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GWAS and meta-analysis identifies 49 genetic variants underlying critical Covid-19

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GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19

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Critical illness in COVID-19 is an extreme and clinically homogeneous disease phenotype that we have previously shown¹ to be highly efficient for discovery of genetic associations². Despite the advanced stage of illness at presentation, we have shown that host genetics in patients who are critically ill with COVID-19 can identify immunomodulatory therapies with strong beneficial effects in this group³. Here we analyse 24,202 cases of COVID-19 with critical illness comprising a combination of microarray genotype and whole-genome sequencing data from cases of critical illness in the international GenOMICC (11,440 cases) study, combined with other studies recruiting hospitalized patients with a strong focus on severe and critical disease: ISARIC4C (676 cases) and the SCOURGE consortium (5,934 cases). To put these results in the context of existing work, we conduct a meta-analysis of the new GenOMICC genome-wide association study (GWAS) results with previously published data. We find 49 genome-wide significant associations, of which 16 have not been reported previously. To investigate the therapeutic implications of these findings, we infer the structural consequences of protein-coding variants, and combine our GWAS results with gene expression data using a monocyte transcriptome-wide association study (TWAS) model, as well as gene and protein expression using Mendelian randomization. We identify potentially druggable targets in multiple systems, including inflammatory signalling (*JAK1*), monocyte–macrophage activation and endothelial permeability (*PDE4A*), immunometabolism (*SLC2A5* and *AK5*), and host factors required for viral entry and replication (*TMPRSS2* and *RAB2A*).

The design of the GenOMICC study and the rationale for focusing on critical illness has been previously described^{1,2}. In brief, patients with confirmed COVID-19 requiring continuous cardiorespiratory monitoring or organ support (a generalizable definition for critical illness) were recruited in 2020–2022. We first performed ancestry-specific GWAS analyses according to the methods that we described previously^{1,2}. Using the results of these GWAS analyses, previously reported results obtained using GenOMICC participants with whole-genome sequencing data² and data from GenOMICC Brazil, we performed trans-ancestry and -platform meta-analyses within the GenOMICC study for a critically ill

COVID-19 phenotype and a hospitalized COVID-19 phenotype (Extended Data Fig. 1). The results of these GenOMICC-only meta-analyses are presented for both critically ill and hospitalized phenotypes (Table 1 and Extended Data Fig. 2). To put these results into the context of existing knowledge, we performed comprehensive meta-analyses, drawing on further GWAS results, including data shared by the SCOURGE consortium and published data from the COVID-19 Human Genetics Initiative (HGIv6, 2021)⁴. The characteristics of the contributing studies are summarized in Supplementary Tables 13 and 14 for the critically ill and hospitalized phenotypes, with further details on each study provided in

Table 1 | Genome-wide significant associations with critical COVID-19, listing independent lead variants

Chr:pos(b38)	rsid	EA	OR	OR _{ci}	P	P _{cond}	Nearest gene	Citation
1:9067157	rs2478868	A	0.92	0.9–0.95	1.5×10 ⁻¹⁰		SLC2A5	GenOMICC ^{new}
1:64948270	rs12046291	A	1.1	1.07–1.13	5.1×10 ⁻¹¹		JAK1	GenOMICC ^{new}
1:77501822	rs71658797	A	1.1	1.09–1.18	2.8×10 ⁻⁹		AK5	GenOMICC ^{new}
1:155066988	rs114301457	T	2.4	1.81–3.18	1.5×10 ⁻⁹		EFNA4	GenOMICC ²
1:155175305	rs7528026	A	1.3	1.25–1.44	1.5×10 ⁻¹⁵		TRIM46	GenOMICC ²
1:155197995	rs41264915	A	1.2	1.17–1.26	7.6×10 ⁻²⁴		THBS3	HGI ¹⁸
1:155278322	rs11264349	A	0.94	0.92–0.97	7.3×10 ⁻⁵	3.9×10 ⁻¹³	HCN3	GenOMICC ^{new}
2:60480453	rs1123573	A	1.1	1.09–1.15	1×10 ⁻¹⁴		BCL11A	GenOMICC ²
3:45796521	rs2271616	T	1.2	1.14–1.23	1.1×10 ⁻¹⁶		SLC6A20	HGI ¹⁸
3:45818159	rs17713054*	A	2	1.96–2.13	7.7×10 ⁻²⁵⁴		LZTFL1	SCGG ¹⁹
3:45873093	rs35482426	CTT	0.53	0.5–0.57	6.1×10 ⁻⁹¹		LZTFL1	SCGG ¹⁹
3:101790631	rs11706494	A	1.1	1.05–1.11	9.4×10 ⁻⁹		NXPE3	GenOMICC ^{new}
3:146522652	rs343314	T	1.2	1.09–1.21	4.6×10 ⁻⁸		PLSCR1	GenOMICC ²
4:25446871	rs7664615	A	1.1	1.07–1.14	1.5×10 ⁻⁸		ANAPC4	GenOMICC ^{new}
4:105673359	rs72670002	A	1.1	1.09–1.21	4.4×10 ⁻⁸		ARHGEF38	GenOMICC ^{new}
4:167824478	rs1073165	A	1.1	1.05–1.11	1.1×10 ⁻⁹		–	GenOMICC ^{new}
5:132422622	rs2269821	A	1.1	1.08–1.16	3×10 ⁻¹⁰		IRF1-AS1	GenOMICC ²
6:31153455	rs111837807	T	0.8	0.77–0.84	8.6×10 ⁻²⁶		CCHCR1	GenOMICC ¹
6:31571991	rs2071590	A	1.1	1.06–1.11	3.1×10 ⁻¹⁰		LTA	GenOMICC ^{new}
6:32702687	rs2858305	T	0.93	0.9–0.95	2.1×10 ⁻⁹		HLA-DQA1	GenOMICC ²
6:41522644	rs41435745	C	1.4	1.31–1.51	1.5×10 ⁻²⁰		FOXP4	HGI ¹⁸
7:75623396	rs1179620	T	0.92	0.9–0.95	2.3×10 ⁻⁹		HIP1	GenOMICC ^{new}
7:100032719	rs2897075	T	1.1	1.06–1.11	8.9×10 ⁻¹¹		ZKSCAN1	GenOMICC ^{new}
8:60532539	rs13276831	T	1.1	1.05–1.1	1.7×10 ⁻⁸		RAB2A	GenOMICC ^{new}
9:21206606	rs28368148	C	0.59	0.49–0.7	5.3×10 ⁻⁹		IFNA10	GenOMICC ²
9:33425186	rs60840586	G	1.1	1.07–1.14	9.7×10 ⁻⁹		AQP3	SCOURGE ²⁰
9:133271182	rs879055593	T	1.1	1.1–1.16	1×10 ⁻¹⁶		ABO	SCGG ¹⁹
10:79946568	rs721917	A	0.93	0.9–0.95	7.6×10 ⁻⁹		SFTPD	HGI ⁴
11:1219991	rs35705950	T	0.86	0.82–0.89	3.8×10 ⁻¹⁴		MUC5B	HGI ⁴
11:34482745	rs61882275	A	0.88	0.86–0.91	1×10 ⁻²²		ELF5	GenOMICC ²
12:112919637	rs2660	A	1.1	1.08–1.13	2.8×10 ⁻¹⁵		OAS1	GenOMICC ¹
12:132481571	rs11614702	A	1.1	1.08–1.13	2.1×10 ⁻¹⁶		FBRSL1	GenOMICC ²
13:112881427	rs12585036	T	1.2	1.12–1.18	9.6×10 ⁻²²		ATP11A	GenOMICC ²
16:89196249	rs117169628	A	1.2	1.12–1.2	2.6×10 ⁻¹⁶		SLC22A31	GenOMICC ²
17:40003082	rs12941811	T	0.93	0.91–0.95	1.1×10 ⁻⁹		PSMD3	GenOMICC ^{new}
17:46085231	rs8080583	A	0.89	0.86–0.91	1.8×10 ⁻¹⁶		KANSL1	21
17:49863303	rs77534576	T	1.3	1.24–1.43	8.7×10 ⁻¹⁶		TAC4	21
19:4717660	rs12610495	A	0.8	0.77–0.82	9.1×10 ⁻⁵¹		DPP9	GenOMICC ¹
19:10352442	rs34536443	C	1.5	1.39–1.61	2.2×10 ⁻²⁸		TYK2	GenOMICC ¹
19:10414696	rs142770866	A	1.2	1.19–1.3	9.4×10 ⁻²¹		PDE4A	GenOMICC ^{new}
19:48702915	rs516246	T	0.9	0.88–0.93	1.4×10 ⁻¹⁵		FUT2	GenOMICC ²
19:50374423	rs35463555	A	1.1	1.07–1.13	1.9×10 ⁻¹³		NR1H2	HGI ⁴
20:6489447	rs2326788	A	0.93	0.9–0.95	1.5×10 ⁻⁸		CASC20	GenOMICC ^{new}
21:33229937	rs188401375	C	0.74	0.66–0.84	3.1×10 ⁻⁶	4.7×10 ⁻⁹	IFNAR2	GenOMICC ¹
21:33237639	rs9636867	A	0.83	0.81–0.85	5.2×10 ⁻⁴⁸		IFNAR2	GenOMICC ¹
21:33287378	rs8178521	T	1.1	1.1–1.17	6.2×10 ⁻¹⁵		IL10RB	GenOMICC ²
21:33980963	rs76608815	T	1.2	1.14–1.23	7.4×10 ⁻¹⁷		ATP5PO	GenOMICC ²
21:41479527	rs915823	A	1.1	1.06–1.13	2.1×10 ⁻⁹		TMPRSS2	GenOMICC ^{new}
X:15523993	rs35697037	A	1	1.03–1.06	6.8×10 ⁻⁹		ACE2	HGI ⁴

