European Cystic Fibrosis Society

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Cystic Fibrosis Research News

Title:

Severity of the S1251N allele in cystic fibrosis is affected by the presence of the F508C variant *in cis*

Lay Title:

Two mutations in one *CFTR* gene copy can influence each other and thereby disease characteristics

Authors:

Senne Cuyx [1], Sofia S Ramalho [2], Isabelle Callebaut [3], Harry Cuppens [4], Arthur Kmit [2], Kaline Arnauts [5], Marc Ferrante [6], Catherine Verfaillie [7], Marjolein Ensinck [8], Marianne S Carlon [8], Mieke Boon [1], Marijke Proesmans [1], Lieven Dupont [9], Kris De Boeck [1], Carlos M Farinha [2], François Vermeulen [1]*, Anabela S Ramalho [10]*

Affiliations:

1 KU Leuven, Department of Development and Regeneration, Woman and Child Unit, CF research lab, B-3000 Leuven, Belgium; University Hospital Leuven, Department of Pediatrics, Pediatric Pulmonology, B-3000 Leuven, Belgium.
2 University of Lisboa, BioISI - Biosystems & Integrative Sciences Institute, Faculty of Sciences, Campo Grande, C8 bdg, 1749-016 Lisboa, Portugal.
3 Sorbonne Université, Muséum National d'Histoire Naturelle, UMR CNRS 7590, Institut de Minéralogie, de Physique des Matériaux et de Cosmochimie, IMPMC, F-75005 Paris, France.
4 Harelias BV, B-1000 Brussels, Belgium.
5 Department of Chronic Diseases, Metabolism and Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium; KU Leuven, Department of Development and Regeneration, Stem Cell Institute Leuven (SCIL), B-3000 Leuven, Belgium.
6 Department of Chronic Diseases, Metabolism and Ageing (CHROMETA), Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium; KU Leuven, Department of Gastroenterology and Hepatology, University Hospital Leuven, B-3000 Leuven, Belgium.
7 KU Leuven, Department of Development and Regeneration, Stem Cell Institute Leuven (SCIL), B-3000 Leuven, Belgium.
8 Laboratory for Molecular Virology and Drug Discovery, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, 3000, Belgium; KU Leuven, Department of Chronic Diseases, Metabolism and Ageing; BREATHE, B-3000 Leuven, Belgium.

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9 KU Leuven, Department of Chronic Diseases, Metabolism and Ageing; BREATHE, B-3000 Leuven, Belgium; University Hospital Leuven, Department of Respiratory Diseases, B-3000 Leuven, Belgium.
10 KU Leuven, Department of Development and Regeneration, Woman and Child Unit, CF research lab, B-3000 Leuven, Belgium.
* equal contribution as senior authors

What was your research question?

When the S1251N mutation is present in the *CFTR* gene, the F508C mutation is usually present on that same copy of the gene. We investigated the impact of having these two mutations in one gene copy.

Why is this important?

For other combinations of *CFTR* mutations on the same copy of the gene, it has already been shown that these mutations influence each other. Such a combination is called a "complex allele". The interaction between these mutations can affect the symptoms of people with CF (pwCF) as well as the response to new CFTR correcting drugs known as CFTR modulators. A more in depth characterisation of these complex alleles could thus aid in predicting the course of the disease and prescription of the right drugs.

What did you do?

A person with CF was observed to have the S1251N mutation but not the F508C in one copy of the *CFTR* gene, and the disease-causing mutation G542X in the other copy. This person had much milder symptoms than usually seen in CF. To understand this rare case, this person was compared to pwCF with both the S1251N and the F508C mutations on one gene. We compared medical data to look at the differences between the S1251N mutation with and without F508C. We also used data from cell models and software modelling.

What did you find?

Compared to pwCF with the usual complex allele of S1251N and F508C, this person had no detectable lung disease and a lower sweat chloride concentration, suffering only from recurrent bouts of pancreatitis. The CFTR modulator ivacaftor did not improve their health.
In cell models, the person's CFTR was confirmed to be dysfunctional, but to a lesser extent than in pwCF with the S1251N and F508C complex allele. The response to CFTR modulators was also lower.

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CFTR models in specialised software showed that F508C might worsen the negative effect of S1251N on CFTR function.

What does this mean and reasons for caution?

In routine genetic testing, complex alleles are often not searched for. However, the findings in this person illustrate how extensive genetic analysis might impact prognosis and treatment with CFTR modulators. The effect of lifelong treatment with these efficient but expensive drugs could vary depending on the presence of complex alleles. Thorough investigation can lead to more adequate prescription of treatments, especially modulators, which is important for both pwCF and the healthcare system.

What's next?

International collaborations will be essential to do further research into complex alleles, because these combinations are even less frequently found than rare mutations on their own. Identifying and understanding complex alleles would allow us to predict the disease course more accurately and tailor treatments towards the specific needs of pwCF.

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