RESEARCH ARTICLE

Genome-wide association study of susceptibility to hospitalised respiratory infections [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: Globally, respiratory infections contribute to significant morbidity and mortality. However, genetic determinants of respiratory infections are understudied and remain poorly understood.

Methods: We conducted a genome-wide association study in 19,459 hospitalised respiratory infection cases and 101,438 controls from UK Biobank. We followed-up well-imputed top signals from the UK Biobank discovery analysis in 50,912 respiratory infection cases and 150,442 controls from 11 cohorts. We aggregated effect estimates across studies using inverse variance-weighted meta-analyses. Additionally, we investigated the function of the top signals in order to gain understanding of the underlying biological mechanisms.

Results: In the discovery analysis, we report 56 signals at $P < 5 \times 10^{-6}$, one of which was genome-wide significant ($P < 5 \times 10^{-8}$). The genome-wide significant signal was in an intron of *PBX3*, a gene that encodes pre-B-cell leukaemia transcription factor 3, a homeodomain-containing transcription factor. Further, the genome-wide significant signal was found to colocalise with gene-specific expression quantitative trait loci (eQTLs) affecting expression of *PBX3* in lung tissue, where the respiratory infection risk alleles were associated with decreased *PBX3* expression in lung tissue, highlighting a possible biological mechanism. Of the 56 signals, 40 were well-imputed in UK Biobank and were investigated in the 11 follow-up cohorts. None of the 40 signals replicated, with effect estimates attenuated.

Conclusions: Our discovery analysis implicated *PBX3* as a candidate causal gene and suggests a possible role of transcription factor binding activity in respiratory infection susceptibility. However, the *PBX3* signal, and the other well-imputed signals, did not replicate when aggregating effect estimates across 11 independent cohorts. Significant phenotypic heterogeneity and differences in study ascertainment may have contributed to this lack of statistical

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replication. Overall, our study highlighted putative associations and possible biological mechanisms that may provide insight into respiratory infection susceptibility.

Keywords

Respiratory infections, GWAS, UK Biobank, electronic medical records

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Introduction

Respiratory infections are a group of diseases characterised by infection and inflammation of the respiratory system. Respiratory infections can be grouped according to their symptomatology, anatomic involvement and causative pathogen¹. Upper respiratory tract infections are typically benign, self-limiting diseases, and include the common cold, pharyngitis and otitis media. However, upper respiratory tract infections can be particularly burdensome for infants and young children². Lower respiratory tract infections, on the other hand, are often life-threatening diseases that require medical intervention. In 2016, over two million deaths worldwide were caused by lower respiratory tract infections, making this group of infectious diseases the sixth leading cause of death in individuals of all ages and the leading cause of death in very young children^{3,4}. Environmental exposures, such as indoor air pollution and inhalation of tobacco smoke, are important risk factors for upper and lower respiratory tract infections⁴. Genetic factors may also contribute to host susceptibility to infection. Indeed, twin studies have demonstrated a genetic component in susceptibility to otitis media^{5,6}, recurrent tonsillitis⁷ and respiratory syncytial virus-related bronchiolitis⁸ with heritability estimates as high as 73%⁵. Identifying associations with genes and pathways that influence host susceptibility to infection may reveal novel therapeutic targets and opportunities for drug development.

Further to the environmental and genetic risk factors described above, primary immunodeficiencies (PIDs) are a group of disorders that affect normal immune function, often leading to increased susceptibility to infections⁹. Activated phosphoinositide-3-kinase δ syndrome (APDS) is one such PID that is caused by gain-of-function mutations in genes encoding phosphoinositide-3-kinase δ (PI3K δ)⁹. In previous studies of APDS^{10,11}, up to 96% of individuals with APDS presented with an upper respiratory tract infection, such as otitis media, and/or a lower respiratory tract infection, such as pneumonia, seemingly distinct respiratory infection diseases. These findings may motivate the need to study a broad respiratory infection phenotype—one that comprises many different kinds of respiratory infection diseases—due to the possibility of shared aetiology between distinct conditions as previously observed in the context of APDS.

In this study, we conducted a genome-wide association study (GWAS) of hospitalised respiratory infections in UK Biobank, utilising the Hospital Episode Statistics (HES) data. We report genetic variants that were putatively associated with hospitalised respiratory infections, of which a subset of well-imputed genetic variants was followed up in 11 independent cohorts. We performed an inverse variance-weighted fixed effects meta-analysis to aggregate effect estimates across the UK Biobank discovery and follow-up cohorts. Finally, we applied a range of statistical approaches in order to achieve greater insight into the biological mechanisms underlying the putative statistical associations.

Methods

Defining the hospitalised respiratory infection phenotype

The hospitalised respiratory infection (HRI) phenotype was a composition of International Classification of Diseases, 10th Revision (ICD-10) codes. We initially extracted all ICD-10 codes under Chapter 10: diseases of the respiratory system. Then, by manually exploring the [online browser](#), we extracted further relevant ICD-10 codes that appear under other chapter headings that would have otherwise been missed. Following careful consideration, we restricted the ICD-10 codes to those most likely to be indicative of a respiratory infection (Table S1, *Extended data*¹²). An ICD-10 code was deemed relevant by screening its text description, retaining those relating to clinical diagnoses and the detection of common respiratory pathogens.

