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Planning a Healthy Baby: The 21st Century Way!

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Abstract

Genetic carrier screening finds a new place in clinical practice today. Consequent to advanced technology coupled with increased awareness among population in the reproductive age group, this seems to be gaining popularity. Indian population is a heterogeneous mix of several sub-populations and the gene pool is quite different from the western or oriental populations. Thus, a need to detect carrier frequency was felt and a pilot study was performed at a tertiary care hospital in North India, on 200 healthy individuals. The study brought out some unexpected results, such as the high frequency of cystic fibrosis in Indian population. This mini-review provides a glimpse into the study and puts together the carrier frequencies of common autosomal recessive disorders as detected from other studies as well.

Keywords: Genetic carrier screening • Population • Disorder • Thalassemia • Spinal muscular atrophy

Abbreviations

ARGD: Autosomal Recessive Genetic Disorders; NGS: Next generation sequencing; *CFTR*: Cystic Fibrosis Transmembrane Conductance Regulator; ECS: Expanded Carrier Screening; CF: Cystic Fibrosis; VUS: Variants of Uncertain Significance; HBB: Hemoglobin Subunit Beta; *SLC26A4*: Solute Carrier Family 26, Member 4; *GJB2*: Gap Junction Beta 2 Protein; *TMPRSS3:* Transmembrane Protease Serine; TMC1: Transmembrane Channel like Protein; *MLC1*: Megalencephalic Leukoencephalopathy with Cysts; ACMG: American College of Medical Genetics; *SMN1*: Survival Motor Neuron 1; VUS: Variants of Uncertain Significance; *CYP21A2*: Congenital Adrenal Hyperplasia; GAA: Glycogen Storage Disease Type II; MMAA: Methyl Malonicaciduria Mut A.

Introduction

As we move ahead in the 21st year of the 21st century, we have evolved from being re-active to becoming more pro-active in our approach. This is especially true in situations which have grave consequences especially when they are avoidable. Genetic disorders have long been recognized to be severe, life-long burdensome and many a times untreatable for which the best approach is a preventive one. With advancements in technology and with Gen-z, the new 'much aware' generation at the forefront, preventative approaches are becoming popular. Genetic carrier screening is now sought after as never before to avoid having a baby affected with genetic disorder.

Each individual carries two copies of the genome with ~20,000 genes, inherited one from each parent. Carriers have only one faulty copy of a gene, with the other copy is normal. This does not 'usually' impact on their lives or create a disease-state, and is called a 'carrier state'. The transformation to disease state occurs in the next generation if the other partner also has a mutation in the same gene and the baby inherits both faulty copies of a particular gene. This possibility would occur only if 'both' parents are 'carriers' of a certain faulty gene and the baby is termed as suffering from an 'autosomal recessive disorder.'

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Literature Review

The history of carrier screening for these disorders dates back to 1960s when it started for beta-thalassemia, one of the most common single gene disorder in the world [1]. The Ashkenazi-Jewish population was the first to start carrier screening among their population for disorders such as Tay-Sach disease which was more prevalent in view of a closed system of marriages [2]. The guidelines for prenatal carrier screening issued by the American College of Obstetrics and Gynecology and American College of Medical Genetics in 2001 included screening for cystic fibrosis, followed by spinal muscular atrophy, hemoglobinopathies, and disorders common in Ashkenazi-Jewish [3-6]. With advanced genetic testing techniques using Next-generation sequencing, it is now possible to test multiple genes together, even the entire genome or exome (collection of all functioning areas of genes).

The inheritance of pathogenic variants in our genes is from our ancestors, hence the ethnicity matters. There are thus fundamentally two approaches for pre-conceptional carrier screening-first is targeted screening for conditions known to be more prevalent in the particular populations, and second is to do the 'extended' carrier screening, applicable to all populations. The first approach is helpful for populations where a closed system of marriages or endogamy is prevalent, while the second approach is applicable to all, and is thus to be preferred.

There have been numerous studies now providing the carrier frequency of the various Autosomal Recessive Genetic Disorders (ARGD) [7-10], but there are none providing data from the Indian population. Lazarus et al. [7] in a study of 23,453 individuals from many obstetric and infertility clinics for 108 disorders for specific mutations showed that 24% of individuals were identified as carriers of at least one of these 108 disorders, while 5.2% were carriers of multiple disorders. In another study of over 30,000 people analyzed by next generation sequencing of over 100 genes, 1 in 3.4 people were carrier of at least one condition [8]. We performed a pilot study to determine the carrier frequency of the presumed common ARGDs in the North Indian population [11].

In the North Indian study of 200 healthy subjects, which included 88 couples, all married non-consanguineously was carried out. Few disorders-beta thalassemia, spinal muscular atrophy, Duchenne's muscular dystrophy and Fragile X syndrome were excluded from the study as either the carrier frequency was already known, or they could not be detected by the NGS method employed [12,13]. The results of the study were very significant and telling.

Next generation sequencing for a predesigned panel of 88 genes was carried out on the blood samples obtained from these individuals. These genes were selected because the disorders related to them were common in this population as observed in our genetic clinic. Using descriptive analysis carrier frequency was calculated and reported as a proportion of total screened (1/n).

