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UTILITY OF COMMUNITY GENETICS TOOLS IN ALLEVIATING HEALTH BURDEN FROM HAEMOGLOBINOPATHIES IN INDIA

KEYWORDS

Haemoglobinopathies, Community genetics, sickle cell disease (SCD), India

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ABSTRACT

Haemoglobinopathies is a genetic disorder highly prevalent among the socio-economically backward castes of India inhabiting different geographical areas. In India there are an estimated 17862455 individuals of sickle cell trait and 1339684 individuals of sickle cell disease. Most of the children with HbSS disease die premature before attaining childhood placing a heavy burden on the already economically underprivileged. An estimated prevalence of sickle cell central India in central India is 0- 40 per cent, in southern India 0- 35 per cent, in western India 0-30 per cent and in eastern India it is 0-20 per cent. Among scheduled tribes HbS ranges from 0 to 48 %, in scheduled castes it ranges from 0 to 20 % while that of sickle cell disease ranges from 0 to 6 %. In other caste groups it ranges from 0 to 9 % while among Brahmin and Muslim populations it ranges from 0 to 4.5 % and 0 to 3 % respectively. Sickle cell present in high frequency among the scheduled tribes as compared to other ethnic groups- castes, scheduled castes and communities.

Since no cure exists for this monogenic disease it can only be managed at high cost. The only avenue available to reduce the health burden of homozygous is by means of massive population screening and counseling to avoid potential homozygous pregnancies. The detailed risk factors across a cross-sectional ethnic communities and efforts to address the problem with a public health perspective are discussed. Haemoglobinopathies is burning global issue from public health point of view which needs to be dealt with on war footing.

INTRODUCTION

Impairments in the synthesis of normal haemoglobins are the most common genetically inherited disorders in human resulting either from quantitative reduction of globin chain or qualitative defect in globin molecules what is called sickle cell disease (SCD). It is a structural variant of haemoglobin in which glutamic acid, an amino acid, at position 6 of beta-globin chain of haemoglobin is replaced by valine (Ingram 1957). This situation occurs due to molecular change of nucleotide, adenine to thymine (GAG→GTG) at codon 6 (Marotta et al., 1977) of β- globin gene located on the short arm (p-arm) of chromosome 11. SCD is the commonest haemoglobinopathy found in India where the frequency sickle cell gene (HbS gene) is between 0 and 48 %.

At present about 5 percents of the world's population are carriers of a potentially pathological haemoglobin gene. Every year about 300000 infants worldwide are born with haemoglonopathies (Angastiniotis & Modell, 1998) which constitute thalassaemia syndrome (30 percent) and sickle cell trait (SCT) (70 percent). About 8 percent of American Negroes possess this characteristic (Pauling, 1949). Globally, the percentage of carriers of thalassaemia is greater than that of carriers of sickle cell, but because of the high frequency of the HbS gene in certain regions the number of affected birth is higher than with thalassaemia (WHO, 2006). While the general incidence of β- thalassaemia trait and sickle cell haemoglobinopathy varies between 3 and 17 percents and 1 and 44 percents respectively, attributed to high consanguinity and caste and area endogamy making the disease a major public and genetic health problem in India SCD is not only confined to tribal groups or the lower castes but it is present in higher castes communities in varying frequencies (Sinha, et al. 2004; Balgir 2006; Urade 2012b). According to Labie et al. (1989), the sickle cell anaemia has got unicentric origin of the mutation in India. Based on RFLP studies on -gene complex numerous haplotypes yielding multiple combinations of restriction site have been reported. It is evident from the literature that the several ethnic groups with varied genetic elements have been assimilated into the mainstream, resulting in population diversity with the passage of time (Russel and Lal, 1916). This situation leads to an increase health care burden across communities.

