# **Research Article**

DOI: 10.5455/2320-6012.ijrms20131112

# Hemoglobin E genotypes and fertility: a study among the Ahom of Upper Assam, India

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Received: 3 July 2013 Accepted: 4 August 2013

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#### **ABSTRACT**

**Background:** Differential fertility is reported in areas where prevalence of hemoglobin E (Hb E) is high. At this backdrop a representative Ahom sample from Upper Assam is studied to examine if differential fertility exist between Hb E and normal Hb A mothers and whether there is significant difference between them with regard to the hemoglobin (Hb) concentration.

**Methods:** Detailed reproductive histories are collected from 119 Ahom couples followed by Hb typing by 'Cellulose Acetate Gel' electrophoresis (pH 8.9) and fetal hemoglobin (Hb F) determined by Acid Elution technique. Hb concentration (in g/dl) is measured by Sahley's method.

Results: The calculated Hb E allele frequencies for the Ahom male and the female subjects are 0.424 and 0.403 respectively.  $\beta$ -carrier frequency in the total sample is found to be 0.42%. There is no differential fertility observed between Hb A/Hb A (AA), Hb A/Hb E (AE) and Hb E/Hb E (EE) mothers. Reproductive performance of the couples revealed that the mothers with an Hb E complement either heterozygous or homozygous are more likely to have a spontaneous abortion or an infant mortality.

**Conclusions**: It may be concluded that Hb E induced anemia may increase spontaneous abortion and infant mortality in AE and EE mothers.

Keywords: Differential fertility, Hb E induced anemia, Spontaneous abortion, Infant mortality

### **INTRODUCTION**

Hemoglobin E (Hb E) is caused by a  $G \to A$  mutation at codon 26 of the  $\beta$ -globin gene which substitutes  $Glu \to Lys$  and gives rise to functional but unstable hemoglobin. The unstable nature may be due to the reduced synthesized rate of Hb E as the mutation creates an alternate splicing site within an exon. Hb E is quite frequent in South-East Asia. North-East India in general and the state of Assam in particular has got a very high prevalence of this allele. The high frequency is perhaps due to the malarial selection pressure and population endogamy in the region because carriers of Hb E appears to enjoy some protection against *P. falciparum* malaria and this inference is supported by both epidemiological  $^{4,5}$ 

and experimental <sup>6-8</sup> studies. In this context it is pertinent to note that in Assam prevalence of *Plasmodium falciparum*, presence of asymptomatic carriers of the parasite and *Anopheles minimus*, the major vector, maintain the perennial transmission of malaria. <sup>9-13</sup> Differential fertility is reported in areas where frequency of Hb E is high. <sup>14-16</sup> Among the Kachari, Ahom and Mishing population groups in Assam it is also found that women homozygous for Hb E have more spontaneous abortion and infant mortality than women who are heterozygous for Hb E and homozygous for the normal Hb A allele <sup>16-18</sup> and it is assumed that iron deficiency is one of the main reasons for high infant mortality among the homozygous Hb E mothers. <sup>16,18</sup> It is further noted that the Hb E homozygous Mishing women in the presumably

malarial environment of Upper Assam might have an advantage up to the point of conception but beyond that there are several factors including the socio economic one which come into play to increase pregnancy wastage and infant mortality in them. <sup>18</sup> At this backdrop it is intended to study a representative Ahom sample from Upper Assam and examine if differential fertility exist between Hb E and normal Hb A mothers and whether there is significant difference between them with regard to the hemoglobin (Hb) concentration.

#### **METHODS**

The study is carried out among the Ahom (originally a Tai speaking group) living under Bokota and Khaloighugura Mouzas within Sibasagar district of Assam. The area is around 60 Km from Dibrugarh town and the Ahom settlements here are predominantly large and one of the oldest in the Upper Assam region. Majority of the Ahom people in this area apparently belong to the middle socio economic status. Initially the villages are surveyed and purpose of study and its importance is explained to the villagers. Couples having a minimum of one child are considered under the present study and care is taken to include only non-pregnant women of reproductive age. With regard to ethical issues the research project is locally evaluated by the concerned Department. Besides, the principles outlined in the Helsinki Declaration of 1975, as revised in 2000<sup>5</sup> are sincerely followed and informed consent is taken from the subjects prior to their selection by random sampling. Detailed reproductive histories are collected from 119 Ahom couples (both husband and wife) through in-depth interview using structured schedule followed by collection of blood samples (2 ml approximately) by vein puncture. Hemoglobin (Hb) typing is carried out by 'Cellulose Acetate Gel' electrophoresis (pH 8.9) while fetal hemoglobin (Hb F) is determined by Acid Elution technique following. 19 Hb estimation is done by Sahley's method. WHO Hb thresholds (<13.0 g/dl for men; <12.0 g/dl for women) are used to classify the subjects as anemic. Statistical methods namely Kruskal Wallis, Kolmogorov-Smirnov, Mann-Whitney and independent sample T-Test are performed through SPSS software whereas Z-Test for proportion is done manually using the formula -

$$Z = \frac{\left| P_1 - P_2 \right|}{\sqrt{\hat{p}\hat{q}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

