Drug-resistant malaria suggests a health policy change for pregnant women and infants

8 September 2010

Malaria remains a serious global health problem, killing more than one million people per year. Treatment of the mosquito-borne illness relies on antibiotics, and the emergence of drug-resistant malaria is of growing concern. In a report published online today in *Genome Research*, scientists analyzed the genomic features of a Peruvian parasite population, identifying the genetic basis for resistance to a common antibiotic and gaining new insights that could improve the efficacy of diagnosis and treatment strategies.

The World Health Organization began efforts to eliminate malaria in the mid-20th century and had made significant strides in curtailing the disease. However, by the 1990s, malaria was again on the rise due to the emergence of drug-resistant parasites, and today much remains unknown about the genetic basis of resistance.

Researcher Elizabeth Winzeler of The Scripps Research Institute and colleagues from the United States and Peru expected that by using genomic methods to analyze the malaria-causing parasite *Plasmodium falciparum* in a geographic area where malaria had been previously eradicated and recently re-emerged, they could identify positively selected regions of the genome that contain genes underlying drug resistance.

Iquitos, a city in the Amazonian lowlands of Peru, was an ideal choice for studying the genomic features of drug resistance as malaria was eliminated there in the 1960s, but re-emerged in the 1990s. Using microarrays to scan the genome of *P. falciparum* isolated from 14 patients in Iquitos, Winzeler's group analyzed and compared genetic variation between the isolates, searching for selected regions.

"We were surprised to find that the parasite populations in Peru were much more homogeneous than expected," Winzeler said. The data suggested that the malaria parasites from Iquitos patients were closely related, with some patients harboring parasites that are nearly clones of each other.

Winzeler explained that although the high similarity of the parasite genomes hindered their efforts to identify regions under selection, their analysis uncovered critical findings that could have a significant impact on the diagnosis and treatment of malaria.

The team's data indicated that there is significant genetic instability in regions near the telomere, the repetitive DNA sequences that protects the ends of chromosomes from damage. Because a malaria rapid diagnostic test relies on detection of a protein encoded by a subtelomeric gene, use of these tests could result in missed diagnoses.

Furthermore, their work identified a gene that could change the course of treatment for some infected patients. A mutation was found in a non-coding RNA gene that the authors predicted would confer resistance to the antibiotic clindamycin, a lincosamide drug commonly administered in combination with quinine to treat pregnant women and infants for malaria in Peru. They then tested the Peruvian isolates for clindamycin sensitivity and confirmed that the parasites were resistant. "This was exciting as it was the first demonstrated case of clindamycin resistance," Winzeler said. "The data also show parasites could be resistant to related compounds, such as mirincamycin, that are under development."

Winzeler noted that although the geographic scope of clindamycin resistance must be examined further, this work strongly suggests that treating pregnant women and infants with clindamycin and

similar antimalarial lincosamide drugs should be reconsidered. "Our findings emphasize the importance of placing new antimalarial compounds in the drug development pipeline," said Winzeler, "especially compounds with novel mechanisms of actions."

More information: Dharia NV, Plouffe D, Bopp SER, González-Páez GE, Lucas C, Salas C, Soberon V, Bursulaya B, Kochel TJ, Bacon DJ, Winzeler EA. Genome-scanning of Amazonian Plasmodium falciparum shows subtelomeric instability and clindamycin-resistant parasites. *Genome Res* doi:10.1101/gr.105163.110

Provided by Cold Spring Harbor Laboratory