

Cystic Fibrosis Research News

Title:

Nonsense mutations accelerate lung disease and decrease survival of Cystic Fibrosis children

Lay Title:

STOP Codon mutations are associated with more severe disease from childhood in people with cystic fibrosis

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What was your research question?

We aimed to study disease severity of people with CF (pwCF) who carry a nonsense mutation on both copies of the gene (alleles) compared to pwCF with other *CFTR* mutations.

Why is this important?

Nearly 5% of people with CF (pwCF) worldwide carry a nonsense mutation on both alleles) resulting in a premature termination codon (PTC). For these pwCF, no efficient *CFTR* targeted therapy is available yet.

What did you do?

We investigated clinical outcomes such as lung function and mortality of pwCF carrying *CFTR* nonsense mutations resulting in PTCs on both alleles (PTC/PTC), pwCF who are compound heterozygous for F508del and PTC (F508del/PTC), and pwCF homozygous for F508del (F508del+/+), based on the European CF Society Patient Registry (ECFSPR) database. We also analyzed *CFTR* activity of specific PTC/PTC genotypes. We specifically focused on genotypes

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leading to incomplete CFTR proteins at, or downstream of codon 1162 (e.g., E585X/R1066C genotypes), which have been shown to be partially functional.

Based on the ECFSPR clinical data of pwCF living in high and middle income European and neighbouring countries, PTC/PTC (n=657) were compared with F508del+/+ (n=21,317) and F508del/PTC (n=4254). CFTR mRNA and protein activity levels were assessed in primary human nasal epithelial (HNE) cells sampled from 22 PTC/PTC pwCF.

What did you find?

As compared to pwCF with F508del on both alleles (F508del +/+), both PTC/PTC and F508del/PTC pwCF exhibited a significantly faster rate of decline in Forced Expiratory Volume in 1 s (FEV₁) from 7 years of age, and probably earlier. This resulted in lower FEV₁ values in adulthood. The mortality rate of paediatric pwCF with one or two PTC alleles was higher than those with the F508del+/+ genotypes. Infection with *Pseudomonas aeruginosa* was more frequent in PTC/PTC versus F508del+/+ and F508del/PTC pwCF. CFTR activity in PTC/PTC pwCF's HNE cells was very low and ranged between 0% to 3% of the expected level. The E585X/R1066C and Y275X/S466X genotypes had the highest CFTR activities.

What does this mean and reasons for caution?

This is the largest study until now comparing the disease severity of pwCF carrying 1 or 2 PTCs compared to F508del homozygotes.

Our study has the inherent limitations of a retrospective (using information on events that have taken place in the past) registry study from different countries. The impact of differences between country such as delay in diagnosis or genotyping, neonatal screening implementation, differences in treatment practices cannot be excluded in interpretation of childhood survival and lung function rates of change. This is counterbalanced by the very large number of pwCF included in the study, the high quality of data collection, and the fact that we only considered high and middle income countries with access to diagnosis, genetic screening and to treatment.

What's next?

Altogether, our findings support implementation of aggressive treatment from birth in children carrying a CFTR non sense mutation and of the urgent need for more research on alternative treatments to CFTR modulators. Nevertheless, the possibility of a positive response to CFTR modulators needs to be investigated for specific PTC variants. Early initiation of CFTR modulators in children with PTC/F508del mutations, to slow down the progression of the disease, should be investigated.



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