#### **RESULTS**

Hemoglobin typing revealed that out of 119 Ahom male individuals there are 37 Hb A/Hb A (AA), 61 Hb A/Hb E (AE), 20 Hb E/Hb E (EE) and one  $\beta$ -carrier. On the other hand in 119 Ahom females there are 42 AA, 58 AE and 19 EE genotypes. The calculated Hb E allele frequencies

for the male and the female sample are 0.424 and 0.403 respectively while the Hb E allele frequency for the total 238 unrelated individuals is 0.414. The  $\beta$ -carrier frequency in the present sample is found to be 0.42%. When AA, AE and EE frequencies are tested for equilibrium no deviation from Hardy-Weinberg expectation is found in either sex. Z-Test for proportion between the two sexes with regard to the frequencies of AA, AE and EE genotypes do not show any significant difference at 5.0% level of probability (Table not shown).

Combination of spouses carrying the four genotypes AA, AE, EE and β-carrier resulted in 10 different couple combinations, viz., ∂AA x ♀AA, ∂AA x ♀AE, ∂AE x  $\bigcirc$ AA,  $\bigcirc$ AE x  $\bigcirc$ AE,  $\bigcirc$ AA x  $\bigcirc$ EE,  $\bigcirc$ EE x  $\bigcirc$ AA,  $\bigcirc$ AE x  $\bigcirc$ EE,  $\bigcirc$ EE x  $\bigcirc$ AE,  $\bigcirc$ EE x  $\bigcirc$ EE and  $\bigcirc$  $\beta$ -carrier x  $\bigcirc$ AA. In the present sample of 119 couples there are seven  $\Im AA \times \Im AA$ , 23  $\Im AA \times \Im AE$ , 24  $\Im AE \times \Im AA$ , 29  $\partial AE \times QEE$ , six  $\partial EE \times QAE$ , four  $\partial EE \times QEE$  and one  $\beta$ -carrier x  $\varphi$ AA. The reproductive outcome of nine different couple combinations excluding one  $\beta$ -carrier x ♀AA couple are presented in a tabular form in Table 1. The mean conception, live birth and living children in the couple categories are ranged between 2.86 to 3.83, 2.43 to 3.33 and 2.43 to 3.0 respectively and they do not show any significant difference when treated with Kruskal Wallis Test (Conception, P = 0.959; Live birth, P = 0.979; Living children, P = 0.931). However it is found that mothers with an Hb E complement either heterozygous or homozygous are more likely to have a spontaneous abortion or an infant mortality. It can be seen especially in the case of the couples where there is a 50 or 100 percent possibility with each pregnancy of having a child with AE or EE genotype. In order to get a clearer picture the reproductive performance of the mothers with AA, AE and EE genotypes are shown separately in Table 2. The mean conception, live birth and living children in AA, AE and EE mothers do not show normal distribution when subjected to Normality Test by using the method Kolmogorov-Smirnov (Table not shown). Thus to compare the means between AA vs AE, AA vs EE and AE vs EE mothers the non-parametric counterpart of independent sample T-Test i.e. Mann-Whitney Test is performed. However, the Mann-Whitney Test does not show any significant difference between the three groups of mother (Table 3). No significant difference is observed even when the induced abortions are excluded from AA, AE and EE mothers. However it is revealed that the frequencies of spontaneous abortion and infant mortality in AE and EE mothers are more than the normal AA mothers. An opposite picture can be seen in the case of the AA mothers where the frequency of induced abortion is found to be much more than spontaneous abortion and infant mortality. The mean Hb concentration in mothers by genotype is shown separately in Figure 1. In AA, AE and EE mothers the mean Hb estimation are 9.83, 9.42 and 8.48 respectively. The mean values are found to follow normal distribution when subjected to Normality Test (Table not shown), as a result independent sample T-Test is performed to compare the means between AA vs AE, AA vs EE and AE vs EE mothers. The t values show significant difference

between AA vs EE (3.032, P=0.001) and AE vs EE (2.519, P=0.014) mothers with regard to Hb concentration.

