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Genetic Variations and Sensitivity to Malaria

Malaria is one of the oldest infectious diseases known to man. It is caused by the parasitic species, *Plasmodium* (Fujioka, 2002). Although *Plasmodium falciparum* is the most common species of this parasitic family that infects the human population, the three other known species include *Plasmodium ovale*, *Plasmodium vivax*, and *Plasmodium malariae* (Fujioka, 2002). It is transmitted to humans by the bite of female mosquitos acting as the vectors for these parasites. Each year there are close to 250 million who suffer from this disease leading to a fatality level that is staggering: more than 1 million people (WHO, 2011). Although the disease is practically eradicated in nations like the U.S, it remains prevalent in most developing countries. The repercussions of this disease include the negative impact it has on the economic expansion of these nations. According to the World Health Organization, as a result of malaria, the annual economic development declines by 1.3% in countries where the disease is most prevalent (WHO, 2011). Thus it is a relevant problem that this world continues to tackle and researchers are using genomics to better understand the disease and to develop a long-term fix through vaccines. One of the ways that researchers are exploring such options is by analyzing the various malaria related genetic polymorphisms present in the human population.

Sensitivity to malaria has evolved throughout human evolution and genetic resistance to malaria is one of most sustained genetic variation preserved through natural selection (Dornamraju, Krishna, Arese, Haldane, 2006). These mechanisms of resistance are highly

selected for, despite some of these variations leading to fetal diseases like those who are homozygotes for sickle cell anemia (HbS). Interestingly, genetic variations resulting in resistance to this disease are constantly changing and various mechanisms of genetic resistance have been adopted by different population groups of the world. Some of these mechanisms of genetic resistance developed as early as 10,000 years ago (Abdalla, Saad, Pasavola, 2004). Different forms of evolutionary selection for malaria resistance developed include, mutation in genes coding for hemoglobin, membrane proteins of red blood cells as well as those of liver cells. One of the most common forms of selectivity to malaria are ones that influence the response of red blood cells to the invasion of a *Plasmodium* parasite.

Pathology of Malaria in the Human Body

After the mosquito bites the human skin, the parasites (sporozoites) present in the mosquito's saliva will enter the blood stream of the individual (Hisashi, 2002). Once inside the body, they attack the liver cells and the sporozoites will mature releasing merozoites which will go to infect blood cells. And these merozoites continue to divide inside the blood cells and these parasites will go and attack other erythrocytes. The human immune system has difficulty implementing an effective defense against this attack because these merozoites have developed savvy techniques to bypass the body's immune response. Obviously, a major problem the immune systems faces is that T-cells cannot attack the red blood cells because erythrocytes lack MHC proteins (Hisashi, 2002). And while it is developing in the liver cells, the parasites remain concealed from the immune system and one possible way that the body's defense system can rid the body of these parasites would be by employing the aid of the spleen. However, these parasites have developed a way to avoid circulating in the blood stream and thus never reaching the spleen. Once these parasites are inside the red blood cells, they produce a series of proteins

that are sent to the surface of the cell (Hasashi, 2002). These membrane-bound proteins bind to adhesive molecules on the endothelial surface of blood vessels (Abdalla, Saad, Pasvol, 2004). Thus when the adoptive immune system cannot tackle the complexities of these parasitic invasions, genetic variations selected for by nature result in decreased sensitivity to the disease.

Mendelian Genetic Disorders and Resistance

Some of the most common mendelian genetic disorders have shown a correlation with a resistance to malaria. Some of these disorders include afflictions brought on by a mutant of the HBB gene: HbS, HbC, and HbE (Kwiatkowski, 2005). HbS and HbC is a variant that is most commonly associated with Africans, African decedents as well as individuals from the middle east. However, HbE is one variation that is common at high frequencies in population of Southeastern Asia. Another variant that results in hemolytic anemia but leads to malaria resistance is variations found in the G6PD gene (Tishkoff, 2001). This gene codes for an enzyme that produces a reducing agent that helps the red blood cells cope with an oxidative stress caused by *Plasmodium* parasites (Tishkoff, 2001). This stress is present as iron is produced when the parasites degrade hemoglobin. There are many more genetic variations such as those listed below which exhibit at high frequency within a few specific populations giving them a genetic advantage over others who do not have such traits (see Figure 1). There is little known about the molecular basis behind how these variations lead to resistance to malaria, while others are well understood and potential therapeutic treatments are being developed as a result.

