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Cystic Fibrosis Research News

Title:

The clinical utility of sequencing the entirety of CFTR

Lay Title:

In-depth examination of the *CFTR* gene finds more disease-causing genetic changes than conventional clinical genetic testing

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What was your research question?

Cystic fibrosis (CF) occurs when a person has disease-causing genetic changes (variants) in each of their *CFTR* genes. Typically, conventional clinical genetic testing identifies both disease-causing variants. We wanted to determine whether more in-depth testing (whole-gene sequencing) of the *CFTR* gene can identify any disease-causing variants when one or no disease-causing variants are identified by conventional testing.

Why is this important?

For individuals with clinical features of CF but an unconfirmed genetic diagnosis (fewer than two disease-causing variants found) there is uncertainty about the diagnosis of CF and

treatment options. Identification of two disease-causing variants using whole-gene sequencing would relieve this uncertainty and inform selection of the most appropriate therapy.

What did you do?

We analysed whole-gene *CFTR* sequencing data for individuals who had previously undergone conventional genetic testing for CF that identified one or no disease-causing variants. Individuals were grouped by the results from previous testing (one or no variants identified) and clinical evidence of CF (diagnostic sweat chloride or non-diagnostic sweat chloride results). We also re-evaluated CF clinical features and searched for other genetic explanations for disease for a subset of people.

What did you find?

Whole-gene *CFTR* analysis successfully found a second disease-causing variant in nearly half of the people who had one previously-identified disease-causing variant and a positive CF-diagnostic sweat chloride test. Success in finding a second disease-causing variant was much lower in those with one previously-identified disease-causing variant and a negative or non-diagnostic sweat chloride value. Whole-gene *CFTR* analysis was unsuccessful (no disease-causing *CFTR* variants found) in people who had no previously identified disease-causing variants. Re-evaluation of clinical features in many individuals showed that CF was not likely to be the correct diagnosis. No other genetic explanations for CF-like disease were found in other genes.

What does this mean and reasons for caution?

Whole-gene *CFTR* analysis can be useful, but only in a subset of people. Those who have good clinical evidence for CF and one disease-causing variant found by conventional clinical genetic testing are expected to benefit the most from more in-depth sequencing of the *CFTR* gene. Individuals who do not meet these criteria may benefit in certain cases, but additional clinical studies, such as repeating sweat chloride testing, should be performed first.

What's next?

Future studies will use newly-developed laboratory techniques to assess the *CFTR* gene for additional disease-causing variants in the group of individuals who have a single disease-causing variant and a positive CF-diagnostic sweat chloride.

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