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Cystic Fibrosis Research News

Title: Complete *CFTR* gene sequencing in 5,058 individuals with cystic fibrosis informs variant-specific treatment

Lay Title: An in-depth study of the CFTR gene enables selection of CFTR therapies for almost all individuals with CF

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What was your research question?

Every individual has two CFTR genes; one inherited from each parent. Individuals with CF should have a genetic variant in each CFTR gene that causes it not to work properly. We tested whether we could find both CF-causing variants in individuals with CF using a technology called full-gene sequencing.

Why is this important?

Genetic testing for CF usually looks at a portion of the CFTR gene (the coding region) – akin to reading a word that is ~4,800 letters long. Full-gene sequencing examines the *entire* gene (coding and non-coding regions); this 'word' is ~186,000 letters long. Genetic variants in *CFTR* are like spelling changes and are important to understand because CFTR modulator treatments target specific *CFTR* variants. Full-gene sequencing also allows identification of other genetic changes in addition to the variants that cause CF. The additional changes may help explain differences in clinical symptoms or CFTR modulator response among patients.

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What did you do?

In 5,058 individuals with CF, we looked at every single letter in both of their 186,000-letter CFTR genes. We catalogued every 'misspelling' (i.e. variant) in every individual and determined the likely effect of each variant.

What did you find?

Nearly everyone in our study (98%) had a CF-causing variant identified in each CFTR gene. This information can be used to select therapy targeted to treat specific CF-causing variants.

What does this mean and reasons for caution?

Full-gene sequencing detected more variants than other methods and it was especially useful in finding large rearrangements in the CFTR gene. While nearly all of those in our study were found to have changes that cause CF in each CFTR gene, a very small fraction could not be resolved. Furthermore, the finding of genetic changes in *CFTR* in addition to the established CF-causing variants – such the common F508del variant – indicates that other changes in the CFTR gene may influence disease severity and /or response to CFTR modulators.

What's next?

A small fraction of individuals with CF carried *CFTR* variants that have to be studied and tested for response to available CFTR modulators. We need to find out why full-gene sequencing did not find any CF-causing variants in a small number of individuals with CF (14 people).

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