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Shielded from harm

For some, covid-19 is fatal, but others have no symptoms at all. How can we predict who will get seriously sick – and how best to protect them? Carrie Arnold reports
The new coronavirus has already infected millions of people, but we are still learning about who is most vulnerable to its attacks. It quickly became clear that older people and those with certain underlying health conditions such as diabetes and cancer were at higher risk. But there have now also been many reports of the disease killing young, otherwise healthy individuals. And even among the high-risk groups, the threat that covid-19 poses varies dramatically.

What’s more, information from several countries now indicates that people from some ethnic minorities are more likely to die. So are men and people who are obese.

Meanwhile, because covid-19 attacks the lungs, we predicted that people with asthma would be among the most vulnerable. But so far, they don’t seem to be in greater danger.

Around the world, efforts to quickly identify risk factors have already helped shape public health advice and direct resources (see “Best behaviour,” page 38). But to understand why these factors make such a difference, we will need to look more closely – not just at the virus, but also ourselves.

“The disease is actually just our response to the pathogen,” says Priya Duggal, an epidemiologist at Johns Hopkins University in Maryland. To work out who gets sick and why, we need to understand what happens once the virus is inside us, and the role our genes play in our body’s response. As well as helping us to better protect the most vulnerable, doing so could guide the development of treatments that ultimately let us live with covid-19.

We tend to think of the SARS-CoV-2 virus – the spiky 85-nanometre parcel of protein and nucleic acid that causes covid-19 – as if it were its own entity. That’s a mistake, says Reid Thompson, a computational biologist at Oregon Health and Science University. “The host is required for a virus to do its work. If you changed humans into turtles, they wouldn’t be infected with SARS-CoV-2,” he says.
Like other viruses, this new coronavirus depends on a host for everything. It needs to break into our cells for food and shelter, and the ability to reproduce. Yet when it comes to understanding how such pathogens work, microbiologists have historically studied them on plates of jellied agar or in flasks of broth that smell of miso soup mixed with raw sewage. It is a strategy that can yield critical insights, but for covid-19, it leaves huge questions unanswered. The most urgent one: how many of us are catching the virus, and possibly passing it on to others, without ever realising it?

By the numbers

Estimates suggest anywhere from half to more than three-quarters of infected people show no symptoms, but until testing is more widespread, this remains a difficult question to answer meaningfully. Children seem just as likely as adults to be infected by the new coronavirus, yet far less likely to experience severe or deadly disease. There are several different hypotheses for why this might be, from the fact that children have fewer of the cell surface receptors in their airways that the virus needs to break in, to the idea that kids’ routine exposure to coronaviruses that cause the common cold provides them with crossover protection against this one.

Another possibility is that young people’s immune systems are less likely to mount an aggressive response that can spiral out of control, or that they haven’t yet been undermined by the ageing process. Indeed, the main reason that older people are thought to be more vulnerable to covid-19 is that our immune systems get weaker as we age.

Age is far from the only consideration. When epidemiologists began to examine statistics about who had been hospitalised by covid-19 and who had died, they noticed something strange: men seem worse affected. One recent analysis of data from several European countries found that men were more than twice as likely to die after infection. Last year, a different group hypothesised that oestrogen promotes a more vigorous immune response, which gives individuals who produce more of the hormone an advantage when fighting disease. The trade-off is that it may also put them at risk of autoimmune conditions such as multiple sclerosis, which disproportionally affects women.

Lifestyle factors could also influence risk for men. Because men tend to be less fastidious about handwashing, it is possible that they are more likely to get infected in the first place or to carry other viruses or bacteria that make them more susceptible to severe infection with the new coronavirus. Then there is the fact that men are more likely than women to smoke cigarettes and develop chronic obstructive pulmonary disease, both of which have been shown to increase the risk of hospitalisation and death from covid-19.

Chronic health problems, including diabetes, high blood pressure and cancer, do seem to put people at higher risk of severe disease, though the reasons why have been the subject of intense debate. The impaired immune function seen in diabetes and cancer provides a likely explanation, but the link with high blood pressure is less clear.

As of 31 March, 89 per cent of people hospitalised in the US because of covid-19 had at least one chronic health condition, according to data from the US Centers for Disease Control and Prevention (CDC). Just under half were obese and had high blood pressure. No one knows whether this represents a statistically significant difference from non-infected adults because 42 per cent of adults in the US have a body mass index over 30, the cut-off for obesity, as do 40 per cent of those hospitalised for covid-19. Obesity isn’t listed in reports from China or Washington state as one of the top 10 conditions associated with a disease caused by a related coronavirus. During the SARS outbreak, males more often wound up in an intensive care unit and were more likely to die. It was the same story with Middle Eastern respiratory syndrome (MERS), another coronavirus disease.

