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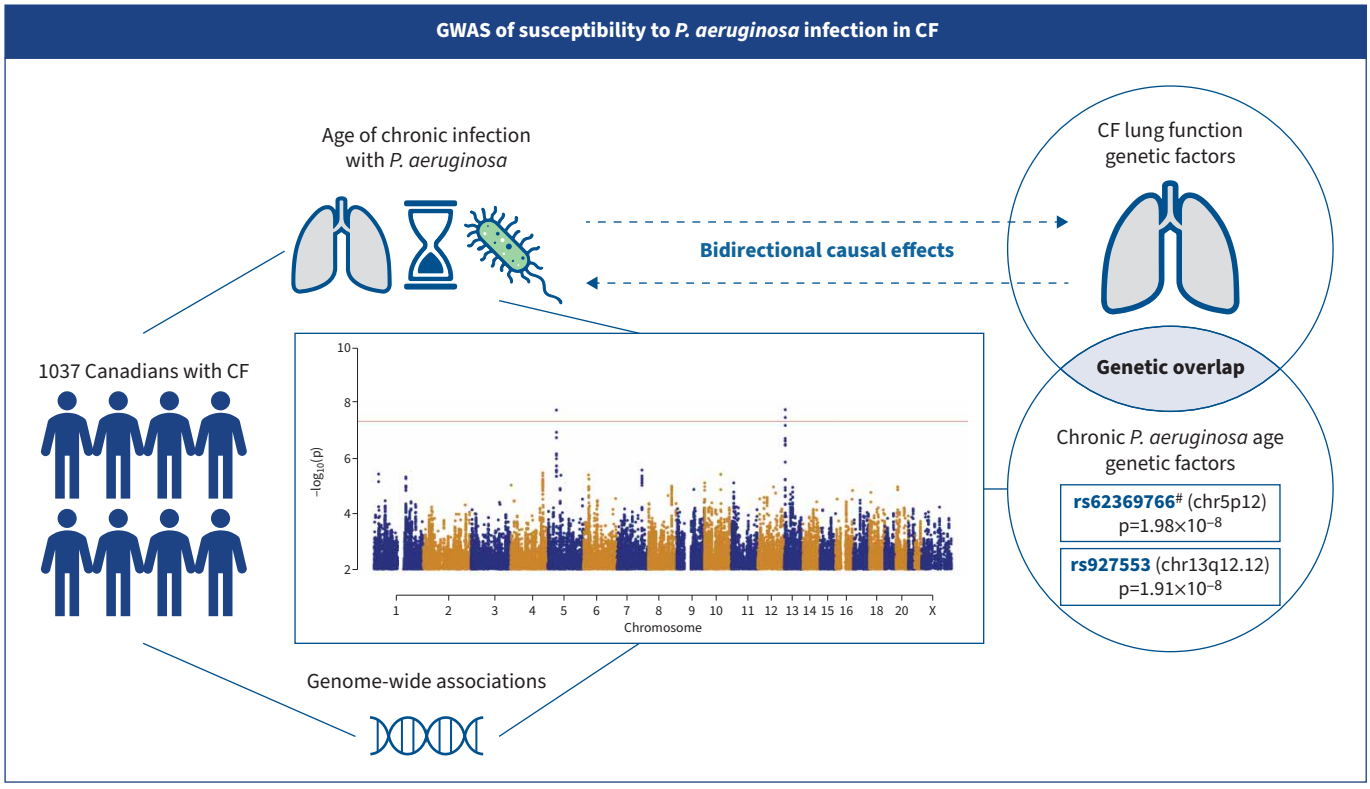

GRAPHICAL ABSTRACT Summary of the study. In a genome-wide association study (GWAS) of 1037 Canadians with cystic fibrosis (CF), we found two novel loci linked to chronic *Pseudomonas aeruginosa* infection age. We found evidence of a shared polygenic component and a potential causal relationship between chronic *P. aeruginosa* infection and lung disease. #: the rs62369766 locus was validated using an independent French cohort (n=501).

Link to published version: https://doi.org/10.1183/13993003.00062-2024

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
B. LIN ET AL.

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Shareable abstract (@ERSpublications)
This GWAS on 1037 Canadians with CF found two novel loci linked to chronic *Pseudomonas aeruginosa* (*Pa*) infection age, along with evidence of a shared polygenic component and a potential causal relationship between chronic *Pa* infection and lung disease https://bit.ly/4fcMeFg

Cite this article as: Lin B, Gong J, Keenan K, *et al*. Genome-wide association study of susceptibility to *Pseudomonas aeruginosa* infection in cystic fibrosis. *Eur Respir J* 2024; 64: 2400062 [DOI: 10.1183/13993003.00062-2024].

This article has an editorial commentary: https://doi.org/10.1183/13993003.01224-2024

Received: 10 Oct 2022
Accepted: 10 July 2024

Abstract

Background *Pseudomonas aeruginosa* is a common pathogen that contributes to progressive lung disease in cystic fibrosis (CF). Genetic factors other than CF-causing *CFTR* (CF transmembrane conductance regulator) variations contribute ∼85% of the variation in chronic *P. aeruginosa* infection age in CF according to twin studies, but the susceptibility loci remain unknown. Our objective is to advance understanding of the genetic basis of host susceptibility to *P. aeruginosa* infection.

Materials and methods We conducted a genome-wide association study of chronic *P. aeruginosa* infection age in 1037 Canadians with CF. We subsequently assessed the genetic correlation between chronic *P. aeruginosa* infection age and lung function through polygenic risk score (PRS) analysis and inferred their causal relationship through bidirectional Mendelian randomisation analysis.

Results Two novel genome-wide significant loci with lead single nucleotide polymorphisms (SNPs) rs62369766 (chr5p12; $p=1.98\times10^{-8}$) and rs927553 (chr13q12.12; $p=1.91\times10^{-8}$) were associated with chronic *P. aeruginosa* infection age. The rs62369766 locus was validated using an independent French cohort (n=501). Furthermore, the PRS constructed from CF lung function-associated SNPs was significantly associated with chronic *P. aeruginosa* infection age (p=0.002). Finally, our analysis presented evidence for a causal effect of lung function on chronic *P. aeruginosa* infection age (β=0.782 years, $p=4.24\times10^{-4}$). In the reverse direction, we observed a moderate effect (β=0.002, p=0.012).

Conclusions We identified two novel loci that are associated with chronic *P. aeruginosa* infection age in individuals with CF. Additionally, we provided evidence of common genetic contributors and a potential causal relationship between *P. aeruginosa* infection susceptibility and lung function in CF. Therapeutics targeting these genetic factors may delay the onset of chronic infections, which account for significant remaining morbidity in CF.