

NEWS RELEASE

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Scientist Searches for Genetic Clues to Stop Malaria's March

FOR IMMEDIATE RELEASE

Malaria kills more people than all inherited human disorders, and is a leading cause of economic stagnation in third-world countries. Despite decades of research and treatment, *Plasmodium*, the single-celled organism that causes malaria, always seems to stay a step ahead of human immune systems and pharmacies.

North Carolina State University geneticist Philip Awadalla wants to close that gap.

Awadalla, assistant professor of genetics, recently received three major research grants from the National Institutes of Health, Human Frontiers Science Program, and National Academies Keck Futures Initiative to study the genetic underpinnings of the human-versus-*Plasmodium* arms race.

“The motive is to identify candidate genes for vaccines and drug targets in malaria, and genes for immunity in humans,” Awadalla said. “But it’s also about interesting biological questions, about understanding the genetics of the co-evolutionary process between humans and malaria.”

To identify genes associated with a particular trait, such as drug resistance in malaria, geneticists rely on a statistical method called association mapping. If, in a large sample of individuals, a particular trait usually co-occurs with a particular gene, that’s a clue that the gene may contribute to that particular trait.

But as any good detective knows, clues sometimes lead to dead ends. Different regions of an organism’s chromosomes, the molecules that contain genetic information, participate differently in the process of sexual recombination – the mechanism by which genomes, or sets of genes, mix and match – thereby affecting the organism’s evolution as well as the results of association mapping.

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Just like humans, *Plasmodium* has a diploid phase to its life cycle, meaning it bears two copies of each chromosome – one from each parent. The two copies are homologous: they are organized the same way and contain the same kind of information, but not necessarily the same details.

In humans, for example, a particular chromosome would always contain a gene for eye color, but one copy could have the allele, or version, for brown eyes while its homologue has the allele for blue. *Plasmodium* doesn't have eyes, but its genes are organized the same way.

As the parental chromosomes prepare for sexual reproduction, the homologues align with one another and trade sections in a process called crossing over. Thus the one copy of a chromosome that an offspring receives is a mosaic of the parent's two copies, and genes can end up with new neighbors on the new chromosome.

If crossing over occurs in large chunks and many genes stay together uninterrupted, it's impossible for association mapping studies to tell which one of those genes is the one that really goes with the trait of interest.

"If there is no recombination, then everything segregates together and it's impossible to do statistics because all the genes appear to be associated with every trait," Awadalla said. Even if there is some recombination, a similar problem can arise. "If recombination happens in blocks, you can tell which block contains the gene of interest, but you can't tell, within that block, which gene is associated with the trait of interest."

Scientists using association mapping get the best results when recombination occurs uniformly across the genome. In that case, if alleles of one gene are always associated with a particular trait, there's a good chance that the gene controls that specific trait.

In studying *Plasmodium falciparum*, the parasite that causes the most deadly form of malaria, Awadalla and his collaborators found that rates of crossing over are definitely not uniform. Some parts of the chromosomes break and trade pieces all the time, forming new combinations of traits, while other regions of the chromosome hardly cross over at all.

Furthermore, the areas with the most recombination, or recombination hotspots, often encompass parts of the genome involved in the human-malaria arms race.

"You see high rates of recombination at genes directly associated with immune avoidance, genes that are in the parasite's best interest to be variable," Awadalla said. "If all parasites are the same, the human immune system will target that gene, so it's good to be variable."

Researchers also found that geography has a lot to do with observed rates of recombination in *Plasmodium*. Africa, home of the "malarial Eve," Awadalla said, has the greatest genetic diversity and is freely recombining. Asia and South America, where malaria arrived later and has been through population bottlenecks associated with selective sweeps due to drugs, have lower genetic diversity, so new genetic combinations arise less often.

Now that geneticists better understand how the malarial genome behaves, they can make more effective association maps and better identify genes relevant to the prevention of malaria. Awadalla and his collaborators are currently sequencing the genes of hundreds of isolates of malaria, contributing to a shared genetic resource that many scientists can use in their studies.

But much of Awadalla's new grant money is earmarked not for studies of malaria alone, but for the genetic interactions between malaria and humans.

“We're starting to survey candidate genes in humans and malaria – how they vary, how they segregate in natural populations, and how they segregate in different populations of humans that are exposed to malaria at different rates,” he said. “We're going to look at all these different populations of humans. They're all variable, and we're interested in the variability associated with who's infected and who's not. But then, there's another layer, because the malaria they're infected with also varies.”

Awadalla's lab will begin sorting through the genetic basis of co-evolution between humans and *Plasmodium* across Africa, starting with a field trip to collect thousands of human blood samples this winter. Many samples will also come from collaborators working at clinical field stations throughout the continent.

Malaria has been infecting primates for millions of years – since before humans and apes split from each other on the evolutionary tree of life, Awadalla said – but he is optimistic that science will continue to reveal important new information for controlling the disease.

“Evolutionary genetics is at its zenith. We've never had the kind of information that we have now,” he said. “We can use a lot of mathematical tools developed over the past hundred years to address questions that are both biologically and practically relevant.”