Genomic study sheds light on protective effects of malaria vaccine candidate

October 21 2015

Credit: National Cancer Institute

An international team led by researchers from the Broad Institute of MIT and Harvard, the Harvard T.H. Chan School of Public Health, and Fred Hutchinson Cancer Research Center have used cutting edge genomic methods to uncover key biological insights that help explain the protective effects of the world's most advanced malaria vaccine candidate, RTS,S/AS01 (RTS,S).

Applying highly sensitive sequencing technology to more patient samples than previously tested, the team was able to determine that genetic variation in the protein targeted by RTS,S influences the vaccine's ability to ward off malaria in young children. The work, which was published online October 21st by the *New England Journal of Medicine* (*NEJM*), could inform future vaccine development.

"This is an example of the benefits of applying genomics to a real world problem of global health importance," said Dyann Wirth, co-director of the Broad's Infectious Disease Program and the Richard Pearson Strong Professor of Infectious Diseases and chair of the Department of Immunology and Infectious Diseases at the Harvard T.H. Chan School of Public Health. Wirth, along with Peter Gilbert of Fred Hutchinson Cancer Research Center, led the study.

Malaria is a global health threat responsible for hundreds of millions of infections and more than half a million deaths annually in tropical and subtropical regions of the world. The disease is caused by intracellular protozoan parasites from the genus Plasmodium, which are transmitted to humans by mosquito vectors.

RTS,S is designed to target a fragment of a specific protein, circumsporozoite (CS), that sits on the surface of the Plasmodium falciparum parasite. The CS protein is capable of provoking an immune response that can prevent parasites from infecting the liver, where they typically mature and reproduce before dispersing and invading red blood cells, leading to symptomatic malaria. RTS,S aims to trigger that response as a way to protect against the disease. However, the CS protein is genetically diverse - perhaps due to its evolutionary role in the immune response - and RTS,S includes only one version (or "allele") of the protein. The current study sought to test whether alleles of CS that matched the one targeted by RTS,S were linked with better vaccine protection.

Through a collaboration with the vaccine division of the healthcare company GlaxoSmithKline, researchers from Harvard and the Broad obtained blood samples from over 5,000 of the approximately 15,000 infants and children who participated in the vaccine's phase 3 trial across 11 study sites in Africa between 2009 and 2013. The researchers were sent samples when the first symptomatic cases appeared in those vaccinated, as well as samples from all participants at month 14 and month 20 following vaccination. By sequencing those samples, the team determined that, while RTS,S provided at least partial protection against all strains of the parasite, it was significantly more effective at preventing malaria in children with matched allele parasites than in preventing malaria with mismatched allele parasites. The same effect was not noted in infants.

Previous studies during the RTS,S's phase 2 trials had not detected an allele-specific effect for this vaccine candidate. However, the current study benefited from a larger sample size and technological advances that made it possible to read the genetic samples with much greater sensitivity that, for instance, allowed for the detection of rare alleles and multiple parasite infections.

"This is the first study that was big enough and used a methodology that was sufficiently sensitive to detect this phenomenon. Now that we know that it exists, it contributes to our understanding of how RTS,S confers protection and informs future vaccine development efforts," said Dan Neafsey, associate director of the Genomic Center for Infectious Diseases at the Broad and co-first author of the NEJM paper.

Combined with the new methodology for generating genetic data, the study used new statistical methods for analyzing the data.

"This uniquely valuable data set posed some challenges to data analysis. The statistical team extended methods previously developed for HIV to

provide interpretable answers about differential vaccine efficacy by malaria genetics," said Gilbert, who is a member of the Vaccine and Infectious Disease Division and director of the statistical center for the HIV Vaccine Trials Network at the Fred Hutchinson Cancer Research Center.

This powerful approach can now be applied not only to malaria but also to other major infectious diseases that involve highly variable vaccine targets. It is already being applied in HIV vaccine trials, and Wirth's team has made plans to apply it in future malaria vaccine trials. Furthermore, the work underscores how a full and comprehensive catalogue of the genetic diversity of key pathogens could inform the design of robust, effective vaccines.

"Now that we understand that at least in the case of this immune response, that there's an allele-specific aspect to it - a particular parasite strain or type creates a certain immune response in the individual - this finding can color how we approach future vaccine discovery and development," said Wirth.

RTS,S is the first malaria vaccine candidate to complete phase 3 trials. Originally designed by scientists at GlaxoSmithKline (GSK) in 1987, development of the vaccine is now being advanced by a public-private partnership between GSK and PATH Malaria Vaccine Initiative.

More information: Daniel E. Neafsey et al. Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine, *New England Journal of Medicine* (2015). DOI: 10.1056/NEJMoa1505819 .

Provided by Broad Institute of MIT and Harvard