How much protein function needs to be restored?

The answer could help doctors decide when to intervene with treatments targeting the mutations that cause cystic fibrosis. **By Benjamin Plackett**

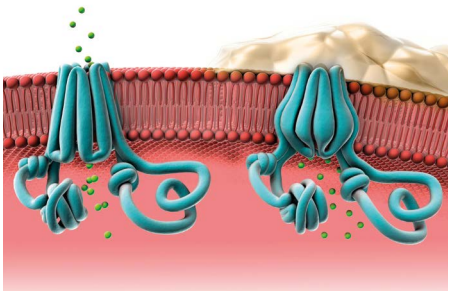
The past couple of decades have seen huge advances in treatments and life expectancy for people with cystic fibrosis. But a fundamental question surrounding the genetic malady remains unanswered. To prevent the disease's symptoms, what percentage of function is required for cystic fibrosis transmembrane conductance regulator (CFTR), the protein that is absent or dysfunctional in cystic fibrosis?

"This is an interesting question and one that's clinically relevant," says Felix Ratjen, a paediatric respiratory specialist at the University of Toronto in Canada. "We know there's a spectrum of CFTR dysfunction and that it varies from organ to organ. So, the question is: at what level of that dysfunction do we need to consider intervention?"

Faulty CFTR proteins, which can be caused by hundreds of genetic mutations, interfere with the movement of salt and water between cells. This interference causes mucus to build up in the body's tube-like structures, particularly in the lungs and digestive system. Those mucus build-ups, in turn, make people with cystic fibrosis more likely to contract infections. And the disease comes with an array of other complications, including liver problems and an increased risk of diabetes.

When to intervene

Testing for the two main CFTR mutations at birth has been routine in the United Kingdom since 2007 and in the United States since 2010. But Ratjen and others fear that some people might be slipping through the cracks. For example, someone with rarer mutations or only one affected organ with late-developing symptoms could miss out on the benefits of early intervention. The opposite is also true. "If we knew that *X* percentage of function was sufficient and never led to problems, then we'd know we don't need to follow that patient and intervene," Ratjen says. "We don't actually know for sure what the drugs' side effects are 50 years down the road." Unnecessary intervention is also expensive.



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Normal (left) and abnormal CFTR proteins.

So, to determine when and how to treat a patient, doctors need to know how much CFTR function is required to effectively eliminate the symptoms of cystic fibrosis. The problem, however, isn't straightforward.

If you were to plot a graph with CFTR function on one axis and the severity of symptoms on the other, you wouldn't get a straight line, but rather a curve. "In other words, a little bit of CFTR function can make a big difference, and then it levels out," says Steven Rowe, director of the Cystic Fibrosis Research Center at the University of Alabama at Birmingham.

Rowe and other researchers have a few ways to draw this curve. "We know the genes that cause cystic fibrosis, and so you can put those versions of the genes into cells and look to see how much function they have," he says. A slightly more sophisticated version of that experiment uses not cells but organoids — multicellular *in vitro* tissue with a structure that reflects the complexity of a full-scale organ. There are also observational studies, in which researchers measure the CFTR function of people with cystic fibrosis and track their symptoms and how long they live for. "The confluence of all these studies is something of a road map for what CFTR level each organ needs in order to be normal," says Rowe.

A drug called ivacaftor was shown to boost CFTR function during clinical trials in 2008 by opening the faulty chloride channels. "Ivacaftor gave 50% more function in the lab, but 30% in real life," says Rowe. That was enough to substantially improve the quality of life of people with the disease, he adds. "It became the cornerstone goal."

Subsequent drugs have pushed CFTR function as high as 85% in the laboratory. Yet despite these advances, cystic fibrosis remains a life-limiting disease. The question of how much CFTR function is needed to eliminate the disease's symptoms remains unanswered.

How much is enough?

"What about people who are carriers, but with no discernible symptoms? You'd initially say they're normal," says Rowe. "Their CFTR function could be as high as 90%." But here again, things aren't so simple, because those seemingly healthy carriers can face a higher risk of a whole host of complications associated with cystic fibrosis. For example, Patrick Flume, who studies cystic fibrosis at the Medical University of South Carolina in Charleston, says: "If you look at patients with chronic sinusitis, you'll see a greater proportion of patients with at least one CFTR mutation than the general population."

This holds true for other complications, too. One study found that 90% of men with congenital absence of the vas deferens, the tube that carries sperm from the testes, have at least one CFTR mutation (M. Wilschanski *et al. Am. J. Respir. Crit. Care Med.* **174**, 787–794; 2006).

Accepting that variations in CFTR function give rise to a spectrum of disorders makes it harder to define who does or does not have cystic fibrosis. "It can be difficult sometimes to know if we're diagnosing cystic fibrosis or related disorders," says Claude Férec, head of the department of medical genetics at the University Hospital of Brest, France.

But that doesn't mean we should abandon the pursuit of working out the level of CFTR function at which a person is regarded as not having the disease, Férec says. "It's always important to have a precise diagnosis to give people a better idea of what they can expect."

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