Researchers identify genes causing antimalarial drug resistance

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Using a pair of powerful genome-search techniques, researchers from the Harvard School of Public Health (HSPH), Harvard University, and the Broad Institute have identified several genes that may be implicated in the malaria parasite's notorious ability to rapidly evade drug treatments. Further testing revealed that one of the genes, when inserted into drug-sensitive parasites, rendered them less vulnerable to three antimalarial drugs.

The successful experiments suggest that the genomic methods are useful tools for probing the genetic mechanisms underlying drug resistance in the Plasmodium falciparum malaria parasite and potentially other types of disease-causing parasites as well.

The study appears online April 21, 2011, in PLoS Genetics, and is timed to coincide with World Malaria Day on April 25.

"Identification of mutations associated with drug resistance helps us understand how the parasite evades the effects of the drug," said Sarah Volkman, senior research scientist at HSPH and a co-senior author of the paper. "Once we understand the processes used by the parasite to avoid the effects of the antimalarial treatment, scientists can develop new drugs that circumvent the strategies employed by the drug-resistant malaria parasite."

In addition, said Volkman, knowing the mutations that signal that a parasite has become resistant to an antimalarial compound allows researchers to develop tools that can be used for monitoring and surveillance of drug-resistant parasites.

Reducing the toll of malaria, which kills nearly a million people a year--mainly young children in sub-Sahara Africa--is a major challenge because of the parasite's talent for swiftly developing resistance to multiple drugs. To counter the shape-shifting parasite's defenses, scientists say they must improve on their meager understanding of the molecular and genetic mechanisms of resistance.

Genetically diverse populations of the blood-borne malaria parasite are endemic in Africa, Asia, and South America. When exposed to antimalarial drugs and the human immune system, Plasmodium falciparum has a remarkable ability to quickly generate resistant clones of parasites, a major obstacle to successful treatment.

For the study, the scientists, including Volkman, Dyann Wirth, and co-first author Daria Van Tyne of HSPH and the Broad, co-first author Danny Park and Pardis Sabeti of the Broad and Harvard University, and Daniel Neafsey and Stephen Schaffner of the Broad, analyzed the DNA of 57 parasites from the three continents, using a high-density genome-wide array that examines more than 17,000 mutations. They also measured the parasites' responses to 13 antimalarial drugs.

The scientists examined diversity of the parasite to identify 20 rapidly evolving loci in the genome, and then carried out a genome-wide association study (GWAS) to identify genetic variants that correlated with or are associated with the drug-resistance trait. These genetic variants are necessarily enriched in the drug-resistant, but not drug-sensitive parasites, allowing the researchers to home in on the candidate genes that are involved in modulating drug responses. That search netted 11 genes implicated in drug resistance - one previously known and others discovered for the first time.

Van Tyne pursued one of the novel genes, PF10_0355, for follow-up functional testing. She used an experimental technique that introduced extra copies of the gene from a resistant parasite into a drug-sensitive one, and found that the formerly sensitive parasite was now rendered more resistant to three standard antimalarial agents.

"This demonstration suggests that the gene is involved in modifying parasite drug response," said Van Tyne, a graduate student in the laboratory of Wirth, chair of the Department of Immunology and Infectious Diseases at HSPH and a co-director of the Infectious Disease Initiative at the Broad. "We feel that this is one gene of potentially many that affect drug-resistance mechanisms. We're now working to follow up and understand how these and the other genes identified work."

Drug resistance is a major concern that threatens to undermine global efforts to control or eradicate malaria. Understanding how the parasite is changing before clinical drug resistance is apparent offers some hope that we might be able to extend the useful life of available drugs and identify new effective antimalarials, said Volkman.

More information: "Identification and Functional Validation of the Novel Antimalarial Resistance Locus PF10_0355 in Plasmodium Falciparum," Daria Van Tyne, Daniel J. Park, Stephen F. Schaffner, Daniel E. Neafsey, Elaine Angelino, Joseph F. Cortese, Kayla G. Barnes, David M. Rosen, Amanda K. Lukens, Rachel F. Daniels, Danny A. Milner, Jr., Charles A. Johnson, Ilya Shlyakhter, Sharon R. Grossman, Justin S. Becker, Daniel Yamins, Elinor K. Karlsson, Daouda Ndiaye, Ousmane Sarr, Souleymane Mboup, Christian Happi, Nicholas A. Furlotte, Eleazar Eskin, Hyun Min Kang, Daniel L. Hartl, Bruce W. Birren, Roger C. Wiegand, Eric S. Lander, Dyann F. Wirth, Sarah K. Volkman, Pardis C. Sabeti, *PLoS Genetics*, online April 21, 2011

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