Scientists pave way for potential cure for severe kidney disease disproportionately affecting Black individuals

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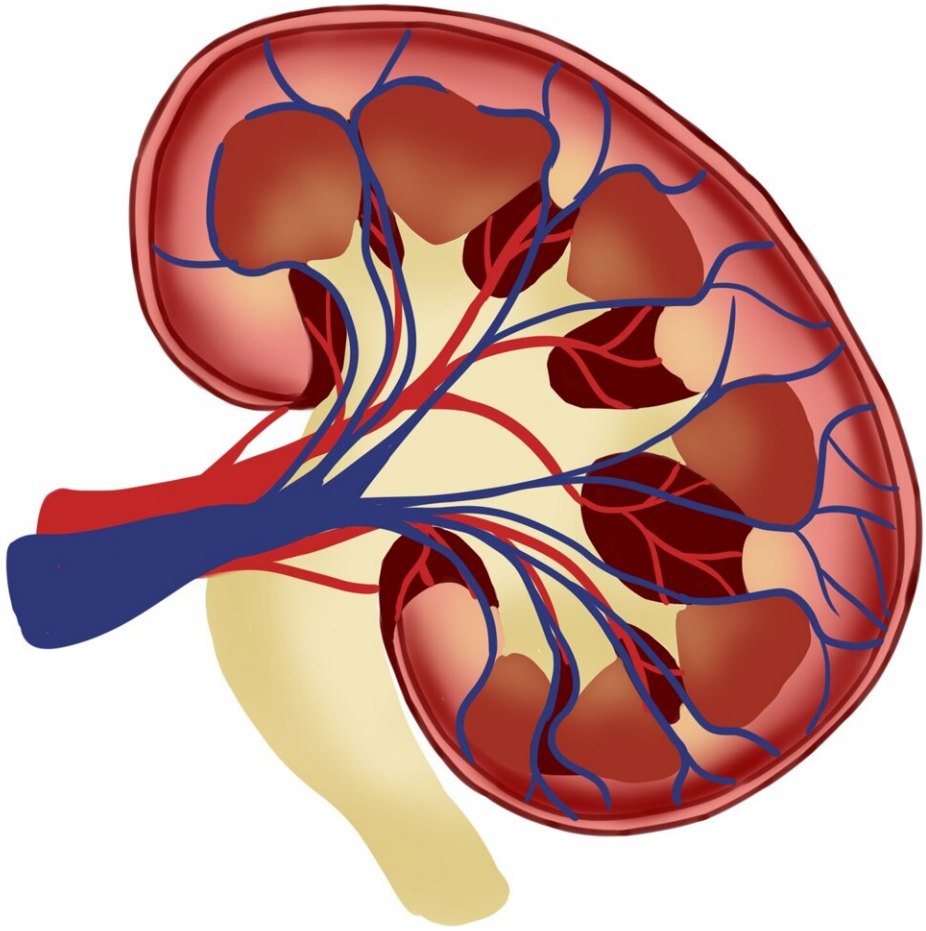

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Today in the United States, about two out of every 1,000 people live with kidney failure. For every one white person who develops the disease, three Black people do. Kidney failure, also known as end-stage renal failure or end-stage kidney disease, is the irreversible loss of kidney function. Regular dialysis or kidney transplant are the only therapies currently available.

Now, an investigational molecule has been shown to improve kidney function in people with one form of chronic kidney disease in a small phase 2 clinical trial. The molecule targets two gene variants that increase the risk of developing kidney disease in people who carry them. These two gene variants—carried by 12% of Americans with recent African ancestry—were identified by BIDMC's Martin Pollak, MD, and David Freidman, MD, in 2010, who are also advisors on the recent clinical trial. Their findings are published in the *New England Journal of Medicine*.

We asked Dr. Pollak, who is chief of the Division of Nephrology at BIDMC, about the journey from research question to potential cure.

Q: You and your colleague Dr. Friedman reported the link between these gene variants and increased risk of kidney disease in 2010. Much of the research on the disproportionate burden of kidney disease among Black Americans focused on social determinants. What made you look into genetic factors?

