ISSN 2321 – 7359 EISSN 2321 – 7367

discovery

Medical Science

The International Weekly Journal for Medicine

Haemoglobinopathies – HbE and HbS among the Gallong Tribe of West Siang District of Arunachal Pradesh, India

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Publication History
Received: 13 February 2014
Accepted: 12 April 2014
Published: 23 April 2014

Citation
Urade BP. Haemoglobinopathies – HbE and HbS among the Gallong Tribe of West Siang District of Arunachal Pradesh, India. *Medical Science*, 2014, 7(26), 83-89

ABSTRACT

The Gallong is a small tribal group of the West Siang district of Arunachal Pradesh in India settled in small hamlets. The Gallong are Tibetan in origin of Mongoloid stock belong to the Tibeto-Burman language. Traditionally they are hunters, gatherers and shifting cultivators. Intravenous 1.blood samples were collected from unrelated 108 individuals of both sexes. The HbE gene is more frequent among Gallong (38.9%) while HbS gene was less frequent (0.98%). The females show higher frequency of HbE homozygous than males. The frequency of haemoglobin-E trait in Northeast ranges from 0 – 55%. HbE is more frequent in population of Northeastern belonging to the Tibeto-Burman linguistic group. The Proto-Australoid populations are less frequent for HbE gene. The pattern of haemoglobin-E variant in Northeast India is similar to that found in Cambodian and Thai populations as revealed from literature. Incidences of 5.55% of consanguinity were recorded among Gallong. The Gallong a Tibeto-Burman linguistic group show a very high frequency of HbE trait.

Key words: HbE, HbS, gene frequency, tribe, North-east, Arunachal Pradesh, India.

1. INTRODUCTION

Haemoglobin E (HbE), is one of the most prevalent haemoglobin structural variants, existing in a very high frequencies in Southeast Asia. It is one of the four abnormal haemoglobins identified (Sturgeon et al., 1955) and has an ancestry of Hindu/Guatemalan/Spanish and Italian (Itano et al., 1954). It is highly prevalent in North-east India, Indonesia, Thailand, Cambodia, Bangladesh, Srilanka, Europe and North America. Its occurrence is up to 50% in Khmer populations living in the borders of Laos, Thailand, Cambodia and North-east India (Wasi, 1983; Deka, 1988). The preponderance of HbE is restricted to tribal groups of North-east and Bengali communities. Sickle cell (HbS, codon 6

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A→ T) and HbE (codon 26 G→ A) are molecular disorders caused by the substitution of a glutamic acid for valine at 6th ($\alpha_2\beta_2^{\ 6\ Glu\rightarrow Val}$) and for lysine at 26th ($\alpha_2\beta_2^{\ 26\ Glu\rightarrow Lys}$) positions respectively of β-polypeptide chain. HbES and homozygous HbE result in hypochromic microcytosis and minimal anaemia but HbSS causes a severe and lethal anaemia. HbE is the second most prevalent Hb variant worldwide and the third most prevalent variant in India, after HbS and β-thalassaemia. HbE is found primarily in Southeast Asia, especially among the Thai population (Tanphaichitr et al., 1995). Clinically the HbE and HbS traits are asymptomatic in nature and have 2:3 ratios of red cells with adult haemoglobin (HbA) but HbE homozygous has 90 to 99 per cent of HbE cells and found to be moderately anaemic (Flatz, 1967; Chernoff et al., 1956; Lehmann et al., 1956).

Whereas, HbSS state in the range of 80 to 90 causes severe anaemia. In Southeast Asia occurrence of a third allele called β-thal in β-globin has a negative correlation between HbE and β-thal (Flatz, 1965; Wasi et al., 1967). These three allele polymorphism exists in Northeast and believed to be maintained through adaptive advantages in the malarial environment (Flatz et al., 1972) and by positive selection against malarial infection (Ohashi et al., 2004). In vitro studies have shown the inhibition of the growth of *P. falciparum* in HbE erythrocytes (Chotivanich et al., 2002; Vernes et al., 1986; Yuthavong et al., 1987).

There are no studies on haemoglobin E among the tribes of Arunachal Pradesh until recently (Sengupta et al., 2002) who studied only 29 adolescent boys of Gallong tribe for HbE. Therefore the present study probably, the first of its kind to study the Gallong tribal group from the most inaccessible part of Arunachal Pradesh for HbE and HbS.

