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Cystic Fibrosis Research News

Title: Emergence and impact of *oprD* mutations in *Pseudomonas aeruginosa* strains in cystic fibrosis

Lay Title:

Relationship between changes in the *oprD* gene of *Pseudomonas aeruginosa* and patient outcomes

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What was your research question?

This study looked at specific strains of the bacterium, *Pseudomonas aeruginosa,* that are shared between some people with CF in Australia. Our main research questions were (1) do these strains have changes in a gene called *oprD* and (2) do particular *oprD* changes relate to

patient outcomes? Notably, changes in *oprD* can result in increased resistance to antibiotics, called carbapenems, and are frequently detected in CF *P. aeruginosa* isolates.

Why is this important?

Understanding the changes that can happen in *oprD* will improve our knowledge of how *P. aeruginosa* bacteria adapt to survive to the lungs and how antibiotic resistance occurs. Earlier research has linked changes in a number of specific genes in *P. aeruginosa* with more rapid progression of lung deterioration. In blood stream infections, changes in *oprD* were related to patient death. Therefore, it is important to know whether changes in *oprD,* could be an indicator of worse patient outcomes in CF.

What did you do?

First, we analysed the DNA sequence (genetic information) of 114 isolates of *P. aeruginosa* strains that are commonly identified in people with CF in Queensland, Australia. We then looked for changes in the *oprD* gene genetic information and compared these changes to how resistant the CF isolates were to antibiotics. Next, we tested the most common changes we saw in the *oprD* genetic information in the laboratory to understand their effect. Finally, we developed a technique to look for these common *oprD* changes in several hundred patient isolates and compared clinical features, such as lung function and survival or the need for a lung transplant.

What did you find?

We found three common *oprD* changes that each resulted in a shorter protein than usual and were characteristic of three *P. aeruginosa* strain sub-groups. In the laboratory, we found that the changes in the *oprD* gene probably contributed to the increased carbapenem resistance observed in the patient isolates. People with CF with lower lung function were more likely to be infected with the isolates with the commonly identified *oprD* changes. However, infection with these isolates did not result in a greater reduction in lung function over time or increase the risk of death or of a lung transplant.

What does this mean and reasons for caution?

P. aeruginosa strains sub-groups with specific *oprD* changes have persisted in Australia suggesting that cross-infection with these particular strain sub-groups between people with CF has occurred. The results suggest that people with CF with lower lung function may be at greater risk of acquiring the strain sub-groups. This could be due to these people having an increased exposure to healthcare environments. Although cause and effect cannot be proven,

the results indicate that acquisition of the strain sub-groups does not relate to worse clinical outcomes over time for those infected.

What's next?

Currently, antibiotic resistance identified in the laboratory does not correlate well with response to treatment of pulmonary exacerbations in CF. A possible future study is to determine if changes in *oprD* have a therapeutic value in predicting responses to antibiotic treatment regimens containing carbapenems.

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