Discovery analysis in UK Biobank

Cases were defined by the presence of one or more of the relevant HRI ICD-10 codes (Table S1, *Extended data*¹²) in the linked Hospital Episode Statistics (HES) data over a 20-year period—from the inception of ICD-10 coding in the UK to the end of the period covered by the version of the HES data we analysed. These data reflect all diagnoses recorded while an individual was a patient in hospital, not just the primary discharge diagnosis, and does not include outpatient hospital diagnoses. We restricted the cases to those with (1) genome-wide imputed genetic data; (2) complete information for age (at recruitment), sex and smoking status (at recruitment); (3) no 2nd degree or closer relative (defined by a kinship estimate >0.0884 from the KING software, provided by UK Biobank) in cases only, and (4) were of European ancestry based on *k*-means clustering of the first two principal components of ancestry. Among the UK Biobank participants who were not defined as cases, we, separately, applied the same quality control measures as described above. Then, controls were randomly selected—to ensure computational feasibility, only a subset of controls was analysed—without replacement from the remaining individuals, using the sample function in R v3.6.1, at a ratio of five controls to every case, such that the distributions of age, sex and smoking status were broadly similar to those of the cases. Following selection of controls, the relatedness was checked between cases and controls. In 2nd degree or closer related pairings, controls were preferentially excluded in order to maximise the number of cases in the analysis.

Genotyping was undertaken using the Affymetrix Axiom UK BiLEVE¹³ and UK Biobank¹⁴ arrays. Genotype imputation was conducted using the Haplotype Reference Consortium panel and the merged 1000 Genomes phase 3 and UK10K panels¹⁴. Imputed genotypes with a minor allele count >20 (in all UK Biobank participants with genome-wide imputed genetic data) and an imputation quality score >0.5 were tested for association with the HRI phenotype.

PLINK 2.0¹⁵ was used to perform the genome-wide association study. We assessed autosomal variant associations under an

additive genetic model adjusted for age (at recruitment), age², genotyping array, sex, smoking status and the first ten principal components of ancestry. We analysed variant dosages in order to account for genotype uncertainty.

LD score regression¹⁶ was used to quantify genome-wide inflation in the test statistics due to possible confounding of the genotype-phenotype associations, for example, by population stratification.

Initial signal selection and conditional analyses

We initially defined primary signals of association according to the following criteria: minor allele frequency >0.1% (in cases and controls combined), Hardy-Weinberg exact test $P > 1 \times 10^{-6}$ (in cases and controls combined), and an association $P < 5 \times 10^{-6}$.

All genetic variants ± 1 Mb from the sentinel variant in each association signal were extracted. A conditional analysis was used to identify further, conditionally independent association signals within the 2Mb regions, using GCTA^{17,18}. Conditionally independent signals were defined according to the same criteria as for the primary signals.

Effect of smoking behaviour

The discovery analysis was adjusted for ever-smoking status. However, this may not have fully adjusted for the effect of smoking behaviour. Therefore, we assessed whether any of the association signals for HRIs were driven by smoking behaviour by testing the association between the sentinel variants from the HRI GWAS and smoking initiation (189,159 ever smokers versus 224,349 never smokers), smoking cessation (150,906 current smokers versus 45,075 ex-smokers), the number of cigarettes smoked per day (categorised, 136,391 total individuals), and heaviness of smoking index, a measure of nicotine dependence, (categorised, 31,766 total individuals). We also assessed the association with HRIs in never smokers only (8123 cases and 42,361 controls). These smoking behaviour phenotypes are discussed in more detail in the Supplementary Material (*Extended data*¹²). We used a P -value corrected for the number of sentinel variants tested to define a significant association with a smoking behaviour phenotype.

Follow-up cohorts

The following cohorts were included in the follow-up analysis: The Institute for Personalized Medicine BioMe Biobank (BioMe), Cardiovascular Health Study (CHS)¹⁹, Electronic Medical Records and Genomics Network (eMERGE)^{20,21}, Estonian Biobank²², Generation Scotland: Scottish Family Health Study (GS:SFHS)²³, Northern Finland 1966 Birth Cohort (NFBC1966)²⁴, Orkney Complex Disease Study (ORCADES), Partners Biobank, Penn Medicine Biobank, Trøndelag Health Study (HUNT)²⁵ and Viking Health Study Shetland (VIKING). A brief summary of each of the cohorts included in the follow-up analysis is given in the Supplementary Material (*Extended data*¹²).

The Cardiovascular Health Study and Partners Biobank cohorts defined the HRI phenotype using ICD-9 codes. For this, we

mapped the HRI ICD-10 codes to their ICD-9 counterparts, where possible (Table S2, *Extended data*¹²).

