Title:
SHOULD DIFFUSE BRONCHIECTASIS STILL BE CONSIDERED A CFTR-RELATED DISORDER?

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What was your research question?

Diffuse bronchiectasis (DB) is characterized by abnormal and irreversible destruction of bronchi resulting in respiratory failure. Several comprehensive studies have evaluated the role of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene as the cause of DB. However, the theory of implication of CFTR gene in DB remains controversial and we proposed additional molecular evidence to prove or disprove this theory.
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Why is this important?

DB is the main structural damage of CF lung, it promotes microbial stasis and infections, setting up a vicious cycle of further infection and inflammation ultimately leading to airways destruction that often lead to death of CF patients. Answering whether DB is a CFTR-Related Disorder (CFTR-RD), i.e. a classical autosomal recessive disease with two mutations detected (one severe/one mild or two mild), is an important question for DB patients for defining the cause of their disease and giving optimal genetic counselling to families.

What did you do?

To determine whether we should still consider DB as a CFTR-RD, we compared the DNA sequence of the CFTR gene between 47 adult patients with DB and 47 healthy subjects (controls). A combination of severe mutations on both CFTR alleles usually leads to severe forms of classical Cystic Fibrosis (CF). Other mutations that retain residual CFTR function (above 10%) result in mild CF or incomplete phenotypes. For instance CBAVD patients carry two mild mutations or are compound heterozygous for a severe and a mild alteration of the CFTR gene; CBAVD being considered as a CFTR-RD.

The differences (mutations) in DNA sequence for the CFTR gene in the DB group were then classified using computer predictive analyses; lab experiments to test DB CFTR protein amount; and data from previous research publications, to assess whether these mutations potentially affect CFTR protein functioning. Finally, the patient’s mutations in the CFTR gene were cross checked with their actual clinical symptoms or biological parameter, to see if there was any match between predicted mutation severity and actual health of the patient.

What did you find?

CFTR mutations (severe, mild mutations, unclassified variants (VUCs) and rare polymorphisms) were identified in 24 patients with DB and in 27 controls. Three DB patient’s had two mutations. Lab experiments confirmed a deleterious effect for detection of known severe and mild mutations. Matching patient mutation type to actual clinical symptoms, highlighted that sweat chloride level is an appropriate biochemical indicator to discriminate DB patient’s carrying at least one CF gene. Patients with at least one no neutral
variant (NNV), mild or severe CF gene mutation have a slighter risk (but not significant) to have lower respiratory capacity values.

**What does this mean and reasons for caution?**

Our findings suggest that DB should not be systematically considered as a CFTR-Related Disorder. Only a few DB cases in our study carried two fundamental or probably contributory CF mutations, suggesting that other genetic or environmental causes could lead to DB. The major limitation to this study is the number of patients involved. In addition, we showed that some other non-severe mutations of the CFTR gene (polymorphisms or VUCs) do have a possible impact on CFTR gene functioning in the lab. So we classified these mutations as NNV, but other studies including larger numbers of patients with DB are needed to make firmer conclusions.

**What’s next?**

Other studies are needed to determine if these NNV actually impact on chronic lung diseases. Mutations in other genes such as SLC26A9 (an epithelial chloride/bicarbonate channel) have also been reported to contribute to DB, hence further research must be completed in this area to answer all the questions.

**Original manuscript citation in PubMed**

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