Chr:pos(b38), chromosome and position on human genome build 38; rsid, lead variant rsid; EA, effect allele; OR, odds ratio; OR_{ci}, odds ratio confidence interval; P, P value against null hypothesis of odds ratio of one; P_{cond}, P value in conditional analysis in variants with P>5×10⁻⁸; nearest gene, the nearest or most plausible nearby gene; citation, the first report of genome-wide significant association. ‘GenOMICC^{new}’ indicates findings presented in this Article. Additional details are provided in Supplementary Table 15 and full results of conditional analysis are provided in Supplementary Table 16. Supplementary Table 17 contains details of lead variants from the analysis of the hospitalized phenotype.

the Supplementary Information. We used a mathematical subtraction approach, as done in our previous work², to remove signals of previous GenOMICC releases from HGIv6, yielding an independent dataset.

As no replication cohorts exist for these meta-analyses, we used the heterogeneity across studies to assess the reliability of individual findings (Supplementary Table 15). Owing to the unusually extreme phenotype in the GenOMICC study, some heterogeneity is expected for the strongest associations when compared with studies with more permissive inclusion criteria. Importantly, significant heterogeneity was not detected for any of the findings that we report here (Supplementary Table 15). Comparing effect estimates between studies using a regression approach that takes into account estimation errors (Methods), we detected systematic differences in effect sizes between studies (Extended Data Fig. 3). For example, effects for the HGI critical illness phenotype (which was designed to parallel the GenOMICC inclusion criteria) are smaller than those obtained using prospective recruitment in GenOMICC by a factor of 0.68. As the effect sizes in GenOMICC are consistently larger than other studies, and GenOMICC contributes a disproportionately large signal to meta-analyses of both critical and hospitalized phenotypes (Extended Data Fig. 4), between-study heterogeneity is likely to reflect the careful case ascertainment and extreme phenotype in GenOMICC compared with other studies.

We found 49 common genetic associations with critical COVID-19 meeting our criteria for genome-wide significance in the absence of heterogeneity (Extended Data Fig. 2 and Table 1). Findings from previous reports were consistently replicated (Extended Data Table 2). Conditional analysis revealed two additional lead variants (Table 1) and statistical fine-mapping provided credible sets of putative causal variants for a majority of lead variants (Supplementary Figs. 27–44 and Supplementary Table 5). Gene-level analyses found 196 significantly associated genes at a Bonferroni-corrected threshold (Supplementary Table 10). There were no genome-wide significant differences in the effects between sexes in a sex-stratified meta-analysis using a subset of cohorts (Supplementary Fig. 1).

Therapeutic implications

Our analysis is limited to common variants that are detectable on genotyping arrays and imputation panels. Although most lead variants are not directly causal, in some cases, they highlight molecular mechanisms that alter clinical outcomes in COVID-19, and may have direct therapeutic relevance. To investigate the disease mechanisms, we first quantified the effect of inferred gene expression on critical illness in three relevant tissue/cell types. Many of the genes that we have found to be implicated in critical COVID-19 (refs. 1,2) are highly expressed in the monocyte–macrophage system, which has poor coverage in existing expression quantitative trait loci (eQTL) datasets. For this reason, we constructed a new TWAS model in primary monocytes obtained from 176 individuals (Methods). We found significant associations after Bonferroni correction between critical COVID-19 and predicted gene expression in lung (33), blood (21), monocyte (37) and all-tissue (107) meta-analysis (Supplementary Table 2 and Supplementary Table 11). We extended these findings using generalized summary-level data Mendelian randomization (GSMR) for RNA expression (Fig. 2, Extended Data Table 1, Supplementary Figs. 11–18 and Supplementary Table 4).

In parallel, we assessed the effect of genetically determined variation in circulating protein levels on the critical illness phenotype using GSMR⁵. We identified 15 unique proteins linked to critical illness, as summarized in Extended Data Table 1 (Supplementary Table 3). Of the significant results, we found causal evidence implicating five new proteins in comparison to our previous GSMR analysis²: QSX2, CREB3L4, myeloperoxidase (MPO), ADAMTS13 and mannose-binding lectin-2 (MBL2) (Supplementary Fig. 10). These include well-studied biomarkers and potential drug targets in sepsis—the innate immune pattern recognition receptor MBL2 and the neutrophil effector enzyme

MPO. ADAMTS13 modulates von Willebrand-factor-mediated platelet thrombus formation and may have a role in the hypercoagulable state in critical COVID-19 (Extended Data Fig. 5).

Three genes containing non-synonymous protein-coding changes associated with severe disease were also found to have significant effects from differential gene expression: *SLC22A31* (ref. 2) (Fig. 1), *SFTPD*⁴ (Fig. 1) and *TKY2* (ref. 1) (Extended Data Fig. 6). Further biological and clinical research will be required to dissect the genetic evidence at these loci. In the example of *TKY2*, there is now a therapeutic test of the genetic predictions. Our previous report of association between higher expression and critical illness¹ led directly to the inclusion of a new drug, baricitinib, in a large clinical trial; the result demonstrated a clear therapeutic benefit³. This therapeutic signal is consistent across multiple trials, providing the first proof-of-concept for drug target identification using genetics in critical illness and infectious disease.

To assess the immediate therapeutic use of our results for repurposing of existing compounds, we considered the drug therapies under consideration by the UK COVID-19 Therapeutic Advisory Panel (UK-CTAP), a national independent review group supported by an expert due-diligence panel⁶. Consistent evidence from gene-level GWAS (Supplementary Table 6 and Supplementary Table 10) and post-GWAS analyses was identified for several licensed compounds (Supplementary Table 12). For example, we found an association in another gene encoding a protein that is inhibited by baricitinib and other JAK inhibitors—the intracellular signalling kinase, *JAK1*, which is stimulated by numerous cytokines including type I interferons and IL-6. Mendelian randomization analysis of RNA expression revealed a significant positive association between the expression of the gene encoding a canonical inflammatory cytokine, tumour necrosis factor (*TNF*), and severe disease (Fig. 2). This suggests that inhibition of TNF signalling may be an effective therapy in severe COVID-19.