Meta-analysis of discovery and follow-up cohorts

Of the sentinel variants in each association signal achieving $P < 5 \times 10^{-6}$ in the discovery analysis, a subset was followed up in the 11 independent cohorts described above according to the following criteria: all sentinel variants with a minor allele frequency >1%, and any sentinel variant with a minor allele frequency between 0.1% and 1% that additionally had an imputation quality score >0.8. This latter criterion was used to ensure greater confidence in the genotype imputation in lower-frequency sentinel variants and, hence, in the statistical associations.

Where necessary, proxy variants, with a minimum R^2 of 0.6, were substituted based on UK Biobank LD. We used the LDpair tool in the LDlink²⁶ suite of online applications to match the effect allele of proxy variants to that of the corresponding sentinel variant.

We conducted an inverse variance-weighted (IVW) fixed effects meta-analysis of association results from the follow-up cohorts and, separately, combined with the discovery analysis using the *meta* package in R v3.6.1. We used $P < 5 \times 10^{-8}$ in the overall meta-analysis (discovery with follow-up) and a Bonferroni-corrected P -value threshold in the meta-analysis of follow-up cohorts only, corrected for the number of variants followed up, to define a replicated signal.

Identifying putative causal genes

Fine-mapping. In order to restrict the variants in each association signal defined in the discovery analysis to those most likely to be causal, we performed fine-mapping using a Bayesian method²⁷. This approach derives approximate Bayes' factors from GWAS summary statistics, from which the posterior probability of a variant being the true causal variant (under the assumption that the true causal variant was analysed) can be calculated. The variants at each association signal can be sorted by the posterior probability and combined to create a set of variants that is 95% probable to contain the true causal variant, i.e. 95% credible set. Posterior probabilities were calculated for all variants ± 1 Mb from the sentinel variant in each association signal that had $R^2 > 0.1$ with the sentinel variant, using $W=0.04$ as the prior parameter, representing 95% belief that the relative risk corresponding to departure from the null model lies between 2/3 and 3/2^{27,28}. Association signals in the HLA region were not included in the fine-mapping.

Functional annotation. To identify putative causal genes, we used the Ensembl GRCh37 Variant Effect Predictor (VEP)²⁹ to annotate all variants in the 95% credible sets. We used the following criteria to annotate variants as deleterious (all criteria implemented in VEP): labelled "deleterious" by SIFT, labelled "probably damaging" or "possibly damaging" by PolyPhen, had a CADD scaled score ≥ 20 , labelled "likely disease causing" by REVEL, labelled "damaging" by MetaLR or "high" by MutationAssessor. The union of the variants defined

by each of these methods was taken to be the set of potentially deleterious variants.

Gene expression. We tested whether any variants in the 95% credible sets were associated with gene expression from three expression quantitative trait loci (eQTL) databases: 48 tissues from GTEx v7³⁰, three major human immune cell types (CD14⁺ monocytes, CD16⁺ neutrophils, and naïve CD4⁺ T cells) from BLUEPRINT³¹, and *cis*- and *trans*-eQTLs in blood from eQTLGen³². A false discovery rate (FDR) of 5% was used to define a significant association with gene expression.

Colocalisation with expression quantitative trait loci (eQTLs)

Where a variant (or variants) in the 95% credible set was found to be associated with expression of a particular gene, we assessed whether there was a shared causal variant underlying the corresponding HRI GWAS association signal and expression of the implicated gene in the highlighted tissue or cell type. We performed colocalisation using the *coloc*²⁷ package in R v3.6.1 (with default prior probabilities) and all variants within 1Mb of the sentinel variant in the corresponding HRI GWAS signal for which $P < 0.01$ in either the HRI GWAS or the eQTL analysis.

In addition, we also used PICCOLO, which performs colocalisation in the absence of full summary statistics³³, for example if the association results for a sentinel variant only were available. In addition to eQTL data from the three eQTL databases described above, PICCOLO incorporates quantitative trait loci (QTL) data from additional sources, including protein quantitative trait loci (pQTL) data from four studies^{34–37}. These four studies collected pQTL data for blood plasma^{34,35}, sputum from chronic obstructive pulmonary disease (COPD) patients³⁶, and serum from asthma patients³⁷.

We used a posterior probability of >80% to identify colocalisation between the GWAS and eQTL traits for both methods described, i.e. >80% probability of a shared causal variant.

Pathway analysis

We tested for enrichment of genes harbouring association signals in pathways defined in the MetaBase³⁸ and Gene Ontology: Biological Processes^{39,40} (GOBP) databases using Pascal⁴¹. With Pascal, variants are mapped to genes by genomic position. To ensure computational feasibility, only GOBP pathways with >10 and <1000 genes were tested. A false discovery rate (FDR) <5% was used to define a significantly enriched pathway.