Normal haemoglobin (HbA) consists of 2 α-globin chains and 2 β-globin chains. Both HbS and HbE are inherited autosomal recessive variations of the β-globin chain. The normal β-globin chain has a glutamic acid at 6th position, located on p-arm of chromosome 11. The HbS results from substitution of valine for glutamic acid (glu→val) while HbE occurs due to substitution of lysine for glutamic acid at 26th position (glu→lys). Sickle cell trait (HbAS) results when a single copy of mutated gene inherited from one parent and one copy of normal gene from other parent. Likewise, haemoglobin E trait results when one copy of mutated gene inherited from one parent and a normal copy of healthy gene from other parent. Thus, if mating between two carriers takes place, one child they produce will receive defective genes from each parent and will have a disorder (25% normal, 50% carrier and 25% affected children).

There are 4693 communities in India (Singh, 1998) including different castes, tribes and religious groups. About 450 tribes constitute 8.2% of the total India's population and Arunachal Pradesh has 0.95 million tribal populations (Census of India, 2011). There are more than 750 dialects mainly classified into Austro-Asiatic, Dravidian, Tibeto-Burman and Indo-European linguistic families. Indian tribal communities follow endogamy inhabiting mostly in the forests and hilly terrain areas.

The Gallong is a small tribe of the West Siang district of Arunachal Pradesh settled in small hamlets. The Gallong are homogeneous population consists of several groups which include the Karka, Bogum, Iaktu, Korga, Tator-Tani and Lodu. The Gallong are Tibetan in origin of Mongoloid stock belong to the Tibeto-Burman language, lived on the fringes of the Indo-Tibetan frontier but established permanent settlements. Traditionally they are hunters, gatherers and shifting cultivators.

2. MATERIALS AND METHODS

For DNA Polymorphism project, blood samples were collected from 28 villages of remote area in West Siang district of Arunachal Pradesh, India. Before drawing intravenous blood every individual was well explained about the purpose of research for which necessary consents (approved by the Ethical Committee) were obtained from all individuals. Following standard protocols 4-5 ml intravenous blood samples were drawn in BD vacutainer (USA) containing liquid EDTA from healthy and unrelated 108 individuals comprising both sexes (age 18 –71 years). Prior to DNA extraction, about 200 µl (micro-liter) of blood from each sample was taken out in 1.5 ml tube to prepare haemoglobin lysates. The erythrocytes (RBC) were washed with normal saline. 1-2 droplets of MQ (the processed distilled water) were added to all washed RBCs and kept in refrigerator at -20°C for about ½ an hour to haemolyse the erythrocytes. All haemolysed samples were washed with CCl_4 at room temperature and centrifuged at 8000 rpm. The clear supernatant (protein) was taken out in a separate test tube. These lysates were subjected to electrophoresis at alkaline pH 8.9 on cellulose acetate membrane along with the known controls (procedure laid down by Dacie and Lewis, 1968). TEB buffer (Tris-EDTA-Boric acid) was used as media. The results were noted down according to the position of HbE-band after running the electrophoresis for about ½ an hour. The age and sex-wise distribution of sample is given in Table 1.

3. RESULTS

Table 2 portrays the sex-wise occurrence of haemoglobin (HbE and HbS) variants among the Gallong tribe of Arunachal Pradesh. As HbE is common in Southeast Asia with over 30 per cent population affected, the Gallong is no exception to this phenomenon where the frequency of 38.9 % was recorded. Both the sexes show a similar pattern of

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Table 1

Age and sex-wise distribution of sample among the Gallong

Population	Sex	No.	Age cohort					
			>20	21-30	31-40	41-50	51-60	60+
Gallong	M	54	3	10	20	10	7	4
	F	54	3	25	10	10	2	4
	Total	108	6	35	30	20	9	8

Table2

Sex-wise frequency distribution of HbE and HbS among the Gallong tribe

			HbAA	HbAE	HbEE	HbAS
Population	Sex	N	%	%	%	%
Gallong	M	54	34 (31.48)	19 (17.60)	1 (0.92)	-
	F	54	31 (28.71)	19 (17.60)	3 (2.78)	1 (0.98)
	Total	108	65 (60.19)	38 (35.19)	4 (3.70)	1 (0.98)

