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Haemoglobin E Distribution in Four Endogamous Populations of Manipur (India)

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Abstract

The present paper is a report on the prevalence of Haemoglobin E (HbE) among four endogamous populations of Manipur (India) namely the Kabui, Koireng, Simte and the Meitei. The average allele frequency of HbβE observed among the Meitei is 0.101. However, the frequency of HbβE ranges from 0.045 to 0.226 among various sections of the Meitei. The frequency of HbβE among the Phayeng Chakpa shows the highest value (0.226) while the Ningthoukhong Meitei shows the lowest (0.045). The frequency of HbβE among the hill Kabui population is 0.035 followed by the Koireng (0.029) and the Simte (0.012). The frequency of HbβE among the various tribal populations of malaria endemic zones of Manipur is below 0.04. It is indicative that the ethnic origin and marriage system may be the responsible factors for variation in the frequencies of HbE gene among the populations of Manipur. In the present study, neither protective advantage of HbβE against malaria nor harmful effect of homozygous (HbEE) genotype could be satisfactorily established.

Keywords: *Haemoglobin E, malaria, endogamous, populations of Manipur*

Introduction

Haemoglobin E (HbE) is the most popular haemoglobin variant in Southeast Asia as well as in Northeast India. It is abnormal haemoglobin with a single point mutation where glutamic acid is replaced by lysine at position 26 of the beta globin chain. The first case of HbE was concurrently reported by Itano et al. (1954) and Chernoff et al. (1954). Subsequently many studies on the distribution and prevalence of haemoglobin E were carried out in Southeast Asia and Northeast India.

Reports of the prevalence of haemoglobin E in Northeastern India were mainly from the states of Assam and Meghalaya that too was not complete and there are meager reports from rest of the northeastern states like Arunachal Pradesh, Manipur, Mizoram, Tripura, etc. From Manipur, there are a few reports on the prevalence of haemoglobin E among the Meiteis, Brahmins, Phayeng, Khurkhul, Ningthoukhongs, Thadou, Kabui, Gangte, and the Muslim (Chakraborty and Roy, 1979; Singh et al., 1986;

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Singh and Singh, 2008, 2009*a*). The present paper is a report on the distribution of HbE among four endogamous populations of the state, named, the Kabui, Koireng, Simte and the Meitei. They are racially mongoloid and speak dialects of Tibeto-Burman language of the Sino-Tibetan family. The Kabuis is one of the representatives of the Naga group of Manipur. The Kabuis nowadays call themselves Rongmei. The Kabui or Rongmei are mainly concentrated in the Tamenglong district of Manipur and there are a number of Kabui pockets in Imphal Valley. The Koirengs are one of the tribes of the old Kuki group inhabiting Manipur. But now they identify themselves as Naga. The Simtes is one of the representatives of the Kuki-Chin group inhabiting mainly in the Churachandpur District of Manipur. The Meiteis, on the other hand, are the numerically dominant ethnic group of Manipur, India. They speak Mieteilon and it is used as lingua franca of the state. The main reason for choosing these populations in the present study is, they have been living in this region from times immemorial under similar environmental condition showing affinity both in culture and biology. It was due to the influence of religion in the later part of history which makes them different. So, the study on such groups can give a picture on the antiquity of the trend of HbE frequency in the region.

Land

Manipur is situated in the extreme north-eastern corner of India and lies between 23.80°N and 25.68°N latitudes and 93.03°E and 94.78°E longitudes. The state is bounded on the east by the Somra tract and the upper Chindwin areas of Myanmar, on the west by the Cachar hills of Assam, on the north by the Naga Hills of Nagaland, and on the south by the Chin Hills of Myanmar. The total geographical area of the state is 22,327 sq km. It is predominantly a mountainous state with a central bowl shaped valley formed by the deposits of alluvial soil. The state can be divided into two major regions namely the central valley with an area of 2230 sq km (10.02%), at the elevation of 750 - 900 metres above the mean sea level and the surrounding mountain covering an area of 20,089 sq km. The Imphal basin covers an area of 1813 sq km.

