Genes that protect African children from developing malaria identified

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Credit: CDC

Published today in *Nature*, the findings detail a new gene locus that can explain why, in communities where everyone is constantly exposed to malaria, some children develop severe malaria and others don't. Now, researchers can be sure that this particular stretch of our DNA plays a crucial role in the progression of the disease.

In 2013, the World Health Organisation estimated that worldwide 584 000 people died from malaria, 90% of which were children under five living in Africa, while 198 million were infected.

The research was conducted by MalariaGEN, an international network of scientists and clinicians spread across Africa, Asia and other malaria-endemic regions of the world, largely funded by the Wellcome Trust. In this study they analysed data from eight different African countries: Burkina Faso, Cameroon, Ghana, Kenya, Malawi, Mali, The Gambia and Tanzania.

To identify the new locus, researchers performed a genome-wide association study (GWAS) that compared the DNA of 5,633 children with severe malaria with the DNA of 5,919 children without severe malaria. They then replicated their key findings in a further 14,000 children.

The new locus they have identified is near a cluster of genes which code for proteins called 'glycophorins' that are involved in the malaria parasite's invasion of red blood cells. Although many different malaria resistance loci have been postulated over the years, this is one of very few that have stood up to stringent testing in a large multi-centre study; the others include the genes for sickle cell and the O blood group.

A particularly strongly-protective variant, known in genetics as an 'allele', was found most commonly among children in Kenya in East Africa. Having this allele reduces the risk of severe malaria by about 40% in Kenyan children, with a slightly smaller effect across all the other populations studied. The authors speculate that this difference between populations could be due to the genetic features of the local malaria parasite in East Africa.

Researchers have known for decades that the glycophorin cluster of

genes is highly variable, but it was not possible to show that this genetic variation was responsible for protecting people against severe malaria. Now, with improved GWAS methodology, and the ability to collect samples from across different African countries, researchers are better able to understand the complexity in the patterns of DNA and, crucially, accurately measure their effects on an individual's level of resistance to the disease.

Intriguingly, the new genetic resistance locus lies within a region of the genome where humans and chimpanzees have been known to share particular combinations of DNA variants, known as haplotypes. This indicates that some of the variation seen in contemporary humans has been present for millions of years. The finding also suggests that this region of the genome is the subject of 'balancing selection'.

Balancing selection happens when a particular genetic variant evolves because it confers health benefits, but it is carried by only a proportion of the population because it also has damaging consequences. The classic example is the sickle cell gene - people with one copy of the gene are strongly protected against malaria but those with two copies of the gene develop a life-threatening condition known as sickle-cell disease.

Professor Dominic Kwiatkowski, one of the lead authors of the paper, from the Wellcome Trust Sanger Institute and the Wellcome Trust Centre for Human Genetics, said: "We can now say, unequivocally, that genetic variations in this region of the human genome provide strong protection against severe malaria in real-world settings, making a difference to whether a child lives or dies.

"These findings indicate that balancing selection and resistance to malaria are deeply intertwined themes in our ancient evolutionary history.

"This new resistance locus is particularly interesting because it lies so close to genes that are gatekeepers for the malaria parasite's invasion machinery. We now need to drill down at this locus to characterise these complex patterns of genetic variation more precisely and to understand the molecular mechanisms by which they act."

Professor Ogobara K. Doumbo one of the co-authors from the Malaria Research and Training Center at the University of Bamako in Mali, said: "This type of discovery is made possible by a strong collaboration between malaria investigators in the field and northern collaborators who have the technology platform and the capacity to analyse big data.

"These findings provide new insights into the human and plasmodium genetic interaction that are determined by their co-evolution. How these findings could be used in public health settings, as a marker of individual and population risk of malaria infection, is the next step. Applying the findings in this way will only be possible by training a critical mass of African scientists in genomics and big data management and analysis. Both are addressed by the MalariaGEN Consortium and the next Wellcome Trust DELTAS Africa programmes."

Professor Kevin Marsh, a co-author of the study from the Kemri-Wellcome Research Programme in Kilifi, Kenya, said: "This work is an excellent example of how genuine large-scale collaboration can tap into the power of modern genomic science. The risk of developing severe malaria turns out to be strongly linked to the process by which the malaria parasite gains entry to the human red blood cell. This study strengthens the argument for focusing on the malaria side of the parasite-human interaction in our search for new vaccine candidates."

More information: A novel locus of resistance to severe malaria in a region of ancient balancing selection, *Nature*, dx.doi.org/10.1038/nature15390

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