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Research letter

# Genetically proxied interleukin-6 receptor inhibition: opposing associations with COVID-19 and pneumonia

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# Genetically proxied interleukin-6 receptor inhibition: opposing associations with COVID-19 and pneumonia

*To the Editor:*

The inflammatory cytokine interleukin-6 (IL-6) is central to orchestrating the immune system [1]. The pathophysiological process underlying severe coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2, consists of an exaggerated host immune response and elevated circulating levels of inflammatory cytokines, including IL-6 [2, 3]. As such, immunomodulatory agents are being investigated for the treatment of COVID-19. Glucocorticoids may limit inflammation-mediated lung injury in patients with severe COVID-19, and consequently reduce progression to respiratory failure and death. The RECOVERY trial found that administration of dexamethasone resulted in lower 28-day mortality among hospitalised COVID-19 patients who were receiving either invasive mechanical ventilation or oxygen alone at randomization, but not among those who were not receiving any respiratory support [4]. IL-6 receptor (IL6R) inhibition may represent another potential immunomodulatory strategy for treating COVID-19 [5, 6], and a recent meta-analysis of mean IL-6 concentrations demonstrated 2.9-fold higher levels in patients with complicated COVID-19 compared with patients with non-complicated disease [7].

Genetic variants that proxy IL6R inhibition may be used as instrumental variables in the Mendelian randomization paradigm to investigate corresponding drug effects. Here, we conducted a Mendelian randomization investigation to assess the potential effect of IL6R inhibition on COVID-19 susceptibility and hospitalisation and risk of pneumonia.

IL6R inhibition was proxied using seven single-nucleotide polymorphisms within or adjacent to the *IL6R* locus that were associated with C-reactive protein (CRP; downstream molecule of IL-6 signaling) concentrations at the genome-wide significance threshold in 204 402 individuals of European ancestry [8]. These genetic variants also had associations with fibrinogen, IL-6 and soluble IL-6 receptor in a pattern consistent with their effect on IL6R inhibition [8]. The variance in CRP concentrations explained by each variant ranged from 0.04% to 0.34%.

Summary-level genetic data for COVID-19 were acquired from: 1) The COVID-19 Host Genetics Initiative genome-wide association meta-analysis (release 4, 20 October 2020; without the 23andMe study) [9], which included 17 965 COVID-19 cases *versus* 1 370 547 population controls, 7885 hospitalised COVID-19 cases *versus* 961 804 population controls, and 4336 very severe respiratory confirmed COVID-19 cases *versus* 623 902 population controls; and 2) a genome-wide association study involving 1610 hospitalised patients with severe COVID-19, defined as having respiratory failure and requiring some degree of respiratory support, and 2205 control participants (healthy volunteers, blood donors and outpatients of gastroenterology departments) from seven hospitals in Italy and Spain [10]. Corresponding data for pneumonia were obtained from: 1) the FinnGen consortium, including 15 778 cases of all pneumoniae (International Statistical Classification of Diseases and Related Health Problems – 10th Revision codes: J12-J16, J18), and 119 867 control participants [11]; and 2) the UK Biobank cohort (through the MRC-IEU consortium via the MR-Base platform [12]), which included 6572 self-reported pneumonia cases (id:UKB-b:4533) and 456 361 control participants. The genetic association estimates in all studies were adjusted for sex and ancestry. Only summary-level data were analysed in this study, for which appropriate ethical approval and participant consent had previously been obtained.

The Mendelian randomization analyses were performed using the multiplicative random-effects inverse-variance weighted method and accounting for correlations between genetic variants. Analyses

were conducted in R (version 3.4.3) using the MendelianRandomization package [13]. Our results showed that genetically proxied IL6R inhibition, scaled per 0.1 standard deviation decrease of natural log-transformed CRP concentrations, was associated with a reduced risk of being infected and hospitalised with COVID-19, but also with an increased risk of pneumonia (Figure 1).

Our findings provide evidence supporting that IL6R inhibition reduces the risk of being infected and hospitalised with COVID-19. Importantly, they also go further to provide genetic evidence that IL6R inhibition may increase susceptibility to pneumonia. While we considered a broad definition of pneumonia from any cause, our results may be of relevance to secondary lung infections that can complicate COVID-19. The neutral finding of a recent randomized controlled trial of IL6R blockade for the treatment of hospitalised COVID-19 [14] may reflect discrepancies related to effects on the systemic inflammatory response driven by COVID-19 and the pneumonic process specifically.

It is important to appreciate that our analyses investigated associations of genetically proxied IL6R inhibition with susceptibility to COVID-19 and pneumonia, and caution should be taken when extrapolating these findings to assume the effect of a clinical intervention targeting this. Furthermore, our analysis did not directly investigate the effect of IL6R inhibition in individuals suffering with COVID-19, and therefore should not be assumed to offer insight into IL6R blockade as a target for treating COVID-19. It is similarly important to appreciate that the pneumonia analyses are likely to be dependent upon the case definition used. A further potential shortcoming is that variants proxying IL6R inhibition were only available at the *IL6R* locus. However, genetic associations at this locus have previously been shown to be concordant with observed effects of tocilizumab, an interleukin-6 blocker, supporting our claim that variants in this locus can be used as proxies for IL6R inhibition. Another limitation is that the amount of variability in CRP concentrations explained by the seven variants is small. Finally, the COVID-19 Host Genetics Initiative genome-wide association meta-analysis consists of mixed-population, which

could induce bias by ancestry-difference. However, results were similar in the analysis based on the genome-wide association study comprising Italian and Spanish participants, which would be expected to be less influenced by population stratification bias.

