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Red Cell Genetic Markers in Malarial Susceptibility and Selective Advantage Hypothesis

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Abstract: Malaria is still a serious public health challenge in many parts of the world including India. Human genetic susceptibility to malaria varies from individual to individual depending upon the genetic constitution and from region to region based on geo-ecological and climatic conditions. In the present study, intravenous 334 random blood samples of unrelated adult individuals belonging to Mongoloid ethnic stock were taken after informed consent from the endemic localities of Arunachal Pradesh, Assam and Nagaland to find out the relationship between the abnormal hemoglobin and G6PD enzyme deficiency, and susceptibility to malaria. Abnormal hemoglobin E and G6PD enzyme deficiency seem to interact with malarial parasite in such a way that they probably provide decreased susceptibility or inhibitory effect or increased resistance. Genetic alterations in human genome are maintained in the specific population by natural selection to protect the host against the malarial infection. These findings are consistent with those studies which support the notion of selective genetic advantage hypothesis against the malaria infection.

Key Words: Red cell genetic markers; Hemoglobin E; G6PD deficiency; Malaria susceptibility; Natural selection; North-Eastern India.

Introduction:

It is fascinating that at certain geographical locations, some people are less susceptible to particular type of disease, whereas, at other places they are more prone to specific genetic abnormalities. Similarly, all individuals might not be equally susceptible to particular disease. What determines this anomaly? The question is important for several reasons. The genetic constitution (make - up) of an individual is a paramount of the health and disease conditions. Man is blessed with numerous advantageous genes and plagued by deleterious ones. Certain mutations that may be

disadvantageous or even fatal to the homozygotes are beneficial to the heterozygotes and are maintained in the population through the mechanism of Natural selection.[1] Genes influence at the level of individual, family, and the population. The maintenance of deleterious genes in a population by heterozygote advantage is referred to as the balanced polymorphism.

The study of genetic markers provides a useful tool to unfold the mystery associated with the susceptibility (friendship) or non-receptivity of an individual towards a particular person or disease. In human day to day life, the same genetic affinities or disaffinities, or absurdities also play a major role in determining the human behavioral relationships. The high incidence of a particular genetic marker in a population indirectly indicates the operation of some protective mechanism. Hemoglobinopathy and glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency are two very important genetic markers that are maintained as the balanced polymorphisms in certain populations of the world including in India. To study the relationship between these human red cell genetic markers with high frequency in malaria endemic areas of North Eastern region of India[2-4] and the susceptibility to malaria is the focus of the present study.

Materials and Methods:

The subjects for the present study were the inhabitants of North-Eastern region of India, particularly from the malaria endemic rural localities of the states of Arunachal Pradesh, Assam and Nagaland. These were the tribal people belonging to the ethnic stock of Mongoloid origin. They invariably practice clan-exogamy. This study was a part of the project undertaken for the investigations of genetic markers among the tribal populations of the North Eastern region. From each individual, detailed history about malaria was recorded along

with the personal particulars such as age, sex, marital status, domicile, etc.

For confirmation whether the person ever suffered from malaria in its life time was made by thoroughly cross examining and questioning the subject regarding the symptoms, prognosis, treatment and cure of malaria[5] such as feeling of cold with rapidly rising the temperature, shivering, teeth chattering, dryness of skin, pale extremities, curling of patient in the bed, rapid pulse rate, headache, tiredness, rapid respiration, feeling of thirst, sudden perspiration on face and body (sweating), feeling of drowsiness, weakness, irritability with poor appetite, periodicity (recurrence) of fever, etc. The patients could not be grouped according to *Plasmodium falciparum*, *Plasmodium vivax* or mixed infection as the information was based on the verbal dialogue.

About 2ml. of blood was collected intravenously in EDTA containing vials from unrelated adult individuals. A total of 334 blood samples were randomly collected from different tribal populations. For determining the G6PD deficiency, Brilliant Cresyl Blue decolorization test was performed.[6] The screening for abnormal hemoglobins was done by electrophoresis on cellulose acetate strips at alkaline pH (8.9) as described by Dacie and Lewis[7] and quantification of A2 fraction of adult hemoglobin was done by elution method.[7,8] The value more than 3.5% of A2 fraction of adult hemoglobin was taken as cut off point for determining the β -thalassemia trait. Those individuals having the very high hemoglobin A2 value, i.e. more than 10% were suspected to have Hb A2 plus Hb E. Estimation of fetal hemoglobin was done according to technique described by Weatherall.[8]

Three cases of homozygous E hemoglobin were encountered which were excluded from the present study. They neither ever suffered from malaria nor from G6PD enzyme deficiency.

