



## Letter to the Editor

### Genetic variation of Golgi membrane protein 1 is associated with COVID-19 disease



Dear Editor

We read with interest a recent work by Zoha Kamali and colleagues, who found IL-13 as a risk factor for severe COVID-19.<sup>1</sup> Similarly, other investigators discovered that interleukin (IL) pathways, including IL-1, IL-1R1, and IL-6, *etc.* were associated with the severity of COVID-19 disease.<sup>2,3</sup>

In the present work, we used the previously identified association of single-nucleotide polymorphisms (SNPs) for circulating Golgi membrane protein 1 (GOLM1) levels to evaluate its causal role in COVID-19.<sup>4</sup> GOLM1, also known as GOLPH2 and GP73, is a type II transmembrane protein that cycles across membrane compartments. Once considered a valuable serum marker for hepatocellular carcinoma,<sup>5</sup> GOLM1 was shown to exacerbate CD8<sup>+</sup> T cell suppression in liver cancer by facilitating exosomal PD-L1 trafficking into tumor-associated macrophages.<sup>6</sup> More recently, it was discovered that GOLM1 connects SARS-CoV-2 infection with dysglycemia.<sup>7</sup>

In order to infer potential causality of risk factor-disease associations, we used the promising approach of Mendelian randomization (MR).<sup>8</sup> This strategy is based on the premise that genetic variations are distributed randomly during meiosis, hence minimizing confounding bias. The design for this MR study is shown in Suppl. Fig. 1.

The GOLM1 genetic instrumental variables (IVs) were selected on the basis of cis-protein quantitative trait loci (cis-pQTLs) identified in recent proteomics genome-wide association study (GWAS) including 3,301 European individuals.<sup>4</sup> pQTLs strongly associated with GOLM1 at a threshold of  $p < 5e-6$  were chosen. Linkage disequilibrium (LD) analysis by the LDlinkR package was used to eliminate cis-pQTLs ( $r^2 > 0.1$ ) based on the 1000-genome European reference panel. F statistics were assessed to determine the instrument strength, and  $F \geq 10$  indicates strong instruments. Finally, the candidate GOLM1 genetic IVs were listed in Suppl. Table 1.

The instrumental variables for COVID-19 were retrieved at the genome-wide significance ( $p < 5e-8$ ) from the largest GWAS meta-analysis of COVID-19 to date, by the COVID-19 Host Genetics Initiative.<sup>9</sup> In total, we used twenty COVID-19 GWASs for COVID-19 severity (e.g. “Severe COVID-19 infection with respiratory failure, id:ebi-a-GCST90000256”, *etc.*) or susceptibility (e.g. “COVID-19 RELEASE 5, id:ebi-a-GCST011072”, *etc.*) respectively. Summary statistics about twenty COVID-19 GWASs of persons with European ancestry are shown in Table 1, and GWAS summary datasets are available in <https://gwas.mrcieu.ac.uk/datasets/>.

The independent GOLM1 genetic IVs from twenty COVID-2019 GWAS datasets were then standardized. Potential proxy SNPs were identified by the LD proxy tool ( $r^2 > 0.80$ ) when these IVs could

not be found. The association of these IVs with the twenty COVID-19 GWAS datasets is shown in Suppl. Table 2.

