Genome-wide association study of chronic sputum production implicates loci involved in mucus production and infection

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Shareable abstract (@ERSpublications)
Genome-wide association study in UK Biobank identifies six novel loci associated with chronic sputum production at genome-wide significance in a disease agnostic population. These include a *FUT2* locus, highlighting a possible target for drug development. https://bit.ly/3IRVJeT

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Abstract

Background Chronic sputum production impacts on quality of life and is a feature of many respiratory diseases. Identification of the genetic variants associated with chronic sputum production in a disease agnostic sample could improve understanding of its causes and identify new molecular targets for treatment.

Methods We conducted a genome-wide association study (GWAS) of chronic sputum production in UK Biobank. Signals meeting genome-wide significance ($p<5\times10^{-8}$) were investigated in additional independent studies, were fine-mapped and putative causal genes identified by gene expression analysis. GWASs of respiratory traits were interrogated to identify whether the signals were driven by existing respiratory disease among the cases and variants were further investigated for wider pleiotropic effects using phenome-wide association studies (PheWASs).

Results From a GWAS of 9714 cases and 48 471 controls, we identified six novel genome-wide significant signals for chronic sputum production including signals in the human leukocyte antigen (HLA) locus, chromosome 11 mucin locus (containing *MUC2*, *MUC5AC* and *MUC5B*) and *FUT2* locus. The four common variant associations were supported by independent studies with a combined sample size of up to 2203 cases and 17 627 controls. The mucin locus signal had previously been reported for association with moderate-to-severe asthma. The HLA signal was fine-mapped to an amino acid change of threonine to arginine (frequency 36.8%) in HLA-DRB1 (*HLA-DRB1*03:147*). The signal near *FUT2* was associated with expression of several genes including *FUT2*, for which the direction of effect was tissue dependent. Our PheWAS identified a wide range of associations including blood cell traits, liver biomarkers, infections, gastrointestinal and thyroid-associated diseases, and respiratory disease.

Conclusions Novel signals at the *FUT2* and mucin loci suggest that mucin fucosylation may be a driver of chronic sputum production even in the absence of diagnosed respiratory disease and provide genetic support for this pathway as a target for therapeutic intervention.