Results obtained were statistically tested applying chi-square test for the significance of the difference, if any.

Results:

Out of 334 subjects studied, 92 (27.5%) suffered from malaria during their life time, 46 (13.8%) had the G6PD enzyme deficiency and 70 (21%) subjects had the abnormal hemoglobin E in heterozygous form. Thus, the prevalence of G6PD enzyme deficiency was recorded to be 13.8% and that of abnormal (Hb AE) hemoglobin 21% among the tribal populations, particularly of the Mongoloid ethnic origin of the North Eastern region of India.

Genetic Markers	Malaria Positive [No. (%)]	Malaria Negative [No. (%)]	Inter-group difference
G6PD Normal	88 (30.6)	200 (69.4)	p<0.01
G6PD Deficient	4 (8.7)	42 (91.3)	
Hemoglobin AA (Normal)	81 (30.7)	183 (69.3)	p<0.02
Hemoglobin AE	11 (15.7)	59 (84.3)	

G6PD= Glucose-6-phosphate dehydrogenase.

The subjects ever suffered from malaria were subgrouped according to the deficiency of G6PD enzyme and abnormal hemoglobin. The distribution is given in Table 1. It is interesting to note from Table that the proportion of the subjects ever suffered from malaria is much smaller in the G6PD deficient group (8.7%) than in the normal cases (30.6%). This difference between the two groups, i.e. G6PD deficient and normals, was statistically significant (p<0.01).

Similarly, the subject suffering from abnormal hemoglobin E in heterozygous form, were less susceptible to malaria infection than the normal individuals. The difference between the subjects possessing the normal and abnormal hemoglobins and the prevalence of malarial infection in them was statistically found significant (p<0.02).

Discussion:

Human red cell genetic markers and disease association have been the focus of study throughout the world in the recent years. High prevalence of polymorphism of genetic traits in particular geo-ecological locality has prompted the speculation that they may provide some selective advantage against the prevalent diseases.[9-13] This was the focus of the present study for understanding the individual variations regarding the unequal susceptibility towards a disease under the prevailing malaria endemic environment. Human red cell markers and malaria parasite appear to be good example to examine this case.

The genetic abnormalities of human erythrocytes have been found to decrease their susceptibility to malarial parasites.[11] Hemoglobin is the major intra-erythrocytic component. Abnormal hemoglobin and G6PD deficiency are, therefore, likely to influence the interaction. The present study throws some light on the interaction between the genetic constitution – normal or abnormal of an individual with respect to hemoglobinopathy and G6PD deficiency and malarial infection. These abnormalities of the human genome by selection give heterozygote advantage to the affected individual. The possible protection of the individual may occur at the level of invasion of erythrocytes and intra-erythrocytic development or at a more subtle level involving the host response, rheologic and other extra-erythrocytic determinants.[14] Abnormal erythrocytes are not as susceptible to parasite infection as the normal. The genetic abnormality appears to augment the inhibitory effect. Results with hemoglobin E erythrocytes show a tendency towards protection or rather suppression of the parasite development. Abnormal shapes of erythrocytes may also play a significant role in the protection to the host.

It is interesting that the parasitism, particularly the intra-cellular exhibits extreme biological interactions between cells with diverse genomes. Human erythrocytes and malaria parasite appear a good example of such interaction operable at the sequential stages of selection, invasion, intra-red cell development and liberation of merozoites.[15] It is thought that genetically controlled characteristics of the host red blood cells such as hemoglobin E and G6PD enzyme deficiency are likely to influence the life cycle of the malarial parasite. This may occur in the components of the surface coat of the red blood cell or in the intra-cellular components and their metabolic pathway. The erythrocytes possessing genetic alterations, showing apparent normalcy may interact vigorously when parasitized by the malaria parasites.[16] There is a decreased concentration of parasites in the G6PD enzyme deficient cells although the reason is uncertain – it may be that the parasitized cells are rapidly removed from the circulation.[17]

Contrary to the earlier contention[18], the findings of the present study give support to the hypothesis that abnormal hemoglobin and G6PD enzyme deficiency protect the individual from malarial infection or give reduced susceptibility to malaria by way of inhibitory action. These results are consistent with those of the other workers.[19]

Implications of the present study are many folds in health and disease conditions. Those individuals who are genetically susceptible to malarial infection get severe attacks of malaria; whereas, those individuals who are genetically not prone to malaria get milder attacks of malaria and the malarial parasites do not survive for longer duration among such heterozygote hosts with either abnormal hemoglobins or

G6PD deficiency. Thus, they are maintained in the population to counter lethal malaria and have low malarial parasite density and get selective genetic advantage over the normal individuals.

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