Materials and methods

Blood samples from 270 unrelated Kabui (Hill), 174 Koireng, 164 Simte and 626 Meitei, i.e. a total of 1,234 apparently healthy individuals belonging to both sexes, were collected in EDTA by finger pricks from March 2005 to October 2009. The Kabui samples were drawn from the Tamenglong district, the Koireng samples from Senapati district, the Simte from Churachandpur district and the Meitei from Imphal East and West districts of Manipur (Figure 1). The haemoglobin types were screened by electrophoresis on Cellulose Acetate/cellogel strips along with known control samples (Dacie and Lewis, 1991). Fetal haemoglobin is estimated by an alkali denaturation technique, while haemoglobin A2 quantification by elution method. The present data have been compared with available reports of Chakraborty and Roy (1979), Singh et al. (1986), and Singh and Singh (2008, 2009*a*) of the state.

Results

Table 1 displays the occurrence of haemoglobin variants in the four endogamous populations, viz., the Meitei, Kabui, Koireng and Simte of Manipur. Haemoglobin E, the most common abnormal haemoglobin variant in the whole Southeast Asia and Northeast India, is also found to be common in the present four populations of Manipur. The Meitei shows the greatest incidence of HbE, with 18.207% of them possessing HbβE.

Among them 15.81% are heterozygous, 1.917% homozygous and 0.48% compound heterozygous. Incidence of HbE among the Hill Kabui is 6.67% of which 6.30% is heterozygous and only 0.37% homozygous. No homozygous individual has been found in the remaining two populations. Percentage frequencies of heterozygous individuals in the latter are: 5.75 and 2.44 among the Koireng and Simte respectively. It is noteworthy that homozygous HbEE is found among the Meitei and Hill Kabui only. It is, most likely, an indication of early introduction of the HbβE gene either by mutation or by gene flow to these populations.

