What DNA can tell us about cystic fibrosis

In the age of personalised medicine, understanding the impact of genetic variations is increasingly important. Here we explore some of the genetic variations that have been found in CF so far and what needs to be done next.

Since the CFTR gene was discovered 30 years ago – a significant step forward in understanding and treating cystic fibrosis – precision medicines that modify the CF gene have been licensed, newborn screening has been implemented and we know a lot about what the 'CFTR' protein does in the body, both in the lungs and elsewhere.

As we learn more about CF, we see lots of variations in what symptoms develop and how, what bugs people grow and how people respond to treatments. The genetic make-up of someone with CF determines some of this variation, along with socioeconomic and environmental factors.

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Everyday genetic variations

Genetic variations affect us every day of our lives without us realising. We can see these genetic variations by comparing people in the queue at the bus stop, our school friends or work colleagues – things like different hair and eye colour, or how tall people are. There are many different genetic variations, and understanding them is at the heart of the development of personalised medicines.

Just as there are genetic variations in our physical appearance, there are lots of variations in how our bodies work; in the hundreds of chemical reactions taking place in your body as you read this. Most of the time they don't make a difference to how you go about your day-to-day life. However, every now and then you might notice things that make you different to your friends and family, and some of these are due to you having a different version of a gene.

For example, perhaps you've noticed an espresso after dinner will keep you awake much longer than it does your friends? If so, you're not alone! Around a third of people in the UK break down caffeine slower than the other two thirds, as they have a slower form of the enzyme that breaks down caffeine (you'll find out why this is important later). In some situations, a different genetic variation can be an advantage and in others it can be a disadvantage.

Variations can change how a condition develops

The known genetic variations in our biochemistry can affect how long drugs stay in our bodies, make us more or less likely to develop a particular condition or disease, or even affect the way diseases develop.

We know which genetic variation affects how caffeine breaks down because the enzyme involved also breaks down some drugs. If a particular drug is broken down by the 'caffeine enzyme', researchers need to know this when working out the safe dosage for the drug. That's because, for those that are kept awake by an evening espresso, the drug will stay in their body longer.

When it comes to genetic variations, however, the subtler the effects they have, the harder they can be for researchers to find.

Twins to the rescue

With so many different factors that could contribute to why one person has a different experience of a condition to another, it can be hard to work out whether that variation is due to someone's genetics, or whether it's due to environmental or socioeconomic factors. One way of doing this is to conduct 'twin studies'.

Twin studies work by comparing the symptoms and disease patterns of identical twins with non-identical twins. As they are likely to grow up with the same socioeconomic and environmental factors, it's much easier to spot whether these symptoms and patterns are due to genetic differences or not.

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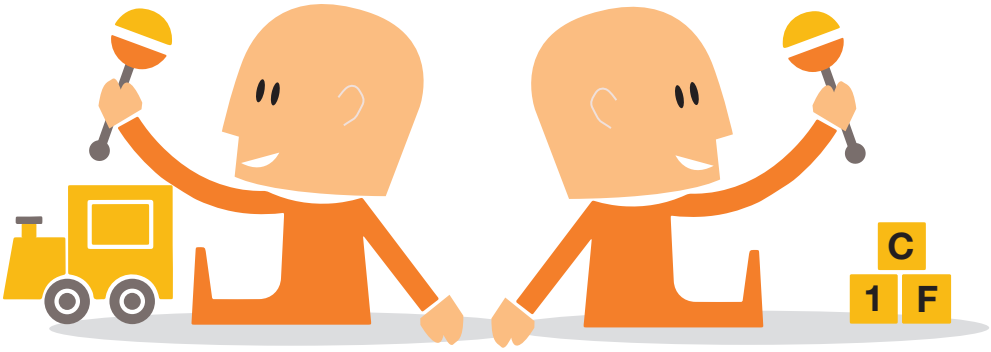
If it is genetic differences that affect a particular symptom, you would expect the symptoms in the identical twins to match all of the time (in the caffeine example, they would either both be kept awake by the espresso, or both wouldn't), but the symptoms in non-identical twins would only match some of the time. If there is no genetic component to a symptom, then the



chances of seeing the symptom in either set of twins should be the same.

Researchers in the USA found that identical twins with CF who also had CF-related diabetes (CFRD) would be more likely to both have the condition than non-identical twins, and so researchers concluded that there was a genetic link to whether people with CF would develop CFRD. They found that CFRD is not entirely due to genetic changes, and that other things contribute to why it develops too. Research is underway to explore the genetic links to CFRD in more detail, and to work out how to apply this new knowledge.

Learning from research into other conditions

Another logical approach to understanding more about the influence of genetic variations in CF is to learn from other conditions. Genetic variations for similar conditions may also affect how the symptoms of CF develop. For example, there are a number of genetic variations that increase a person's risk of developing type 2 diabetes in the general population. Cystic fibrosis researchers wondered whether these risk factors also increased the risk of someone developing CFRD (which has a mix of symptoms related to type 1 and type

2 diabetes). When they looked for the known diabetes genetic variations in people with CF, they found that these genetic variations altered the age of onset of CFRD. If a person with CF had the 'at risk' variations for type 2 diabetes, then they were likely to develop CFRD at a younger age.

The power of large numbers

Comparing DNA samples from thousands of people with CF to thousands of people who don't have the condition is another method for identifying genes that may modify different people's experience of cystic fibrosis. If a genetic modifier is linked to CF, then it will be found more frequently in DNA from people with CF than in people who don't have the condition. The more samples that are analysed, the less likely it is that the findings are 'false positives,' or unreliable. This type of approach is the genetic equivalent of looking for a needle in a haystack. However, new knowledge and modern technology (in terms of lab equipment and number-crunching capacity) has made this much easier than it was 20 years ago – and it is getting quicker, easier and cheaper all the time.

Filling in the genetic gaps

Genetic technology gets better and cheaper with every passing year, meaning that ever more detailed analysis is possible. The level of detail with which it is now possible to analyse our DNA means we can be more accurate than ever before

in pinpointing the DNA change that affects how people with CF have different experiences of their condition.

An important step in this type of genetic analysis has been to work out how the changes in someone's DNA can affect the symptoms of CF they experience. This can be done by collecting information about someone's symptoms at the same time as taking a DNA sample (by taking their blood). Such a link can be done anonymously and is done with the person's knowledge and consent.

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A more powerful way of taking this test would be to link a person's DNA sample with information from a CF registry - like the UK CF Registry - as this could help us to understand quickly if many people with the same CF genotype genetic variations experience the same symptoms in the same ways.

Our DNA still holds the answers to many questions we have about why each person's experience of CF is different. The good news is that research to unlock these answers is within our grasp. Together, the worldwide CF research community is working to piece together the complicated jigsaw of genetic variations to improve the symptoms of people with cystic fibrosis.