Genome secrets of elusive human malaria species revealed

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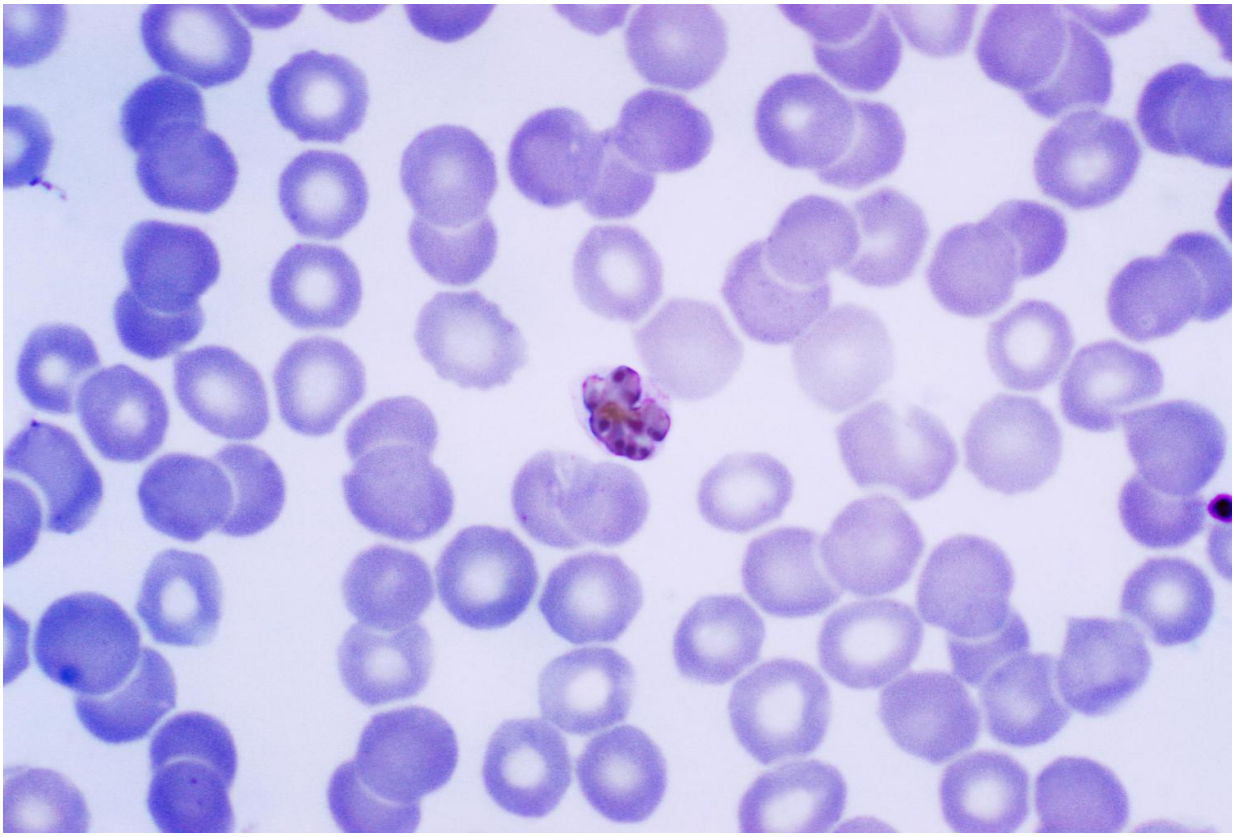

This photomicrograph shows a mature Plasmodium malariae schizont within an infected RBC. This mature P. malariae schizont is contained within a normal sized RBC. The parasite contains 6-12 merozoites with large nuclei, and has a coarse, dark brown pigment. Credit: CDC/Dr. Mae Melvin

The genomes of the two least common species of human malaria parasites are revealed today in *Nature* by a team of scientists from the Wellcome Trust Sanger Institute and their international collaborators. These sequences will enable improved surveillance and diagnosis of these rarer parasites that still cause more than 10 million malaria cases every year.

The research has important implications for malaria eradication worldwide, and casts light on a malaria vaccine target.

Malaria is caused by *Plasmodium* parasites, which are spread to humans by mosquitos. The genomes of three human infective *Plasmodium* species are relatively well studied, especially *P. falciparum*, the most common malaria parasite. However, very little was known about *Plasmodium malariae* and *Plasmodium ovale*, which are believed to cause up to five per cent of malaria worldwide, corresponding to approximately 10 million cases annually. These species can remain hidden in the host for years.

The researchers determined the genome sequences of these *Plasmodium* parasite species. By comparing these new genomes with those of the malaria parasites already sequenced, the researchers were able to identify genes that could be involved in human infection and in adapting to the human host. They found that up to 40 per cent of the *P. malariae* and *P. ovale* genomes contain genes that are probably involved in evading an immune response.

The study revealed that *P. malariae* contains two new families of genes that are similar in shape to a vital gene in *P. falciparum*, known as RH5. This gene is essential for the *P. falciparum* parasite to invade human red blood cells and is one of the top targets for malaria vaccine design. It is likely that the novel *P. malariae* genes are also involved in binding to host cell receptors.

Gavin Rutledge, first author on the paper from the Wellcome Trust Sanger Institute, said: "It is really hard to study these parasites because we can't grow them in the lab. Here, we isolated the parasites from blood samples of malaria patients and determined these final Plasmodium genome sequences. This will help us understand the evolution of the Plasmodium species, and maybe even give us an idea which routes to drug resistance these parasites may possess."

Professor James McCarthy from QIMR Berghofer Medical Research Institute, said: "Although they are less lethal than Plasmodium falciparum, the rarer malaria species are likely to be much more difficult to eliminate. Better tools to diagnose these parasites, as well as drugs and vaccines to control them will be essential. These new genomes should now make it possible to develop improved diagnostic tools for these Plasmodium species, to ensure that drugs work against them and to assist vaccine development."

P. ovale actually consists of two distinct species, *Plasmodium ovale* wallikeri and Plasmodium ovale curtisi. The authors showed that the split between these species was ancient and occurred long before the much more virulent *P. falciparum* emerged. The researchers also sequenced *Plasmodium* parasites taken from chimpanzees living in a sanctuary in Gabon. They compared these with the human samples, and existing data from other Plasmodium parasites that also infected chimpanzees, offering insights into how malaria parasites have adapted to different host species.

The new genetic information is already available for other scientists in the malaria research community to use via the Sanger Institute GeneDB database or the European Nucleotide Archive at the European Bioinformatics Institute.

Dr Thomas Dan Otto, lead author from the Sanger Institute, said: "This

study provides long awaited reference genomes for the malaria research community. The parasites are present in malaria zones worldwide yet researchers have limited knowledge about their biology. The genomes of these more neglected species will enable the development of tools to study malaria transmission and spread, which will be essential to achieve the goal of complete malaria eradication."

More information: Plasmodium malariae and P. ovale genomes provide insights into malaria parasite evolution, *Nature*, nature.com/articles/doi:10.1038/nature21038

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