Assessment of sentinel variants in published GWAS

We assessed whether any of the sentinel variants in the association signals were associated with other traits and diseases from existing GWAS. The traits studied included, but were not limited to, UK Biobank baseline measures (from questionnaires and physical measures), curated health outcomes from primary and/or secondary care data, and self-reported diseases and medications. $P < 5 \times 10^{-8}$ was used to define a significant association between the sentinel variants and existing

GWAS traits. Further, likely relevant, traits were also highlighted at $P < 5 \times 10^{-6}$.

In addition, we investigated the association between the sentinel variants and four COVID-19 phenotypes from the COVID-19 Host Genetics Initiative⁴² meta-analyses (release 6) ranging from 8779 cases (very severe COVID-19) to 112,612 cases (any COVID-19) from up to 165 cohorts worldwide. A significant association between a sentinel variant and a COVID-19 phenotype was defined using $P < 5 \times 10^{-8}$.

Ethics statement

UK Biobank: The human samples were sourced ethically, and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol (16/NW/0274).

Estonian Biobank: This study and the use of data acquired from biobank participants was approved by the Research Ethics Committee of the University of Tartu (Approval number 288/M-18).

Ethical approval for the GS:SFHS study was obtained from the Tayside Committee on Medical Research Ethics (on behalf of the National Health Service).

The HUNT study was approved by the Regional Committee for Medical and Health Research Ethics and written informed consent was given by all participants.

The research protocols of NFBC1966 have been approved by the Ethics Committee of the Northern Finland Ostrobothnia Hospital District and all participants have given their written informed consent.

No further ethics approvals were required for the analyses of these data.

Results

Defining the hospitalised respiratory infection phenotype

Our hospitalised respiratory infection phenotype was a composition of 114 ICD-10 codes (Table S1, *Extended data*¹²). Due to the specificity of certain codes (for example, “pneumonia due to *Klebsiella pneumoniae*” versus the more generic “pneumonia, unspecified”), 59 (51.8%) of these 114 ICD-10 codes occurred in fewer than 10 individuals, and 28 (24.6%) codes did not occur at all. Furthermore, 95% of cases were captured by the 16 most frequently recorded codes – the most common code, “J22 unspecified acute lower respiratory infection”, accounted for more than one third (37.8%) of all cases (Figure 1).

Discovery analysis in UK Biobank

Following quality control, 19,459 cases and 101,438 controls were included in the association testing of 52,488,101 genetic variants. The intercept of LD score regression¹⁶ was found to be 1.013, hence we did not correct the GWAS results for inflation (*Methods*). We defined 56 signals showing association at

Figure 1. Frequency of individual ICD-10 codes used to define the hospitalised respiratory infection phenotype. Frequency (log₁₀ scale) of individual ICD-10 codes used to define the hospitalised respiratory infection phenotype. To improve visualisation, only codes that occurred in 10 or more individuals are shown. Individuals may contribute to the overall count of more than one ICD-10 code. A description of each ICD-10 code, as well as the ICD-10 code itself, is shown.

$P < 5 \times 10^{-6}$ with hospitalised respiratory infections (HRIs), including one signal on chromosome 9 that was genome-wide significant ($P < 5 \times 10^{-8}$; Table S3, *Extended data*¹²). The sentinel variant, rs10564495 (risk allele: A, risk allele frequency: 65.0%), in the genome-wide significant signal was located in an intron of *PBX3*, a gene that encodes pre-B-cell leukaemia transcription factor 3, a homeodomain-containing transcription factor. The conditional analysis¹⁸ did not identify further conditionally independent signals in any of the 2Mb regions.

Effect of smoking behaviour

We assessed the association between the sentinel variants in the 56 signals and smoking behaviour traits (*Methods* and *Supplementary Material, Extended data*¹²). The rs10564495 variant was found to be significantly associated with smoking cessation ($P = 1.53 \times 10^{-4}$; Table S3, *Extended data*¹²). The A allele for this variant was associated with 3.1% (odds ratio (OR): 0.969; 95% CI: 0.954-0.985) lower odds of quitting smoking and 7.6% (OR: 1.076; 95% CI: 1.051-1.101) greater odds of HRIs.

In a stratified analysis, the association between this variant and HRIs was stronger in never-smokers than in both ever-smokers and in the overall GWAS: 8.9% (OR: 1.089; 95% CI: 1.051-1.129) greater odds of HRIs in never-smokers versus 6.6% (OR: 1.066; 95% CI: 1.034-1.099) greater odds of HRIs in ever-smokers (effect size for overall GWAS as above). These latter findings may suggest that the effect of the rs10564495 variant was not mediated by smoking behaviour.

Meta-analysis of discovery and follow-up cohorts

Across the 11 follow-up cohorts (*Methods*), there were 50,912 additional cases and 150,442 additional controls, bringing the total number of cases to 70,371 and controls to 251,880, effectively more than tripling the number of cases included in the discovery analysis in UK Biobank (Table 1).

