CORONAVIRUS

What Do Your Genetics Have to Do With Your Chances of Dying From Coronavirus?

Our genes might make some of us more susceptible to COVID-19—but *which* genes? Geneticists are sharing their vast DNA databases to find out.

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Medical personnel test people for COVID-19 using rapid antibody testing kits. BY EZRA ACAYAN/GETTY IMAGES.

Six weeks ago, with little fanfare, a network of geneticists launched an obscure but potentially game-changing initiative. Their aim: to learn why people with particular DNA profiles end up dying from the coronavirus—or completely avoiding its effects. Ultimately, they want to devise ways for scientists to cook up new therapies that might alter how our nanosize genes operate as a way of reversing or accelerating the pathogen's progress. Called the COVID-19 Host Genetics Initiative, the project now involves close to 700 scientists and researchers, worldwide, who are busily comparing DNA data from pandemic victims to literally millions of existing DNA profiles of millions of people.

To appreciate how our genes might be impacted by the onslaught of COVID-19, imagine this: that a tiny, invisible bug is hovering over the surface of a cell inside your body—say a lung cell. You don't know it yet, but you've just been infected with SARS-Cov-2. Maybe it came from that jogger who whizzed past you on the sidewalk, or that tabletop you touched before rubbing your eyes. Whatever its source, there it is, circulating inside you: a fuzzy, sphere-shaped pathogen that's less than 1/1000 the width of a human hair. Prickly, with spikes on its outside, it's searching for a place to plug into and enter your cell. It's a little like a key and a lock, where the key (the virus) wants to slip into the keyhole (a receptor on the cell) and then release a payload that will be up to no good.

Except that, in some people, the virus-key doesn't fit the lock and is blocked from entering the cell. In others, it slips right in, leading to illness and sometimes to rapid deterioration and even death. One potential difference—say geneticists who are working day and night to better understand how SARS-Cov-2 invades and attacks our cells—might be because your DNA code differs from mine. Yours might inherently spurn the virus at the cellular level; mine might make me more susceptible.

So what determines who gets dangerously sick? "We know that people who are older and have underlying diseases like diabetes and heart disease are at higher risk for having a bad response to COVID-19," explained **Mark Daly,** a 52-year-old geneticist and the director of the Institute for Molecular Medicine in Helsinki, Finland. Other factors include higher risk "biases" that involve ethnicity, class, vocation, geographic location, and the medical resources available at the time of treatment. And yet, according to Daly, "this doesn't explain why relatively healthy people, including young people, are sometimes having severe and life-threatening reactions" such as very high fevers, pneumonia, and difficulty with breathing that requires oxygen and sometimes a ventilator. "Most likely this has something to do with differences in their genes."

Daly should know. With his Paul Revere–like ponytail, circular hippie glasses, and lean, determined face, he's a pioneer of modern genetics who was a key player during and after the Human Genome Project, the huge international effort in the 1990s and early 2000s that sequenced the first-ever human genome. And as the pandemic has been raging, Daly, a physicist, decided to help spearhead a remarkable "hive-mind" effort: the COVID-19 Host Genetics Initiative.

THE RACE FOR THE CODE

The project was announced on March 16 in a tweet posted by Daly's cohort **Andrea Ganna:** "Goal: aggregate genetic and clinical information on individuals affected by COVID-19." The response was immediate. Within days, scientists from over 150 organizations in more than 30 countries on six continents agreed to join. That's the ideal use of "the hive mind": a conglomeration of big brains and, in this case, their disparate data sources, to solve one huge problem. Participants have come not only from Harvard and MIT (institutions with which Daly has ongoing affiliations) and the usual institutional suspects in North America, Europe, and the wealthier Asian countries, but also from the Qatar Genome Program, Vietnam's SARS-Cov-2 Susceptibility Program, and CLHORAZ—based in Burkina Faso.

The underlying quest: to identify which specific genes in a person's 20,000-plus gene sequence of DNA actually impact our response to COVID-19. By cracking the inner DNA code behind severe reactions to the virus, scientists might then be able to design better treatments and even vaccines that might modify genetically induced responses to the coronavirus. Daly and his colleagues also want to concoct a DNA test that might reliably predict if a healthy person has a genetic predisposition to becoming compromised.

"This [initiative] is happening really fast," said Ganna, who is a group leader at the Institute for Molecular Medicine—he comes from Northern Italy, where COVID-19 has been particularly harsh. "It also is completely inclusive and open. For instance, I'm helping a researcher organize a collection [of human DNA] in Kenya." Diverse DNA is key: For too many years, genetic research has favored Caucasians, without a broader picture of how the virus affects everyone.

Each partner in the consortium has agreed to assemble applicable DNA sequencing data from COVID-19 victims who, in the past few weeks, have been tested and treated in hospitals and clinics in their regions. Then, in a process called "mining," the geneticists compare each patient's DNA to corresponding data collected over the past few years from data sets in lab after lab and country after country, sometimes drawing from the DNA samples of hundreds of thousands of people in a given area.

These records include a patient's age, ethnicity, and preexisting conditions, along with their symptoms (and severity), as well as their ultimate outcome. Biobank FinnGen, which Daly helped launch, contains genetic data and medical histories of 220,000 people, collected over a three-year span. Thus far, they have identified the DNA profiles of 200 people in their database who have since tested positive for the virus. (Some 85,000 Fins have been tested for COVID-19; 4,995 came out positive; 211 have died.)

"When you combine all of the sequences from these 150-plus programs," said project partner **Robert Green,** a physician and medical geneticist at Brigham and Women's Hospital, "you start reaching numbers that can really tell you something."

THE MAGIC GENES

The hive mind is investigating some intriguing possibilities. These include a gene called ACE-2, which provides genetic instructions for our bodies to create the receptor protein (the keyhole) that sits on the surface of lung cells and other cells and is one of major entry points for the virus. "Differences in our genetic code for ACE-2," Green maintained, "may be one of the factors that's protecting us or making us more vulnerable to the virus entering our cells."

Geneticists have identified over a dozen other gene candidates. Some, like ACE-2, seem to involve the mechanisms around *how* the virus infects the body. Others impact the immune response to COVID-19. These include several genes (including ACE-2) that are located on the X chromosome. This may be one reason that twice as many men are succumbing to the disease as women. "We know that the X chromosome actually has a lot of genes involved in immune response and immunology," said **Aleksandar Rajkovic,** a pathologist and geneticist at the University of California at San Francisco. "Men are definitely more susceptible by having just one X chromosome. Women have two X chromosomes. So that offers some protection to them."

Scientists are also searching for genetic variants that can shield people from COVID-19 in the same way that a version of a gene called CCR5 prevents people who carry it from being infected by HIV, the virus that causes AIDS. About one percent of people exposed to HIV

have a rare sequence of DNA in CCR5 that seems to make them effectively immune to the virus. A slightly different version of this genetic code provides some level of defense for about 15% to 20%.

Then there is the search for the unknown—genes yet to be identified. According to Ganna, "Researchers are running 'genome-wide association studies' that look for signals coming from new genetic variants that might tell us something new about how our bodies are reacting to the coronavirus."

Six months into the pandemic, we still don't really know the reasons that the novel coronavirus is killing some people and not others, or even why many people remain asymptomatic. But in Daly's view, a clearer picture of the underlying genetics may emerge by mid- to late-summer.

In the long run, the efforts of this hive mind are likely to help us "host organisms" be in a better position to fend off future bugs—spiky or not—that will inevitably appear in the years to come.

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