Researchers uncover genetic factors for severe Lassa fever

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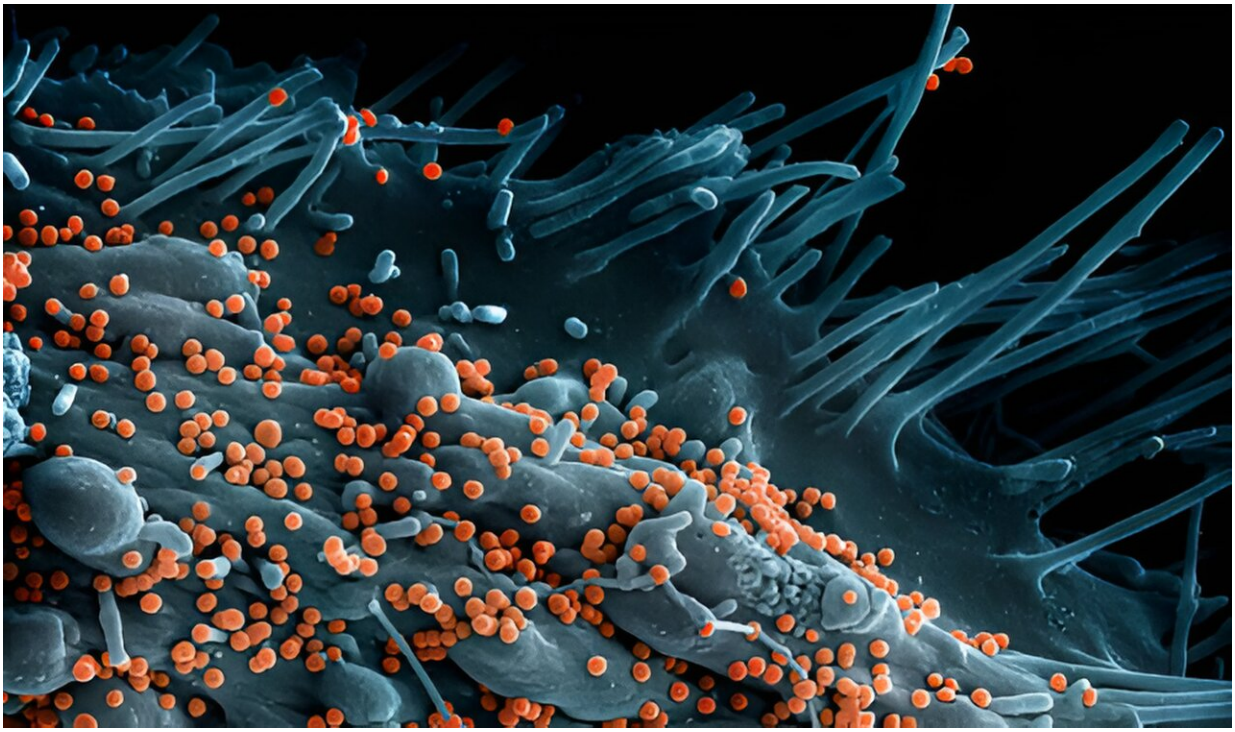

Scanning electron image of the Lassa virus budding off a cell. Credit: NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland

While combing through the human genome in 2007, computational geneticist Pardis Sabeti made a discovery that would transform her research career. As a then-postdoctoral fellow at the Broad Institute of MIT and Harvard, Sabeti discovered potential evidence that some

unknown mutation in a gene called LARGE1 had a beneficial effect in the Nigerian population.

Other scientists had discovered that this gene was critical for the Lassa virus to enter cells. Sabeti wondered whether a mutation in LARGE1 might prevent Lassa fever—an infection that is caused by the Lassa virus, is endemic in West Africa, and can be deadly in some people while only mild in others.

To find out, Sabeti decided later in 2007, as a new faculty member at Harvard University, that one of the first projects her new lab at the Broad would take on would be a genome-wide association study (GWAS) of Lassa susceptibility. She reached out to her collaborator Christian Happi, now the Director of the African Center of Excellence for Genomics of Infectious Diseases (ACEGID) at Redeemer's University in Nigeria, and together they launched the study.

Now, their groups and collaborators report the results of that study in *Nature Microbiology*—the first ever GWAS of a biosafety level 4 (BSL-4) virus. The team found two key human genetic factors that could help explain why some people develop severe Lassa fever, and a set of LARGE1 variants linked to a reduced chance of getting Lassa fever. The work could lay the foundation for better treatments for Lassa fever and other similar diseases. The scientists are already working on a similar genetics study of Ebola susceptibility.

