Putting an Old Hypothesis to the Test

Scientists have known for years that having sickled red blood cells can protect humans against malaria because sickled red blood cells are harder for the malaria-causing parasite to infect. **Sickle cell trait,** the phenotype associated with having one sickle cell allele and one normal allele (genotype *HbAS*), is an example of **heterozygote advantage** because in an environment where malaria is common, being homozygous in either direction—either having all sickled red blood cells (*HbSS*) or having all no sickled red blood cells (*HbAA*)—is a disadvantage. It is therefore unsurprising that scientists have observed a high rate of sickle cell anemia among populations living in areas where malaria is very common. (After all, what happens when two carriers for sickle cell anemia have children together?) What might be surprising, however, is that although scientists have understood the importance of the link between malaria and sickle cell anemia for many years, it wasn't until 2015 that a group of researchers set out to gather firsthand data.

Before 2015, most of the data that scientists had used was taken from historical records of malaria prevalence. To get a more up-to-date picture, a group of scientists from the Research Institute for Development (IRD) in France undertook an epidemiological study to observe the patterns of health and disease with relation to sickle cell anemia and malaria in the Republic of Gabon (see **Figure 1**). **Epidemiology** is a branch of medicine that studies the factors influencing health and disease in populations. In this case, the researchers were curious about whether sickle cell anemia and malaria occur in the same places. Their prediction was that they would, because the presence of malaria favors individuals with sickle cell trait, and when two individuals with sickle cell trait have children, there is a 25% chance that the child will have sickle cell anemia.

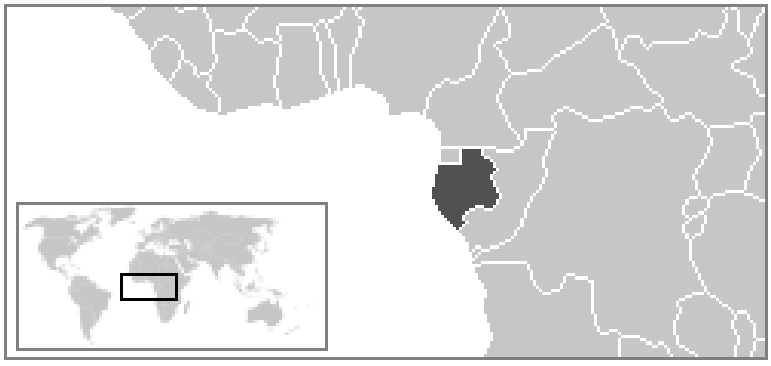


Figure 1. Republic of Gabon. Map shows the location of the Republic of Gabon in western Africa. *Source:* Modified from Wikimedia Commons.

To test their prediction, the scientists randomly selected 220 villages out of the 2,056 villages that comprise Gabon. Within these villages, they screened 4,349 blood samples for both malaria infection and the presence of sickle cell anemia or sickle cell trait. To test for malaria infection,

the researchers extracted all the DNA contained in the blood samples and looked for parasite DNA. If parasite DNA was present, it indicated an infection. To screen for sickle cell anemia and sickle cell trait, the researchers broke open the red blood cells to analyze the hemoglobin found within. Why didn't they just look at red blood cells under a microscope? Well, it turns out that blood cells don't always look the same after they're taken out of the body. To ensure that they were properly distinguishing between sickling and normal red blood cells, the researchers had to directly analyze the hemoglobin.

The researchers found evidence that supported their prediction: The more malaria was in a population, the more likely it was that members of that community carried one or more copies of the sickle cell anemia allele. That is, wherever malaria infections occur, sickle cell anemia tends to be passed from generation to generation more often. The study not only confirmed previous data, but was the first large-scale epidemiological study of sickle cell and malaria in a modern population. Researchers were able to look for both diseases in the same samples, rather than relying on historical data for one or the other. Their findings provided the strongest evidence yet in support of the link between malaria and sickle cell anemia.

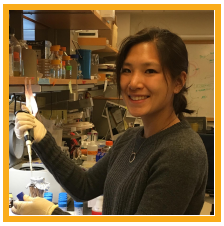
And so, the short answer to why sickle cell anemia has not disappeared from the population is that having sickle cell trait protects against another deadly disease. In this way, an infectious disease—malaria—has shaped human evolution by favoring individuals with sickle cell trait. Thus, when rates of malaria rise, rates of sickle cell anemia rise. It seems safe to infer, therefore, that a dramatic decrease in the occurrence of sickle cell anemia is likely dependent on finding a way to completely get rid of malaria and prevent it from coming back.

References

Elguero, Eric, Délicat-Loembet M. Lucrèce, Virginie Rougeron, Céline Aranthay, Benjamin Roche, Pierre Becquart, Jean-Paul Gonzalez, Dieudonné Nkoghe, Lucas Sica, Eric M. Leroy, Patrick Durand, Francisco J. Ayala, Benjamin Ollomo, François Renaud, and Franck Prugnolle. 2015. "Malaria continues to select for sickle cell trait in Central Africa." *Proceedings of the National Academies of Sciences of the United States of America* 112(22): 7051–7054. doi: 10.1073/pnas.1505665112

Piel, Frédéric B., Anand P. Patil, Rosalind E. Howes, Oscar A. Nyangiri, Peter W. Gething, Thomas N. Williams, David J. Weatherall, and Simon I. Hay. 2010. "Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis." *Nature Communications* 1:104. doi: 10.1038/ncomms1104.

BiteScientist Profiles



Katherine J. Wu is a staff writer at The Atlantic, where she covers science. She's also a senior editor at The Open Notebook, and a senior producer for The Story Collider. She completed her PhD at Harvard University, studying the microbes that cause the lung disease tuberculosis.

Emily Berman's research at Wesleyan University focused on how women with affective disorders make decisions and take risks. Emily also spent time doing ecology and conservation fieldwork in Ecuador, specifically around the impacts of environmental education. She currently teaches at Blackstone Academy Charter School in Pawtucket, Rhode Island.