To investigate this trend, in 2017 Stanley Perlman at the University of Iowa carried out mouse studies of the SARS coronavirus. He and his colleagues found that male mice – and females that couldn’t produce oestrogen – were more likely to die after infection. Last year, a different group hypothesised that oestrogen promotes a more vigorous immune response, which gives individuals who produce more of the hormone an advantage when fighting disease. The trade-off is that it may also put them at risk of autoimmune conditions such as multiple sclerosis, which disproportionally affects women.

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with covid-19 mortality, yet according to some preliminary data from physicians working in New York, it may increase the risk of severe disease. As yet, it is unclear whether obesity plays a role directly, or if it is instead via its association with other chronic conditions.

One alarming trend emerging from patient data in several Western countries is the finding that minority populations make up a disproportionate number of those who become seriously ill with covid-19. The reasons don’t appear to be biological, but only 20 per cent of cases reported to the CDC specify the patient’s ethnicity, so it is hard to draw conclusions. Duggal suggests that this difference may be driven by lack of access to healthcare, medical bias and the immune-eroding stress of poverty, which is more common among ethnic minorities. All of these issues lead to a host of health disparities, including a greater prevalence of chronic diseases such as high blood pressure and diabetes, and now covid-19.

Identifying these broad trends can help guide the difficult decisions that policy-makers and public health officials are having to make as this pandemic rolls on. But to gain deeper insights that will ultimately allow us to offer more targeted protection and treatments, a growing number of researchers believe that studying the people who are exceptions to these trends may be key.

This idea dates to the genetics revolution of the late 1990s and early 2000s, when scientists began to understand how people’s DNA can make them more vulnerable – or resilient – to infectious disease.

**Immune to infection**

In the mid-1990s, teams in New York and Boston discovered that certain individuals somehow avoided infection with HIV, the virus that can lead to AIDS, despite multiple exposures via sharing needles to inject drugs or by having unprotected sex with infected partners. It turned out that people carrying certain mutations in a gene called *CCR5* were completely resistant to HIV.

The CCR5 protein wedges itself into the outer membrane of immune cells called T-cells and acts as a lock that HIV has to pick to enter. People with certain mutations of the gene that codes for this protein had unpickable

“**For HIV, some people have cells with unpickable locks. This is the kind of thing we want to find with covid-19**”

locks. This discovery, published in 1996, was a breakthrough in understanding how HIV enters cells and directed us to potent new approaches for antiviral treatments.

“These are the findings we want to move towards as we study covid-19,” says Martin Ferris, a geneticist at the University of North Carolina, Chapel Hill.

A similar approach has been taken with hepatitis C. Most people who contract the hepatitis C virus (HCV) will develop chronic infection, but about a quarter somehow clear the virus. To find out why, in 2013 Duggal made use of newly available genetic technology that enabled her to search through entire genomes. These genome-wide association studies enabled her and others to identify several genetic variations that affected whether someone could clear HCV without pharmaceutical help, and how
likely they were to respond to antiviral therapy. 

Our genes don’t just influence our vulnerability to viruses, but to bacterial infections too. “Human genetics is actually a big driver of many diseases we think are caused by a pathogen,” says Ferris. Consider *Streptococcus pneumoniae*. Pulmonologist Stephen Chapman at the University of Oxford has seen plenty of people hospitalised with pneumonia caused by infection with this bacterium, but the devastating nature of these illnesses is surprising given that one in 15 healthy adults in the UK carry the microbe harmlessly in their respiratory tracts. In his efforts to understand why, Chapman has identified several gene variants associated with immune function that influence whether these bacteria cause people harm.

“Two patients that may look quite similar on the outside can be very different on the molecular level when it comes to their immune response,” he says.

The idea that genes contribute to infectious disease risk is still new. “A physician will ask about family history of heart disease or cancer, but they never ask about infection,” says Chapman. “They just say infection is bad luck.”

Where to look

Now scientists want to use this approach to figure out who gets sick from the new coronavirus, and why. In February, Santa Clara county in California had some of the first US cases of community spread of covid-19. Alarmingly, Manuel Rivas at Stanford University in California contacted fellow geneticists Mark Daly and Andrea Ganna at the University of Helsinki in Finland, who had already started to gather genetic data from covid-19 patients.

“It made sense to pool our data and expertise,” says Rivas. When other researchers heard of the project, they wanted to contribute, so the trio launched the Covid-19 Host Genetics Initiative. It now boasts 151 studies and counting – run by more than 500 scientists around the world.