Our additional expression data in monocytes reveal a marked tissue-specific effect on expression of *PDE4A*. This phosphodiesterase regulates the production of multiple inflammatory cytokines by myeloid cells. In contrast to the negative correlations seen in the lungs and blood, we show that a genetic tendency for higher expression of *PDE4A* in monocytes is associated with critical COVID-19 (Supplementary Table 11). Inhibition of PDE4A by several existing drugs is under investigation in multiple inflammatory diseases⁷, reduces pulmonary endothelial permeability⁸ and appears to be safe in small clinical trials in patients with COVID-19.

The postulated biological role of genes associated with critical COVID-19 in GWAS, TWAS and GSMR results is shown in Extended Data Fig. 5, which highlights the preponderance of genes with expression or functions in the mononuclear phagocyte system. This includes *SLC2A5*, encoding the GLUT5 fructose transporter, which is strongly inducible in primary macrophages in response to inflammatory stimulation⁹, and *XCRI*, a dendritic cell receptor with a critical role in cytotoxic T cell-mediated antiviral immunity¹⁰. *NPNT*, a significant meta-TWAS association in the genome-wide significant region on chromosome 4 (chr4:105673359; Supplementary Table 11), encodes a pulmonary basement membrane protein that may have a protective role in acute lung injury¹¹.

Host–pathogen interaction

Our results also demonstrate the capacity of host genetics to reveal core mechanisms of disease. Multiple genes implicated in viral entry are associated with severe disease. In addition to *ACE2*, we detect a genome-wide significant association in *TMPRSS2*, a key host protease that facilitates viral entry that we have previously studied as a candidate gene¹². This effect may be viral-lineage specific¹³. A strong GWAS association is seen in *RAB2A* (Table 1), with TWAS evidence suggesting that more expression of this gene is associated with worse disease (Supplementary Table 11). *RAB2A* is highly ranked in our previous

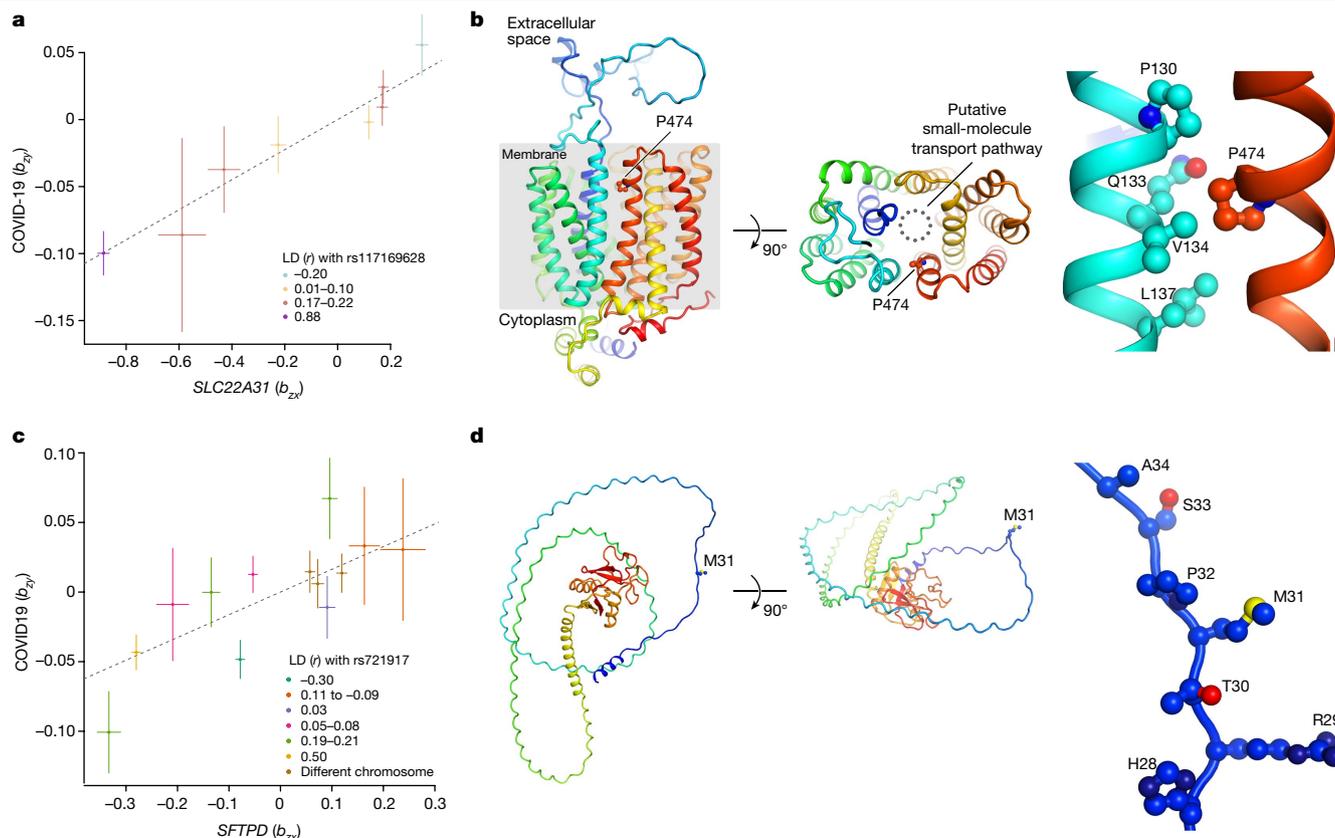


Fig. 1 Functional genomics analyses for *SLC22A31* and *SFTPD*. **a**, Effect-size plot for the effect of multiple variants on *SLC22A31* expression (eQTLgen, x axis) against increasing susceptibility to critical COVID-19 ($\beta_{xy} = 0.11$; $P_{xy} = 1.3 \times 10^{-9}$). The colour shows linkage disequilibrium (LD) with the missense variant rs117169628. **b**, Three cartoon views of an AlphaFold²² model of putative solute carrier family 22 member 31 (*SLC22A31*; UniProtKB: A6NKX4). The side chains of Pro474 and interacting amino acids are shown as connected spheres. A putative channel for small-molecule transport across the cell membrane is indicated by a dashed circle. Pro474 is predicted to be located in the transmembrane helix and point towards a putative transport pathway of a small molecule. The risk variant, P474L (Ala at rs117169628) would be expected to introduce more flexibility to

the transmembrane helix and might therefore affect the transport properties of *SLC22A31*. Pro474 is predicted to be in a tightly packed environment, and may therefore affect the folding of *SLC22A31*. **c**, Effect-size plot for effect of multiple variants on *SFTPD* expression (eQTLgen, x axis) against increasing susceptibility to critical COVID-19 ($\beta_{xy} = 0.16$; $P_{xy} = 9.7 \times 10^{-6}$). Colour shows linkage disequilibrium with the missense variant rs721917. **d**, Three cartoon views of an AlphaFold²² model of pulmonary surfactant-associated protein D (*SFTPD*; UniProtKB: P35247). The side chain of the variant Met31 is shown as connected spheres. Met31 is predicted to be located in the secondary-structure-lacking region of *SFTPD*. In the diagram on the right, oxygen and nitrogen atoms are coloured red and blue respectively, and the sulfur atom is coloured yellow.

meta-analysis by information content¹⁴ study of host genes implicated in SARS-CoV-2 interaction using in vitro and clinical data¹⁵, and is consistent with CRISPR screen data showing that *RAB2A* is required for viral replication¹⁶.