In the meta-analysis of the discovery and follow-up cohorts, no variants achieved $P < 5 \times 10^{-8}$ (Table S5, *Extended data*¹²). Furthermore, in the meta-analysis of follow-up cohorts alone, no variants met a Bonferroni-corrected P -value threshold for 40 tests ($P < 0.05/40 = 1.25 \times 10^{-3}$). The effect estimates in the follow-up cohorts for rs10564495-A, or its proxy rs10819083-T, were consistently in the opposite direction, or were close to the null value, to the effect estimate from the UK Biobank

discovery analysis (Figure 2). In the meta-analysis of the discovery and follow-up cohorts for the rs10564495 variant, we observed an I^2 statistic of 70.8% (95% CI: 45.9%-84.2%; $P = 0.0002$), representing significant heterogeneity in the meta-analysis for this variant.

Identifying putative causal genes

Fine-mapping. There were 107 variants in the 95% credible set at the genome-wide significant locus from the discovery analysis. The sentinel variant, rs10564495, at this locus was assigned 16.2% probability of being causal, the highest probability in the corresponding 95% credible set (Table S6, *Extended data*¹²).

Functional annotation. According to the criteria defined in *Methods*, there were six variants in five unique genes across four signals that were annotated as deleterious (Table S7, *Extended data*¹²): *DNAH6* (rs72832548 and rs72836490), *ZNF608* (rs10040793), *PBX3* (rs7849076 and rs1411352), *RNU6-457P* (rs2172310) and *RBFOX1* (rs2172310). The two missense variants in *DNAH6* (rs72832548 and rs72836490) were low frequency (minor allele frequencies of 0.55% and 0.56%, respectively) and result in amino acid changes from serine to glycine and alanine to threonine, respectively. The consequence(s) of these base changes has not been reported. *DNAH6* encodes a

Table 1. Summary demographics of the case-control populations in the UK Biobank discovery cohort and each of the follow-up cohorts. Demographics of the case-control populations in the UK Biobank discovery cohort and in each of the follow-up cohorts. *The HUNT cohort provided average year of birth rather than average age. For age, the mean and standard deviation are reported in cases and controls separately. For sex and smoking status, the number and proportion of females and never-smokers are reported in cases and controls separately.

Cohort	Sample size		Age, mean (SD)		Sex, n (%) - female		Smoking status, n (%) - never-smoker	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
UK Biobank (discovery)	19,459	101,438	59.1 (7.7)	59.0 (7.7)	9280 (47.7)	48,312 (47.6)	8123 (41.7)	42,361 (41.8)
BioMe	585	2182	60.0 (17.2)	56.9 (17.4)	335 (57.3)	1058 (48.5)	328 (56.1)	1205 (55.2)
CHS	1098	2169	72.5 (5.1)	72.3 (5.5)	647 (58.9)	1342 (61.9)	476 (43.4)	1088 (50.2)
eMERGE	26,353	33,252	67.3 (24.0)	58.6 (24.8)	11,644 (44.2)	16,964 (51.0)	18,265 (69.3)	26,938 (81.0)
Estonian Biobank	4420	19,937	59.2 (17.9)	58.9 (17.6)	2961 (67.0)	13,230 (66.4)	2446 (55.3)	10,916 (54.8)
GS:SFHS	1133	15,729	41.8 (17.3)	47.4 (14.4)	651 (57.5)	9223 (58.6)	535 (47.2)	8271 (52.6)
HUNT*	9887	58,243	1940 (16.8)	1950 (17.7)	4794 (48.5)	31,203 (53.6)	3106 (31.4)	25,153 (43.2)
NFBC1966	1340	2899	31.1 (0.4)	31.1 (0.4)	534 (39.9)	1795 (61.9)	820 (61.2)	1628 (56.2)
ORCADES	141	1886	55.6 (19.5)	53.6 (15.0)	93 (66.0)	1131 (60.0)	86 (61.0)	1159 (61.5)
Partners Biobank	3342	4386	62.5 (15.5)	59.0 (16.6)	1959 (58.6)	2387 (54.4)	2023 (60.5)	2797 (63.8)
Penn Medicine Biobank	2488	7755	69.7 (13.6)	70.5 (13.6)	916 (36.8)	2569 (33.1)	953 (38.3)	3398 (43.8)
VIKING	125	2004	45.4 (16.8)	50.1 (15.1)	71 (56.8)	1208 (60.3)	72 (57.6)	1100 (54.9)
Total	70,371	251,880			33,885 (48.2)	130,422 (51.8)	37,233 (52.9)	126,014 (50.0)

Figure 2. Forest plot for the sentinel variant in the genome-wide significant signal from the discovery analysis following meta-analysis of discovery and follow-up study level results. Forest plot for the sentinel variant, rs10564495, in the genome-wide significant signal identified in the UK Biobank discovery GWAS following inverse variance-weighted fixed effects meta-analysis of discovery and follow-up study level results. The A allele for this variant was taken to be the coded allele. Where a proxy variant was used, which was consistently the rs10819083 variant, the T allele was taken to be the allele that corresponds to the A allele of the rs10564495 variant, as reported by the LDpair tool in the LDlink²⁶ suite of online applications.

protein that is involved in regulating motile ciliary beating^{43,44} and has been implicated in primary ciliary dyskinesia⁴⁵, a disorder characterised by chronic respiratory tract infections. *PBX3* houses the genome-wide significant signal from the discovery analysis. However, the two variants in *PBX3* annotated as deleterious were non-coding (Table S7, *Extended data*¹²).