PREVALENCE OF SICKLE CELL GENE (HbS) IN INDIA

Community-wise prevalence of HbS gene in India reveals 15.07% in scheduled tribes, 11.06% in lower castes, 6.89% in middle castes, 6.71 in Muslims and 6.39% in higher castes. The prevalence rate across India varies from region to region amongst many Indian populations. The highest prevalence of HbS gene was encountered in Chhattisgarh while the least was recorded in Bihar. Balgir (2005, 2006) reported higher prevalence of sickle cell among the general castes (0.3-20.7%) followed by scheduled castes (0-8.9%) and scheduled tribes (0-5.5%). The prevalence of sickle cell trait (SCT) is high in tribal communities and lower castes but it is highest among the middle castes groups (Kurmi, 55% and Teli, 53%) of Chhattisgarh (Patra et al. 2010).

Table-1 State-wise Prevalence of sickle cell gene in India

State	HbS%
Andhra Pradesh	0-36
Assam	0-35
Bihar	0-0.7
Chhattisgarh	0-55
Gujarat	0-31.4
Karnataka	0-43.7
Kerala	0-32
Maharashtra	0-35
Madhya Pradesh	0-40
Manipur	0-31
Orissa	0-44.4
Rajasthan	0-33.3
Tamil Nadu	0-43.1
Utter Pradesh	0-18.5
West Bengal	0-1.2
Jharkhand	0-0.7

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ETHNIC SITUATION OF HbS GENE IN INDIA

SOUTHERN INDIA:

In India the HbS gene was first reported from Tamil Nadu (Nilgiri Hills). Gradually HbS gene has spread in seventeen states of India. During the first decade of discovery the research was confined to southern states. In Tamil Nadu the Irula tribe exhibit the highest HbS gene (40%) followed by Paniyan (34.43%), Kurumba (26.92%), and Kurumba-Mullu (19.8%) (Kirk et al. 1962; Sanghvi et al. 1981; Negi, 1976; Sastry 1990). In Kerala the Adiyan and Paniyan exhibit high magnitude of HbS gene ie., 32% and 29.73% respectively (ICMR, 1986; Buchi, 1959; Negi, 1976). In Karnataka the Yerawa (33.33%) and Soliga (26.09%) show highest HbS gene compared to other ethnic groups.The tribal groups inhabitant of Andhra Pradesh like Pardhan (34.65%) and Koya Dora (24.24%) possess high frequency of HbS gene (Blake et al. 1981; Sudhakar Babu et al. 1980) compared to other ethnic groups. The Kolam and Raj Gond however show a similar distribution of HbS gene as they linguistically belong to larger Dravidian family cluster. The Mullukuruman of Kerala exhibits low frequency of HbS (Urade 2012c). In some of the tribal groups (eg. the Kurichian and the Kota) however, sickle cell gene is absent. During 1952 to 1976 for about 25 years the prevalence rate of sickle cell gene was 0-19% in tribal populations of south India. The situation became worst by doubling the prevalence (above 40%) of HbS gene in the same area attributed to high consanguinity and less marital distance (Urade, 2012).

WESTERN INDIA

In western India the frequency ranges from 0 to 31.4% among the Gamit, the Dhanka, the Bhil, the Dhodia and the Naik of Gujarat. The Garasia of Rajasthan shows very high frequency of HbS gene (Negi, 1976). Some tribal groups of Maharashtra show very high frequency of sickle cell. Apart from scheduled tribes, lower caste, and middle castes, higher castes communities like Maratha, Brahmin, Kalar and Muslim also exhibit moderate frequency of HbS gene. However, HbS gene is absent among Mahadeo Koli, Dhangar,Halba, and Mana tribal groups belong to Maharashtra (Undevia et al. 1985;Rao and Bhatia, 1988; Kate, 2001; Urade 2012).

