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How malaria is shaping the human genome

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For millennia, malaria has been a major killer of children in Africa and other parts of the world. In doing so, it has been a major force of evolutionary selection on the human genome.

Research by an international consortium that includes members from The University of Western Australia has found that small genetic changes result in improved survival against malaria, and that children carrying these genes have a better chance of passing them on.

Associate Professor Laurens Manning, Winthrop Professor Timothy Davis and Dr Moses Laman from UWA together with Papua New Guinean collaborators contributed clinical data and genetic material from PNG, the representative site in Oceania.

For the first time, researchers have seen a biological trade-off through different forms of the same disease. The finding highlights the complexity in the way the human genome may have been shaped by malaria and other infectious diseases.

The researchers found that genetic variants become balanced in the population if there is a downside to carrying the gene. Sickle cell haemoglobin (HbS) is considered a classic example of this process whereby children carrying one copy of the gene are almost completely protected from cerebral malaria, a very severe form of malaria that has a mortality of around one in five children affected. However, if a child has two copies of the genetic variant, they develop sickle cell disease and usually die before adulthood.

It is highly likely that other genetic variants exist. Indeed, many other genetic variants, or polymorphisms have been reported as associated with susceptibility or protection from malaria. But other than HbS, most of these have shown discordant results or haven't been replicated elsewhere.

The Malaria Genomic Epidemiology Network (MalariaGEN), led by Professor Dominic Kwiatkowski from the Welcome Trust Centre for Human Genetics in Oxford, is a large, multicentre case-control study of severe malaria. Previously reported associations of genetic variants have been reappraised at 12 sites in 11 countries enrolling nearly 12,000 children with severe malaria and comparing their genes with 17,000 controls without severe malaria.

The results published online in *Nature Genetics* last week demonstrate that associations for many previously reported genetic variants have not been replicated. Strong and consistent protective effects were observed for HbS (86%), blood group O (26%) and three other genes (ATP2B4, HbC and CD40L). The most striking finding however was in a gene

encoding glucose-6-phosphate dehydrogenase (G6PD). Although there was no effect overall, Children carrying the deficiency variant of G6PD were protected from cerebral malaria but susceptible to severe anaemia, another form of severe malarial disease.

Provided by University of Western Australia

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