Researchers show new evidence of genetic 'arms race' against malaria

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For tens of thousands of years, the genomes of malaria parasites and humans have been at war with one another. Now, University of Pennsylvania geneticists, in collaboration with an international team of scientists, have developed a new picture of one way that the human genome has fought back.

The international team was led by Sarah Tishkoff, a Penn Integrates Knowledge professor with appointments in the genetics department in Penn's Perelman School of Medicine and the biology department of biology in the School of Arts and Sciences, and Wen-Ya Ko, a postdoctoral fellow in the genetics department at the medical school. They performed a genetic analysis of 15 ethnic groups across Africa, looking for gene variants that could explain differing local susceptibility to malaria.

Their research will be published online in the journal American Journal of Human Genetics on June 2.

Malaria remains one of the deadliest diseases on the planet, annually killing about a million people, 90% of whom live in Africa. Different populations show different responses to the parasites that cause malaria; the team conducted the largest cross-population comparison ever on a pair of genes related to malaria's ability to enter red blood cells.

"When you try to identify the variants that are associated with disease susceptibility, it's important to do a very fine scale study," Ko said.
"Different populations evolve independently, to a certain degree, so different populations can come up with unique mutations."

The life cycle of malaria depends on infecting red blood cells by binding to their surfaces, which is why mutations, such as sickle cell anemia, that change the overall shape of those cells are thought to have experienced positive selection.

"Both host and the parasite try to fight back with mutations; it's a co-evolution arms-race that leaves a signature of selection on the genes," Ko said. "We've identified several single-nucleotide polymorphisms that are candidates for that signature."

Across the 15 population sets, the researchers focused on polymorphisms in a pair of genes that code for proteins called glycophorin A and glycophorin B. These proteins exist on the surface of red blood cells, and changes to their shape affect the ability of the parasite causing malaria to bind to them and to infect the cells.

There are, however, two conflicting theories of why changes to glycophorin shape influence rates of malaria. One theory suggests that glycophorin A acts as a decoy, making itself more attractive to binding so that pathogens don't infect more vulnerable cells. Another theory suggests that glycophorin A mutates so that malaria parasites can't bind at all.

The researchers observed differing patterns of natural selection acting on the different regions of the two genes. They noted an excess of genetic variation being maintained in the region of glycophorin A that plays a critical role of entry of the malaria parasite into the blood cell.

"This signature of selection was strongest in populations that have the highest exposure to malaria," Tishkoff said.
In addition, the researchers identified a novel protein variant at glycophorin B in several populations with high levels of malaria that may also be a target of natural selection.

Comparisons to chimpanzee and orangutan genomes showed that these mutations occurred after the human lineage split from these closely related primates. But a process known as "gene conversion," in which similar genes can acquire mutations from one another during cell division, complicates tracking the exact history of the mutation's spread.

"The genes for glycophorin A and B arose through gene duplication. They are more than 95 percent similar to each other on the sequence level," Ko said. "Because they are so similar, sequences of A might bind to B during recombination, which means a mutation that occurs on one can be shared with the other."

That aspect of gene conversion may be a key to helping humans in the genetic arms race against malaria.

"The parasite's genome is very highly mutable, and its generation time is short, as compared to humans, so having more mutations more quickly is helpful in keeping up," Ko said. "This is one tool in the arms race. It may not win the war, but it's another way to increase variation."

A better understanding of the interplay between the genes of the malaria parasite and that of its human hosts could also give researchers an artificial advantage - drugs or vaccines - in the fight against the disease.

"Any new information about how malaria infects cells and how humans have evolved natural defense mechanisms against that infection adds to the body of knowledge about the pathology of malaria," Tishkoff said. "This information could aid in the development of more effective treatments against malaria."