CENTRAL INDIA

Research on haemoglobinopathies had begun in Central India when Negi (1963) reported the presence of sickle cell gene in the Hill Maria and the Gond of Chhattisgarh. Since then few studies have been carried out in central India (Shukla and Solanki, 1958; Negi, 1963, 1964, 1976; Das et al. 1967; Papiha et al. 1978; Tiwari et al. 1980; ICMR 1986; Bhatia and Rao 1986; Saha and Goswami 1987, Urade et al. 2008; Khan et al. 2010; Patra et al. 2011, Deore and Urade 2013). HbS gene is highly prevalent among some tribal groups of central India such as Panka, Halba, Bhilala, Gond, Bhil, Gond-San Batra, Hill Maria, Gond Muria, Bison Horn Maria. However, some tribal groups exhibit negligible HbS gene like, Kawar, Kamar, Dhurwa, Oraon, and Korku. Some middle caste (backward) groups show a very high (62%) HbS gene than the scheduled tribes (15%), and the scheduled castes (18%) in Chhattisgarh state (Khan et al. 2010). The vulnerable primitive tribal groups of Chhattisgarh like Baiga and Abujmaria also exhibit high frequency of HbS gene.

EASTERN INDIA

In eastern India the prevalence rate for HbS gene varies from 0-20.7 (Kirk et al. 1962, Chaudhuri et.al. 1967; Das et al. 1974; Kate et al. 1978; Balgir and Sharma 1988; Saha et al. 1988; Balgir 2006; Urade 2012b). Sickle cell disease was wide spread in almost all castes and communities in Orissa (Kar and Devi 1997). The HbS gene has sparsely spread in some ethnic groups of West Bengal and Bihar but is absent in the Mundari speaking tribes inhabit mostly in eastern, north-eastern region of India. The Austro-Asiatic speakers migrated from Africa to India and then south-east Asia (Nei and Ota 1991; Chu et al. 1998; Su et al. 1999; Majumder, 2001) but were free from sickle cell gene.

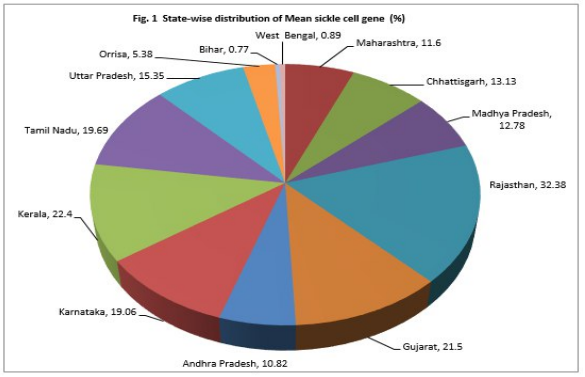
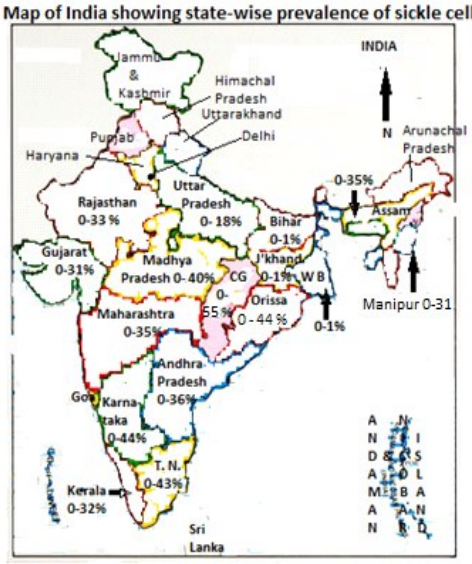


Fig. 1 Map of India showing state-wise prevalence of sickle cell gene



NORTH-EASTERN INDIA

In Assam and Manipur the prevalence rate is unexpectedly high (Shah et al. 2012) due to migration of people as tea garden laborers (Mukherjee and Das, 1990). for which a validation is needed. Population screening at large is the need of hour to establish the fact as the mutation for sickle haemoglobin is very rare among the Tibeto-Burman and Austro-Asiatic linguistic groups.

DISCUSSION

In south India, Paniyan, Kurumba, Mullukuruman and Irula have high incidence of HbS gene. In central India it is very high among the middle castes than the lower castes followed by few pockets of eastern and western India. In central India some of the lower castes possess moderately high frequency of HbS gene. In eastern India the middle castes and lower castes exhibit higher frequency of HbS compared to higher castes. The variation in frequency of HbS gene is largely depends upon the sample selection and geographical location.