There was this persistent question of why is severe kidney disease so much more common in Black individuals than in other groups. There was some evidence to suggest that there was a strong genetic component, including the way disease clustered in families. Then, two papers

published in 2008 suggested that a lot of the risk was attributable to something in a genetic region on chromosome 22. We weren't directly involved in that work, but that got us very interested in trying to define the specific genetic drivers for this disease.

Clearly genetics and social determinants both play a role—these aren't opposing views at all. About 12% of people who identify as Black have this APOL1 genotype and certainly not all of them get kidney failure. Meanwhile, not everyone who is Black and has kidney failure has this genotype. So we know the social determinants of health—less access to high quality health care, environmental contributors, economic stability, etc.—are also a factor here. The genotype does increase the risk tremendously, and the risk is then compounded by those social determinants of health.

Q: Your team's hypothesis is that the two gene variants common among people of recent African ancestry may have evolved to protect against parasitic disease, but that survival advantage came with an increased risk of kidney disease. It's analogous to the way the genes for sickle cell anemia help protect against malaria, but cause their own set of health concerns. What evidence led you to this idea?

A very smart post doc, Giulio Genovese, noticed these statistical patterns that suggested that natural selection was acting differently on these variants (or alleles) that carry risk than on non-risk alleles at this locus. The risk-alleles were brought to relatively high-frequency in the population very quickly. That was probably because of natural selection; that is, those alleles conferred a survival advantage, so evolutionary pressures were acting on them.

Q: What is it the risk alleles do to prevent disease and/or injure kidneys?

A lot of those details still are not really clear—we're still conducting experiments to answer those questions. We are all protected against the African trypanosome parasite, called T. brucei. It doesn't cause human disease because we have this protection against it. The parasite gets in the blood stream through the bite of a tsetse fly. It seems as though (the gene product) APOL1 circulates in the blood and gets taken up by these parasites. APOL1 inserts itself into the cell membrane of the parasite and causes it to die, to lyse, by creating a pore or a channel in the cell membrane that is not compatible with the parasite living.

But, there are sub species of the trypanosome parasite that cause really serious human disease. The presence of these gene variants expand the protection provided by APOL1. We are not yet sure precisely how the mechanism works.

Q. This is a research project with an extraordinary outcome. Has it been a typical scientific process?

The moment we realized it was these two variants driving disease—that was sort of an unusual milestone in the journey. But overall, the work has been mostly incremental progress in understanding how these variants actually cause human disease.

This has been a highly collaborative process from the start. We've worked with teams across BIDMC, the National Institutes of Health, Vertex and beyond. We've been aided by efforts of the human genome project, the thousand genomes project, sequencing and genotyping technologies. While it would have been possible to figure it out 10 years earlier, it definitely would have been harder. If we hadn't figured it out,

someone else would have. It was there to be figured it out.

Q: But you and your team are among the major contributors. What does that feel like?

Feels good! This published study is still early—we don't know whether or not the results will be replicated in bigger studies. However, this work shows that understanding genetics can lead to better treatment. It shows this should be a form of kidney disease we can treat with personalized medicine. I am pretty optimistic.

Q: What happens next?

We will be advisors to phase 3 follow-up experiments and we'll continue to do research collaboratively. My colleague Dr. Freidman and I are focused on trying to understand the mechanism of this disease—how do these variants actually damage the kidney. We've developed a mouse model that replicates the disease and we're also doing studies at the cellular and biochemical levels.

It's a nice example of using genetics to help inform development of therapies. I'm excited that basic research into human genetics can lead us to what may be a way to make big dent in the amount of kidney disease we see in the world. These genotypes are really a big contributor to kidney disease worldwide. I'm optimistic that we are moving toward being able to prevent and treat kidney disease much more effectively.

More information: Ogo Egbuna et al, Inaxaplin for Proteinuric Kidney Disease in Persons with Two APOL1 Variants, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2202396

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