Although our focus on critical illness enhances discovery power (Extended Data Fig. 4), it has the disadvantage of combining genetic signals for multiple stages in disease progression, including viral exposure, infection and replication, and development of inflammatory lung

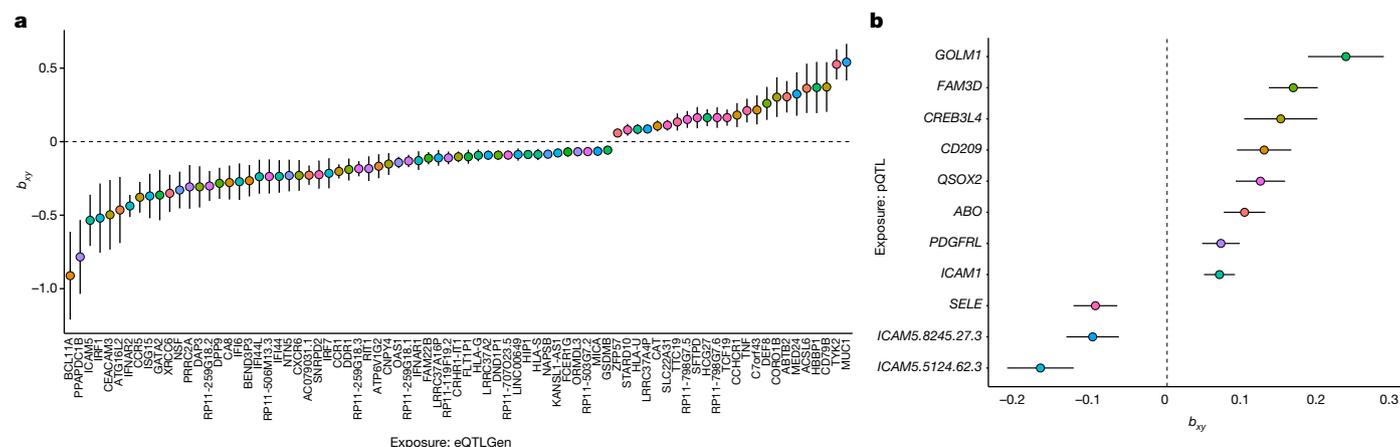


Fig. 2 GSMR effect sizes. **a, b**, The predicted effect of change in protein concentration (**a**) and gene expression (**b**) on the risk of critical COVID-19 is shown for proteins and genes significantly linked to critical COVID-19 by GSMR (false-discovery rate (FDR) < 0.01). The bars show 95% confidence intervals.

disease. From these data alone we cannot identify when in disease progression the causal effect is mediated, although clinical evidence helps to make some predictions¹⁷ (Extended Data Fig. 5). As most cases included were recruited before vaccinations and treatments became available (Extended Data Fig. 7), at present, our study does not have sufficient statistical power to dissect the genetic effects of treatments or vaccination. These effects may include the masking of true associations, or the detection of genetic effects mediated by vaccine or drug response, rather than COVID-19 susceptibility. However, the absence of divergent genetic effects between studies (Supplementary Figs. 2–5) or consistent changes in effect allele frequency among cases over time (Supplementary Figs. 45–48) suggests that treatment and vaccination have not substantially affected the association between the specific variants that we report and the risk of critical illness.

As we performed a meta-analysis of multiple studies that may have slightly different definitions of the phenotype, effect sizes differ between studies (Supplementary Figs. 2–5). This, together with ancestry-specific effects¹, may explain the heterogeneity in strong GWAS signals, such as the LZTFL1 signal in Table 1. Different studies also have sets of variants that are not completely overlapping, so *P* values between variants in high linkage disequilibrium are more different than expected. Although most of the studies contain individuals from multiple ancestries, a large majority of the individuals are of European ancestry. In future research, there is a scientific and moral imperative to include the full diversity of human populations.

Together, these results deepen our understanding of the pathogenesis of critical COVID-19 and highlight new biological mechanisms of disease, several of which have immediate potential for therapeutic targeting.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-023-06034-3>.

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Article

Methods

Hospitalization meta-analysis

The hospitalized phenotype includes patients who were hospitalized with a laboratory-confirmed SARS-CoV2 infection. In this analysis we included GenOMICC, GenOMICC Brazil, GenOMICC Saudi Arabia, ISARIC4C, HGIv6 B2 phenotype with subtraction of GenOMICC data, SCOURGE hospitalized versus population and mild cases, and 23andMe broad respiratory phenotype. A summary description of each analysis is given above, a table with the included studies can be found in Supplementary Table 14 and an extended description can be found in Supplementary Table 1.

Critical illness meta-analysis

The critically ill COVID-19 group included patients who were hospitalized owing to symptoms associated with laboratory-confirmed SARS-CoV-2 infection and who required respiratory support or whose cause of death was associated with COVID-19. In the critical illness analysis, we included GenOMICC, patients with critical illness from ISARIC4C, HGIv6 phenotype A2 with subtraction of GenOMICC data, SCOURGE severity grades 3 and 4 versus population controls, and 23andMe respiratory support phenotype. A summary description of each analysis can be found above, a table with the included studies can be found in Supplementary Table 13 and an extended description can be found in Supplementary Table 1.

Meta-analyses

All meta-analyses across studies were performed using a fixed-effect inverse-variance weighting method and control for population stratification in the METAL software²³. Allele frequency was calculated as the average frequency across studies with the METAL option AVERAGE-FREQ. *P* values for heterogeneity in effect sizes between studies were calculated using a Cochran's *Q*-test implemented in METAL. For variants in the same position with different REF and ALT alleles across studies, the GenOMICC variant in the European population was selected and the rest were removed. Finally, variants with switched ALT and REF alleles between HGIv6 and GenOMICC were also removed on the basis of differences in allele frequency of the alternative allele. Variants were annotated to the closest genes using dbSNP v.b151 GRCh38p7 and BionR R package (v.2.46.3)²⁴. As each single-nucleotide polymorphism (SNP) of the meta-analysis can be present in different subsets of cohorts, there may be large differences in *P* values in SNPs with a high level of linkage disequilibrium, which may have an effect on downstream analyses. For this reason, variants that were not present in one of the three biggest studies—GenOMICC European ancestry, HGIv6 or SCOURGE—were filtered out from post-GWAS analysis.

Conditional analysis

We performed a step-wise conditional analysis to find independent signals. As European-specific data are not available in some cohorts but European ancestry is largely predominant (87.2% of cases with critical illness), we performed the conditional analysis using a European reference panel and the meta-analysis results of the whole cohort. To perform the conditional analysis, we used the GCTA (v.1.9.3) --cojo-slc function²⁵. The parameters for the function were $P = 5 \times 10^{-8}$, a distance of 10,000 kb and a co-linear threshold of 0.9 (ref. 26), and the reference population for the conditional analysis was individuals of European ancestry with whole-genome sequence available in the GenOMICC study and whole genomes from the 100,000 Genomics England project².

Credible set fine-mapping

We performed fine-mapping using the SuSiE model²⁷ to construct credible sets for the independent signals identified using conditional analysis. As for conditional analysis, we used a European reference panel and the meta-analysis results of the whole critical illness cohort.

We performed analyses in 1 Mb windows centred on the lead variants identified through conditional analysis. In cases in which windows for multiple variants overlapped, they were joined into a single window. For each window, we fitted the SuSiE summary statistics model setting the expected number of independent signals to the number of identified though conditional analysis. Models for three windows did not converge in 500 iterations and have been excluded. As a reference, we used the publically available linkage disequilibrium information for non-Finish Europeans from the GNOMAD 2.1.1 release. Full data for all variants included in credible sets are included in Supplementary Table 5.

Gene-level analysis

We performed an analysis summarizing the genetic associations at the gene level using the mBAT-combo method²⁸. We used the COVID 'all critical cohorts' meta-analysis (GenOMICC, HGIv6 phenotype A2, SCOURGE and 23andMe) summary statistics. As this is a trans-ethnic meta-analysis, we used a mixed ancestry linkage disequilibrium reference panel, consisting of 3,202 1000 Genomes phase 3 samples. We considered a list of protein-coding genes with unique ensemble gene ID based on the release from GENCODE (v.40) for hg38, which can be found on the mBAT-combo website (<https://yanglab.westlake.edu.cn/software/gcta/#mBAT-combo>). A gene region was taken to span 50 kb upstream to 50 kb downstream of the gene's untranslated regions.

Sex-stratified meta-analysis

To test for differences in genetic effects, we performed sex-stratified GWAS of the COVID-19 critical illness phenotype in the European ancestry GenOMICC WGS and genotyped cohorts and SCOURGE. We then performed a meta-analysis for each sex following the same methods as for the main analysis. We tested for differences in effects between the meta-analyses of the two sexes following previously described methods²⁹.