Gene expression and colocalisation with expression quantitative trait loci (eQTLs)

Using GTEx v7³⁰ data, the genome-wide significant signal from the discovery analysis was found to colocalise (PP>80%) with *PBX3*-specific eQTLs in heart atrial appendage tissue, tibial artery tissue, not-sun-exposed suprapubic skin tissue, stomach tissue, lung tissue, aortic artery tissue, and sigmoid colon tissue (Figure 3 and Supplementary Figures, *Extended data*¹²). The HRI risk alleles were consistently associated with decreased *PBX3*-specific gene expression in all of the aforementioned tissues (Table S8, *Extended data*¹²). We also found colocalisation between the genome-wide significant signal and expression of the proximal *GOLGA1* gene in sun-exposed lower leg skin tissue (PP=81%). We did not identify additional colocalisation using BLUEPRINT³¹ or eQTLGen³² data.

Using PICCOLO³³, the genome-wide significant signal from the discovery analysis was found to additionally colocalise (PP>80%) with *PBX3*-specific eQTLs in CD4/8⁺ naïve T cells, coronary artery tissue and whole blood (Table S11, *Extended data*¹²). PICCOLO did not highlight colocalisation between eQTLs

and any proximal genes to *PBX3*. At the time of analysis, PICCOLO did not provide effect estimates for the eQTL traits. Therefore, we queried the Open Targets Genetics⁴⁶ portal in order to assess directionality for these additional eQTL traits. The HRI risk alleles were associated with decreased *PBX3*-specific expression in coronary artery tissue. Summary statistics for the T cell and whole blood traits were not available, however.

For the remaining signals, the chromosome 5 signal (sentinel variant: rs7730012) was found to colocalise with *ZNF608*-specific eQTLs in tibial artery tissue (GTEx v7³⁰) using the *coloc*²⁷ method (Supplementary Figure 1, *Extended data*¹²). Additional results from PICCOLO³³ can be seen in Table S11 (*Extended data*¹²).

Pathway analysis

We tested for significant enrichment of genes from the HRI GWAS in known pathways: 1383 pathways from the MetaBase³⁸ resource and 6405 pathways from the Gene Ontology: Biological Processes^{39,40} resource (*Methods*). We did not identify any significantly enriched pathways at a false discovery rate of 5%.

Assessment of sentinel variants in published GWAS

The A allele of the rs10564495 variant was associated with increased overall health rating, increased odds of requiring the use of dentures and decreased standing height at $P < 5 \times 10^{-8}$ (Table S12, *Extended data*¹²), and decreased lung function and increased odds of various respiratory disease phenotypes,

Figure 3. Hospitalised respiratory infection GWAS versus eQTL for *PBX3* in lung tissue (GTEx v7): probability of colocalisation = 87%. Each point corresponds to a genetic variant, with genomic position (GRCh37) on the x-axis and $-\log_{10}(p\text{-value})$ on the y-axis. The top plot shows regional association results for the genome-wide significant signal (sentinel variant: rs10564495) from the hospitalised respiratory infection GWAS. The bottom plot shows regional association results for the genome-wide significant signal from the eQTL analysis. The plotting window extends 1Mb either side of the sentinel variant in the region. The sentinel variant is represented by a blue triangle, with all other genetic variants in the region coloured according to the extent of pairwise linkage disequilibrium with the sentinel variant: red points reflect genetic variants that have $r^2 > 0.8$ with the sentinel variant, orange points reflect genetic variants that have $0.5 < r^2 \leq 0.8$ with the sentinel variant, yellow points reflect genetic variants that have $0.2 < r^2 \leq 0.5$ with the sentinel variant, and grey points reflect genetic variants that have $r^2 \leq 0.2$ with the sentinel variant. The area shaded in light pink represents the gene implicated by the eQTL analysis. The red dashed line represents a p -value threshold of 5×10^{-8} .

including respiratory infections, at $P < 5 \times 10^{-6}$ (Table S13, *Extended data*¹²). Significant associations for the other sentinel variants are presented in Tables S12&S13 and include various respiratory infection phenotypes such as acute pharyngitis and pneumonia.

Finally, there were no significant associations found between any of the sentinel variants and the four COVID-19 phenotypes from the COVID-19 Host Genetics Initiative⁴² (Table S14, *Extended data*¹²).

Discussion

We conducted one of the largest GWAS of respiratory infections to date, combining data from UK Biobank and 11 international cohorts.