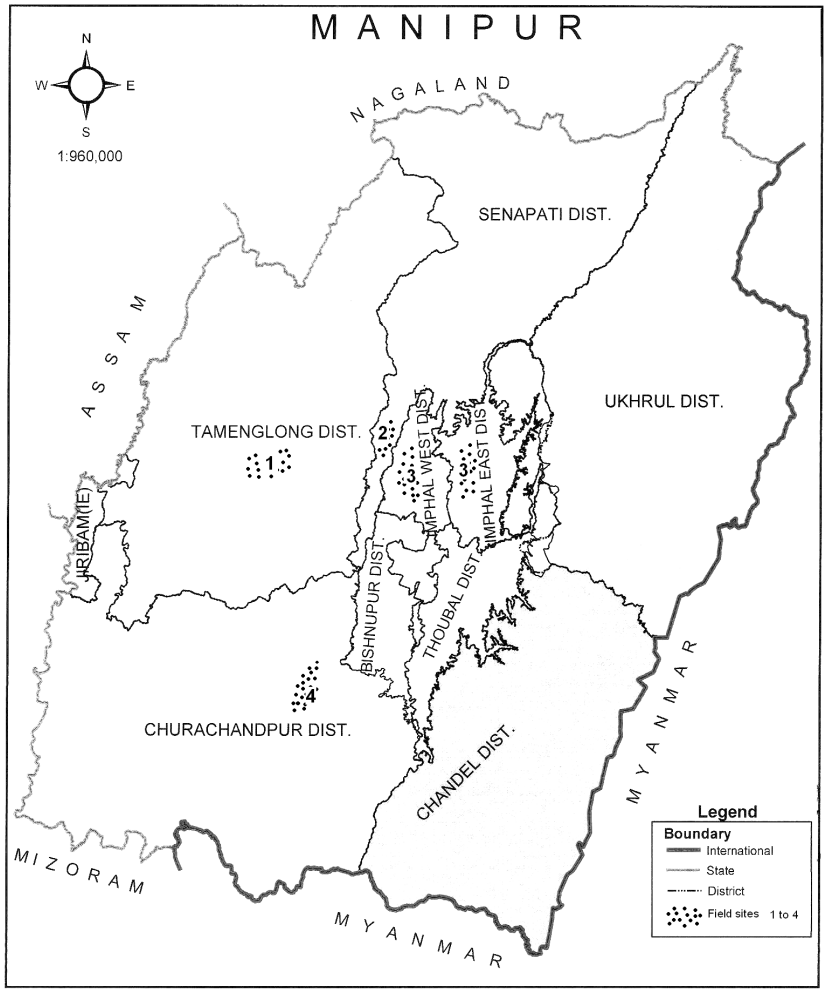

Figure 1: Map of Manipur showing the field sites.

Table 1: Percentage frequency of haemoglobin types in four populations of Manipur

Population	Sample size	HbAA (%)	HbAE (%)	HbEE (%)	HbE/beta-thal (%)	Beta-thal trait (%)	Unknown (%)
Meitei	626	81.31	15.81	1.92	0.48	0.32	0.16
Hill Kabui	270	93.33	6.30	0.37	-	-	-
Koireng	174	94.25	5.75	-	-	-	-
Simte	164	97.56	2.44	-	-	-	-
Total	1234	87.93	10.53	1.05	0.24	0.16	0.08

The allelic frequency of haemoglobin types among four endogamous populations of Manipur are shown in Table 2 along with available data of Chakraborty and Roy (1979), Singh et al. (1986), and Singh and Singh (2008, 2009*a*). In the present research

the greatest frequency of allele HbβE, 0.101, is found among the Meitei. It is successively followed by the hill Kabui (with a frequency of 0.035), Koireng (0.029) and the Simte (0.012). The frequency of HbβE among the Meitei agrees with the earlier reports of Chakraborty and Roy (1979) and Singh et al. (1986), who found in another Meitei samples from Manipur a frequency of 0.071 and 0.101 respectively. The hill and valley Kabuis show a similar picture in the frequency of HbE albeit the varied ecological niche. It is pertinent to mention here that in early historic period the Kabuis of Imphal valley have come mainly from Tamenglong, one of the malaria endemic districts of Manipur. They have been living in the valley from many generations, protecting their cultures and tradition.

Table 2: Allelic frequency of haemoglobin types in various populations of Manipur

Population	Sample size	HbA	HbE	β-thal	Unknown	Reference
Meitei	626	0.895	0.101	0.004	0.001	Present
Kabui	270	0.965	0.035	-	-	Present
Koireng	174	0.971	0.029	-	-	Present
Simte	164	0.988	0.012	-	-	Present
Meitei	203	0.929	0.071	-	-	Chakraborty and Roy, 1979
Meiteis	104	0.899	0.101	-	-	Singh et al., 1986
Brahmins	108	0.972	0.028	-	-	Singh et al., 1986
Phayengs	104	0.774	0.226	-	-	Singh and Singh, 2008
Khurkhuls	123	0.915	0.085	-	-	Singh and Singh, 2008
Ningthoukhong	122	0.955	0.045	-	-	Singh and Singh, 2009*a*
Kabui	162	0.963	0.037	-	-	Singh and Singh, 2009*a*
Thadou	115	0.965	0.035	-	-	Singh and Singh, 2009*a*
Gangte	117	0.970	0.030	-	-	Singh and Singh, 2009*a*
Muslim	136	0.941	0.059	-	-	Singh and Singh, 2009*a*

When we observed the present results and compared with other reports from Manipur, the greatest frequency of allele HbβE, 0.226, is found among the Phayeng. It is successively followed by the Meitei (with a frequency of 0.101), Khurkhul (0.085), Meitei (0.071), Muslim (0.059), Ningthoukhong (0.045), Plain Kabui (0.037), Hill Kabui (0.035), Thadou (0.035), Gangte (0.030), Koireng (0.029), Brahmin (0.028) and Simte (0.012).

