Could genetics explain the confusing array of SARS-CoV-2 symptoms?

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A dry cough. Loss of smell. Diarrhea. Fever. All of these have been considered possible symptoms associated with SARS-CoV-2 infection, along with the complete absence of symptoms at all. In the absence of a sufficient testing capacity, many areas in the United States are being compelled to allocate their limited tests to only those who seem to have COVID-19 symptoms. But, given the difficulty of determining which symptoms actually indicate a likely infection, those are difficult decisions to make.

The bewildering array of symptoms also raises questions about why people respond so differently to the same virus.

Figuring out what’s going on in the midst of a pandemic is an incredible challenge. We’re going to take a look at some preliminary reports about one way of doing so—not because the results are likely to hold up as more research comes in, but because it reveals some of the ways that researchers are using to try to understand the virus’s infection.

Symptom or coincidence?

Currently, the CDC website lists a variety of symptoms associated with COVID-19. Some of these are what you'd expect for a viral infection of the lungs: fever and chills, cough, shortness of breath, and a sore throat. But there are also some less obvious ones, like headaches, muscle pain, and loss of the sense of smell.

Lists like these are typically prepared by aggregating medical reports, as doctors take and update a person's symptoms as they're admitted and treated. But the lack of testing poses significant problems for this effort. For one, we're struggling to understand how many people have been infected without requiring medical care. The arrival of the pandemic was also coincident with flu season and the onset of seasonal allergies, which can produce an overlapping set of symptoms.

Finally, the list of symptoms is generally a product of the patient's own memory as they're asked to describe the onset of the problems. Memories can be problematic, as the need for medical care itself can enhance recall of symptoms that might otherwise be ignored. The wide awareness of lists of symptoms like the CDC's can serve the same purpose.

Complicating matters further, some problems seem to strike a relatively small subset of infected people. Various reports have implicated SARS-CoV-2 in blood-clot formation, possibly through its infection of the lining of blood vessels. Similar things are true for the gastrointestinal symptoms. And the receptor that the virus uses to enter cells is also found in the kidneys, which could potentially explain why a number of hospitalized patients have needed dialysis. Why some patients appear vulnerable to severe symptoms yet others have an asymptomatic infection remains unclear.

Figuring out what's going on with some of this will ultimately require a lot of lab work—we'll need to find out if the virus

can reproduce in kidney cells and explore the nature of any kidney damage, for example. But another group of researchers has been looking for ways to understand the onset of COVID-19 symptoms in real time.

What happens when?

Two recent draft papers have described the early results of a collaboration between health researchers at Harvard and King's College London. They've worked with an application development company to put together a simple application for mobile devices called COVID Symptom Tracker that asks its users a series of questions daily. These are focused on known symptoms of COVID-19 (and can be updated as that lists expands), as well as any test results and treatments received.

This approach has some downsides. Its users are self-selected and have smartphones, which probably means a younger population. And the app only asks about the symptoms that the developers have enabled. But the approach trades these limitations for some significant advantages. The first is simply scale. Between the US and UK, the app already had 2.2 million users before the end of March. The second is that it doesn't suffer from recall bias—people enter their symptoms as they arise, *before* they know they're associated with a positive diagnosis. Later, the early symptoms and even treatments can potentially be correlated with patient outcomes.

How's it working out? A draft describing the application presents some initial analysis of its users. It found that people typically got tested after reporting coughing and/or fatigue, but these weren't actually strongly linked to the test coming back positive. The same was true if someone had diarrhea but no other symptoms. Instead, positive diagnoses went up if cough and/or fatigue was associated with diarrhea or the loss of smell. In fact, the results suggested, loss of

smell was more common than fever among those who would eventually test positive for the virus.

Last week, the team posted a follow-up draft that starts looking at the features associated with these symptoms. It does so by looking at a population of twins in the UK who have volunteered to take part in health research. A number of them (a bit over 2,500) have been using the application, and the researchers have used that to try to tease out whether genetics might influence the symptoms that people experience.

Limitations

The problem here is that not enough of them have received a diagnosis to do any sort of analysis. So the researchers weren't correlating anything to actual SARS-CoV-2 infections; instead, they correlated it to a prediction of a positive diagnosis, as determined in their earlier draft manuscript. That's clearly the biggest single weakness of this work. The second is that it covered an extremely short period: March 25 through April 3.

Given those cautions, you should take the results with an entire salt flat. But there are some interesting potential results that seem worth following up on with longer-term tracking. They suggest that there's a significant genetic component to who is likely to end up with a COVID-19 diagnosis, with a likely value of 50-percent genetic (though the error range was from 30 to 80 percent). In addition, many symptoms also seemed to be linked by genetics, including fever, fatigue, loss of smell, and diarrhea. Others, like coughs, chest pains, and abdominal pains, were not.

While this study isn't going to change our understanding in its current form, it does provide an interesting model for how a higher-quality study would work—that's a potential reason for posting a draft publicly in the first place. And it's clear that this study could eventually be what we're looking

for, as there’s no reason we couldn’t eventually test every single participant and get a clearer picture of what’s going on. Longer-term, rather than relying on twins, we might want to also do genome-wide studies with unrelated individuals, which could greatly expand the study population.

Although this study shouldn’t be viewed as much more than a hint of what’s possible, something is clearly influencing the body’s response to this virus in different individuals. Genetics is a reasonable candidate for one of the influences there.

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