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Cystic Fibrosis Research News

Title:

"Mild" *CFTR* genetic variants might be associated with a lower than expected probability of developing CF

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What was your research question?

We aimed to get insight into the risk for neonates screened positive for cystic fibrosis (CF) and identified with an inconclusive diagnosis to develop clinical CF. This study was based on population genetics data and focused on certain genetic variants.

Why is this important?

A number of infants detected positive through newborn screening are identified with an inconclusive diagnosis. Reasons are that the sweat test values and/or the genotype cannot confirm or refute the diagnosis of CF. The majority of these infants will remain asymptomatic throughout their life but few may develop symptoms suggestive of CF in infancy or in adolescence or adulthood. It is thus important to evaluate as best as possible the probability of these clinical outcomes depending on the variants carried. This should allow to adapt medical care and follow-up and to prevent over or under medicalisation and parents' anxiety.

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What did you do?

We selected 15 variants of the *CFTR* gene, five severe, including F508del, and 10 mild, and compared their frequency in the population of asymptomatic individuals and in the population of people with CF. Based on the data of newborn screening for CF in France between 2002 and 2017, we also evaluated the probability that a neonate who carries one of these 15 variants in combination with F508del on the other parental chromosome be detected through newborn screening.

What did you find?

The probability that a neonate carrying two copies of F508del or F508del in combination with another severe variant be detected was about 100%. The probability that a neonate carrying a mild variant in combination with F508del be detected varied from 0.03% to 53%, depending on the variant. It was very low in particular for the so-called 5T or T5 variant. This means that 98%-99% of neonates carrying a T5 variant in combination with F508del will not be detected at birth.

What does this mean and reasons for caution?

Clinical databases provide useful information about the symptoms observed in people carrying given variants. However, they represent the tip of the iceberg of all possible clinical presentations, such as CFTR2 that collects clinical information on CF patients exclusively. Data in asymptomatic individuals, such as in the gnomAD database, should also be taken into account. Low probabilities of developing CF when carrying certain mild variants may impact on one hand on medical care and follow-up, and on the other hand on genetic counselling for parents who wish to have other children and for relatives.

What's next?

As this study has revealed a low probability of detecting neonates for certain mild variants, the actual probability to develop symptoms of CF might even be lower, as previously shown for the R117H variant, but this remains to be evaluated for the other mild variants.

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