Table 1

Common Erythrocyte Variants That Affect Resistance to Malaria

Gene	Protein	Function	Reported Genetic Associations with Malaria
FY	Duffy antigen	Chemokine receptor	FY*O allele completely protects against <i>P. vivax</i> infection.
G6PD	Glucose-6-phosphatase dehydrogenase	Enzyme that protects against oxidative stress	G6PD deficiency protects against severe malaria.
GYPA	Glycophorin A	Sialoprotein	GYPA-deficient erythrocytes are resistant to invasion by <i>P. falciparum</i> .
GYPB	Glycophorin B	Sialoprotein	GYPB-deficient erythrocytes are resistant to invasion by <i>P. falciparum</i> .
GYPC	Glycophorin C	Sialoprotein	GYPC-deficient erythrocytes are resistant to invasion by <i>P. falciparum</i> .
HBA	α -Globin	Component of hemoglobin	α^0 Thalassemia protects against severe malaria but appears to enhance mild malaria episodes in some environments.
HBB	β -Globin	Component of hemoglobin	HbS and HbC alleles protect against severe malaria. HbE allele reduces parasite invasion.
HP	Haptoglobin	Hemoglobin-binding protein present in plasma (not erythrocyte)	Haptoglobin 1-1 genotype is associated with susceptibility to severe malaria in Sudan and Ghana.
SCL4A1	CD233, erythrocyte band 3 protein	Chloride/bicarbonate exchanger	Deletion causes ovalocytosis but protects against cerebral malaria.

developing

vaccines

Kwiatkowski, Dominic. "How Malaria Has Affected the Human Genome and What Human Genetics Can Teach Us about Malaria." *Genet* 77 (2005): 171-90. Print.

Variation in gene has been one adaptation that is in their hopes for

for malaria (Dornamraju, Krishna, Arese, Haldane, 2006). This gene codes for the Duffy antigen that is associated with the surface of red blood cells. This antigen is not expressed in some regions of Africa and it is a genetic variation that results in a resistance to the parasitic variant, *P. Vivax*. This genetic variation led researchers to find a parasitic derived protein that binds to this Duffy antibody (Kwiatkowski, 2005). With this knowledge, current research is looking into developing vaccines that will manipulate the parasites's ability to bind to the body's Duffy receptor.

Another variation leading to decreased sensitivity to malaria is the gene HLA-B (Dornamraju, Krishna, Arese, Haldane, 2006). This gene codes for an antigen-presenting protein (MHC like protein) and a variant of this gene has been shown to exist at a high frequency in populations of Western Africa. This led researchers to begin looking at possibilities that include examination of malaria resistance at the liver level before it crosses to red blood cells. Unlike erythrocytes, hepatic cells are able to make these MHC proteins and a variant of this protein is able to offer genetic resistance to malaria (Hisashi, 2002). Such knowledge has led many researchers in search of vaccine development to look for the possibility of manipulating the immune response at the hepatic stage of malaria's pathogenesis.

Besides genetic variations resulting in resistance to malaria, environmental resistance has also been noticed as a factor that influences population susceptibility to malaria. So there does exist an environmental influence on resistance to malaria. Numerous studies conducted on the resistance to malaria have perceived declining rate of sensitivity to the disease from childhood to adulthood (Kwiatkowski, 2005). One study conducted on the progressive resistance of malaria by kids in Kenya showed that the heterozygous genetic trait of sickle cell anemia collaborates with the adoptive immune system to protect the body from infection. Starting from when the

child is 2 years old, resistance level of these kids was 20% but increased to 56% once they were about 10 years old (Williams, 2005). This adoptive nature may explain the variety and abundance of genetic variation selected for malaria resistance. Thus far, we have looked at genetic variations found as result of known genetic disorders leading to resistance to malaria. Yet, there are other sources of genetic variation which researchers are currently looking for by conducting a GWAS study.

Current GWAS Study: Malaria Resistance

In the past few years GWAS studies have become instrumental in finding genetic associations that have yet to be explored. The knowledge attained from GWAS studies can aid in diagnosis but most importantly preventive care. In the case of malaria the discovery of new genes associated with malaria can lead to possible methods of preventive care as well as a better understanding of the molecular biology of the disease. One recent international GWAS research was able to examine the susceptibility to malaria in a total of 6000 Gambian children (Muminatou, Jallow, 2009). The group looked at more than half a million SNPs to conduct this study. They were able to confirm some of the genetic variations that are discussed above including, more than 10 located very near to the HBB gene on chromosome 11. They also found strong associations for genes not yet known to have been correlated with Malaria. These include, CAMTA1, (P appx. = 10^{-5}) a calmodulin associating transcriptional factor and RYR2 (P appx. = 10^{-5}), a type of calcium channel membrane protein. They also discovered a few other associations on chromosome 7, 2, 5 and 14. Thus far, these studies have identified these genes but hope that further studies can explore these similar SNPs and analyze if these results can be replicated. The study was just looking at Gambian children and an expansive SNP analysis of other population groups can help broaden the knowledge we may have about the

causality of these variations. However, the ultimate goal is to learn more about the disease and to better understand the mechanisms which it uses to attack the body. And a GWAS study is only a step in that direction which may eventually lead to the discoveries of vaccines for the millions suffering with this disease.

Conclusion

In the past decade or so, there has been a surge in the use of genomics to analyze the genetic variations related to malaria resistance. There are countless malaria-resistance genes in the human population and the variations exhibited by different groups in the world show that the selection for some of these genetic modifications must have occurred in recent years. Thus far, there have been countless research conducted on this very subject and many have lead to a better understanding of the disease as well as possibilities related to vaccine manipulations. Recent studies with GWAS have become even more promising, giving researchers the ability to identify many more malaria-related genes in the human genome. Malaria-resistance variation is not only a mechanism for one to study natural selection and the evolutionary history of human population but it is now also a source of hope in the research for malaria vaccination development.

Work Cited

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