Conclusion

Occurrence of HbβE in a relatively greater frequency among the autochthones like the Meitei, particularly the Chakpa and appearance of this gene in all the populations so far examined, implies that this is a very old gene in Manipur. The Khurkhul, who shows a comparatively high frequency of HbβE, is believed to have Shan origin. They are historically identified as a section of the Shans, whose ethnic compatriots are found today in the Shan tribe of Burma (McCulloch 1859). They might have either carried the gene with them or received from the neighbour, both are possible. This state, being situated at the crossroad of Indian subcontinent and Southeast Asia, is believed to have been a route of racial movement since pre-historic times. This must be the reason for her advanced unique culture and multi ethnic composition, an outcome of the contributions made by various ethnic groups. Introduction of HbβE to the people of this region must have taken place in the same manner.

HbE is the most popular haemoglobin variant in Southeast Asia as well as in Northeast India. Prevalence of HbE in high frequencies (0.6455) among the Bodo-Kachari and other Tibeto-Burman speaking populations of Assam is a mind-boggling

subject now (Deka et al., 1988). How did the HbβE gene appear in these populations and what had caused the elevation of its frequency to such an extent as seen today? Brumpt et al. (1958) reported that in Cambodia HbE-β thalassaemia disease was associated with Chinese-Khmer parents, and that HbE was invariably transmitted by Khmer parents. On the basis of this data Flatz (1967) presumed a hypothesis of association of HbE and Mon-Khmer (Austroasiatic) language speaking people. Entire Southeast Asia was believed to have occupied by the Austroasiatic speakers during prehistoric and early historic times, and HbE probably originated in these populations. Accordingly, Flatz et al. (1972) initiated an investigation on haemoglobin variant in Northeast India by selecting the Austroasiatic (Mon-Khmer) speaking Khasi of Meghalaya and a Siamese-Chinese (Tai) speaking Ahom of upper Assam, who entered the region in the thirteenth century. As expected, the study revealed HbβE in these populations with frequencies of 0.225 and 0.352 among the Khasi and Ahom respectively, which were comparable with that of the Khmer of Cambodia. Further studies among the Tibeto-Burman speakers of the regions, however, discovered a much unexpected picture (Das et al., 1975; Deka, 1981). In contrast to very low frequency of haemoglobin E among the Tibeto-Burman populations of Tibet, Nepal, South China and Thailand, Tibeto-Burman populations of Assam displayed frequencies of haemoglobin E above 50%. High prevalence of haemoglobin E (>50%) were observed among the Soui, Thai Khmer, So, Yor and Puthai populations inhabiting the region near Cambodia and Laos (Sriboonlue et al., 1985; Flatz et al., 2004; Fucharoen et al., 2002). It is pertinent to mention here that the Phayeng belongs to a section called Chakpa of the Meiteis, the larger community of the state. The other Chakpa groups are the Sekmai, Andro, Leimaram, Koutruk, Chairel, etc. From where and when the Chakpa came in Manipur is not known. They represent one of the oldest settlers of the state. They are, however, still retaining their old pristine beliefs and practices. There is a mention in Cheitharol Kumpapa, a noted Royal Chronicle of Manipur (Parratt, 2005), which points to the possibility of matriarchal society of the Chakpas in the past. The Chakpa is now a section of the Meitei and speaks Manipuri (Meiteilon) even though they used to have their own dialect in the past. Very little is known about Chakpa language today. Nobody can say whether it is a Tibetoburman, Austroasiatic or Siamese-Chinese. Grierson (1967) was also not sure about the family of Chakpa language. A research on Chakpa language will, therefore, be of great academic importance. If it were an Austroasiatic dialect, we can believe in the existence of Austroasiatic matrilineal race, like the Khasi of Meghalaya, in Manipur too in the past. If it is true, relatively higher frequency of HbE in the Phayeng (a Chakpa) of Manipur can be taken as a favour on the hypothesis of association of Austroasiatic race and HbE, as presumed by Flatz (1967).