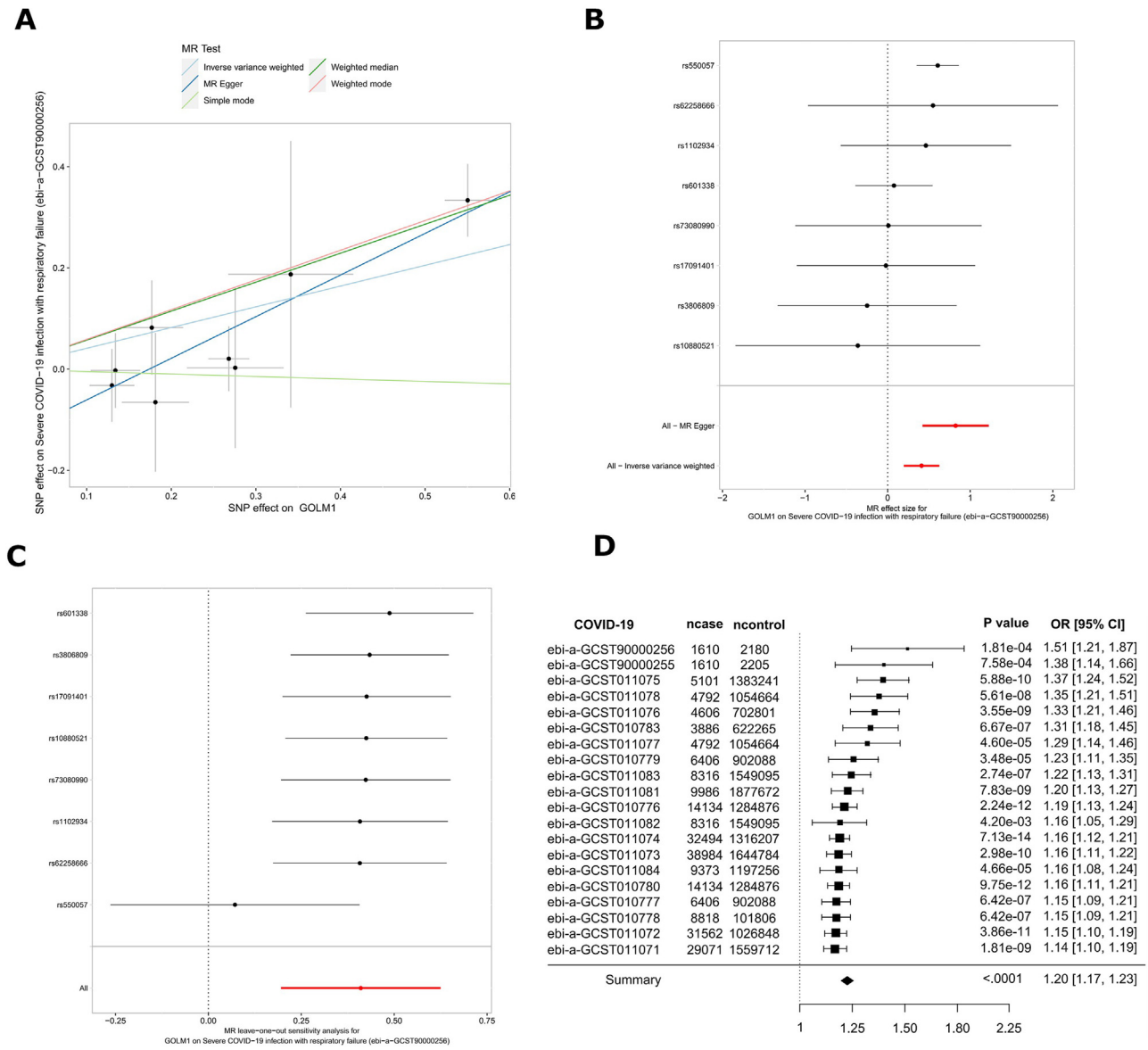
The MR-PRESSO, MR-Egger\_intercept, MR-Egger, and Inverse variance weighted (IVW) methods in Cochran's Q statistic were used to examine the pleiotropy or heterogeneity of the independent GOLM1 genetic IVs in the COVID-19 GWASs. No evident pleiotropy or heterogeneity of these IVs was seen in the COVID-19 GWAS datasets (Suppl. Table 3). Consequently, all identified GOLM1 genetic variations may be regarded as effective IVs in our MR investigation.

Further, we used MR to analyze the effect of the GOLM1 genetic IVs on the risk of contracting COVID-19. Interestingly, we found that as GOLM1 genetically increased, the risk of severe respiratory COVID-19 (ebi-a-GCST90000256) had an increased trend using MR Egger (Beta = 0.823,  $p = 6.96E-03$ ; OR = 2.277), weighted mode (Beta = 0.587,  $p = 2.07E-03$ ; OR = 1.799), weighted median (Beta = 0.573,  $p = 9.81E-06$ ; OR = 1.773), and IVW (Beta = 0.410,  $p = 1.81E-04$ ; OR = 1.507) (Fig. 1; Suppl. Table 4). In addition, the impact of a single SNP on COVID-19 risk rose as the effect of a single SNP on GOLM1 increased, as measured by IVW, weighted median, simple mode, and weighted mode (Fig. 1A). Critically, each effect size (Fig. 1B) and leave-one-out sensitivity (Fig. 1C) suggested that each effect of GOLM1-associated SNPs on COVID-19 risk were robust. Our MR results were replicated in other 19 COVID-19 GWASs to ensure robustness and reduce false positives (Suppl. Table 4; Suppl. Fig. 2–4).

In summary, we found an OR of about 1.20 for COVID-19 per 1 SD increase in GOLM1 levels and replicated in multiple independent datasets (Fig. 1D). Warranting further investigations, severe cases of SARS-CoV-2 infection are related with high blood glucose levels and metabolic complications. Recent research suggested that GOLM1 is a glucogenic hormone that contributes to the SARS-CoV-2-induced change in systemic glucose metabolism and increased hepatic gluconeogenesis.<sup>10</sup> We then conducted a MR study to investigate the associations of genetically predicted GOLM1 with glucose (Suppl. Table 5). Our MR result of a favorable impact of GOLM1 on glucose levels is consistent with a prior finding that plasma GOLM1 levels are increased in COVID-19 patients and positively correlate with blood glucose levels.<sup>10</sup>

This study has several limitations. First, GOLM1 genetic IVs and COVID-19 GWAS are from European ancestry. Our conclusion need be proven in other ancestries. Second, GOLM1 blockade with an antibody inhibits excessive glucogenesis stimulated by SARS-CoV-2 in vitro and lowers elevated fasting blood glucose levels in infected mice.<sup>10</sup> It is necessary to clarify whether inhibiting GOLM1 could reduce the risk of severe respiratory COVID-19 in the future research.

