Genetic differences key to why sub-Saharan Africans have lower rates of COVID infections and fewer severe cases than other population groups

hy did COVID-19 impact certain populations more than others?

That mystery is slowly coming into focus. For the first time, genetic researchers are including ethnically diverse Africans rather than exclusively investigating European whites or Asians, which is typical of most genome-wide COVID studies to date. According to the University of Pennsylvania, scientists at Penn have found 41 variants in the ACE2 gene, one of the genes linked to SARS-COV-2 infections, that could have impacted who contracted the virus and its severity. And Africans are far more likely to have these variants than any other population group yet studied.

“Although these variants were rare when the team looked at the pooled global population,” wrote Penn’s Katherine Unger Baillie, “among a population of Central African hunter-gatherers three variants were common.”

Some news outlets reported these findings as a “breakthrough”, but this is not news to the Genetic Literacy Project. The GLP has produced multiple reports over the past two-and-a-half years documenting evidence that there are population-linked genetic components that impact contracting the disease or protecting COVID victims from more severe outcomes. And those gene proclivities are not random. Despite predictions by the UN and other global agencies that Africa was likely to face a ‘disease Armageddon’, in part because of its poor health facilities, sub- Saharan African populations faced far lower rates of COVID infections than any other region in the world — less even than China which imposed a vigorously-enforced shutdown in an attempt to contain the disease.

(As the GLP article explains, the relatively higher rates of COVID infections among blacks in the US can be explained in most part because they are a much older population cohort and their health profiles, because of social conditions, are on the whole particularly poor.)

Three months after the US declared the virus a pandemic, in May 2020, the GLP ran the first of a series of articles offering a science-based explanation for why Africa had emerged as the global ‘cold spot’ for contracting or dying from the fast-spreading virus. We analyzed a host of genetic factors, including the fact that Africans are much more likely to carry more protective variants of the ACE2 gene than any other population cohort. The GLP article posed this question:

> *Despite the fact that the social conception of ‘race’ does not neatly mirror human biological differences, could genetic factors based on population differences thousands of years in the making account for some of the difference in health outcomes between different human groups?*

What’s ‘race’ got to do with it? Sub-Saharan Africa emerges coronavirus ‘cold spot’, offering clues to develop COVID-19 vac

Given the odious racist history of biological beliefs about human differences, this was a fraught question to ask. But the startling global differences in how different regions experienced the COVID crisis, it's an issue that needs answering. Although geneticists and the general population generally avoid using the term "racial" to characterize disease proclivities that show up more in one population than others, ancestry matters.

Perhaps the 'racial' components helps explain why, over the past three years, so many scientists have side-stepped exploring a genetic connection to explain at least part of the sub-Saharan African mystery. But not all. More than two years before the University of Pennsylvania claimed that its 'breakthrough' study had identified a link between COVID-19 and the dozens of variants of the ACE2 receptor gene — scientists had already found links between COVID and a variety of genetic factors, including the ACE2 receptor gene in the lungs.

"A number of ACE2 variants could reduce the association between ACE2 and S-protein in SARS-CoV," a team of Chinese scientists reported in a study published in February 2000.

A few months later, in May, a research team at the University of Hawai'i Cancer Center announced that it too was examining the role of variants of the ACE2 gene and its links to specific population groups. "Epidemiological studies indicate that populations carry different variants of the ACE2 gene," said Maarit Tiirikainen, an associate professor at the University of Hawai'i M?noa, who partnered on the study.

> *This variation in the gene coding for the ACE2 receptor may have an effect on the number of ACE2 receptors on the lung cells, as well as on how effectively the virus binds to the receptor. There may also be genetic differences in immunity and other important genes explaining why some people get more sick than others.*

"Based on genetics, certain individuals and populations may be impacted more severely," said Cyril Moukarzel, CEO of LifeDNA, a partner in the University of Hawai'i study.

Only one news outlet in Hawai'i—and the GLP—picked up on this apparently taboo twist, and no other research centers explored this population-linked explanation. A broad research effort could have saved perhaps millions of lives. In a follow up article in March 2021 published simultaneously by the GLP and Quillette, we pointedly asked (and answered): "Why are we afraid to talk about" these racial, population-based differences?

