and carrier frequency of these disorders	Researchers used heparinized peripheral samples of blood among children for this systematic review by analysing four year reports within their health care centre among many couples and pregnant women.	Different tests have been developed by researchers within this study such as Specimen required, cell cultures, Resolution of Chromosomal, TAT, Chromosomal anomaly detected types, and Chromosomal anomaly non-detectable types.	Consanguinity, or the marriage of closely related individuals, is a major contributor to spinal muscular atrophy, which is an example of autosomal recessive inheritance. When partners who are carriers for the condition reproduce, there is a 25% chance of having a homozygous affected offspring, a 25% chance of having a homozygous unaffected offspring, and a 50% chance of having a heterozygous unaffected carrier offspring. In the event that the affected individual is homozygous and their partner is a heterozygous carrier, there is a 50% chance of having an affected offspring. This phenomenon is known as pseudo dominance and is present in common recessive conditions with a high carrier frequency in the population. A thorough knowledge of the patterns of inheritance is essential in genetic counselling of families with genetic disorders. Once the pattern of transmission is known, the family can be counselled about the risk of recurrence and appropriate preventive measures like prenatal diagnosis and presymptomatic genetic testing can be adopted. A thorough knowledge of the patterns of inheritance is essential in genetic counselling of families with genetic disorders. Once the pattern of transmission is known, the family can be counselled about the risk of recurrence and appropriate preventive measures like prenatal diagnosis and presymptomatic genetic testing can be adopted. The progress made in genetic research so far is significant, and the future holds great promise for further discoveries.
4.	Yasheswinee *et al.* 2022 [14]	To highlight how carrier frequency testing can detect neuromuscular disorders, specifically focusing on spinal muscular atrophy, at an early stage	In this quantitative study design Asian population has been selected as the sample size.	Researchers collected blood samples among the population and transferred it for further tests	The study found that only 1 in 10,000 individuals had this disorder. The prevalence of the disorder was estimated to be 1-2 out of 100,000 individuals, with Asian populations having a higher prevalence of carriers. SMN1 gene is implicated in the disorder, and individuals with one copy of this gene can have carrier status for the condition. The presence of mutation in one copy of the gene can be detected by a dosage analysis of SMN1 with a 95% accuracy rate. While the number of SMN2 copies can determine the severity of the disorder, this information is not always reliable for prediction. Awareness of carrier status for genetic disorders should begin with understanding family history and seeking diagnosis for high-risk individuals with affected relatives. Technological advancements have improved diagnostic outcomes, but reliable testing and resources are necessary for validation purposes.

S.No.	Author(s) and Year	Objective	Sample(s) and Study Design	Methodology	Results
5.	Singh *et al.* 2020 [15]	To identify the frequency of carriers and the harmful genetic variations related to prevalent neuromuscular disorders in the north Indian population, accomplished through next-generation sequencing	In this Pilot study the sample size included two hundred (200) unrelated individuals - 101 male and 99 female - aged between 20 and 60 years. These individuals were visiting the Medical Genetics and Obstetrics and/or Gynaecology out-patient clinic for unrelated health reasons and were enrolled in the study following	The research spanned a period of 22 months, from October 2016 to June 2018, and was conducted with the appropriate ethical clearance (Ethical clearance number EC/08/16/1066). The molecular analysis was carried out at Medgenome Laboratories Ltd. in Bangalore.	Among the 200 participants, 52 individuals (or 26 percent) were identified as carriers, having one or more disorders with decreasing costs of NGS panels, carrier screening is being increasingly utilised in recent times in India. Due to the falling costs of NGS panels, there has been a rise in the usage of carrier screening in India. As medical treatments for genetic diseases often are not covered by state-sponsored programs, family finances are often limited, making this screening method potentially valuable in reducing the burden of such diseases. However, a key flaw of the pilot study is that it overlooked spinal muscular atrophy, based on the assumption that it would be less accurately detectable through the use of NGS technology, or could be screened with ease via haematological tests.

It is important to note that advancements in genetic testing and increased awareness of SMA have likely contributed to the identification of more carriers. As more individuals undergo genetic testing and become aware of their carrier status, the apparent carrier frequency may increase. This underscores the significance of accessible and accurate genetic testing facilities and awareness campaigns to identify carriers and provide appropriate support and information to individuals and families at risk.

Furthermore, it is crucial to consider the diversity within the Indian population when discussing carrier frequencies. Different ethnic groups in India may have varying carrier frequencies due to unique genetic variations specific to each group. This highlights the need for comprehensive studies that encompass different regions and ethnicities to capture the complete picture of SMA carrier frequencies in India.

Understanding the carrier frequency of SMA in India has implications for genetic counseling and carrier screening programs. Accurate knowledge of the carrier frequency helps in providing informed guidance to at-risk individuals and families, facilitating family planning decisions and offering appropriate support. Additionally, it enables the development of targeted interventions, such as implementing population-based carrier screening programs, to identify carriers and potentially prevent the occurrence of SMA in future generations.

Studies conducted in India have shown that the carrier frequency of SMA varies among different regions and ethnic groups within the country.

4. Conclusion

The overall study is mainly focused on identifying the role of "carrier screening" in detecting SMA. It has been found as one of the most used prediction processes in India and also plays a vital role in detecting the disease in the earlier stages. A blood sample is used in this determining process which is also considered as a factor which increases its use in this context as this sample collection process is most reliable and error-free in India. The determination of SMA through "carrier screening" is enhanced as it has the ability to predict the changes in genes in an effective course of action. In conclusion, while specific data on the carrier frequency of SMA in India might be limited, available evidence suggests that it is comparable to global estimates. Continued research, genetic testing programs, and awareness campaigns are essential in better understanding the prevalence of SMA and improving support for affected individuals and their families in India.

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