Mendelian randomization

GSMR⁵ was performed. We used the COVID 'all critical cohorts' meta-analysis (GenOMICC, HGIv6 phenotype A2, SCOURGE and 23andMe) as the outcome, protein expression quantitative-trait loci (pQTLs) from ref. 30 and RNA expression quantitative-trait loci (eQTLs) from eQTLgen³¹ (2019-12-23 data release) as exposures, and 10,000 individuals of European ancestry randomly sampled from the UK Biobank as the linkage disequilibrium reference cohort (50,000 for linkage disequilibrium to missense variant plots). GSMR was performed for all exposures for which we were able to identify two or more suitable SNPs. SNPs were chosen to meet the following criteria: (1) SNP to exposure association $P < 5 \times 10^{-8}$; (2) linkage disequilibrium clumping lead SNPs only (± 1 Mb, $r^2 < 0.05$); (3) SNP not removed by HEIDI-outlier filtering (for the removal of SNPs with evidence of horizontal pleiotropy) at the default threshold value of 0.01. eQTLGen effect sizes and standard errors were estimated as described in supplementary note 2 of ref. 32. We considered as significant those exposure-outcome pairs with $FDR < 0.05$.

TWAS analysis

To perform TWAS analysis in GTExv8 tissues³³, we used the MetaXcan framework and the GTExv8 eQTL and sQTL MASHR-M models available for download online (<http://predictdb.org/>) and the 'all critical cohorts' meta-analysis. We first calculated individual TWAS for whole blood and lungs using the S-PrediXcan function^{34,35}. We next performed a meta-TWAS including data from all tissues to increase the statistical power using s-MultiXcan³⁶. We applied Bonferroni correction to the results to choose significant genes and introns for each analysis.

Monocyte gene expression

To detect eQTLs, untreated primary monocytes were prepared from 174 healthy individuals of Northern European (British) ancestry recruited

through the Oxford Biobank. Poly(A) RNA was paired-end 100 bp sequenced in the Oxford Genome Centre using the Illumina HiSeq-4000 machines (median = 47,735,438 reads per sample). Reads were aligned to CRGh38/hg38 using HISAT2 with the default parameters. High mapping quality reads were selected on the basis of MAPQ score using bamtools. Duplicate reads were marked and removed using picard (v.1.105). Samtools was used to pass through the mapped reads and calculate statistics. Read count information was generated using HTSeq and normalized using DESeq2. Sample contamination and swaps were detected by comparing the imputed SNP-array genotypes with genotypes called from RNA-seq using verifyBamID. Genotyping was performed with Illumina HumanOmniExpress with coverage of 733,202 separate markers. Genotypes were pre-phased with SHAPEIT2, and missing genotypes were imputed with PBWT. Poly(A) RNA was paired-end sequenced at the Oxford Genome Centre using the Illumina HiSeq-4000 machines. vcftools (v0.1.12b) was applied on genetic variation data in the form of variant call format (VCF) files to filter out indels and SNPs with a minor allele frequency of less than 0.04.

TWAS analysis for monocyte data was performed using genotyping and monocyte RNA-sequencing data from 174 individuals. Using a region of 500 kb around each gene, we calculated gene expression models using the Fusion R package³⁷. For each gene, three models were calculated adding as covariates the two first principal components calculated from the genotype: blup, elastic networks and lasso. The model with a better r^2 between predicted and measured expression in a fivefold cross-validation was chosen. Then SNP genetic heritability was calculated for the 500 kb region for each gene and those genes with a nominal significant SNP heritability estimate ($P \leq 0.01$) were chosen for the TWAS analysis. Summary statistics for the ‘all critical cohorts’ meta-analysis and the best model for each gene were then used to perform the TWAS.

Colocalization

Significant genes in the TWAS and metaTWAS were selected for a colocalization analysis using the coloc R package. The lead SNPs and a region of 200 Mb around the gene were used to colocalize with significant genes in the TWAS with eQTL summary statistics data on the region from GTExv8 lung, GTExv8 whole blood, eQTLgen or monocyte eQTL. As in our previous analysis², we first performed a sensitivity analysis of the posterior probability of colocalization (PPH4) on the prior probability of colocalization (P12), going from $P12 = 10^{-8}$ to $P12 = 10^{-4}$, with the default threshold being $P12 = 10^{-5}$. eQTL signal and GWAS signals were deemed to colocalize if these two criteria were met: (1) at $P12 = 5 \times 10^{-5}$ the probability of colocalization $PPH4 > 0.5$; and (2) at $P12 = 10^{-5}$ the probability of independent signal (PPH3) was not the main hypothesis ($PPH3 < 0.5$). These criteria were chosen to allow eQTLs with weaker P values, owing to lack of power in GTEx v.8, to be colocalized with the signal when the main hypothesis using small priors was that there was not any signal in the eQTL data.

Effect comparison

We compared the estimates of effect sizes between the individual GWASs used in the meta-analysis, for all variants that were genome-wide significant in at least one of the individual GWASs. To this end, we regressed the effects obtained using critical illness and hospitalization in the SCOURGE and 23andMe cohorts, as well as the HGI meta-analyses on the effect estimates obtained using the GenOMICC cohort. To account for estimation errors present in both the dependent and independent variables of the regression we used orthogonal distance regression³⁸.

Weight of studies

To calculate the weight of GenOMICC, we downloaded the leave-one-out data of HGIv7. As the meta-analysis is performed using a variance-weighted method, we can recover the variance for each SNP as $v = \frac{1}{s.e.^2}$,

for the meta-analysis of all of the cohorts and for each one of the leave-one-out analysis. The total weight is $w_{tot} = \frac{1}{v}$ and the weight leaving out a specific study is $w_{100} = \frac{1}{v_{100}}$. The weight of a cohort is then $w_{tot} - w_{100}$. We calculated the weight for each the significant SNPs in our analysis for each study and normalized it using the total weight. Finally, we calculated the mean and s.d. from the significant SNPs for each cohort.

Forest plots

To compare effects between cohorts, we first performed a trans-ancestry meta-analysis for GenOMICC and 23andMe using METAL²³. Then, we used the metagen and forest functions of the meta R package to produce forest plots for critical illness and hospitalization separately.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Downloadable summary data are available through the GenOMICC data site (<https://genomicc.org/data>). Summary statistics are available, but without the 23andMe summary statistics, except for the 10,000 most significant hits, for which full summary statistics are available. The full GWAS summary statistics for the 23andMe discovery dataset will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. For further information and to apply for access to the data, see the 23andMe website (<https://research.23andme.com/dataset-access/>). All individual-level genotype and whole-genome sequencing data (for both academic and commercial uses) can be accessed through the UKRI/HDR UK Outbreak Data Analysis Platform (<https://odap.ac.uk>). A restricted dataset for a subset of GenOMICC participants is also available through the Genomics England data service. Monocyte RNA-seq data are available under the title ‘Monocyte gene expression data’ within the Oxford University Research Archives (<https://doi.org/10.5287/ora-ko7q2nq66>). Sequencing data will be made freely available to organizations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research through a data access agreement. Sequencing data have been deposited at the European Genome-Phenome Archive (EGA), which is hosted by the EBI and the CRG, under accession number EGAS00001007111.

Code availability

Code to calculate the imputation of P values on the basis of SNPs in linkage disequilibrium is available at GitHub (https://github.com/bailielab/GenOMICC_GWAS).

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Competing interests The authors declare no competing interests.