An adverse effect of IL6R inhibition on risk of pneumonia risk is biologically plausible, and respiratory tract infections, including pneumonia, are a well-known complication of IL6R blockade [15]. Respiratory disease is a main feature of severe COVID-19, and the potential of IL6R blockade to increase risk of pneumonia warrants vigilance and caution in their application to treat COVID-19.

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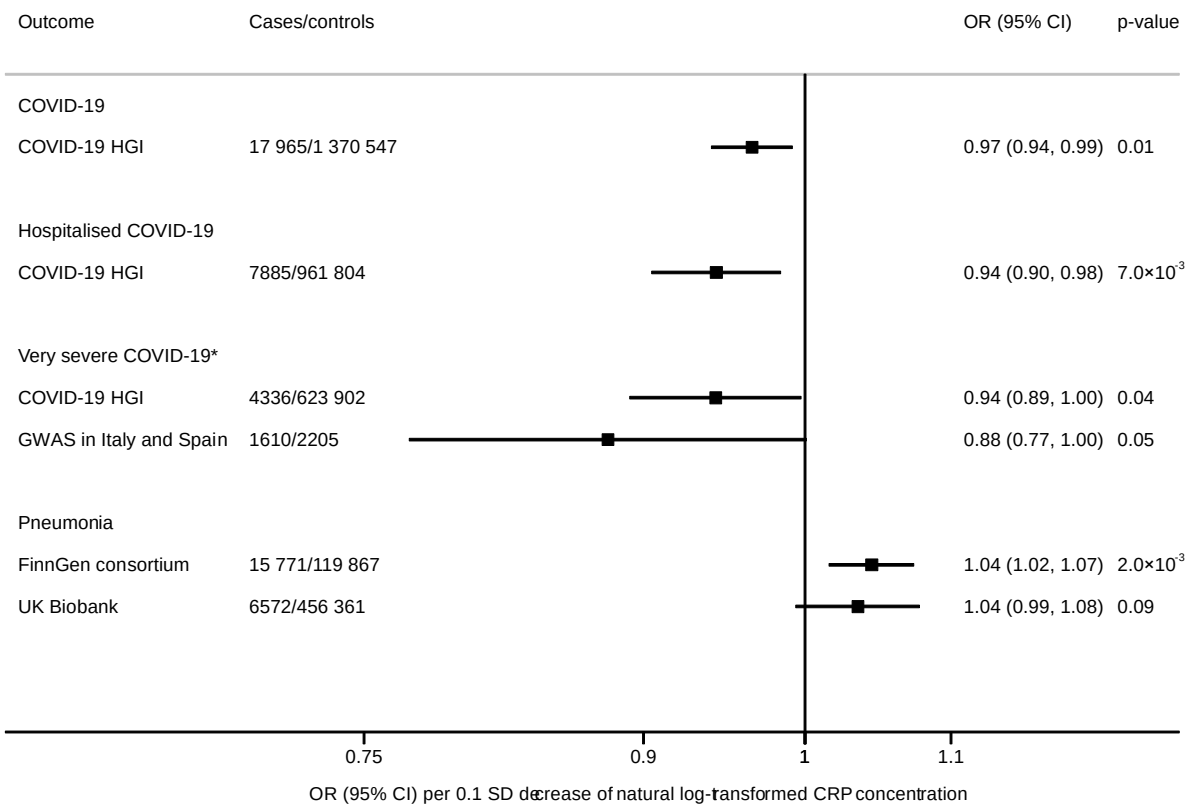
**FIGURE LEGEND**

**FIGURE 1.** Associations of genetically proxied IL6R inhibition with COVID-19 and pneumonia. Estimates were derived using the multiplicative random-effects inverse variance weighted method and accounting for the correlations between the seven genetic variants in or adjacent to the *IL6R* locus. *Defined as severe respiratory confirmed COVID-19 in the COVID-19 HGI and as COVID-19 with respiratory failure in the genome-wide association study in Italy and Spain. CI: confidence interval; CRP: C-reactive protein; GWAS: genome-wide association study; HGI: Host Genetics Initiative; OR: odds ratio; SD: standard deviation.


Outcome
Cases/controls
OR (95% CI)
p-value
COVID-19
COVID-19 HGI
17 965/1 370 547
0.97 (0.94, 0.99)
0.01
Hospitalised COVID-19
COVID-19 HGI
7885/961 804
0.94 (0.90, 0.98)
7.0×10-3
Very severe COVID-19*
COVID-19 HGI
4336/623 902
0.94 (0.89, 1.00)
0.04
GWAS in Italy and Spain
1610/2205
0.88 (0.77, 1.00)
0.05
Pneumonia
FinnGen consortium
15 771/119 867
1.04 (1.02, 1.07)
2.0×10-3
UK Biobank
6572/456 361
1.04 (0.99, 1.08)
0.09
0.75
0.9
1
1.1
OR (95% CI) per 0.1 SD decrease of natural log-transformed CRP concentration