Table 3

Distribution of Haemoglobin variants of North-east population

Population		Haemoglobin variants %			Frequency of	References
	N	HbA	HbAE	HbEE	HbE gene	
Ahom	82	41.46	45.12	13.41	0.36 ± 0.037	Das et al., 1971
Ahom	129	41.86	46.51	11.63	0.35 ± 0.029	Flatz et al., 1972
Ahom	119	36.15	47.05	16.8	0.4	Deka et al., 1988
Ahom (Sibsagarh)	89	52.81	41.51	5.62	0.26 ± 0.033	Das et al., 1975
Ahom (Dibrugarh)	181	42.54	46.41	11.05	0.34 ± 0.025	Das et al., 1975
Assamese (Lower assam)	112	81.32	15.93	2.75	0.11 ± 0.016	Flatz et al., 1972
Assamese (Upper Assam)	133	76.69	19.55	3.76	0.14 ± 0.021	Das et al., 1975
Kachari (Upper Assam)	555	24.14	49.73	26.13	0.51 ± 0.015	Das et al., 1975
Kachari (Lower Assam)	131	21.37	47.33	31.3	0.55 ± 0.030	Das et al., 1978
Kachari (Sonowal)	106	37.74	45.28	16.98	0.4	Deka et al., 1988
Karbi	110	62.73	29.09	8.18	0.23	Deka et al., 1988
Khasi	80	58.57	38.75	2.5	0.22 ± 0.033	Dsa et al., 1971
Khasi	120	59.29	36.43	4.29	0.23 ± 0.025	Flatz et al., 1972
Garo	135	31.85	37.04	31.11	0.5 ± 0.093	Das et al., 1978
Rabah	128	18.75	55.47	25.78	0.54 ± 0.031	,,
Lalung	114	29.82	50.88	19.3	0.45 ± 0.032	,,
Mikir	131	66.41	27.48	6.11	0.2 ± 0.019	,,
Rajbanshi	164	45.12	39.63	15.24	0.35 ± 0.025	,,
Rajbanshi	102	58.83	36.27	4.90	0.23	Deka et al., 1988
Meitei	203	87.57	11.03	1.40	0.07	Chakravarty and Roy, 1979
Meitei	104	80.77	18.27	0.96	0.10	Singh et al., 1986
Brahmin	109	94.45	5.55	0	0.03	Singh et al., 1986
Brahmin	98	89.80	10.2	0	0.05	Deka et al., 1988
Kalita	104	78.85	19.23	1.92	0.12	,,
Kaibarta	101	74.26	24.75	0.99	0.13	,,
Muslim	104	80.77	18.27	0.96	0.10	,,
Chutia	62	46.78	46.77	6.45	0.30	,,
Lepcha	61	95.08	4.92	0.00	0.03	Bhasin et al., 1986
Lepcha	32	90.63	9.37	0.00	0.05	,,

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Bhutia	104	98.08	1.92	0.00	0.01	,,
Sherpa	45	100	0.00	0.00	0.00	,,
Tamang	38	100	0.00	0.00	0.00	,,
Gurung	38	100	0.00	0.00	0.00	,,
Ria	38	97.37	2.63	0.00	0.01	,,
Limboo	51	100	0.00	0.00	0.00	,,
Pradhan	35	100	0.00	0.00	0.00	,,
Hill Kabui	270	93.33	6.30	0.37	-	"
Koireng	174	94.25	5.75	-	-	"
Simte	164	97.56	2.44	-	-	"
Gallong	108	60.19	35.19	3.7	0.21	Present study

Table 4

Distribution of Haemoglobin variants of West Bengal population

Population		Haemoglobin Variants (%)			Frequency of	References
	N	HbA	HbAE	HbEE	HbE gene	
Poliya	85	20	61.18	18.82	0.49	Das et al., 1991
Deshi	103	16.5	44.66	38.84	0.61	,,
Tiyor	95	76.84	21.05	2.11	0.13	,,
Lepcha	75	96.00	4.00	0.00	0.02	Saha et al., 1987
Lepcha	140	95.71	4.29	0.00	0.02	,,
Rava	90	87.78	12.22	0.00	0.06	Kate et al., 1984
Rajbanshi	63	79.37	20.63	0.00	0.10	,,
Mech	26	65.39	34.61	0.00	0.17	,,
Toto	116	80.17	19.83	0.00	0.10	Choudhury et al., 1962
Oraon	202	100.00	0.00	0.00	0.00	Saha et al., 1988
Brahmin	115	96.52	3.48	0.00	0.02	Ghosh et al., 1983
Kayastha	120	97.50	2.50	0.00	0.01	,,
Vaisya	71	98.59	1.41	0.00	0.01	,,
Other castes	132	98.49	1.51	0.00	0.01	,,
Rarhi Brahmin	42	92.86	7.14	0.00	0.04	Kate et al., 1984
Vaidya	29	93.11	6.89	0.00	0.04	,,
Jalia Kaibarta	89	94.39	5.61	0.00	0.03	,,
Lodha	197	90.36	9.64	0.00	0.05	,,
Munda	161	95.03	4.97	0.00	0.03	,,
Bagdi	180	95.00	5.00	0.00	0.03	,,
Brahmin	253	100.00	0.00	0.00	0.00	Choudhury et al., 1969
Kayastha	229	97.38	2.62	0.00	0.01	,,
Vaidya	129	99.23	0.77	0.00	0.00	,,
Kaora	102	99.02	0.98	0.00	0.01	Das et al., 1974
Anglo Indian	89	100.00	0.00	0.00	0.00	,,
Santal	102	99.01	0.99	0.00	0.00	Giri et al., 1982
Bhumij	95	100.00	0.00	0.00	0.00	,,