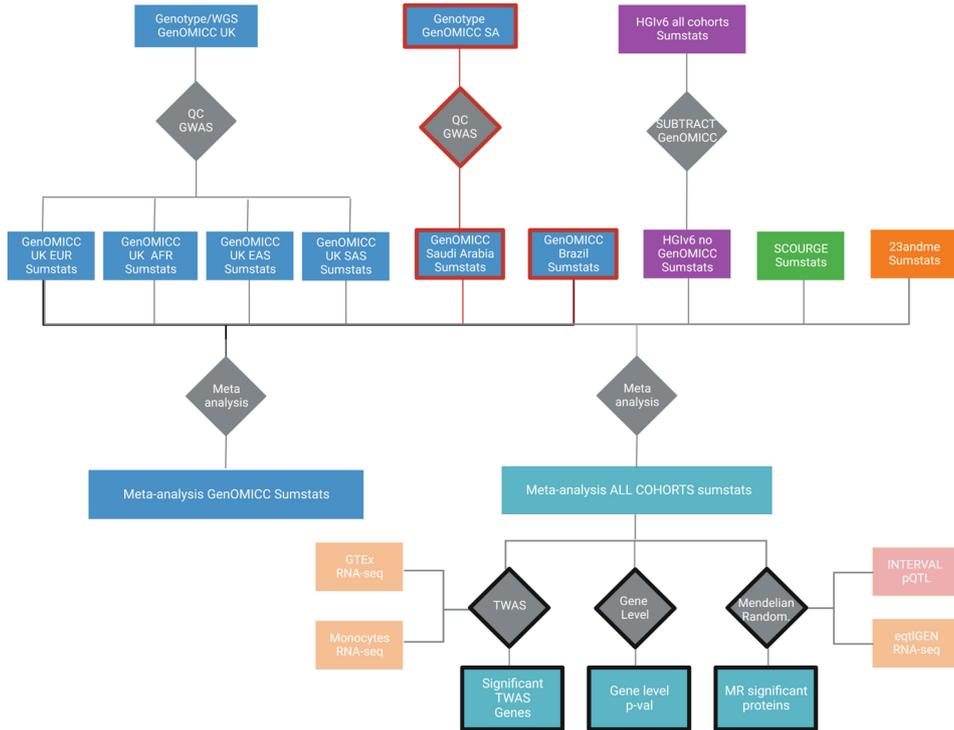
Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41586-023-06034-3>.

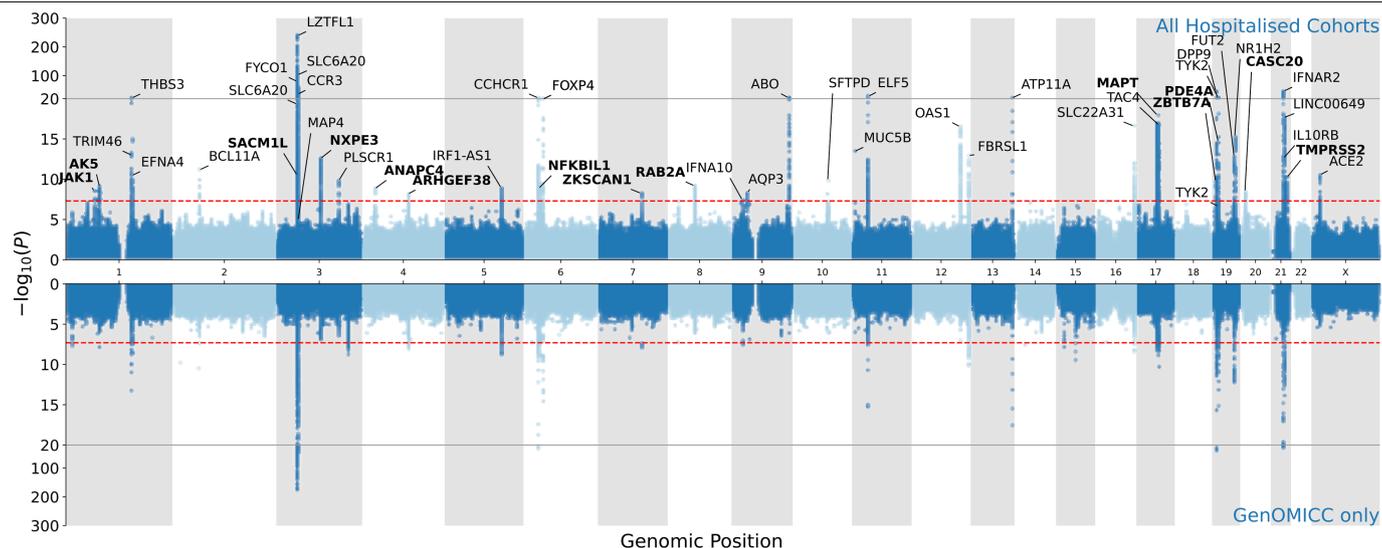
Correspondence and requests for materials should be addressed to J. Kenneth Baillie.

Peer review information *Nature* thanks Jacques Fellay and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

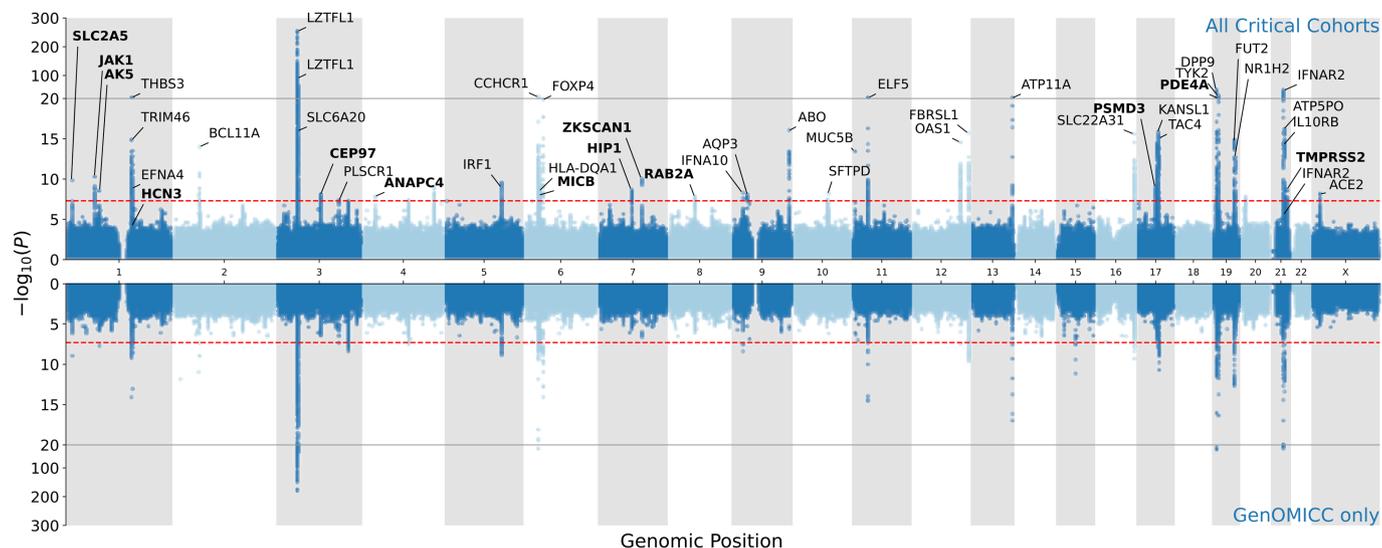
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Extended Data Fig. 1 | Pipeline of meta-analysis and post-GWAS analyses. Red border indicates that the data is only available for the hospitalized phenotype, while a black border indicates that the analysis was performed for the critical illness phenotype.