Quillette

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Taboo: Why Is Africa the Glob
COVID 'Cold Spot' and Why A
Afraid to Talk About It?

Penn scientists confirm previous studies linking population genetics to COVID

If the University of Pennsylvania study is any indication the taboo is finally breaking. It is one of the first major research centers to address population-based factors influencing COVID disease proclivities. Researchers recently identified four genes critical to SARS-CoV-2 infection, including the ACE2 gene, that were targets of natural selection and associated with health conditions seen in COVID-19 patients. According to the news release. The study included “ethnically diverse Africans and a highly diverse dataset from the Penn Medicine BioBank. Including these often-overlooked groups revealed new variants that may be clinically significant”.

According to Sarah Tishkoff, a co-corresponding author on the work and a Penn Integrates Knowledge University Professor with appointments in the Perelman School of Medicine and the School of Arts & Sciences, the research team focused on :signatures of natural selection to identify functionally important variants that impact health and disease. Nature has already done a lot of the screening and can give us clues as to what parts of a gene like ACE2 are important for infection.”

Dr. Sarah Tishkoff is a co-author of the study. Credit: University of Pennsylvania

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Signals of selection

The researchers used genomic data from 2,012 ethnically diverse Africans, including people who practice traditional hunter-gatherer, pastoralist, and agriculturalist lifestyles, as well as 15,977 people of European and African heritage from the Penn Medicine BioBank.

As Baille reported, “Looking for variations in these genes that showed evidence of being selected through evolutionary time, the researchers found 41 variants in the ACE2 gene that affected the amino acid sequence of the protein. Although these variants were rare when the team looked at the pooled global population, among a population of Central African hunter-gatherers three variants were common.”

Tishkoff elaborated on how African roots likely played a key role in this evolutionary process:

> *This is a group that lives in a tropical environment and continues to forage for bush meat, spending a lot of time in the forest,” Tishkoff said. “They’re likely exposed to all kinds of viruses introduced from animals. And, of course, SARS-CoV-2 is believed to have jumped from an animal to humans. So even though this population wouldn’t have been exposed to this exact virus in the past, they could have been exposed to similar types of viruses.*

The variants offered protection against viruses with similarities to SARS-CoV-2. “From an African and specifically Central African perspective, the discovery of three non-synonymous variants at ACE2 in Cameroonian indigenous populations is significant,” the article quotes Alfred K. Njamnshi, a coauthor and professor of neurology and neuroscience at Cameroon’s University of Yaoundé. “The regulatory variants found at ACE2 do suggest targets of recent natural selection in some African populations, and this may have important disease risk or resistance implications that warrant further investigation.”

The ACE2 variants likely not only reduced the number of Africans from contracting COVID, they also appear to contain the severity. Why was COVID so much milder across Asia? The researchers found “ variations in the ACE2 regulatory region that may increase ACE2 expression, which could influence the degree to which SARS-CoV-2 infects host cells”.

“To know for sure, we need to test the function of this variant and see whether we can get some indication that changes in this region are related to COVID infection susceptibility and severity,” said Yuanqing Feng, another Tishkoff lab postdoc who shared first authorship on the paper. Researchers also found hat the “ACE2 receptor does not only play a role in binding to the SARS-CoV-2 spike protein; it is also involved in blood pressure regulation, and thus variants may affect health outside of just COVID infection.”

The next step, already underway at Penn, is to apply this focused research to better understand how specific genetic variants are associated with a host of linked conditions, including respiratory disorders, infection with respiratory syncytial virus, and liver disease.

“From a medical point of view, you could identify novel therapeutic targets, or even provide some personalized medicine depending on which variants a person had,” said Giorgio Sirugo is a clinician scientist and senior research investigator in Penn’s Perelman School of Medicine.

The researchers emphasized how critical it was to look at populations to help identify genetic patterns of disease. Some of the clinically significant variants were only identified in populations—in this case sub-Saharan Africans— that had not been investigated in this way previously.

“That is a deeply important and unique aspect of this study,” Tishkoff said.

Read the original University of Pennsylvania news release here