Cell surface mutation protects against common type of malaria

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A mutation on the surface of human red blood cells provides protection against malaria caused by the parasite *Plasmodium vivax*, research led by Case Western Reserve University School of Medicine shows.

The minute change, at a single position of red blood cell surface protein called the Duffy blood-group antigen, has been known for years. But the researchers found this difference makes it harder for the parasite to lock onto the cell and gain entry.

No entry, no infection.

The research is now published online in the Early Edition of the Proceedings of the National Academy of Sciences.

"The finding has practical implications as medical researchers continue attempts to develop a vaccine for vivax malaria," said Christopher King, a professor of international health, medicine and pathology at the Center for Global Health and Diseases at Case Western Reserve University School of Medicine, and lead author.

The protective aspect of the mutation was discovered in campus labs and confirmed through a population study in the Amazon region of Brazil.

Malaria is caused by four different parasites; the majority of cases in Asia and the Americas are caused by *P. vivax*.

"Plasmodium vivax carries a Duffy binding protein that binds to the Duffy antigen on the surface of the red cell, a critical step to invading the cell," Dr. King explained. "Both parasite and human proteins appear to be needed for the parasite to invade the cell."

King's lab had been studying the parasite's protein, as a target for a vaccine. He teamed with Peter A. Zimmerman, a professor of international health, genetics and biology, also at the Center for Global Health and Diseases. Zimmerman's lab was studying the mutation in the DNA sequence of Duffy blood group gene.

While investigating the binding process, they found that Duffy binding protein interaction with red blood cells varied between samples.

They performed the genetic tests for the single-point mutation. Antigens with the mutation are called Duffy 'A' and those without, Duffy 'B'.

They found the parasite bound to red blood cells expressing Duffy 'B' about twice as often as the parasite bound to cells expressing Duffy 'A'.

The researchers wanted to see if the finding translated to real life.

They collaborated with Marcelo U. Ferreira, an investigator at the Department of Parasitology, Institute of Biomedical Sciences, University of Sao Paulo, to analyze data from 400 individuals tracked for malaria infections for more than a year in northwest Brazil.

In northwestern Brazil, where a mixture of Duffy 'A' and 'B' variants are inherited, the researchers found that people expressing the Duffy 'B' variant experience *P. vivax* malaria more often than those who expressed the Duffy 'A' variant.

"Therefore, stronger binding to Duffy 'B' leads to greater success at red

cell invasion and more vivax malaria, Zimmerman said. "Seen from the other side of this relationship, weaker binding to Duffy 'A' appears to reduce red cell invasion and is therefore protective against vivax malaria."

The analysis showed that those with the Duffy 'A'/Duffy 'A' genotype had a 29 percent reduced risk of vivax malaria. Those who had the Duffy 'A'/Duffy 'B-negative' (a varient that has no antigen) genotype, had an 80 percent reduced risk. Reduced risk was not associated with an increase in antibodies in either case.

Those with Duffy 'B'/Duffy 'B' or Duffy 'B'/Duffy 'B-negative' genotypes had an increased risk of 220 to 270 percent for vivax malaria.

A vaccine's effectiveness therefore may depend on whether a recipient carries one or two copies of the Duffy 'A' or 'B' mutation in his DNA Dr. King said.

"The Duffy 'B' variant is ancestral to Duffy 'A'. We know this because all non-human primates carry the Duffy 'B' variant," Zimmerman said. "So a case can be made for the Duffy 'A' variant arising as protection from vivax malaria."

In a further analysis, the researchers found no association with the Duffy 'A' varient and *Plasmodium falciparum*, the parasite that causes the majority of infections in sub-Saharan Africa and the cause of 66 cases among the 400 individuals studied.

Provided by Case Western Reserve University