To conclude, our study provides evidence for a causal effect of GOLM1 on COVID-19. As such, further investigation is warranted exploring GOLM1 as a potential novel biomarker and therapeutic



**Fig. 1.** Causal relationships of GOLM1 genetic liability on COVID-19. (A) Individual estimates about the causal effect of GOLM1 on COVID-19 GWAS dataset ebi-a-GCST90000256. The x-axis and y-axis show the SNP effect and SE (standard error) on GOLM1 and COVID-19, respectively. The regression line for MR Egger, weighted median, IVW, simple mode, and weighted mode is shown. (B) Forest plot of GOLM1 associated SNPs with risk of COVID-19. The x-axis shows MR effect size for GOLM1 on COVID-19. The y-axis shows the analysis for each of SNPs. (C) MR leave-one-out sensitivity analysis for the effect of GOLM1 on COVID-19. (D) The association between genetically increased GOLM1 and Odds of multiple COVID-19 GWAS.

target for COVID-19 patients or those at risk of acquiring severe symptoms.

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**Authors' contributions**

JY conceived and initiated the project, and were responsible for the design of the study. F-JT, L-YX, FX and L-JM access all the data in the study and took responsibility for the accuracy of the data analysis. JY and F-JT performed the statistical analysis. All authors

were involved in the writing and revision of the article, and all authors approved the submitted version to be published.

**Declaration of competing interest**

The authors have no potential conflicts of interest to disclose.

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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jinf.2022.07.013](https://doi.org/10.1016/j.jinf.2022.07.013).

**Table 1**  
Corona Virus Disease 2019 (COVID-19) GWAS datasets.

GWAS ID	trait	ncase	ncontrol	nsnp	population
ebi-a-GCST011074	COVID-19 (RELEASE 5)	32494	1316207	8666451	European
ebi-a-GCST0110776	COVID-19 (RELEASE 4)	14134	1284876	11435708	European
ebi-a-GCST0110780	COVID-19 (RELEASE 4)	14134	1284876	12508741	European
ebi-a-GCST011072	COVID-19 (RELEASE 5)	31562	1026848	7750967	European
ebi-a-GCST011073	COVID-19 (RELEASE 5)	38984	1644784	8660177	European
ebi-a-GCST011071	COVID-19 (RELEASE 5)	29071	1559712	8103014	European
ebi-a-GCST010781	COVID-19 (predicted covid from self-reported symptoms vs predicted or self-reported non-covid) RELEASE 4	3204	35728	11379674	European
ebi-a-GCST010778	COVID-19 (covid vs lab/self reported negative) RELEASE 4	8818	101806	12832272	European
ebi-a-GCST011075	COVID-19 (very severe respiratory confirmed vs population) RELEASE 5	5101	1383241	9739225	European
ebi-a-GCST011076	COVID-19 (very severe respiratory confirmed vs population) RELEASE 5	4606	702801	7475770	European
ebi-a-GCST011078	COVID-19 (very severe respiratory confirmed vs population) RELEASE 5	4792	1054664	9817241	European
ebi-a-GCST010783	COVID-19 (very severe respiratory confirmed vs population) RELEASE 4	3886	622265	11678750	European
ebi-a-GCST010777	COVID-19 (hospitalized vs population) RELEASE 4	6406	902088	12832272	European
ebi-a-GCST010779	COVID-19 (hospitalized vs population) RELEASE 4	6406	902088	11272365	European
ebi-a-GCST011077	COVID-19 (very severe respiratory confirmed vs population) RELEASE 5	4792	1054664	7496658	European
ebi-a-GCST011084	COVID-19 (hospitalized vs population) RELEASE 5	9373	1197256	7534178	European
ebi-a-GCST90000256	Severe COVID-19 infection with respiratory failure (analysis II)	1610	2180	8095992	European
ebi-a-GCST90000255	Severe COVID-19 infection with respiratory failure (analysis I)	1610	2205	8095360	European
ebi-a-GCST011082	COVID-19 (hospitalized vs population) RELEASE 5	8316	1549095	6814406	European

GWAS ID: Genome wide association study identity; ncase: the number of COVID-19 case; ncontrol: the number of the control; nsnp: the number of single-nucleotide polymorphism.

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