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Researchers find extreme genetic variability in malaria parasite

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Researchers at the University of Maryland School of Medicine Center for Vaccine Development (CVD) have charted the extreme genetic differences that occur over time in the most dangerous malaria parasite in the world. While there is no approved vaccine for malaria, various experimental vaccines are in development. The CVD study suggests that developing a broadly protective vaccine for malaria may be challenging because the parasite's genetic makeup is so variable, constantly changing.

If a vaccine targets only a single protein in the parasite, and there are many different versions of that protein, the parasite becomes a moving target for vaccine development. Drug-resistant malaria has been a major barrier to treating the disease, and this CVD study suggests that "vaccine-resistant" malaria may also become a problem. The study is being published in the Oct. 14 issue of the journal *Science Translational Medicine*.

Scientists and health officials worldwide have made eradication of the disease a priority, with an effective and broadly protective vaccine a critical step toward that goal. Malaria — a parasite spread to humans through mosquito bites — is prevented by avoiding mosquito bites using bed nets or by killing mosquitoes with insecticides. The parasite is treatable using medications, although drug resistance is a relatively common problem. According to the World Health Organization, a child dies of malaria every 30 seconds. There are approximately 300 million malaria cases annually worldwide, resulting in more than one million deaths, most of them African children.

Certain regions within a key parasite protein — a protein targeted by some experimental malaria vaccines — seem to affect the human immune response more than others, and targeting those areas could help develop a better vaccine, according to the study led by Shannon Takala, Ph.D., assistant professor of medicine at the University of Maryland School of Medicine and a research scientist in the CVD. The study was conducted in collaboration with researchers at the University of Bamako in Mali, West Africa, and at the Center for Bioinformatics and Computational Biology and Department of Biology at the University of Maryland, College Park.

"This brings us one step closer to being able to design a broadly protective malaria vaccine," says Dr. Takala. "Though there are medications that are used to treat malaria, drug resistance is a recurring problem. An effective vaccine could help us eliminate malaria altogether, a public health goal that is attracting more global support than ever before."

"In addition to its home campus in Baltimore, the University of Maryland School of Medicine employs hundreds of researchers in 23 countries around the globe," says E. Albert Reece, M.D., Ph.D., M.B.A., dean of the School of Medicine, vice president for medical affairs of the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor. "This study is an example of how our global footprint allows School of Medicine researchers to study diseases such as malaria in the very regions of the world in which they are devastating to the population."

A research team of Malian and American scientists at the CVD's outpost in Mali, West Africa tested malaria parasites from 100 children in Mali over a three-year period. The children, who had not been vaccinated against the disease, all experienced repeated malaria infections during the three years. The CVD researchers, including Christopher Plowe,

M.D., M.P.H., Howard Hughes Medical Institute investigator, professor of medicine and chief of the Malaria Section at the University of Maryland School of Medicine, looked at the genetic diversity in a surface protein of the Plasmodium falciparum — the AMA-1 protein — that is the target of some candidate malaria vaccines.

By tracking the changes in the AMA-1 protein each time a child became infected with malaria, researchers found a surprising amount of genetic diversity. Among more than 500 separate malaria infections the children experienced throughout the study, researchers found 214 distinct types of the AMA-1 protein. The scientists also found that the genetic differences in certain parts of the protein but not others corresponded to whether or not a child got sick the next time they were infected with malaria. It was easier for a child's immune system to defend itself against illness in a subsequent infection if the protein in the second parasite was genetically similar to the parasite that caused their first illness.

Working with Michael P. Cummings, Ph.D., associate professor of biology at the University of Maryland, the researchers were able to track which variants of the AMA-1 protein were present in each infection and compare that data to the symptoms each child experienced during the infections.

"Applying a molecular evolutionary perspective to the study of the malaria parasite gave us new information about why it has been so challenging to develop an effective malaria vaccine," says Dr. Cummings, who is affiliated with the University of Maryland's Center for Bioinformatics and Computational Biology. "The genetic diversity we found in the AMA-1 protein was so high that it could potentially thwart the usefulness of any vaccine based on this protein."

By narrowing their focus to those specific regions of the protein that are

recognized as distinct by the immune response, the researchers were able to reduce the number of immunologically important AMA-1 types from 214 to just 25. By targeting those specific regions of the protein, scientists could possibly develop a more broadly protective malaria vaccine.

"The emergence of drug-resistant malaria was one of the main reasons eradication of the disease didn't work when it was tried 50 years ago," says senior author Dr. Plowe. "We want people to begin thinking now about the possibility that 'vaccine-resistant malaria' could be just as much of a problem for the new global eradication effort. We need to come up with ways to beat vaccine-resistant malaria before we start losing vaccines to resistance the way we have lost so many good drugs."

Source: University of Maryland Medical Center