They aren’t the only ones doing this. At the Rockefeller University in New York, immunologist Jean-Laurent Casanova will focus his efforts on young people hospitalised because of the coronavirus who don’t have any conditions known to make the illness worse. Because only a tiny fraction of young adults develop the life-threatening complications of covid-19, Casanova believes that it happens because of genetic differences in immune function. This focus, he hopes, will improve his chances of identifying human genetic contributors to coronavirus severity.

Even if the mutations that cause the differences are rare, they may show us where to look in other patients, says Casanova. “Perhaps patients without this mutation are severely ill because the derailment of their physiology is similar to that caused by the mutations.”

Duggal, too, is focusing her attention on these outlier cases, sifting through whole genome data in search of relevant variations. And Ferris is turning to mice to identify genetic contributions to covid-19, a strategy he hopes
will allow him to control for environmental factors that may also play a part.

Researchers in China are also on the case, identifying links between certain blood types – which are determined by our DNA – and increased severity of disease among more than 2200 people treated for covid-19 at hospitals in Wuhan, where the virus originated, and Shenzhen. They and researchers in New York have found that people with type O blood seemed to be somewhat protected from serious disease after infection with the coronavirus.

Rivas says these preliminary studies provide some good hypotheses, but the relatively small number of patients involved and the fact that the results have yet to be peer reviewed means we can’t draw any solid conclusions (see page 12). Most genes are likely to have only a small impact on disease susceptibility, and studies in psychiatric genetics show that tens of thousands of genomes are often required to separate the signal from the noise. “This is really hard to do in the context of an ongoing outbreak,” says Ferris.

Thompson has run a computer analysis to examine potential genetic links. He and his colleagues have looked at how well small pieces of protein derived from the covid-19 virus can bind to various human leukocyte antigen (HLA) proteins, which are cell surface proteins that regulate immune system function. Put simply, the more strongly a viral protein binds to an HLA protein, the more vigorous the immune response it triggers. The team also investigated whether exposure to other human coronaviruses could provide cross-protection against the covid-19 virus.

The analysis predicted that several HLA variants might result in a more vigorous immune response, and identified others that might leave individuals more vulnerable. The team suggests that these same variants influenced response to the SARS coronavirus, and possibly other coronaviruses too. It is only very early work, but if it is confirmed, it will provide crucial hints about certain genetic vulnerabilities to covid-19.

What’s more, says Thompson, HLA analysis is cheap and readily available. Combined with reliable covid-19 testing, which is critical to determine who has been infected so that we can then evaluate their response, it could give us a powerful way to identify individuals at high risk of developing severe disease.

These are the types of tools that the world is desperately waiting for. “We’re operating in the dark here. We need to be pooling all our data to get some answers,” says Thompson.

Another aspect that geneticists are investigating has to do with how, once on the loose in our bodies, the new coronavirus gains access to our cells. To break in, the virus binds to a cell surface protein called ACE2. Smokers and people with both type 1 and type 2 diabetes and conditions such as high blood pressure seem to make more ACE2, which has raised questions about whether variations in this surface protein play a role in people being more or less resilient to severe disease.

To predict how well the covid-19 virus binds to known ACE2 variants, researchers recently analysed genomic data sets including more than 290,000 samples, and were able to identify several mutations that appear to be associated with disease susceptibility. That work still needs to be validated, too. For now, any role that these variants play in linking high blood pressure to covid-19 risk remains the subject of much speculation.

**Under pressure**

Yet many are watching this ongoing work closely, because the link between covid-19 deaths and high blood pressure, heart disease and diabetes has led to concern not just about the role of these gene variants, but also about drugs used to control these conditions – ACE inhibitors, which target an enzyme that works alongside ACE2 to regulate blood pressure. Right now, we just don’t know whether taking these drugs influences risk.

As we come to better understand how our genes contribute to the severity of covid-19, another major challenge will be to work out how these interact with environmental factors such as smoking, exposure to pollution, the impact of crowded living spaces and many other things. As more and more of these findings come out, the influence that our individual genes and circumstances can have on our risk for infection and disease severity will become ever clearer. The whole planet is watching how this virus affects seemingly similar people very differently, says Casanova.

For now, we may be able to learn the most from those who have succumbed to covid-19, but the hope is that with more comprehensive testing in the not-too-distant future, we will be able to learn more about people at the other end of the spectrum – the ones who are shielded against this scourge.

Casanova and others believe this pandemic will forever change the way we think about infection, and the influence of individual differences down to our DNA. “All of a sudden,” he says, “people are realising that there’s something other than the virus at play.”

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