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New Research Finds "Vivax" Malaria Could Have Multiple Ways to Cause Infections; Potential Risk for Millions in Africa Thought to be Resistant

At ASTMH Annual Meeting, scientists present new genome sequence data indicating world's most common species of malaria may be evolving to become bigger threat

Washington, D.C. (November 15, 2013)—Provocative new research shows that the *Plasmodium vivax* parasite, responsible for nearly 20 million cases of malaria in 2010, may be "rapidly evolving" to overcome the natural resistance conferred by a blood type found in millions of Africans, scientists reported today at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH).

In large swaths of sub-Saharan Africa, some 95 percent or more of the population have been considered protected from vivax malaria because of something they lack on their red blood cells: the "Duffy blood group protein." The absence of this protein has been well known for decades to hinder the ability of invading vivax malaria parasites to gain entry into red blood cells.

But over the last five years malaria researchers have been surprised to see a growing number of reports from Africa and South America of infections in people who are Duffy-negative and should be resistant to vivax malaria. While not regarded to be as deadly as malaria caused by the *Plasmodium falciparum* parasite, vivax malaria threatens almost as many people worldwide--some 2.49 billion are at risk. But that number could be significantly higher if the blood type is not as fully protective as previously believed.

"We discovered previously unknown genetic mechanisms in the *P. vivax* parasite that could give it other ways to invade red blood cells and help explain why we are seeing these vivax malaria infections in people who are Duffy-negative," said Peter Zimmerman, PhD, of Case-Western Reserve University, a co-author of two new studies to be published November 21 and December 5 in the journal *PLOS Neglected Tropical Diseases*.

The studies conclude that vivax malaria appears to be "rapidly evolving" and also find that previous genome sequence analyses may have missed "important genes" that allow the parasite to make people sick.

Zimmerman's colleague, David Serre, PhD, of the Cleveland Clinic's Genomic Medicine Institute, said that while there is not yet enough evidence to conclude that the *P. vivax* parasite is gaining virulence, "we think the genetic mechanisms we have uncovered could dramatically change our understanding of this very important form of malaria that doesn't get as much attention as falciparum malaria, even though it causes severe disease and may be more deadly than many think."

Also, vivax malaria is in one respect more dangerous than falciparum malaria: the *P. vivax* parasite has the ability to "hide" in the liver and re-emerge multiple times in the bloodstream to cause relapse infections.

Kevin Baird, PhD, an expert in vivax malaria at the Eijkman-Oxford Clinical Research Unit in Indonesia, said the "expanding reports of vivax malaria in Duffy-negative individuals are alarming." But Baird, who was leading discussions at the ASTMH Annual Meeting on improving vivax malaria diagnostics and treatment, said it remains to be seen whether "this is an emerging problem or a low-probability event that has always been around." He also noted that research identifying infections in Duffy-negative individuals indicates that, overall, people who lack the protein still seem less likely to get vivax malaria, even if they may not be fully protected.

In Madagascar, a Surge in Duffy-Negative Infections

Zimmerman and his colleagues looked for biological mechanisms that might explain "Duffy-negative infections" by sequencing the genome of several *P. vivax* parasites, including parasites gathered in Madagascar. Madagascar has been of particular interest, they said, because infections in Duffy-negative individuals have been occurring there at a comparatively high rate.

In the study published today, they report finding something that had not been seen before in *P. vivax* parasites: two copies of the gene that encodes the parasite's Duffy-binding protein. Subsequent analysis of blood samples taken from infected subjects around the world revealed that duplication of the parasite's gene is occasionally found in other areas where vivax malaria is common. But the highest prevalence was in Madagascar. For example, less than 10 percent of the 33 samples tested from Cambodia had the duplicate gene, while it was found in over 50 percent of the 189 samples taken from Madagascar.

"It was particularly striking that most of the parasites that contained the duplicate gene came from areas where we see the population divided between Duffy-positive and Duffy-negative individuals," Serre said.

The researchers believe one possibility is that in such split populations, the Duffy-positive individuals keep parasites circulating in their communities, allowing them to frequently attempt to infect individuals who are Duffy-negative. Such repeated encounters, they say, increase the chances that a *P. vivax* parasite could develop a new way to penetrate red blood cells.

In Cambodia, Evidence of a New "Invasion Mechanism"

In the second study, the researchers analyzed the genome of a *P. vivax* parasite from Cambodia. They found a previously unknown gene that "harbors all the key features" of an "invasion protein" for gaining access to red blood cells. For example, the protein expressed by this gene is similar to proteins used by other *Plasmodium* parasites, including *P. falciparum* to cause infections.

Subsequent investigation found that this new gene is widely present in contemporary *vivax* parasites around the world, but with a notable exception: it is not found in the *vivax* parasite sequenced in 2008 that has been used by malaria scientists as the "reference" genome for studying the genetics of the parasite.

The ASTMH Annual Meeting is the premier international gathering for those working in malaria, noted ASTMH President David H. Walker, MD, and "in recent years it has significantly added to the efforts to raise the visibility and understanding of the global burden of vivax malaria."

"These studies are sure to generate robust discussions among attendees on the future of vivax in sub-Saharan Africa, particularly given the recent progress against falciparum malaria," he said.

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About the American Society of Tropical Medicine and Hygiene
ASTMH, founded in 1903, is a worldwide organization of scientists, clinicians and program professionals whose mission is to promote global health through the prevention and control of infectious and other diseases that disproportionately afflict the global poor.