European Cystic Fibrosis Society

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Cystic Fibrosis Research News

Title:
The multi-faceted nature of 15 *CFTR* exonic variations: impact on their functional classification and perspectives for therapy.

Lay Title:
Effect of variants in the *CFTR* gene on the CFTR transcripts and protein to improve patients care.

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What was your research question?

Cystic fibrosis (CF) is caused by a mutation in a single gene – the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene contains DNA "letters" that spell out the instructions to make a specific protein. When the protein is not made correctly, it can lead to multiple problems.

We aimed to determine the consequences, on the production and function of the CFTR protein, of 15 variants located in the part of the *CFTR* gene used for the production of the CFTR protein (*i.e.*, producing not all parts of the gene are used), in order to better understand why they cause CF and to adapt an individuals' care and therapy.

Why is this important?

New treatments for CF have been available for a few years, but only for some people with CF according to the *CFTR* disease-causing variants they carry. These treatments specifically target the molecular defect caused by a given variant. However, not all variants are characterized and the expected impact of a variant does not always match reality, in particular for variants in the coding sequence which can have various consequences on protein production and activity, which cannot all be corrected by current therapies.

What did you do?

We selected 15 variants in the *CFTR* gene, identified in people suspected to have CF and analyzed in collaborating laboratories The variants were artificially generated in a vector that contains the sequence of the *CFTR* gene. We used cell cultures, by growing a sample of human cells in a petri dish, in which we introduced the different vectors. We then assessed the effect of the variants on the different steps of CFTR protein production and activity: (1) assessment of quality and quantity of ribonucleic acid (RNA) (which converts the genetic information of DNA into protein), the mandatory intermediary between the gene and the protein that ensure the production of a complete and functional protein, (2) assessment of quality and quantity of the CFTR protein, and (3) ability of CFTR to transport chloride ions through the cell membrane.

What did you find?

We showed that five of the variants studied had an impact on the quality of RNA by causing the loss of different parts of the RNA sequence and thus producing an incomplete and non-functioning protein. One variant impacted both the RNA sequence and the quality of the

protein. Two variants had consequences only on CFTR protein quality and function. Finally, seven variants showed no harmful consequence on CFTR, according to our results.

What does this mean and reasons for caution?

As our study has been performed on cultured cell lines (i.e., artificial system), our results must be confirmed on materials derived from individuals carrying those variants. However, variants that alter the quality of RNAs are currently not targetable by CFTR modulators, as the mutant incomplete protein is mainly degraded and thus not accessible for correction by molecules. Thus, determine the consequences of the variants is important to know if a treatment has a chance of being effective or not. Testing the efficacy of targeted therapies on individuals' materials may also be useful to support or prevent the use of these therapies.

What's next?

Finally, these findings can be used for future developments in CF-targeted therapy, which should include therapies that restore the RNA. This would offer new drug perspectives for people with CF who carry this type of variants and for whom current treatments are not effective.

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