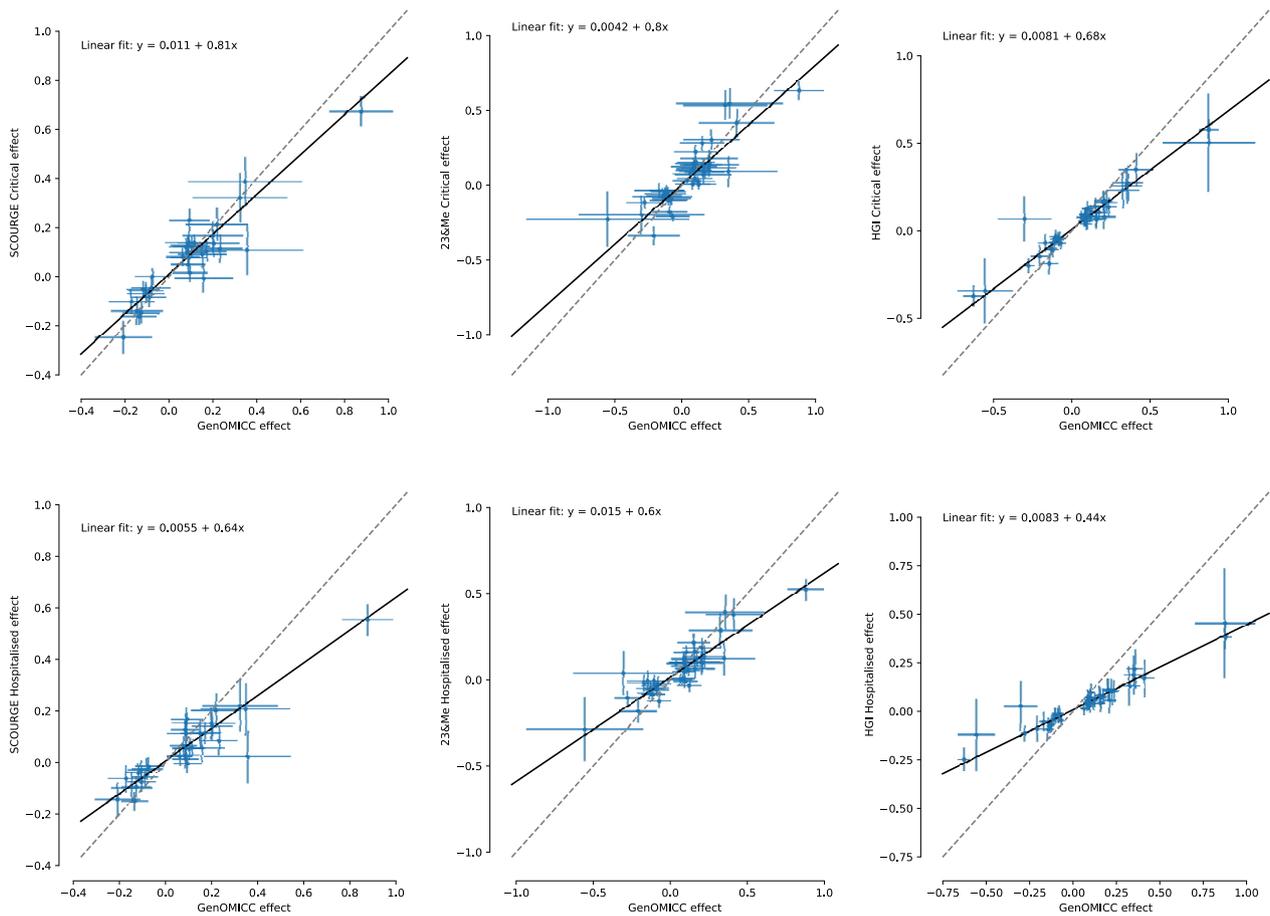
(a)



(b)

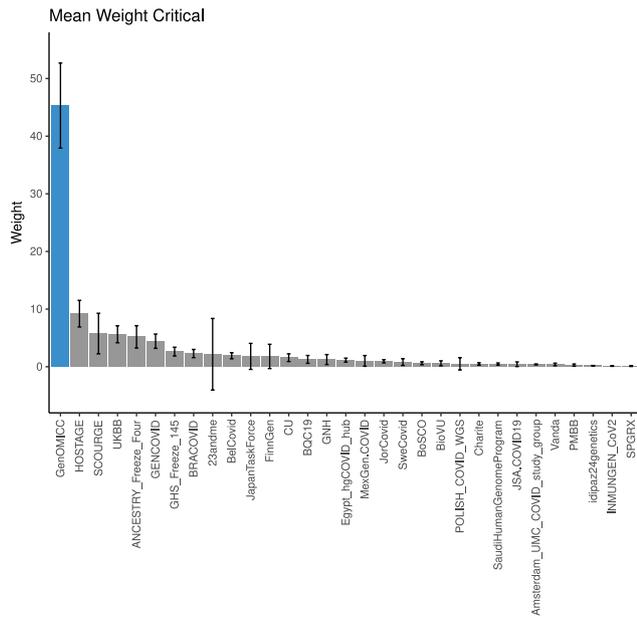
Extended Data Fig. 2 | Miami plots. Meta-analysis results are shown for a) critical and b) hospitalized phenotypes. In each plot results obtained using all cohorts are shown at the top and using GenOMICC data only at the bottom.

Independent lead variants in the analyses of all cohorts are annotated with associated genes. Genome-wide significant associations that have not been previously reported are indicated in bold.

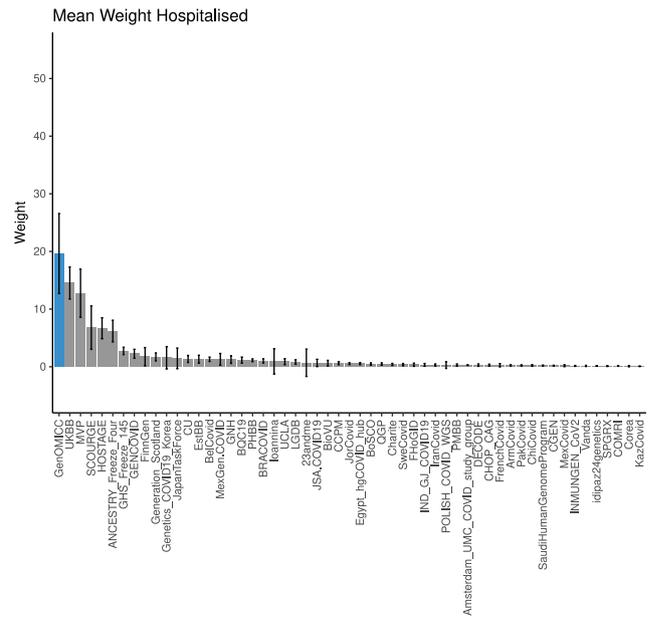


Extended Data Fig. 3 | Comparison of effect size estimates. GenOMICC is compared with the critical and hospitalized phenotype definitions in the SCOURGE, 23andMe, and HGI analyses. The black line indicates the best linear

fit, given by the equation in each plot, obtained using Orthogonal Distance Regression to account for estimation errors in both sets of effects in the comparison.

