New insights into our multi-millenia battle with malaria

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Humans have long been thwarted by 'the fever'. References to malaria's infamous febricity are found across antiquity, from writings by the four thousand-year-old Vedic sages of ancient India to the Greek physician

Hippocrates. But the disease, caused by a group of parasites belonging to the Plasmodium genus, has troubled our ancestors and close relatives for much longer. A range of malaria species infect apes, monkeys and birds across the tropical world and we now know that about 50,000 years ago the ancestors of Plasmodium falciparum, the parasite responsible for most of the current human burden of the disease, transformed from infecting gorillas to parasites that can infect us.

This means that throughout our history, wherever the ecological conditions have been able to support the mosquitoes that transmit the disease (including the marshes of Kent well into the 19th Century) we've been accompanied by the blood parasite which many believe to be one of the largest killers of people in human history. Reports of malaria killing half of the people who have ever lived are likely to be wide of the mark, however.

Given this shared history, you might expect humans to have evolved ways to neutralise the devastating impact of malaria. In evolutionary terms, the stakes are high—falciparum malaria is most deadly in young children—so there is a clear advantage to adapting to beat the parasite. And, because evolution works with new mutations in DNA that cause genes to work in new and different ways, adaptations that gave our ancestors one up against the parasites should be found across the human genome.

One such adaptation was discovered in the 1950 when Anthony Allison observed that there tended to be more people with sickle cell trait in malarial areas than places without the disease. Perhaps, he thought, because sickle cell trait affects the function of people's blood cells, it afforded some sort of protection against malaria parasites, which thrive by infecting their host's blood cells. This idea was a development of the 'Malaria Hypothesis', invented in 1948 by famed geneticist JBS Haldane, which proposed that certain human traits, particularly those involving

blood groups, rise to high frequencies in some populations because they protect people from malaria. The relationship between sickle cell and malaria was soon confirmed when children in Uganda with sickle cell trait were shown to have fewer malaria parasites in their blood than those without the trait. Sickle cell trait is now known to be caused by a single letter change in the genetic code and is the canonical example of human evolution to infectious disease.

Epidemiological research over the intervening years has provided further evidence of human adaptation to malaria. But to go further and investigate the impact of malaria on our DNA requires large well curated datasets of DNA from across the tropics. And, because much of the burden of malaria is in Africa, whose populations are among the most genetically diverse on earth, we also need to think carefully about the statistical approaches that can tease out the real genetic signals from background variation.

Addressing old problems with new data

Big datasets and statistical methods have recently become available thanks to large long-term international collaborative efforts. One such collaboration is the Malaria Genomic Epidemiology Network (MalariaGEN), a global network of malaria researchers that have worked together over the last 20 years to build the largest dataset of human genomes yet assembled for malaria research.

In a new paper using data from over 17,000 people from nine African countries, Vietnam and Papua New Guinea, we explored the extent to which adaptation to malaria has left footprints in the human genome. We used a method called Genome Wide Association Study (GWAS) which compares the DNA of people who have suffered from severe malaria with a control set of people who did not have the disease. The concept of a GWAS is straightforward: you scan these two groups of genomes to

look for systematic differences in the genetic code between the malaria cases and the population controls. In practice though this is incredibly difficult as there are many places in the genome where these two groups might differ for reasons that have nothing to do with malaria. Nevertheless, with appropriate care, it is possible to identify regions of the genome where such differences occur, and these provide evidence of association with malaria susceptibility and hint that they might have played a role in evolution against malaria.

Blood cell evolution

Our GWAS found five regions of the genome with convincing evidence of association with malaria. Encouragingly, four of these regions contained genes involved with blood cell formation and function, which one might expect given that this is where the parasites attack. The most compelling case for genetic association with malaria is the gene controlling sickle cell trait, mentioned above. Individuals with this trait were up to ten times less likely to get malaria than those without. We found further evidence of protection from malaria at the gene that controls the main human ABO blood groups. Our analysis supports previous work that has shown that being blood group O in Africa offers some protection from severe malaria. But this association is complex, and strangely, you are at a greater risk of contracting severe malaria in Papua New Guinea with this blood group. Our analysis also corroborated our recent discovery that the individual's carrying the Dantu blood group are protected from malaria. This blood group is rare however, and currently mainly found in people from East Africa, particularly Kenya.

Whilst we are confident that all five of these regions are associated with malaria, together they only account for about 10% of the genetic contribution to malaria susceptibility. Given the size of the dataset this a conundrum: it suggests that although we know that there are more genetic variants that influence an individual's malaria susceptibility, we

don't know what they are. One possibility is that malaria susceptibility is controlled by many genetic variants spread across the whole genome, each with a small individual effect. This so-called polygenic model of adaptation is increasingly being used to explain predisposition to a number of diseases, and although our method is less good at picking up these types of signal, it's an avenue for future work. Another possibility is that variation in especially complex regions of the genome, that are hard to access using our current data, is involved. Finally, it's also possible that the parasite has itself evolved to overcome human adaptation in an evolutionary arms race. Parasites and humans may have been adapted to each other in slightly different ways in different parts of the world, so the mutations that help against the parasite in East Africa might not be so helpful in West Africa. Future work is planned to explore the fascinating idea of human-parasite coevolution.

So, have the loci we've discovered been driven to high frequency by natural selection, as Haldane suggested? Well yes and no. We found that these variants are systematically more likely to be found in individuals from sub-Saharan Africa than from regions where malaria has been less prevalent, showing how the genomes of Africans have been shaped through millennia of onslaught from the malaria parasite. But the variants themselves are quite different to each other, with some being very rare except in specific geographical locations, and some found at high frequency all over the globe. This suggests that further factors might be at play. Our paper highlights the potential advances in understanding that large, coordinated data sharing networks can provide in the battle against this most ancient foe.

The full paper, 'Insights into malaria susceptibility using genome-wide data on 17,000 individuals from Africa, Asia and Oceania,' can be read in *Nature Communications*.

More information: undefined undefined. Insights into malaria

susceptibility using genome-wide data on 17,000 individuals from Africa, Asia and Oceania, *Nature Communications* (2019). DOI: 10.1038/s41467-019-13480-z