frequency of HbE variant in heterozygous (17.60% each sex). The frequency of homozygous HbEE in females was 2.78% while that of male it shows 0.92%. Only one case of female was seen with sickle cell trait (SCT). The frequency of consanguineous marriages among the Gallong was 5.55%. Merely 0.93% of HbE (for consanguinity) with 7.77 km (SD ± 3.62 km) mean marital distance was recorded among them.

4. DISCUSSION

In North-east India the frequency of HbE ranges from 0 to 55 % while in West Bengal it ranges from 0 to 61% (Table 3). Some populations of North-east like Kachari, Rabah and Garo display the highest gene frequency (0.5) followed by

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Lalung and Ahom (0.4) and Rajbanshi and Chutia (0.3). In some Hindu caste populations and Proto-Australoid tribal groups of West Bengal, the frequency of HbE gene is very low (Kate et al., 1984; Chaudhuri et al., 1962; Bhasin et al., 1986). However, the gene is completely absent in some of the populations of Northeast like Lepcha, Bhutia, Sherpa, Tamang, Gurung, Limboo, Pradhan and Oraon, Brahmin, Podmaraj, Anglo Indian and Bhumij of Eastern India (Table 3 & 4), (Chaudhuri et al., 1962; Ghosh et al., 1981; Giri et al., 1982; Choudhury et al., 1969; Saha et al., 1987; Hurst et al., 1983).

It is evident from the present study that the frequency of the HbE variant is very high and largely restricted to the north-eastern and eastern region of the Indian subcontinent. The children of Cambodian refugee in California (USA) showed 19% HbE (Sanguansermsri et al., 1987). In population from Phnom Penh, Cambodia confirmed high frequency of HbE (Fucharoen et al., 1998). Frequency of HbE reaches 50 % in north-eastern region of Thailand (Fucharoen et al., 2003). Historical evidence exists for their migration from India and neighbouring countries. Similar observations were made in the populations of Ahom, Kachari, Karbi, Lalung, Garo, Rabha and Khasi of north-east Indian that can be comparable with those of Khmer speaking of Cambodia. There is similarity in Mon-Khmer speaking Khasi of Meghalaya and Khmer speaking Cambodian. Consanguineous marriages are responsible for maintaining high incidence of genetic disorders (Das et al., 1971) but the present study differs from this view where no close association was seen between the consanguinity and incidences of HbE among the Gallong. The obvious reason for threefold frequencies of homozygous HbE in female is that each parent of such homozygous individuals must have transmitted one copy of HbE variant as it is autosomal inherited disorder. Presence of HbS in Upper Assam was due to admixture with tea garden labourers who migrated from Orissa and Bihar (Dunlop and Mozumder, 1952; Batabyal and Wilson, 1958; Das et al., 1991). Mere one incidence of HbS in present study may be due to admixture or migration or independent mutation. This incidence in Gallong occurred at least three generation before considering the age of the individual who possesses HbS trait. In-depth molecular study is required to establish this fact as gene diversities exist in sickle cell haemoglobinopathy.

