



# CFTR variants are associated with chronic bronchitis in smokers

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Cigarette smokers who carry one deleterious *CFTR* variant have higher rates of chronic bronchitis, while presence of two *CFTR* variants associates with COPD. These results indicate that genetically mediated reduction in *CFTR* function contributes to COPD. <https://bit.ly/3GSWUXw>

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## Abstract

**Introduction** Loss-of-function variants in both copies of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene cause cystic fibrosis (CF); however, there is evidence that reduction in *CFTR* function due to the presence of one deleterious variant can have clinical consequences. Here, we hypothesise that *CFTR* variants in individuals with a history of smoking are associated with chronic obstructive pulmonary disease (COPD) and related phenotypes.

**Methods** Whole-genome sequencing was performed through the National Heart, Lung, and Blood Institute TOPMed (TransOmics in Precision Medicine) programme in 8597 subjects from the COPDGene (Genetic Epidemiology of COPD) study, an observational study of current and former smokers. We extracted clinically annotated *CFTR* variants and performed single-variant and variant-set testing for COPD and related phenotypes. Replication was performed in 2118 subjects from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study.

**Results** We identified 301 coding variants within the *CFTR* gene boundary: 147 of these have been reported in individuals with CF, including 36 CF-causing variants. We found that CF-causing variants were associated with chronic bronchitis in variant-set testing in COPDGene (one-sided  $p=0.0025$ ; OR 1.53) and in meta-analysis of COPDGene and ECLIPSE (one-sided  $p=0.0060$ ; OR 1.52). Single-variant testing revealed that the F508del variant was associated with chronic bronchitis in COPDGene (one-sided  $p=0.015$ ; OR 1.47). In addition, we identified 32 subjects with two or more *CFTR* variants on separate alleles and these subjects were enriched for COPD cases ( $p=0.010$ ).

**Conclusions** Cigarette smokers who carry one deleterious *CFTR* variant have higher rates of chronic bronchitis, while presence of two *CFTR* variants may be associated with COPD. These results indicate that genetically mediated reduction in *CFTR* function contributes to COPD related phenotypes, in particular chronic bronchitis.