There are proponents of protective advantage of HbβE against tropical malaria. Kruatrachue et al. (1969), in their study in Thailand, provided further data relevant to the hypothesis that heterozygosity for haemoglobin E and thalassaemia offers some selective advantage in *P. falciparum* infections. This has been corroborated by in vitro parasitaemia studies in erythrocytes (Bunyaratvez et al., 1986). Myint-Oo et al. (1995) investigated the relationship between the incidence and severity of malaria infection and various red cell disorders in Myanmar and no seemingly difference were found in the mean parasitaemia levels of individuals with normal haemoglobin AA or with heterozygous haemoglobin E. But they found lower mean parasitaemia levels among the patients with alpha or beta thalassaemia trait or with severe glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Hutagalung, et al. (1999), in their hospital based study in Thailand, suggested that haemoglobin E trait may ameliorate the course of acute falciparum malaria. The findings of Chotivanich, et al. (2002) suggested that HbAE erythrocytes have an unidentified membrane abnormality that renders the ma-

jority of the RBC population relatively resistant to invasion by *Plasmodium falciparum* supporting the Haldane hypothesis of heterozygote protection against severe malaria for haemoglobin E. Win et al. (2005), in their study among the Kayin and Bamar of Myanmar, reported higher prevalence of HbE in the Bamar populations than in the Kayin, regardless of malaria endemicity. This finding indirectly documents that malaria endemicity is less important than race in the maintenance of high frequency of HbE in Myanmar. Correspondingly, Than et al. (2005) reported the high incidence of alpha-thalassemia, hemoglobin E, and glucose-6-phosphate dehydrogenase deficiency in populations of malaria endemic Southern Shan State of Myanmar and their results showed that race was the dominant factor affecting the frequencies of red cell genetic disorders in malaria-endemic areas of Myanmar. Naka et al. (2008) revealed that the sample allele frequency of HbE was not significantly different between mild and cerebral malaria patients. They remark that the HbA/HbE polymorphism would not be a major genetic factor influencing the onset of cerebral malaria in Thailand. With contrast to the above reports Sharma et al. (2009) observed a positive correlation of HbβE gene frequency and mean incidence of *P. falciparum* infection in malaria endemic zones of Northeast India. A study in Thailand by Flatz et al. (1965) suggested the possibility of selective disadvantage of HbβE homozygous females. Deka (1981), however, did not find evidence of reduced fertility of HbβE homozygous females among the Sonowal Kachari of Assam. This state was a highly malarious area until recently, before taking up malaria eradication measures in 1950s. Deka et al. (1987), therefore, suggested two possibilities with regard to Hbβ globin polymorphisms in Assam. First, both the HbE heterozygotes and homozygotes are at an advantage in comparison with the normal HbA homozygotes in malarial environment of Assam. This implies a transient genetic polymorphism. Secondly, malaria might have caused increased fitness of the heterozygotes. Poor nutritional and hygienic conditions could have lowered the fitness of the HbE homozygotes in the past, while the normal HbA homozygotes were disadvantageous in the malarial environment. If this being the case, the present frequencies of HbβE near 0.5 in the populations of Assam would represent the equilibrium stage of a balanced genetic polymorphism.

Besides abnormal haemoglobins a number of other red cell defects like thalassaemia, G-6-PD deficiency; blood group systems- Knops blood group system, Duffy blood groups, ABO blood groups; and the genes like GYPA, CD36, etc. are playing a protective role against malaria. Just to cite an example, Uneke (2007) systematically reviewed the relationship between *P. falciparum* and ABO blood group using available information and data from malaria endemic regions of the world. The findings from all the studies suggested that individuals of blood group O are relatively resistant to severe disease caused by *P. falciparum* infection. That means when malarial infection is considered, various protective genes are involved.

