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Cystic Fibrosis Research News

Title:

Phenotypic spectrum of patients with cystic fibrosis and cystic fibrosis-related disease carrying p.Arg117His

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What was your research question?

WE were interested in learning about individuals carrying a specific CFTR mutation - R117H – as depending on the accompanying gene mutations, people with this mutation can have classical cystic fibrosis (CF) or the milder form diagnosis of CFTR-related disease (CFTR-R).

Why is this important?

All people with R117H are eligible for the new drug Kalydeco. One study of Kalydeco suggested that only adults show clinical benefit with this drug. Individuals with R117H can additionally have either 5T or 7T as part of their CFTR gene defect and generally, those with R117H and 5T have classical CF, whereas those with R117H and 7T have CFTR-R. In the Kalydeco study, (there were more adults with R117H 5T) than R117H-7T and this may explain why adults appeared to improve more. We wanted to see whether having a specific R117H type (5T or 7T) makes a difference in the severity of the disease. This is important as it might influence how we think about allocating the new CFTR-drugs.

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What did you do?

We studied the Toronto patient database and also the charts of some individuals with R117H. We specifically looked at each person's exact genetic analysis, sweat tests, lung function over time, sputum results, weight and height and pancreas status. We then tested whether lung function or a certain sputum result differed between those with R117H-7T or R117H-5T. We also studied whether the sweat test result was different in R117H patients with more severe lung disease. Lastly, we also compared adults with R117H to infants with R117H. These infants screened positive in the Ontario CF Newborn screening program and did not have any signs of clinical disease.

What did you find?

Generally, those with R117H -5T are sicker compared to those withR117H -7T in terms of low lung function and the presence of bacteria in the sputum. However, there are some individuals with R117H - 7T who are just as severely ill and require the same medical therapy as R117H-5T patients. So knowing whether an individual carries 5T or 7T with R117H does not help to tell how sick they might get. The sweat test result also does not tell whether an individual might get sick or not. We could observe that those people with certain bacteria in their sputum had lower lung function. Furthermore, we were surprised to see that the infants with R117H have the same sweat test results and sputum results as the R117H adults.

What does this mean and reasons for caution?

Based on these results we recommend monitoring all those with R117H, no matter whether they have the 5T or 7T type. This is because we currently do not have any markers which help us tell who will develop severe disease or who will not. This is particularly important for infants who should be regularly monitored for the possible onset of CF-like lung disease. We believe that early intervention in lung disease is key to preventing long-term damage. Our findings should also be considered when debating the prescription of CFTR-drugs.

What's next?

This was a retrospective study, meaning we looked backwards when collecting patient's data, which has limitations. We are now planning a prospective (forward-looking), study in adults as well as infants with this R117H mutation. We aim to identify any markers that can help us to better tell who might get bad lung disease and who might not.

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