In our UK Biobank discovery analysis, the strongest association signal was in an intron of the *PBX3* gene, which encodes the pre-B-cell transcription factor 3 protein. *PBX3* contributes to DNA-binding transcription factor activity and sequence-specific DNA binding. The hospitalised respiratory infection risk alleles at this locus were associated with decreased expression of *PBX3* in lung tissue (Table S8, *Extended data*¹²). In a recent preprint, *PBX3* was found to be associated with pneumonia in almost 25,000 cases from UK Biobank

and FinnGen⁴⁷. The authors also found that genetic variants in *PBX3* were associated with *PBX3* expression in lung tissue (effect direction not reported). In a study of a range of infectious diseases using 23andMe data, including some respiratory infections such as pneumonia and childhood ear infections, neither *PBX3*, nor any neighbouring genes, were found to be associated with the diseases studied⁴⁸. However, it should be noted that the respiratory infection phenotypes in the 23andMe study were defined from self-reported questionnaire data which may have been subject to recall bias, particularly for diseases that occurred during childhood.

Evidence that *PBX3* is a functionally significant transcription factor in a range of cancers, in addition to its expression being linked to more aggressive disease and shorter overall survival, has been reported⁴⁹. Cancer patients are more susceptible to infections for a number of reasons. One such reason may be due to the receipt of immunosuppressants compromising the individual's immune system, resulting in greater risk of opportunistic infection, as has been observed in lung cancer patients⁵⁰.

We followed up 40 signals from the UK Biobank discovery analysis in 11 independent cohorts. None of the 40 signals surpassed $P < 5 \times 10^{-8}$ in the meta-analysis of follow-up and

discovery cohorts, highlighting the importance of statistical replication and the potential influence of winner's curse bias in our UK Biobank discovery analysis. However, it is possible that there was significant phenotypic heterogeneity between cohorts owing to differences in exposure to circulating pathogens, health care systems and coding practices which may have influenced the representation of particular infections in the medical record data. For example, the respiratory infection phenotype in UK Biobank was defined using ICD-10 codes (Table S1, *Extended data*¹²). In two of the follow-up studies, the corresponding phenotype was defined entirely or partly by ICD-9 codes (Table S2, *Extended data*¹²). As there is no exact mapping between ICD-9 and ICD-10 codes, the resulting phenotypes may differ and give rise to greater heterogeneity between cohorts. In addition, controls were not selected for similar distributions of age, sex and smoking status in the follow-up cohorts which, in some cases, led to large differences in the distributions of the aforementioned factors between cases and controls for some cohorts (Table 1). Differences in the prevalence of certain comorbidities may have also contributed to the lack of statistical replication. In addition, the manner in which individuals were ascertained should be considered as some cohorts recruited individuals from the general population whereas others recruited from hospitals and other healthcare settings.

We applied a range of statistical techniques to further understand the biological mechanisms underlying the statistical associations identified in the UK Biobank discovery analysis. Following fine-mapping²⁸, the sentinel variant, rs10564495, in *PBX3* was attributed 16.2% probability of being causal for the GWAS trait among a set of 107 genetic variants that was attributed 95% probability of containing the true causal variant. These 107 genetic variants were located in, or slightly upstream of, *PBX3*. We found two variants in *PBX3* that were annotated as deleterious. However, these variants were non-coding. Further work is needed to understand the role of these particular variants in influencing susceptibility to hospitalised respiratory infections. In a colocalisation analysis, the *PBX3* signal was found to colocalise with *PBX3*-specific eQTLs in a range of tissues and cell types including, but not limited to, lung tissue, CD4/8⁺ T cells and whole blood. At the *PBX3* locus, the alleles that were associated with increased risk of hospitalised respiratory infections were also associated with decreased expression of *PBX3* in the tissues and cell types highlighted and may implicate *PBX3* as a candidate causal gene. Furthermore, we found that the *PBX3* sentinel variant was associated with overall health rating, denture use and standing height at $P < 5 \times 10^{-8}$, and a broader respiratory system disease phenotype and FEV₁ at $P < 5 \times 10^{-6}$ when looking across a large number of published GWAS. These associations, particularly those with FEV₁ and standing height, may implicate lung function as a driver of the *PBX3* association signal.

As with all research based on medical records, misclassification of diagnoses may have occurred, and we did not have the benefit of microbiological or virological data to confirm the infective agent. Nevertheless, the use of medical records

enabled us to study much larger sample sizes than have been attained in studies that do not use such data—historically, GWAS that define cases of respiratory infection by other means included fewer than 1000 cases^{51–56}. We combined multiple respiratory infection codes to define our overall phenotype, motivated by previous findings in the context of APDS, which resulted in a larger sample size but likely increased heterogeneity. Controls were individuals with no evidence of having had a respiratory infection in hospital, but we did not consider other data sources, such as primary care data, where there may be records of respiratory infection among the controls, reflecting misclassification and a possible loss of statistical power. Finally, we restricted our analysis to unrelated individuals of European ancestry in order to limit the potential impact of population stratification and cryptic relatedness. However, this may limit the generalisability of the results we report.

