Population Genomic Data Leads to CNVs Related to Severe Malaria Risk

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NEW YORK (GenomeWeb) – A new genomic analysis suggests copy number changes impacting genes coding for invasion receptor-related proteins on human red blood cells may protect individuals infected with the *Plasmodium falciparum* parasite from severe malaria.

An international team led by investigators at the University of Oxford and the Wellcome Trust Sanger Institute sifted through new and available genome sequence data for thousands of individuals with or without severe malaria, searching for host sequences influencing interactions with *P. falciparum*. As reported online today in *Science*, the search led to copy number changes in glycophorin-coding genes related to red blood cell invasion receptors that were more common in populations from sub-Saharan Africa and appeared to dial down the risk of severe malaria.

"These findings link structural variation of red blood cell invasion receptors with natural resistance to severe malaria," University of Oxford researchers Dominic Kwiatkowski and Chris Spencer, the study's corresponding authors, and their colleagues wrote.

The researchers began by doing whole-genome sequencing on 765 individuals from populations in the Gambia, Burkina Faso, Cameroon, and Tanzania — a sample set that included more than 200 parent-child trios.

They then folded these data in with sequence clues from the 1000 Genomes Project to put together a genetic reference panel representing variants in 1,269 individuals from Africa and in 2,000 individuals from other populations around the world.

With that reference set, the team was able to impute variants in another 4,579 individuals with severe malaria and 5,310 unaffected controls from Gambia, Kenya, and Malawi for a genome-wide association study focused on copy number changes and other variants related to severe malaria susceptibility.

The investigators focused particularly on parts of the genome suspected of influencing malaria severity based on past GWAS results or predicted biological functions, including genes coding for glycophorin invasion receptors on human red blood cells.

Their initial search for copy number variants over-represented in African individuals led to dozens of

duplications or deletions, spanning 3,200 to more than 200,000 bases — a copy number variant set that included five types of deletions affecting the glycophorin-coding gene GYPB and additional variants involving hybrids between the GYPB and GYPA glycophorin genes or the GYPE and GYPA genes.

The study's authors noted that "CNVs in the glycophorin region were observed more frequently in Africa than other parts of the world."

In the non-African populations, just over 1 percent of individuals had glycophorin CNVs, they reported. But the glycophorin CNV allele frequency jumped to around 11 percent in individuals from the African populations considered.

When they took a closer look at glycophorin CNVs with potential ties to malaria severity, meanwhile, the researchers narrowed in on a complex structural rearrangement that led to GYPB loss, as well as a glycophorin hybrid gene gain that dialed down severe malaria risk by an estimated 40 percent.

"The discovery that a specific alteration of these invasion receptors confers substantial protection provides a foundation for experimental studies on the precise functional mechanism," the authors concluded, "and may lead us toward novel parasite vulnerabilities that can be utilized in future interventions against this deadly disease."

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