Table 1: Reproductive performance of the Ahom couples.

	Couples									
Husband (♂) x Wife (♀)	♂AA x ♀AA	∂AA x ♀AE	∂AE x ♀AA	∂AE x ♀AE	∂AA x ♀EE	∂EE x ♀AA	∂AE x ♀EE	∂EE x ♀AE	∂EE x ♀EE	
N	7	23	24	29	7	10	8	6	4	
Offspring genotype	Only AA	2AA:2AE	2AA:2AE	1AA:2AE:1EE	Only AE	Only AE	2AE:2EE	2AE:2EE	Only EE	
Conception	26	74	72	91	20	31	26	23	14	
Mean±SE SD	3.71±0.95 2.5	3.22±0.22 1.08	3.0±0.35 1.72	3.14±0.47 2.56	2.86±0.64 1.68	3.10±0.74 2.33	3.25±0.67 1.91	3.83±1.49 3.66	3.50±0.64 1.29	
Induced abortion	5	8	8	5	1	1	2	0	1	
(%)	(19.23)	(10.81)	(11.11)	(5.49)	(5.0)	(3.22)	(7.69)	0	(7.14)	
Spontaneous abortion	0	3	1	5	2	1	1	3	1	
(%)	-	(4.05)	(1.39)	(5.49)	(10.0)	(3.22)	(3.85)	(13.04)	(7.14)	
Still birth	1	1	1	1	0	1	0	0	0	
(%)	(3.85)	(1.35)	(1.39)	(1.10)	-	(3.22)	-	-	-	
Live birth	20	62	62	80	17	28	23	20	12	
Mean±SE SD	2.86±0.74 1.95	2.69±0.19 0.93	2.58±0.35 1.72	2.76±0.45 2.40	2.43±0.57 1.51	2.80±0.66 2.10	2.87±0.61 1.73	3.33±1.38 3.39	3.0±0.70 1.41	
Infant mortality	0	1	2	6	0	0	1	2	1	
(%)	-	(1.61)	(3.22)	(7.69)	-	-	(4.35)	(10.0)	(8.33)	
Child mortality	0	1	1	1	0	1	0	0	0	
(%)	-	(1.61)	(1.61)	(1.28)	-	(3.57)	-	-	-	
Juvenile mortality	1	0	0	0	0	1	0	0	0	
(%)	(5.0)	-	-	-	-	(3.57)	-	-	-	
Living children	19	60	59	73	17	26	22	18	11	
Mean± SE SD	2.71±0.64 1.70	2.61±0.16 0.78	2.46±0.31 1.53	2.52±0.43 2.32	2.43±0.57 1.51	2.60±0.50 1.58	2.75±0.65 1.83	3.0±1.24 3.03	2.75±0.63 1.26	

Table 2: Reproductive performance of the Ahom mothers.

Hb type of the mothers (♀)	Conception Mean±SE SD	Induced abortion (%)	Spontaneous abortion (%)	Still Birth (%)	Live birth Mean±SE SD	Infant mortality (%)	Child mortality (%)	Juvenile mortality (%)	Living children Mean±SE SD
AA (N = 41)	129 3.15±0.31 1.98	14 (10.85)	2 (1.55)	3 (2.32)	110 2.68±0.28 1.81	2 (1.82)	2 (1.82)	2 (1.82)	104 2.54±0.24 1.53
AE (N = 58)	188 3.24±0.29 2.21	13 (6.91)	11 (5.85)	2 (1.06)	162 2.79±0.27 2.05	9 (5.55)	2 (1.23)	0	151 2.60 ± 0.25 1.93
EE (N = 19)	60 3.16±0.38 1.64	4 (6.67)	4 (6.67)	0	52 2.74±0.35 1.52	2 (3.85)	0	0	50 2.63±0.35 1.53

Table 3: Test of significance: Reproductive performance of the Ahom mothers.

	Number of conception	Number of live birth	Number of living children
AA vs AE			
Mann-Whitney U	1164.500	1135.500	1187.000
P	.859	.696	.988
AA vs EE			
Mann-Whitney U	372.000	362.000	371.500
P	.777	.654	.768
AE vs EE			
Mann-Whitney U	537.500	536.500	532.500
P	.871	.860	.821

Table 4: Role of the Ahom fathers in determining the reproductive performance of their spouses.

