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AN OVERVIEW ON SIGNIFICANT HUMAN GENETICS MODIFICATION IN THE PROTECTION AGAINST SEVERE *Falciparum* MALARIA

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ABSTRACT
This paper was aimed at expatiating the relevance to which falciparum malaria are protected due to various genetically modified factors which include Hemoglobin S, Hemoglobin E, Hemoglobin C, Hemoglobin F, Alpha and beta thalassemia, ovalocytosis, Glucose – 6- Phosphate dehydrogenase deficiency, Human leucocyte antigen (HLA) – BW53, DRBI 1302, DQBI 0501, Pyruvate kinase or PKLR gene. However, human genetics is one of the elements can be used in planning of co-ordinated attack on disease, since it sometime give an avenue to differentiate those groups or individual who are susceptible from those who are not.
Key words: malaria, hemoglobin, genetically modified factors.

INTRODUCTION

Severe *Plasmodium falciparum* is major cause of death in Sub-Saharan Africa, particularly in children younger than five years age. Inter-individual variation in susceptibility and manifestation can be attributed particularly to innate host factors such as sickle cell traits. Substantial epidemiological, clinical, autopsy and culture evidence is now available to suggest that the following genetics red cells traits afford relative protection against death from malignant tertian *malaria*: *hemoglobin* S, and E; *hemoglobin* C and F; alpha and beta *thalassemia*; *ovalocytosis*; G-6 PD deficiency; HLA – BW53; DRB1, 1302-DQBI 0501; PKLR (Adetokumbo and Herbert. 2003. Some people are naturally protected from malaria. Research from Canada suggest that sometime this resistance can be explained by DNA difference in these people's pyruvate kinase or PKLR gene, this in not surprising result since researchers had shown before that mice with differences in their PKLR gene are more resistant, the differences here in that the researchers showed that having this DNA differences might affect peoples symptoms too, blood diseases and malaria red blood cells lack mitochondria which PKLR is so important, the parasite that cause malaria, *Plasmodium falciparum*, spends parts of its time in red blood cells. Anything that affect red blood cells might make thing easier or harder for this parasite. Changes in the PKLR gene definitely affect how red blood cells works. PKLR is a key gene in how they get their energy, red blood cells are unique in that they have no nucleus or mitochondria. The lack of mitochondria means that red blood get their energy differently than most other cells. The researchers showed that carriers for pyruvate kinase deficiency may get the benefits of less severe malaria symptoms too. The mechanisms by which erythrocyte containing abnormal *hemoglobins*, are partially protected against P. falciparum infection are not fully understood, although these has been no shortage of suggestions. During the peripheral bloods stage of replication malaria parasites have a high rate oxygen consumption (Vaidya and Mather, 2009) and ingest large amount of hemoglobin (Elliott *et al* 2008). It is likely that HbS in *endocytic* vesicles is deoxygenated, polymerizes and is poorly digested. In red cells containing abnormal *hemoglobins*, or which are G-6-PD deficiency, oxygen radicals are produced, and malaria parasite induce additional oxidative stress (Kuross *et al,* 1988). This can result in changes in red cells membrane, including translocation of phosphatidyl serine to their surface, followed by macrophage recognition and ingestion (Foller *et al,* 2009).

Objectives of the study

- To review how genetic modification render protection against severe falciparum malaria
- To review various red cell traits mechanisms by which relative protection against falciparum malaria is afforded.

Hemoglobin* S protection against *Plasmodium Falciparum

There is clean evidence that the heterozygotes enjoys a selective advantage against the lethal effect of falciparum malaria:

- Sickle cell genes in found in its highest prevalence in areas where p. falciparum malaria is, or was until recently, endemic.
- In areas of stable malaria, high *P. Falciparum* densities are significantly less commonly found in children with sickle cell traits (As) than in normal children (AA)
- The post mortem studies have revealed that death from cerebral malaria rarely occurs in the S. heterozygotes (AS)
- The prevalence of sickle cell traits in a population increases with advancing years, suggesting a differential survival with greater loss of normal genes
- Some studies showed that mothers with sickle cell traits had slightly higher fertility and lower still birth rate, and the birth weights of their children tended to be slightly higher than those of non-sickle cells mothers.

- Studies in vitro have demonstrated that p. falciparum parasite do not survive in cells with AS or SS haemoglobin when oxygen tension is decreased. (Adetokumbo and Herbert. 2003) despite the heavy genetic load of the sickle cell disease, a severe hemolytic syndrome suffered by homozygotes SS, heterozygote AS are healthy and are protected from severe malaria (Verra *et al,* 2007).

Hemoglobin* C Protection against *Plasmodium Falciparum

Hemoglobin C. is present in high frequencies in a localized part of west Africa around Burkina Faso and Ghana. Cells from the homozygotes CC are refractory to parasite growth in culture; however AC cells support parasite growth normally. In west Africa where S gene frequencies are also very high, individuals carrying one S gene and one C gene (SC) are not uncommon and parasite growth is poor in SC cells (Adetokumbo and Herbert 2003) an extensive control slightly carried out in Burkina Faso conclusively described its protective role: the study demonstrated that the protection against clinical malaria is about 90%in homozygosis and 30% in heterozygosis. (Verra et al, 2007).