The global epidemiological studies established that SCD and sickle-cell trait are present at high levels in parts of sub-Saharan Africa, the Saudi Arabian peninsula, India, and certain parts of Southern Europe. Allison (1954), opined that possession of a single mutant gene must confer a survival advantage and be positively selected at the population level.

The disease originated in at least 4 places in Africa and in the

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Indian/Saudi Arabian subcontinent. It exists in almost all parts of India and in areas where HbS carrier have migrated. It is most common in West, Central, southern and eastern India. Some tribal communities have 2 in 5 chances of being carrier for sickle cell trait, lower castes 1 in 8, middle castes 1 in 11 and higher castes 1 in 18 of being sickle cell carrier. In India there are an estimated 17862455 individuals of sickle cell trait and 1339684 individuals of sickle cell disease (SCD) (Census of India, 2011). Most of the children with HbSS disease die premature before attaining childhood per year placing a heavy burden on the already economically underprivileged.

Sickle cell gene finds its way and spread very rapidly in few generations owing to caste endogamy. Due to many historical events and migration during ancient time there exist enormous diversity in various ethnic groups and linguistic families in India. In every geographical niche, the population has also subjected to subdivision in to various small endogamous groups with or without sickle cell gene.

In India, occurrence of SCD is very high as compared to other haemoglobin variants; however, no in-depth study has yet been carried out covering all geographical regions. Studies in the states of Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Tamil Nadu, Kerala, Orissa and Andhra Pradesh have been reported by several researchers. The HbS gene has spread over the central belt from Rajasthan through Gujarat, to Orissa in east and gradually spread over the entire south India that has become a major concern from public health point of view. Thus three major tracks can be formed where HbS gene has preponderance: (1) North-Western track from Rajasthan to Maharashtra (2) Central-East track from Madhya Pradesh to Orissa and (3) South-Western track from Kerala to Maharashtra. Thus in these three tracks, the sickle cell gene is found in various ethnic groups of tribes, lower castes, middle castes, and higher castes of Indian caste hierarchy and Muslim irrespective of ethnic origin.

Community Genetics

Community genetics defined as "the art and science of the responsible and realistic application of health and disease-related genetics and genomics knowledge and technologies in human populations (communities) to the benefit of individual persons." (ten Kate et al., 2010). The ultimate aim of the community genetics is to detect the genetic abnormality at community level and provide counseling to the prospective individuals and families of congenital disorders and genetic diseases, so that prevalence of congenital disorders and genetic diseases could be prevented to establish healthy and abnormality free families in the society. Preventing congenital disorders and genetic diseases is reducing the prevalence and health impact of congenital disorders and genetic diseases of the community. Community genetics services require mass screening and detection of genetic abnormality of the population at molecular level by using advance technology such as PCR and DNA analysis. This helps in promoting and maintaining health and preventing genetic diseases in a particular community. Community genetics services include a number of activities for the diagnosis, care and prevention of genetic diseases at community level (WHO, 2011). Anthropological Survey of India had launched a National Project- Community Extension Programme with Special Reference to Sickle Cell Anaemia and Thalassaemia in Central India in 2005. Since then this premier organization has been screening (using solubility test, NESTROFT, capillary electrophoresis and DNA) populations of premarital age groups from various communities in different parts of central India and offering genetic counseling to the families of sickle cell patients and carriers. Some carrier individuals for both HbS gene and β-Thal were referred to Indian Council of Medical Research, Mumbai for pre-natal diagnosis lessening the burden of genetic load on the communities.

SCREENING AND COUSELING

Population based mass screening is important for balancing the interest of individuals, communities and society. The ultimate goal of developing therapies is to emphasize on prevention and alleviation of genetic diseases. In India though the treatment has improved for sickle cell patients and life expectancy has improved but the frequency remained unchanged. Prenatal diagnosis, selective abortion, artificial insemination by donor, adoption or childlessness etc are the challenging ethical issues in Indian societies. The most important criterion is ethnicity and personal and family history. Proper guidelines should be developed to survey the high risk target populations, the informed consents must be obtained from the individual concerned, pregnant woman for prenatal diagnosis, parents of neonatal child and adult populations to respect individual autonomy.