Hb type of the fathers (ී)	Conception in spouses Mean ±SE SD	Induced abortion in spouses (%)	Spontaneous abortion in spouses (%)	Still Birth in spouses (%)	Live birth in spouses Mean ±SE SD	Infant mortality in spouses (%)	Child mortality in spouses (%)	Juvenile mortality in spouses (%)	Living children in spouses Mean ±SE SD
AA (N = 37)	120 3.24 ± 0.25 1.52	14(11.67)	5(4.17)	2(1.67)	99 2.67 ±0.20 1.25	1(1.01)	1(1.01)	1(1.01)	96 2.59± 0.18 1.12
AE (N = 61)	189 3.10± 0.27 2.15	15(7.94)	7(3.70)	2(1.06)	165 2.70 ±0.26 2.04	9(5.45)	2(1.21)	0	154 2.52± 0.25 1.95
EE (N = 20)	68 3.40 ± 0.57 2.54	2(2.94)	5(7.35)	1(1.47)	60 3.0 ± 0.52 2.34	3(5.0)	1(1.67)	1(1.67)	55 2.75±0.44 1.97

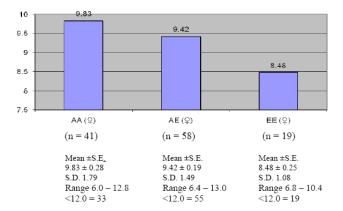


Figure 1: Mean Hb estimation (in g/dl) in the Ahom mothers.

The contribution of the fathers with AA, AE and EE genotypes in determining the reproductive performance of their respective spouses is shown in Table 4. As in the mothers when the mean number of conception, live birth and living children of the spouses of AA, AE and EE fathers are subjected to Mann-Whitney Test between AA vs AE, AA vs EE and AE vs EE fathers it does not show any significant difference in any of the groups (Table not shown). It is also noted that the highest frequency of spontaneous abortion and infant mortality is found in mothers when the fathers are either EE or AE. The mean Hb concentration in fathers with regard to the three genotypes is shown in Figure 2. The mean Hb estimation in AA fathers is 11.17 while in AE and EE fathers the mean values are 10.71 and 10.08 respectively. Normality Test (Table not shown) carried out for the mean Hb values are found to follow normal distribution and as a result independent sample T-Test is performed to compare the mean Hb values between AA vs AE, AA vs EE and AE vs EE fathers. The t value (2.362, P = 0.022)shows significant difference between AA vs EE fathers with regard to the mean Hb concentration.

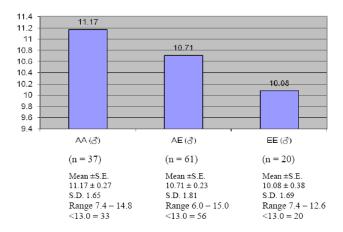


Figure 2: Mean Hb estimation (in g/dl) in the Ahom fathers.

#### DISCUSSION

The Hb E allele frequency found in the present Ahom sample support earlier studies carried out in this population. 20-23 However, it is observed that there is a overall increase of 0.05 in the allele frequency of this variant between the studies carried out in the early 1970's and later part of 1980's. This perhaps suggests that the Hb E allele is on an ongoing process of multiplication presumably in a favorable environment resulting in better fitness for Hb E genotypes. Whether fitness of Hb E genotypes are more than Hb A is difficult to answer from the present finding as the overall reproductive performance of AE, EE and the normal AA mothers do not show any significant difference between them. A study carried out among the Ahom and Kachari of Assam also found no significant variations in fertility performance between AE, EE and AA mothers. 17

Higher fertility found among the EE Kachari mothers <sup>16</sup> and higher conception in EE Mishing mothers <sup>18</sup> of Upper Assam is not observed among the Ahom. The present study also do not corroborate with a couple of studies from Thailand which reported a higher fertility in Hb E heterozygotes and a reduced fertility in Hb E homozygotes in areas with endemic malaria. <sup>14,15</sup>

Spontaneous abortion and infant mortality found in AE and EE Ahom mothers is in accordance to studies carried out in the Upper Assam region <sup>16-18</sup> although its frequency is relatively less than those reported in the Kachari <sup>16</sup> and the Mishing. <sup>18</sup> Earlier studies recorded highest number of reproductive wastages in the EE mothers but in the present Ahom sample although spontaneous abortion is found more in the case of the EE mothers but with regard to infant mortality the frequency is more in AE mothers. There is also no still birth and child mortality found in the EE mothers.

From the present findings Hb E seems to be a neutral allele with regard to fertility and this may perhaps be attributed to the relatively better socio economic conditions found among the Ahom. If Hb E is considered as a neutral allele then reasons for increased reproductive wastage in AE and EE mothers should be for reasons other than selection.

