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Cystic Fibrosis Research News

Title:

Reclassifying inconclusive diagnosis after newborn screening for Cystic Fibrosis. Moving forward.

Lay Title:

Improving conclusions after newborn screening for babies with no clear diagnosis

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What was your research question?

In newborn screening for Cystic Fibrosis (CF) sometimes we cannot clearly rule out a diagnosis of CF or disorders related to CFTR dysfunction (CFTR-related diseases).

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Why is this important?

We urgently need to define a strategy to detect infants who might change to be diagnosed with CF or a CFTR-RD in order to plan a suitable follow up and possible access to CFTR modulators.

What did you do?

We followed 23 children with no clear diagnosis after newborn screening for CF for an average of 7.7 years (varying from 4 to13 years). We investigated the whole CFTR gene (whole *CFTR* gene sequencing) as well as, CFTR function in the bowel (intestinal current measurement on rectal biopsies; ICM) and in the nose (nasal potential difference; NPD).

What did you find?

Extensive testing identified genetic variants with varying clinical consequences and 3 variants of unknown significance (VUS); these were all combined with a CF causing mutation. All patients had a normal CFTR activity in the bowel. There were three different NPD profiles: results similar to those found in people with CF (such as people with the F508del/D1152H mutations) and thus qualifying these people as having CF, normal responses, suggesting an extremely low likelihood of developing a CFTR-RD, such as in people with the F508del/TG11T5 mutations; partial CFTR function above 20% of the normal, highlighting a risk, albeit low, of developing CFTR-RD, such as in people with the F508del/F1052V mutations. Two of the 3 VUS were reclassified by experiments as causing disease (D537N, T582I) and one had no clinical consequence (M952T).

What does this mean and reasons for caution?

It is important to combine genetic and functional investigations to assess the possibility of babies with inconclusive diagnosis at neonatal screening later being diagnosed with CF or CFTR-RD.

What's next?

CFTR function should be studied in such babies, ideally in cells taken from the nose which can be sent to central laboratories to be grown and investigated.

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