It is therefore indicated from the present study that frequency of HbβE in Manipur is notably lower than in Assam. If at all malaria plays the selective role of HbβE in the Kachari populations of Assam, as suggested by Deka et al. (1987), why didn't it (malaria) do the same in other populations of Northeast India? Manipur is another malarial endemic zone in Northeast India. Malaria eradication programme in the region is a very recent activity and not successful as yet. Every year there are reports of malarial outbreak and deaths from it, in different places of Manipur till today. In such a situation and if haemoglobin E plays a protective role against this disease, one can expect elevation of HbE in the populations of Manipur. But the present data from Manipur do not favour this hypothesis. How can the Phayeng Chakpa only have HbβE as high as a frequency of 0.226 and the others has below 0.05, when all of them have been exposed to the same malarial environment? Elevation of HbβE among the Phayeng must have

been due to high rate of intra village marriage, so to say village endogamy rather than malarial selection. ManiBabu (1997) also reported a high rate of village endogamy (80.17%) among the Phayeng. Subjective activity of a gene in different populations of similar environment is unlikely in scientific jargon. It is pertinent to mention here that racial movements between Southeast Asia and Indian subcontinent passed through Manipur, being situated on the cross road, since pre-historic times. For example, the Ahoms, the first Tai immigrants who reached Assam in the thirteenth century A.D., were also believed to have passed through Manipur during the course of their migration. Moreover, nexus of the Meiteis of Manipur with the Tai (called Pong) could be traced back as early as 3rd century A.D. That means arrival of Tai racial element in Manipur took place much earlier than in Assam. Antiquity of HbβE in Northeast India, concomitant with racial migrations, cannot be established as yet. When and how HbβE appear in this region? Molecular analysis does not suggest independent mutational origin of the gene among the Kacharis of Assam as well as the Meiteis of Manipur as the DNA is characterized by framework 2, which is also common among the Thais, Laotians and some Cambodians (Antonarakis et al., 1982; Hundrieser et al., 1988; Singh and Singh, 2009*b*). There is, therefore, no substantive ground to assume that HbβE appeared in Assam earlier than in the neighbouring states. Geographically Northeast India may be considered as a single entity and the constituting states as political divisions. There is, in fact, no satisfactory explanation as to the high frequencies of HbβE among the Kacharis and a few other Tibeto-Burman speakers of Assam. Low frequencies of HbβE in the Tibeto-Burman speakers of Manipur and neighbouring states do not favour the hypothesis of malarial selection of HbβE.

Haemoglobin E is just another harmless allelomorph of HbβA (like A, B, O alleles of the ABO blood group system) which is found in the populations of Southeast Asia and extending up to Northeast Indian populations. Deka (1981), in his study among the Sonowal Kacharis, has already demonstrated that there was no fertility depression of the homozygote mothers of HbEE. The present researcher paid special attention to probe into any detectable physical disadvantage of the homozygote (HbEE) subjects by revisiting them. All of them were found living normal life without any sign of distinctive health problem. HbβE's selective advantage against malaria cannot be satisfactorily established by the evidences from Northeast India. Its activity against malaria cannot be taken at par with that of HbS. Variation in the frequencies of HbβE among the populations may be considered as clinal variation of the gene. There is possibility of association of the gene with the populations of certain racial origin. Frequency of such a gene in a population may be increased by inbreeding, due to gradual acceleration of homozygosity, or may be decreased or introduced in a population by miscegenation. The genes that have mild or no clinical effect, like HbβE, once introduced in a population cannot be eliminated easily. Such a gene, even if it plays protective role against malaria, will continue to exist in the absence of malaria. It will not be surprising to find HbE in malaria free zone for intermarriage may introduce the gene and gets multiplied in the long run with no role to play against malaria or anything similar. In the present study, neither protective advantage of HbβE against malaria nor harmful effect of homozygous (HbEE) genotype could be satisfactorily established.

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