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Genetic predisposition to allergic diseases is inversely associated with risk of COVID-19

To the Editor,

The host immune response is integral to determining susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severity of consequent coronavirus disease 2019 (COVID-19).[1] Allergic diseases such as allergic rhinitis (hay fever), atopic dermatitis (eczema) and asthma tend to cluster together in individuals, partly because of shared genetic factors that navigate the immune system.[2] However, it is not yet known whether genetic predisposition to allergic disease also relates to COVID-19 susceptibility. Understanding this relationship may provide mechanistic insight towards uncovering preventative and therapeutic strategies for COVID-19. To this end, we performed a Mendelian randomization analysis investigating how genetic predictors of allergic disease relate to COVID-19 susceptibility.

As genetic instruments for the primary analysis, we considered 136 uncorrelated ($r^2<0.02$) single nucleotide polymorphisms associated with a broad allergic disease phenotype (presence of at least one allergic disease, including allergic rhinitis, atopic dermatitis, and asthma) at $P <3\times10^{-8}$ in a meta-analysis of 13 genome-wide association studies with a total of 180 129 cases and 180 709 controls (without the three allergic diseases), all of European descent.[2] Information on allergic disease was self-reported. The number of cases with each allergic disease are shown in Supplementary Table 1. The association estimates were adjusted for age, sex, and genetic principal components of ancestry.[2] In secondary analyses, we separately considered single nucleotide polymorphisms associated with each allergic disease (Supplementary Material).

Genetic association estimates for COVID-19 susceptibility were obtained from the COVID-19 Host Genetics Initiative genome-wide association meta-analyses (round 4, release October 20,

2020).[3] To minimize population stratification bias, we restricted the analyses to individuals of European ancestry. The publicly available datasets comprising European-descent individuals included 14 134 cases with laboratory confirmed COVID-19 infection (RNA and/or serology-based) or physician confirmed COVID-19 vs. 1 284 876 population controls (everyone that is not a case) and 6406 cases of hospitalised laboratory-confirmed COVID-19 infection vs. 902 088 population controls. Of the 136 single nucleotide polymorphisms associated with any allergic disease, 130 were available in the COVID-19 outcome datasets. Details of the single nucleotide polymorphisms and their associations with COVID-19 are shown in Supplementary Table 2.

We conducted two-sample summary-level Mendelian randomization analyses using the random-effects inverse-variance weighted method (primary analysis) and several statistical sensitivity analysis methods that make different assumptions.[4] Analyses were conducted in Stata/SE (version 14.2) and R (version 3.4.3) using summary-level data only. Ethical approval and participant consent had previously been obtained.

Genetic predisposition to any allergic disease was associated with reduced susceptibility to COVID-19 but not clearly with risk of being hospitalised with COVID-19 (Figure 1). Similar results were observed in statistical sensitivity analyses, although with wider confidence intervals that were likely attributable to lower statistical power (Figure 1). The associations of each single nucleotide polymorphism with allergic disease and COVID-19 susceptibility are displayed in Supplementary Figure 1. Secondary analyses based on genetic variants associated with different allergic diseases did not reveal associations with any particular allergic disease specifically, although the magnitude of the inverse association was most pronounced for allergic rhinitis albeit with broad confidence intervals (Supplementary Figure 2).

Our results provide evidence to support that the genetic factors underlying predisposition to allergic disease are protective against COVID-19. The pathophysiological process underlying COVID-19 involves an exaggerated host immune response.[5] Previous work has highlighted genetic associations between obesity and smoking with both allergic disease and severe COVID-19,[2, 6] supporting immune dysregulation as a common underlying mechanism. Further work is required to unravel the specific pathways linking susceptibility to allergic disease with risk of COVID-19, for the purpose of identifying opportunities for clinical intervention.

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References

1. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020;369:718-724.
2. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet 2017;49:1752-1757.

3. Covid-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. Eur J Hum Genet 2020;28:715-718.

4. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. Wellcome Open Res 2019;4:186.

5. McElvaney OJ, McEvoy NL, McElvaney OF, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. Am J Respir Crit Care Med 2020;202:812-821.

6. Ponsford MJ, Gkatzionis A, Walker VM, et al. Cardiometabolic traits, sepsis, and severe COVID-19: a Mendelian randomization investigation. Circulation 2020;142:1791-1793.

FIGURE LEGEND

FIGURE 1. Associations of genetic predisposition to any allergic disease with COVID-19 with different Mendelian randomization statistical analysis methods with different assumptions. The I^2 value for heterogeneity between individual genetic variants was ≤27%. The P value for the intercept in the MR-Egger analyses was >0.16 in all analyses. No outlier SNP was detected in the MR-PRESSO analysis. CI: confidence interval; Con-Mix, contamination mixture; IVW, inverse-variance weighted; MR, Mendelian randomization; OR: odds ratio; PRESSO, Pleiotropy RESidual Sum and Outlier.

Outcome and method	OR (95% CI)	*P*-value
COVID-19 susceptibility		
IVW	0.89 (0.83, 0.95)	0.001
Weighted median	0.91 (0.83, 1.00)	0.052
MR-Egger	0.90 (0.75, 1.07)	0.241
MR-PRESSO	0.89 (0.83, 0.95)	0.001
Con-Mix	0.88 (0.80, 0.96)	0.005
COVID-19 hospitalisation		
IVW	0.93 (0.83, 1.05)	0.265
Weighted median	0.88 (0.74, 1.04)	0.146
MR-Egger	1.16 (0.83, 1.60)	0.386
MR-PRESSO	0.93 (0.83, 1.05)	0.265
Con-Mix	0.85 (0.69, 1.12)	0.107

0.7 0.8 0.9 1 1.1 1.2

OR (95% CI)