The paper also describes the many challenges the team had to overcome during their 16-year collaborative effort, such as studying a dangerous virus and recruiting patients with a disease that is not well documented in West Africa. Dozens of scientists contributed to the work and spent seven years recruiting patients in Nigeria and Sierra Leone and many additional years establishing the research program and analyzing the results.

"It truly took a village to get this done," said Happi, a co-senior author along with Sabeti.

"Generations of people in our labs, across different institutions and countries, spent significant parts of their careers bringing this to fruition," added Sabeti.

The co-first authors of the study are Dylan Kotliar, an internal medicine resident at Brigham and Women's Hospital and an MD/Ph.D. student in Sabeti's lab while the project was ongoing; Siddharth Raju, a graduate student in Sabeti's lab; Shervin Tabrizi, a postdoctoral researcher at the Broad; and Ikponmwosa Odia, a researcher at Irrua Specialist Teaching Hospital in Nigeria.

Lassa learnings

Sabeti recalls the team's early discussions when launching the project. They knew they had to be cautious at every step: To work with a BSL-4 virus, scientists must wear pressurized suits connected to HEPA-filtered air in a special containment lab. The virus causes fever, sore throat, coughing, and vomiting, but can quickly progress to organ failure in some people.

"This was an extremely challenging study to get off the ground," said Kotliar, who worked on the project throughout his entire Ph.D. in the Sabeti lab. "I think the battle scars, the things we've learned along the way about how to get a project like this done, are going to be important for future research into viruses in developing countries."

Finding participants for the study would be challenging too. There are currently no FDA-approved diagnostics for Lassa, and Lassa virus cases are typically not documented. There are fewer than 1,000 cases reported each year in Nigeria, the most populous country where the virus is

endemic, and cases are often in rural areas far from diagnostic centers, many of which don't have the technology to detect the virus.

Infections with other viruses, and genomic complexity among different strains of the same Lassa virus can complicate analysis. Moreover, African populations have been historically underrepresented in past genetic studies, which reduces statistical power in data analyses and can make it difficult to identify key genetic variants.

When Sabeti began thinking about how to start the project, she reached out to Happi, whom she knew through their mutual work on the malaria-causing pathogen Plasmodium falciparum. With the help of collaborators including Peter Okokhere, a doctor treating Lassa patients at the Irrua Specialist Teaching Hospital, they began recruiting patients from both Nigeria and Sierra Leone. Then, they compared the genomes of about 500 people who'd had Lassa fever and nearly 2,000 who hadn't.

In the Nigerian cohort, the team found that people with a set of variants in the LARGE1 gene—which modifies a cell receptor that binds to certain viruses—were less likely to get Lassa fever. Sabeti, Happi, and their colleagues also found genomic regions associated with Lassa fatality: in the LIF1 gene, which encodes an immune-signaling molecule, and, in the Nigerian cohort, the GRM7 gene, which is involved in the central nervous system. The team then used a large-scale screen called a massively parallel reporter assay to home in on which variants within these genomic regions might be functional and could be targets of new treatments.

Better detection

The researchers say that to improve detection and treatment of Lassa fever, more diagnostic centers and diagnostics that work in the field are needed, along with better health infrastructure to connect remote

locations with major hospitals.

"This really highlights the need for continued investment in understanding African population genetics," added Raju. "Even with a relatively limited sample set, we've increased our understanding of some African populations, specifically in immune-related genes—and that shows how much more there is to do going forward."

Sixteen years after they first started thinking about the genetics of Lassa fever, Sabeti and Happi are excited about the study's findings, which could explain the biological differences between mild and severe illness. They said the work also shows that through thoughtful collaborations between countries, genome-wide association studies of BSL-4 viruses are possible. The researchers have already begun conducting a similar study of Ebola in Sierra Leone and Liberia, and other scientists are calling for increased pathogen surveillance and scientific training in Africa.

"We're standing at a moment where we can actually start developing point-of-need diagnostics for Lassa virus and testing much more broadly," Happi said. "We need better infrastructure, but I think we've shown that this kind of study is a worthwhile pursuit."

More information: Dylan Kotliar et al, Genome-wide association study identifies human genetic variants associated with fatal outcome from Lassa fever, *Nature Microbiology* (2024). DOI: 10.1038/s41564-023-01589-3

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