Hemoglobin* E Protection against *Plasmodium Falciparum

Early studies. Although early laboratory studies suggested that hemoglobin E (HbE retarded the inter-erythrocytic growth of p. falciparum, subsequent, investigation have yielded a complicating result. But recent scientific advances revealed that hemoglobin E.: A balance polymorphism protective against *P. Falciparum* which are present in South East Asia (Thailand), were studied in vitro in a mixed erythrocyte invasion assay, starting at 1% parsitemia p. falciparum invaded preferentially normal (HbAA) compared with abnormal disease (HbE) (NIAID, 2015)

***Hemoglobin* F Protection against Plasmodium Falciparum**

It has been suggest that the presence of F gene for foetal hemoglobin might partially protected the bearer against the effects of p. falciparum malaria. An analysis of the results of various observers who have examined infants living in malarious districts of Africa reveals comparatively low level of malaria infection in infants under 3 months age. An apparent relationship was found in Gambian infants between the disappearance of total hemoglobin and the onset of malaria infection, but no definite evidence exist from population studies that hemoglobin F (HbF) protects against the lethal effects of p. Falciparum. However, recent in vitro studies have shown that parasite growth as opposed to invasion – is impaired in HbF containing red cells, regardless of their source (Adetokumbo and Herbert 2003).

Alpha thalassemia* Protection against *Plasmodium Falciparum

In sub Saharan Africa, α + thalassemia affects up to 50% of the population, but protection of uncomplicated or severe malaria could not be demonstrated so far, we examined weather α + thalassemia in Ghana. In Melenesia, the geographic correlation between endemicity suggest natural selection in one case-control study in papua New Guinea, the risk of severe malaria was reduced by 60% and 34 % in homozygotes and heterozygotes children respectively (Frank *et al,* 2014)

Beta -thalassemia* Protection against *Plasmodium Falciparum

Carriers of beta-thalassemia are indeed relatively protected against the invasion of plasmodia falciparum. However, because of population migration and to a limited extent slave trade, beta-thalassemia is, at present, also common in northern Europe, North and South America, Caribbean and Australia. Beta thalassemia is caused by the reduced (beta+) or absent (beta ^{o}) synthesis of beta globin chains of the hemoglobin (Hb) tetramer, which is made up of two alpha globin and two beta globin chains ($alpha_2$ and $Beta_2$). (Antonio and Renzo 2010).

Ovalocytosis* protection against *plasmodium falciparum

Is a condition in which the majority of circulating erythrocyte are oval in shape. This abnormality is widely distributed among population in South East Asia, and is commonly found in papua New Guinea. Known as Malaysian Ovalocytosis. The prevalence of ovalocytosis was documented when cases was found up to 20% of more of population in some areas of papua New Guinea and Malaysia Ahnound, Punnee, Preyarat, and Yong, (2017). The relationship between human erythrocyte variants and resistant to falciparum Malaria has been suggested by epidemiological data provide the protection against malaria in ovalocytosis. Resistance to invasion by plasmodium falciparum was demonstrated in vitro data from epidemiological study indicate that patients with elliptocytosis in malanesia also have both lower parasitemia and less frequency of infection with other human malarias namely p. vivax and p. malariae. Moreover ovalocytosis were found to be highly resistance to invasion by both p. falciparum and p. knowlesi Ahnoound, Punnee, Preyarat, and Yong, (2017).

Glucose -6 -Phosphate Dehydrogenase Deficiency Protection against *Plasmodium falciparum*

G-6-PD deficiency has been said to provide resistance against malaria infection Dale, (2007). This concept was first examined after scientist noticed a similarity between area of the world where G-6-PD Deficiency in prevalent and malaria infested areas. It has been suggested that G-6-PD gene mutation is nature's way of providing the body with resistance against parasite. This hypothesis is understandable since the discovery of G-6-PD a genetic disorder was partially fueled by the reaction of G-6-PD patients to antimalarial such as primaquine and quinine. But the bottom line is that G-6-PD does afford some protection against severe malaria falciparum for boys but not for girls with only one affected chromosome (partially deficient) (Dale, 2007).

Human *Leucocyte Antigens* (HLA)

The HLA class I *antigen*, HLA-BW53 and HLA class II haplotypes, DRBI *1302

-DQBI*0501 have been associated with reduced susceptibility to severe disease, which both these HLA antigens are common in African populations. (Adetokumbo and Herbert (2003).

Human genetics is one of the elements that can be used in planning of co-ordinated attacks on disease, since it sometimes differentiate those groups or individuals who are susceptible from those who are not (Adetokumb and Herbert, (2003).

The scientific basis of genetics has made tremendous strides in recent years culminating in the completion of the mapping of the human genome. Harnessing these new tools biomedical scientists expects to make rapid, significant advances in many directions: diagnosis of hereditary disorders, identifications of makers of disease susceptibility using molecular epidemiology; Advances in biotechnology to develop diagnostics tools, prophylactic, and therapeutic agents as well as novel vector control methods. (Adetokumbo and Herbert (2003). Interest in genetics was initially stimulated in the tropics by the discovery that high gene frequencies for some genetic traits are maintained by providing protection against falciparum malaria. The hemoglobin genetic makers vary in importance from one area to the other; while hemoglobin S, is the most important abnormal hemoglobin in Africa, it is superseded by *hemoglobin* E and *thalassaemia* in south East Asia. (Adetokumbo, and Herbert, (2003).

Conclusion

Various types of genetic disorders were diagnosed by identification of makers of the disease susceptibility using molecular epidemiology and advanced biotechnology, some of genetic disorders include, *hemoglobin* S, *hemoglobin* E, *hemoglobin* C, *hemoglobin* F, *alpha* and *beta thalassemia*, *ovalocytosis*, G-6-PD deficiency, HLA-BW53, DRBI*1302, DQBI*0501, PKLR. People having the disorders are protected from severe *falciparum malaria* by natural phenomena.

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