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Cystic Fibrosis Research News

Title:

Evaluation of the response to elexacaftor-tezacaftor-ivacaftor of the rare CFTR variants L383S, I507del, L1065P and R1066H in intestinal organoid-derived epithelial monolayers

Lay Title:

Response to CFTR modulators of the rare CFTR variants L383S, I507del, L1065P and R1066H

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What was your research question?

We wanted to evaluate the effect of the modulator combination elexacaftor-tezacaftor-ivacaftor (ETI) on the function of four rare, poorly characterized CFTR variants: L383S, I507del, L1065P and R1066H.

Why is this important?

These are poorly characterized CFTR variants. These findings may guide the development of a personalized medicine approach for the individuals included in this study and for all those carrying these CFTR variants.

What did you do?

We have studied cells derived from rectal biopsies grown in vitro as mini-guts called organoids. We assess the modulator-dependent restoration of the anion secretory function of these variants in a proper genomic context in cells natively expressing CFTR. Organoids grown as 3D structures can increase in volume if CFTR is present and functional in a way we can precisely quantify. Cultured as

epithelial monolayers, we measured the ionic currents. Both methods were used to assess the effect of ETI on CFTR function. We have also studied whether CFTR protein expression was also increased following the same treatment.

What did you find?

The I507del, L1065P and R1066H variants display severely impaired function. ETI treatment markedly enhanced L1065P- and R1066H-CFTR function and protein expression, whereas its effect on L383S- CFTR was less pronounced.

What does this mean and reasons for caution?

ETI may ameliorate disease symptoms in individuals carrying the L1065P or R1066H variant. More tentative, it may also benefit those carrying the L383S variant. Although a limited number of cases have been studied worldwide using this approach there is agreement in the scientific community that these findings may guide the development of a personalized medicine approach for the individuals included in this study and for all those carrying these CFTR variants.

What's next?

Our data align with previous studies on the FRT cell model, presently used to assess the response of rare variants to modulator therapy by FDA. We expect that these models will pave the way to approval by other regulatory agencies and insurances.

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https://pubmed.ncbi.nlm.nih.gov/39979195/