The information provided to the individual concerned should be appropriate to the level of literacy and should be culturally and ethically sensitive. The key elements of informed consent for screening populations are carrier and affected needs to be elaborated to the individual followed by counseling about phenotype, genotype and risk factor in future. The success of the screening programme is depended on the participation by the target population, understanding by them, follow-up by health providers and community. A two stage approach i.e.,conformity test and DNA based screening should be used. Population screening for HbAS, an autosomal recessive disease is aimed at identifying carriers who are at risk of having an affected child if other spouse is also a carrier. Such screening can be conducted on premarital, school children or newly wedded couples to make a choice of reproductive option including avoidance of marriages between two carriers, having no children or the use of a sperm donor, antenatal diagnosis with termination of pregnancy or accepting the risk.

A qualitative solubility test and naked eye single tube reverse osmotic fragility test (NESTROFT) and capillary electrophoresis screening detects all carriers for sickle cell disease and ß-thalassaemia whereas DNA assay detect only specific mutation. Nearly all haemoglobinopathies carrier can be detected by capillary electrophoresis thus; this technique is preferred for screening in the population.

Genetic counseling is a communication process which deals with the human problems associated with the occurrence or the risk of occurrence of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to the individual or family aware of risk of genetic disaeases, discuss disease prevention and management, and benefits of testing in future. Counseling focuses on providing vital, unbiased information and option to the affected couple in decision making process.

After mass screening, the suspected blood samples are taken to lab for confirmatory test. All the family members are then called in centre/school/college/community hall and offered the genetic counseling. Some of the carrier couples for genetic defect are referred to Indian Council of Medical Research (ICMR), Mumbai for prenatal diagnosis. Few of them have terminated their pregnancies after detecting sickle cell gene in the fetus.

CONCLUSION

Earlier researchers have reported that the HbS gene is

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prevalent among those ethnic groups whose economy revolves around food gathering and inhabitants of highly infested malarial area of hills and forest. During evolution, the entire ancestral globins gene was duplicated. One copy with mutated gene developed in to sickle haemoglobin and another copy in to normal haemoglobin making two distinct founder populations. Because of diffusion and fission one group with sickle haemoglobin and other group with normal haemoglobin diverged independently and dispersed in different geographical areas. The migration processes penetrate the HbS gene in to another group of populations paving the way for spreading in different areas. Thus, due to this genetic diversity in some groups of Indian populations sickle cell gene is virtually absent while some ethnic groups have the sickle cell gene even though they share same ancestral history with similar ecological conditions. This would probably suggest the molecular resolution to determine the likely modest impact of historic gene flow to wide spread of HbS gene in north-western, central, south-eastern and southern India on its pre-existing large populations. Because of invasions by many foreigners like the Huns, Greek, Kushan, Moghul, Muslim, British and others, the prehistoric genetic inheritance in Indian indigenous populations the genetic footprints are in existence.

Many ethnic communities living in highly malarial infested areas such as the Himalaya region, the Ganges plateau, the Vindya-Arawali terrain, the Western Ghats, the coastal region surrounded by Bay of Bengal and Arabian Sea are free from sickle cell gene in India.

A researcher should have thorough knowledge about the universe to study a sample of population to offer quantitative test of sickle cell to the prospective partners of sickle cell carriers before marriage. This would help the couple of their future generation through education and counseling. Number of children in homozygous state of sickle cell (SS) phenotype dies before Unless direct functional relation in the structure of sickle haemoglobin in reducing the parasitic load is established, endemicity of malaria responsible for high prevention of sickle cell trait in certain communities cannot really be explained.

Making aware of high magnitude of sickle cell disease through posters, mass media, electronic media, social media, messages, and community drama will help in bringing down the prevalence rate so that the disease can be prevented and managed in transmitting in next generation.

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