The Gallong shows a very high frequency of HbE similar to those found in Ahom, Kachari, Khasi, Garo, Rabah, Lalung, Phayeng, Rajbanshi, Chutia and Karbi (Table 3). In linguistically different populations like Kaibarta, Mikhir, Meitie, Muslim, Kalita, Assamese, Khurkhul and Brahmin HbE is moderately high. In Bengali speaking populations of Poliya, Deshi, Tiyor, Mech, Rajbanshi, Toto, Rava, Lodha, Rarhi Brahimn a very high frequency of HbE has been reported (Table 4). In unrelated Bengalee Hindus 3.9% of HbE has been reported. Ironically, HbE disease in Gallong is less frequent compared to Ahom, Kachari, Karbi, Garo, Lalung, Mikhir, Rajbanshi, Chutia and Khasi. Other studies in Bengal showed cases of HbE trait, Hb-E disease, Hb-Eβ-thalassaemia and Hb-DE disease. Sporadic cases of Hb-E have been reported from Uttar Pradesh, Patiala, Madras, in a Muslim family from Aurangabad and in a family with Bengal-Tamil ancestry (Lele et al., 1962; Chatterjea, 1965; Kochar and Kapadia, 1963; Sukumaran and Master, 1974). Haemoglobin E-thalassaemia was reported in a Bohra family of Bengalee admixture in Maharashtra, a local Muslim mother and a Pathan father and the other in a Bhayya from Gondia in Uttar Pradesh (Sharma et al., 2000; Mehta et al., 1962). One case of Hb-E trait was observed in Trivandrum, and one case of HbEβ-thalassaemia in a Tamil Christian family (Vella, 1958).

Till recently HbE was restricted to Northeast population of mongoloid stock but gradually it is spreading in other regions of Indian subcontinent. There are some cases of HbE in different states of South India (Brahmin in Kerala and Christian in Tamil Nadu), North India (a Hindu Kayastha in Uttar Pradesh), and Western India (Deshastha Brahmin, Maratha and Muslim in Maharashtra) with no evidence of admixture with the population of Mongoloid stock of north-east (Sharma et al., 2000). Whether this situation is due to novel mutation is need to be found out at the molecular level. There is close linkage between Gallong and Sonowal Kachari at the molecular level (Chandrasekar et al., 2009) and this may be the reason why both these groups show very high frequency of HbE trait.

HbE is most frequent among Gallong, Kachari, Khasi, Cambodia, Thai indicating close association between Tibeto-Burman, Mon-Khmer and Austro-Asiatic linguistic population as they share considerable genetic commonalities (Brumpt et al., 1958). The mutation might be restricted to Southeast Asia as the haplotype could have originated by a crossing-over event 5′ to a β^E gene of Southeast Asian origin (Clark et al., 2000). It has been found that the incidences of HbE are 40% in the people living in North-east India, Laos, Cambodia and Thailand thus making a 'haemoglobin E quadrangle'. There is a correlation between Austroasiatic (Mon-Khmer) linguistic group and the prevalence of HbE gene (Deka et al., 1988).

5. CONCLUSION

HbE is not restricted to the populations of Mongoloid stock but has been reported in other genetically diverse populations of Southern, Northern and Western parts of India as seen from the available literature. Tibeto-Burman, Mon-Khmer and Autro-Asiatic linguistic populations share genetic commonalities. The occurrence of larger frequency of HbE in populations of Northeast India, Laos, Thailand and Cambodia forms 'haemoglobin E quadrangle'.

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Historically, the present days so called endogamous groups are admixture genetically ever since the modern man was evolved for the first time. Gradually different haemoglobin variants are spreading all over India with varying degrees irrespective of regions and populations with different genetic stock. Genetic mutation, environment, migration, hybridization and cultural aspects are responsible for the spread of different haemoglobin variants at different rates. To combat the menace of haemoglobinopathies its proper prevention and management, detection of abnormal haemoglobin at premarital age groups, prenatal diagnosis, and genetic counseling are the essential elements.

SUMMARY OF RESEARCH

1. The pattern of distribution of HbE among the Gallong tribal group of Arunachal Pradesh resembles the pattern found in Khasi, Garo of Meghalaya and Karbi and Rajbanshi of Assam states. The frequency of haemoglobin E variant exceeds 50% in some populations of north-east India eg. Ahom, Kachari, Rabha and Lalung.
2. The magnitude of occurrence of HbE among different ethnic groups of north-east region and eastern region is very high. The environmental conditions and cultural practices may be responsible in maintaining high frequency of HbE gene in various ethnic groups of eastern and north-eastern regions.

FUTURE ISSUES

The molecular study will unravel the enigma of high frequency of HbE and also to see if any diversity in the gene exists. Whether the mutation rate for HbE gene is high or certain evolutionary forces are operating in eastern Himalayan region? In-depth studies at micro level help solve this query.

DISCLOSURE STATEMENT

There is no conflict of interest. This study was done for personal research interest.

ACKNOWLEDGEMENT

Author is grateful to the Gallong people who donated blood samples, to my teacher Prof. Moyna Chakravarty and others who are concerned.

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