Serial number	Disorder	Gene	Carrier frequency in Indians (other studies)	Carrier frequency in Indians [Singh et al, 2020 (11)]
1.	β thalassemia	*HBB*	1/33 (Colah et al, 2017 [30]) 1/33 (Kausthubham et al, 2020 [21])	Not tested
2.	Spinal muscular atrophy	*SMN1*	1/44 (Verma et al, 2020 [31]) 1/38 (Nilay et al, 2020 [32])	Not tested
3.	Albinism type I	*TYR1*	1/145 (Kausthubham et al, 2020 [21])	None
4.	Cystic fibrosis	*CFTR*	1/73 (Kausthubham et al, 2020 [21])	1/22
5.	Deafness – *GJB2* (AR)	*GJB2*	1/47 (Kausthubham et al, 2020 [21])	1/66
6.	Deafness – *SLC26A4*	*SLC26A4*	1/69 (Kausthubham et al, 2020[21])	1/40
7.	Deafness – *TMPRSS3*	*TMPRSS3*	1/132 (Kausthubham et al, 2020 [21])	1/66
8.	Glycogen storage disease type II (Pompe disease)	*GAA*	--	1/66
9.	Methyl Malonicaciduria Mut A (Isolated MMA)	*MMAA*	--	1/100
10.	AR polycystic kidney	*PKHD1*	--	1/100

Table 1. Carrier frequencies of various genetic disorders as detected by Singh et al, in comparison with other similar studies.

Among the 200 participants, 52 persons were found to be carrier of one or more disorder (1 in 3.8). The data on carrier frequencies for top ten disorders is listed in Table 1 and compared with that of existing data from other studies. While carrier frequencies seem to differ from study to study, however the disorders listed in terms of commonness are similar, be it deafness related genes or cystic fibrosis.

In the North Indian study, congenital deafness was identified as the most common disorder with a carrier frequency of 1 in 18 for one of the three genes (*SLC26A4, GJB2* and *TMPRSS3* in decreasing order). The pathogenic variants identified in the *GJB2* gene were founder mutations commonly reported in India (p.Trp77Ter and p.Trp24Ter) [14]. Parental perceptions for prenatal diagnosis of a disorder like hearing loss vary in resource poor countries like India with some families opting to plan the management of a child born with deafness and others opting to discontinue the pregnancy [15].

Cystic fibrosis (CF) was the second most commonly identified disorder with a carrier frequency of 1 in 22 in this cohort. No common mutation was identified in the *CFTR* gene and only one individual had the p.Phe508del mutation out of 9 individuals heterozygous for mutations in the *CFTR* gene (11.1%). The remaining variants were outside the recommended ACMG panel of 23 mutations [16] and not confined to any ethnic group in north India. Comparison of p.Phe508del allele frequency with that reported from the West shows that Indians have a low frequency (19%-44%) of the p.Phe508del pathogenic variant [17,18]. Literature from India shows a wide mutation spectrum among CF patients with few recurring mutations [19]. Historically, CF has been regarded as a disease common to Caucasian ethnicity and rarer in Asian Indians. However, growing literature from India as well as other parts of the world suggests that it is not as uncommon as previously thought [19,20]. The high carrier frequency of cystic fibrosis, if substantiated in larger population studies, would be sufficient ground to initiate new-born screening for cystic fibrosis in the Indian population. Partial confirmation of the results comes from the list of common monogenic disorders common compiled form analysis of 1455 clinical and research exomes in India [21]. They reported beta thalassemia to be the commonest, follow by deafness caused by multiple genes, and cystic fibrosis.

This study also brings out several important points before carrier screening is routinely offered in any country. The pathogenic variants observed in many disorders (such as deafness, cystic fibrosis, Pompe disease, Canavan disease, primary hyperoxaluria, junctional epidermolysis bullosa, galactosemia, medium chain acyl CoA deficiency) in this study were different from those commonly observed in the West. The importance of an Indian database in improving the classification of variants is the need of the hour and it is encouraging that several groups are working towards this goal. Gorospe et al. reported a common pathogenic variant in *MLC1* gene causing megalencephalic leucoencephalopathy with subcortical cysts in a small but enterprising North Indian community of Agarwals [22]. Similar founder mutations were later reported by others in *CAPN3* gene (*LGMD2A*), *ALDOB* (HFI) and others in the same community, thus creating a similarity of this community with Ashkenazi Jews [23,24]. Ankala et al. summarized the common founder mutations in various Indian communities, thus creating a need for carrier screening specifically for Indian population [25].

With the increasing availability of ECS, it is required that carrier screening panels be developed in different countries according to the local population. Testing should comprise the study of all the coding exons with its boundaries in the genes through NGS, as all the variants are not well characterized in less studied populations. However variants of uncertain significance (VUS) should not be reported.

Other diseases known or suspected to have a high carrier frequency in Indian population include spinal muscular atrophy and congenital adrenal hyperplasia due to 21 alpha hydroxylase deficiency. Since both these diseases have a high frequency of deletions as pathogenic, causative mechanism it is imperative that any NGS carrier screening panel should include these diseases. Recent literature shows that NGS methods are being developed to accurately detect *SMN1* gene deletion and deletions in *CYP21A2* gene [26-32].

Discussion and Conclusion

The pilot study on ECS in North Indian population strongly suggests the need for studying a larger population in India to confirm some of the observations. It opens for discussion the utility of carrier screening programs in future as Indians are culturally endogamous, newer genetic therapies are far from affordable for the common man and the large population makes state funded treatment for genetic disorders a herculean task. Second to these important findings, it lays stress on the challenges posed by NGS based carrier screening as opposed to targeted screening. Clinically useful carrier screening relies heavily on the presence of trained geneticists and genetic counsellors to manually review all variants identified as potentially disease causing and reclassify them on the best available knowledge to date.

ECS results can be complex to interpret and pre-test and post-test counseling is vital to its successful implementation. Several papers now also focus on the need to allow pregnant women to make their reproductive choice with regards to having or not having a child with a serious disability/disorder.

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