To conclude, genetic variants in *PBX3* were found to be associated with hospitalised respiratory infection susceptibility in UK Biobank, which may implicate transcription factor binding activity in susceptibility to a general respiratory infection phenotype. However, this finding did not replicate in independent cohorts, possibly highlighting replication as a limiting factor for phenotypes defined from electronic healthcare records due to phenotypic heterogeneity across different healthcare systems.

Data availability

Underlying data

This research has been conducted using the UK Biobank resource under applications 648 and 4892. The genetic and phenotypic UK Biobank data can be requested upon application to the UK Biobank resource for all bona fide researchers (see <https://www.ukbiobank.ac.uk/researchers/> for more details).

Figshare: WilliamsAT_prePMID_HRI.tsv.gz. <https://doi.org/10.6084/m9.figshare.16622062>⁵⁷.

Extended data

Figshare: Williams_et_al_extended_data. <https://doi.org/10.6084/m9.figshare.16622191>¹².

This project contains the following extended data:

- supplementary_material.docx (Supplementary material and methods)
- supplementary_figures.docx (Supplementary figures)
- tableS1_icd10_codes.csv (Table S1, ICD-10 codes used to define the hospitalised respiratory infection phenotype).
- tableS2_icd9_codes.txt (Table S2, ICD-9 codes used to define the hospitalised respiratory infection phenotype in CHS and Partners Biobank).
- tableS3_discovery_summstats_sentinels.csv (Table S3, Summary statistics for the 56 sentinel variants from the discovery GWAS in UK Biobank).

- [tableS4_followup_availability_sentinels.csv](#) (Table S4, Availability of the 40 sentinel variants in the 11 follow-up cohorts).
- [tableS5_metaanalysis_sentinels.csv](#) (Table S5, Results of the inverse variance-weighted fixed effects meta-analysis).
- [tableS6_finemapping_results.csv](#) (Table S6, Fine-mapping of the 56 association signals).
- [tableS7_annotation_results.csv](#) (Table S7, Functional annotation of variants in the 95% credible sets).
- [tableS8_geneexpression_results_gtex.csv](#) (Table S8, Association between variants in the 95% credible sets and gene expression across 48 tissues from GTEx v7).
- [tableS9_geneexpression_results_blueprint.csv](#) (Table S9, Association between variants in the 95% credible sets and gene expression across three major human immune cell types from BLUEPRINT).
- [tableS10_geneexpression_results_eqtlgen.csv](#) (Table S10, Association between variants in the 95% credible sets and gene expression (cis-eQTLs) from eQTLGen).
- [tableS11_coloc_piccolo_results.csv](#) (Table S11, Colocalisation results from PICCOLO).
- [tableS12_gwsig_lookup_results.csv](#) (Table S12, Look-up of the sentinel variants in the 56 association signals in existing GWAS).
- [tableS13_suggestive_lookup_results.csv](#) (Table S13, Look-up of the sentinel variants in the 56 association signals in existing GWAS).
- [tableS14_covid19hgi_lookup_results.csv](#) (Table S14, Look-up of the sentinel variants in the 56 association signals in the COVID-19 Host Genetics Initiative meta-analysis results).

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Gregory Joseph Fonseca

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In this study, the authors curate respiratory infections from the UK Biobank and compare genetic variation with controls. The authors find 40 statistically significant variants. The authors then provide functional annotation and predict cell type expression.

- Are the controls patients that have not had a hospitalized respiratory infection? This was unclear to me.
- Is there a control for age bias? Younger patients would have less chance of contracting a respiratory infection.
- Gene expression in healthy tissues may not be a good measure of gene expression during disease. Also, this is missing the resident cells that would direct the initial response.
- If the data is regressed against the smoking state, do the results hold, such as with rs10564495?
- Do the follow-up cohorts represent a distinctly different population? Is this the reason no variants were significant?
- Did the variants not appear in any of the 11 follow-up cohorts? It may be worth testing these systematically in case a few of your cohorts are hiding any results due to an inherent bias in the cohort.
- How many cases were found with variants in PBX3?
- If the PBX3 variants are non-coding, what is the proposed effect? Are they splicing, are they in enhancer-like elements? Are they in non-coding RNA-like elements?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Bioinformatics, genomics, viral infection

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 23 December 2021

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Chikashi Terao

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The authors conducted a GWAS of hospitalized respiratory infection using UKB and 11 other cohort data. They found PBX3 as a potential susceptibility gene but failed to replicate the findings.

While they conducted many downstream analyses, most of these analyses (such as fine-mapping, functional annotation, gene expression, and colocalization with eQTL) should have been done for GWAS significant variants. They conducted an assessment of 'sentinel variants' in published GWAS, but this analysis should be done in a meta-analysis, not in a discovery cohort. I don't think that the work is clearly presented since I cannot understand their analyses, such as conditioning analyses focusing on sentinel variants.

I believe that they first concluded that no GWAS significant signals were identified in the current study and then should move to analyze polygenic architecture, heritability, evaluation of previously reported signals.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Genetics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.