Genetic map offers new tool for malaria research（阅）

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[摘要] December 11, 2006.. An international research team has completed a map that charts the genetic variability of the human malaria parasite, Plasmodium falciparum. The work, published in the Dec. 10 advance online edition of Nature Genetics, has already unearthed novel genes that may underlie resistance to current drugs against the disease.
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An international research team has completed a map that charts the genetic variability of the human malaria parasite, Plasmodium falciparum. The work, published in the Dec. 10 advance online edition of Nature Genetics, has already unearthed novel genes that may underlie resistance to current drugs against the disease.

The study reveals striking variation within the pathogen's genome, including an initial catalog of nearly 47,000 specific genetic differences among parasites sampled worldwide. That's more than double the expected level of diversity in the parasite's DNA. These differences lay the foundation for dissecting the functions of important parasite genes and for tracing the global spread of malaria.

The scientists who created the map are from the Broad Institute of MIT and Harvard, the Harvard School of Public Health and Cheikh Anta Diop University in Senegal, where malaria is endemic.

"Malaria remains a significant threat to global public health, driven in part by the genetic changes in the parasite that causes the disease," said senior author Dyann Wirth, a professor at the Harvard School of Public Health and co

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director of the Broad Institute's Infectious Disease Initiative. "This study gives us one of the first looks at genetic variation across the entire malaria parasite genome

--a critical step toward a comprehensive genetic tool for the malaria research community." Plasmodium falciparum--

the deadliest of the four parasites that cause malaria in humans--

kills one person every 30 seconds, mostly children living in Africa. Despite decades of research, the genetic changes that enable it to escape the body's natural defenses and to overcome malaria drugs remain largely unknown.

To gain a broad picture of genetic variability--worldwide and genome-wide--

the scientists analyzed more than 50 different P. falciparum samples from diverse geographic locations. This includes the complete genome sequencing of two well

-studied samples, as well as extensive DNA analyses of 16 additional isolates.

By comparing the DNA sequences to each other and to the P. falciparum genome sequenced in 2002, the researchers uncovered extensive differences, including 47,000 single

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letter changes called single nucleotide polymorphisms (SNPs). Although there are probably many more SNPs to be found, this initial survey provides a launching point for future systematic efforts to identify parasite genes that are essential to malaria.

"The roles of most of the malaria parasite's genes are still not known," said Sarah Volkman, a research scientist at the Harvard School of Public Health. "An important application of this new tool will be in pinpointing the genes that are vital to the development and spread of malaria."

Volkman and Pardis Sabeti, a postdoctoral fellow at the Broad Institute, are first authors on the paper.

One of the map's strengths is its ability to reveal evolutionary differences among parasites. This information can shed light on the genes responsible for malaria drug resistance

--a major obstacle to adequate control of the disease. Using the map to compare parasites exposed to different anti-

malarial drugs, the scientists identified a novel genome region that is strongly implicated in resistance to the drug pyrimethamine, and also confirmed a region of the genome known to be involved in chloroquine drug resistance.

"The same genetic principles used to study human evolution can provide important clues about malaria," said Sabeti. "This tool has already yielded insights into the genetic changes that correlate with different drug treatments, pointing us to genes that may contribute to drug resistance."

The map can also define the genetic landscapes of different parasite populations. Applying it to parasites from various continents, the scientists discovered genome DNA variability among P. falciparum samples from Africa relative to those from Asia and the Americas. This knowledge guides the selection of genetic markers to track the transmission of distinct parasites, particularly ones that are virulent or drug resistant. It also lays the groundwork for connecting p

"Genomic tools have largely been applied in First World diseases up to now. This project underscores the power and importance of applying them to the devastating diseases of the developing world," said Eric Lander, one of the study's authors and the director of the Broad Institute. "By joining forces among scientists in the U.S., Africa and elsewhere, it should be possible to rapidly reveal the genetic variation in malaria around the world.

"Knowing the enemy will be a crucial step in fighting it," said Lander, who is also a professor of biology at MIT and a member of the Whitehead Institute for Biomedical Research.

The work is one of three large-

scale studies of the parasite's DNA that appear together in Nature Genetics. It was supported by the Bill and Melinda Gates Foundation, the Burroughs

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