It is reported that Hb E associated with other factors may complicate the course of pregnancy in Malaysian aborigines. <sup>24</sup> Equally relevant is a study in the state of Orissa (India) where children with Hb E/ $\beta$ -thalassaemia are reported to be born of couples where the father is AA and the mother is AE with high Hb A<sub>2</sub> (range in %, 25-30) and also that the mother experienced pregnancy wastage and neonatal deaths. <sup>25</sup> Studies have shown that Hb E cases may carry Hb A<sub>2</sub> <sup>26</sup> and Hb F above permissible limits which may again lead to misdiagnosis of Hb E/ $\beta$ -thalassaemia. <sup>27</sup> The present study found only

one case of  $\beta$ -carrier which support the hypothesis that prevalence of β-thalassaemia is almost nil in the tribal populations of Assam.<sup>28</sup> Hb concentration is the most reliable indicator of anemia at the population level <sup>29</sup> and Sahley's method is one of the inexpensive methods to measure the same which is found to be in good agreement with auto analyzer.30 In the present Ahom sample the mean Hb concentration of both fathers and mothers under each couple combination are below the WHO Hb thresholds to define anemia. They are found to have a mean Hb concentration in the manner AA > AE > EE but this arrangement is more distinct in the case of the mothers. The mean Hb concentration in the EE mothers  $(8.48 \pm 0.25)$  is found to differ significantly from AA and AE mothers whereas in the case of the fathers (EE, 10.08)  $\pm$  0.38) significant difference exist only between AA and EE fathers. A similar finding is reported where Hb values are found to be significantly lower in Hb E individuals.<sup>31</sup> Besides Hb estimation no other hematological parameters is measured in the present subjects but from secondary sources it is established that the Hb E mutation has βthalassaemia properties as both EE and AE individuals may show microcytic hypochromic anemia with high proportion of Hb  $\rm A_2$  and Hb F.  $^{25\text{-}27,32,33}$  Studies have shown that Hb E induced anemia may be associated with iron deficiency in the tribal women of Assam <sup>28</sup> and in women and preschool age children of Thailand. <sup>27</sup> It is reported that severe iron deficiency reduces the proportion of Hb E in heterozygotes<sup>34</sup> and this must be more severe in the case of Hb E homozygotes probably due to the vulnerability of Hb production by Hb E.<sup>33</sup> Hence it is assumed that the anemic status of the Ahom mothers in general and Hb E mothers in particular further deteriorates during pregnancy due to inadequate absorption of iron. With regard to iron absorption it is found that iron therapy responds positively among EE individuals both in and without iron deficiency anemia (IDA).<sup>27</sup> Similarly it is observed that iron supplementation can significantly improve the Hb concentration and zinc protoporphyrin/ haem (ZPP/H) ratio in both sickle cell hemoglobin (Hb S) and normal (AA) individuals.36

Despite the fact that prevalence of Hb E is high among the Ahom in a reportedly malarial environment it is found that there is no difference in the fertility performance of AE, EE and the normal AA mothers. The neutrality of the Hb E allele in the present Ahom sample may perhaps be due to the relatively better socio economic condition found in the population. The increased frequencies of pre and post natal mortalities in the AE and EE mothers is not high enough to record differential fertility with regard to a specific Hb E genotype. Nevertheless it is evident from the present study that in populations with frequent Hb E high incidence of Hb E induced anemia may increase spontaneous abortion and infant mortality in AE and EE mothers. Keeping in mind that hematological parameters of Hb E do not change in association with αthalassaemia mutations<sup>27</sup> and that in the tribal populations of Assam the prevalence of  $\alpha$ -thalassaemia is 3.84% <sup>37</sup> a more detailed study which could include looking for  $\alpha$ -thalassaemia mutations in the Hb E cases at a molecular level is warranted for a firm conclusion.

#### **ACKNOWLEDGEMENTS**

This work is funded by the Indian Council of Medical Research (ICMR), New Delhi, India under its Research Associate ship fellowship program (Reference No. 45/6/2010 – Hae/BMS).

Funding: Indian Council of Medical Research (ICMR), New Delhi

Conflict of interest: None

Ethical approval: For ethical issues the research project was locally evaluated by the concerned Department

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DOI: 10.5455/2320-6012.ijrms20131112

Cite this article as: Das B, Sengupta S. Hemoglobin E genotypes and fertility: a study among the Ahom of Upper Assam, India. Int J Res Med Sci 2013;1:378-84.