Cystic Fibrosis Research News

Title:

Clinical presentation and basic defect of the *CFTR* genotype p.Phe508del / p.Arg117His in a mother and her monozygous twin daughters

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What was your research question?

We wanted to resolve whether variable clinical significance of the *CFTR* genotype p.Phe508del / p.Arg117His can even be observed in family members and monozygous twins who share 50% to 100% of their genes and who were exposed to the same living conditions.

Why is this important?

p.Phe508del / p.Arg117His is the most common *CFTR* genotype of variable clinical significance. People carrying this genotype can range from being completely healthy, having some symptoms of CF-like disease or may be affected by full-blown CF.

What did you do?

Cystic fibrosis (CF) is an autosomal recessive trait. Thus, both parents of CF patients are typically healthy heterozygous carriers of a mutation in the *CFTR* gene. Here we report on the first case in where the mother had the p.Phe508del / p.Arg117His mutations and the father was a p.Phe508del gene carrier, so she gave birth to p.Phe508del / p.Arg117His twins. Thus, we had the opportunity to examine the clinical presentation and the basic defect caused by CFTR dysfunction in a setting with the minimal number of variables that modify the manifestation of two *CFTR* mutations in humans. We examined the clinical symptoms of the

mother and her daughters and characterized their basic defect by CFTR bioassays, i.e. sweat test, nasal potential difference (NPD) und intestinal current (ICM) measurements.

What did you find?

The monozygous twins were very much alike in stature, movement habits, facial expression and wording. They shared the clinical symptoms of CFTR dysfunction such as recurrent episodes of discomfort or abdominal pain after high-fat meals. However, when we examined the sisters' extent of CFTR dysfunction by sweat test, NPD and ICM, CFTR-mediated chloride conductance was found to be in the CF range, but not identical in NPD. Treatment with the CFTR-modulating drug ivacaftor abolished the symptoms of abdominal pain in both twins, but normalized CFTR dysfunction in the NPD in only one twin, but not in her sister.
The twins' mother had regularly experienced CF-typical symptoms such as rhinosinusitis and weekly episodes of diarrhea since adolescence. However, she has always worked full time, had normal anthropometry and was never affected by any lung disease. Sweat chloride, NPD and ICM were in the normal range.

What does this mean and reasons for caution?

Until now, the extent of CFTR dysfunction for people with p.Arg117His has been thought to be less variable than the clinical manifestations of CF disease. However, we have learnt from this family that CFTR dysfunction may actually be more variable than the clinical symptoms. This means we need to understand what is determining this difference as it may help improve CF care.

What's next?

The expression of the basic defect and its therapeutic attenuation are governed by numerous non-genetic factors. Cells, organoids and tissues derived from monozygous CF twins or even better from an ultra-rare trio of two-generation shared *CFTR* genotypes as reported here, may be of interest to future researchers to resolve these non-genetic modulators of the electrophysiological phenotype of the most common *CFTR* mutation genotype of variable clinical significance.

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