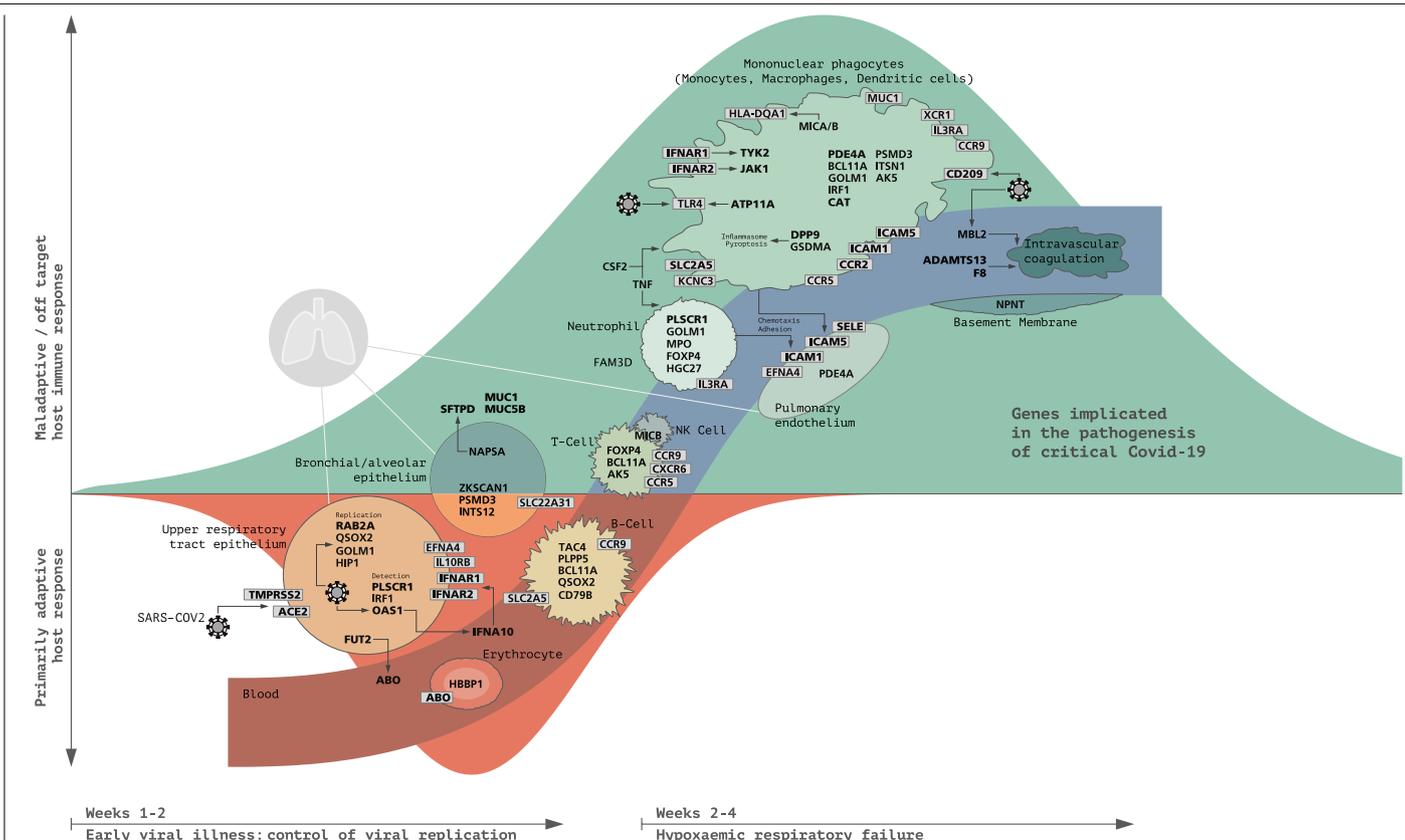


(a)



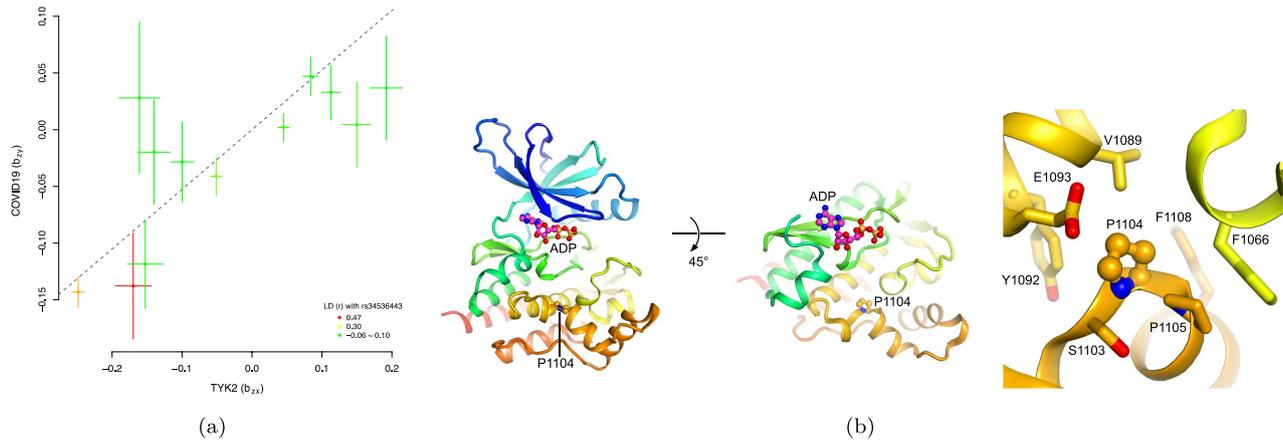
(b)

Extended Data Fig. 4 | Study weightings for (a) critical and (b) hospitalized COVID-19. Mean \pm standard deviation of weights assigned to each data source in meta-analyses for all significant SNPs.



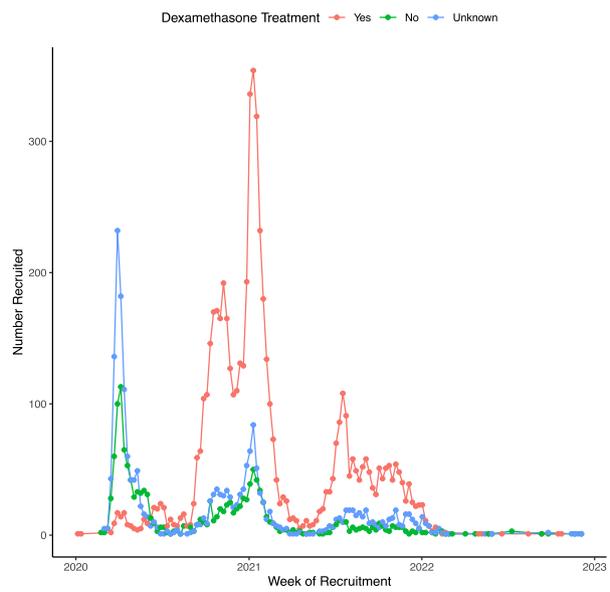
Extended Data Fig. 5 | Cartoon showing postulated roles for genes and mediators implicated in the pathogenesis of critical COVID-19 by GenOMICC GWAS, TWAS and Mendelian randomization. Postulated roles for genetic variants are shown in a highly simplified format to illustrate potential roles in pathogenesis, with the shaded background indicating the hypothetical impact of the host immune response over time¹⁷. Host immune

processes are divided into those that are thought to play a role in controlling viral replication early in disease (orange section, showing “adaptive” response), and those implicated in driving hypoxaemic respiratory failure later in disease (green section, showing “maladaptive” response). Bold type gene names indicate a higher level of confidence in both the gene identification and the biological role.

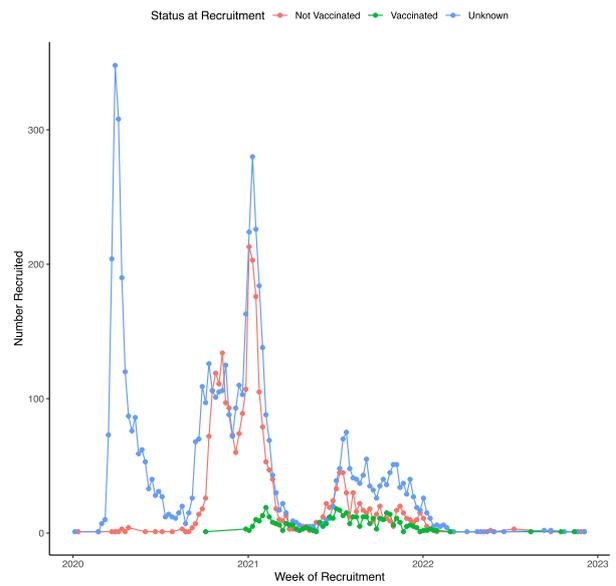


Extended Data Fig. 6 | Functional genomics analyses for TYK2. (a) Effect size plot for effect of multiple variants on TYK2 expression (eQTLgen, x-axis) against increasing susceptibility to critical COVID-19 ($\beta_{xy} = 0.53$; $P_{xy} = 1.2 \times 10^{-23}$). Colour shows linkage disequilibrium (LD) with the missense variant rs34536443. (b) Crystal structure of TYK2 kinase domain (Protein Data Bank ID 4GVJ³⁹) in two views that differ by a 45° rotation around a horizontal axis. The side chain of P1104 is shown as connected spheres with a nitrogen atom

coloured in blue. Carbon, oxygen, nitrogen and phosphorus atoms of ATP are shown as magenta, red, blue and orange connected spheres, respectively. The N-terminal region of the kinase domain is not shown in the second view for clarity. The right-most panel shows a close view of P1104 and neighbouring residues with their side chains shown as sticks. Numbering of residues corresponds to UniProtKB entry P29597. P1104 is in the catalytic kinase domain and proximal to the ATP-binding site; TYK2 P1104A is catalytically impaired⁴⁰.



(a)



(b)

Extended Data Fig. 7 | Steroid treatment and vaccination status. Data are shown for a subset of GenOMICC cases who were also recruited to the ISARIC4C study in the UK.

Extended Data Table 1 | pQTL GSMR results table

Exposure	b	se	p	N_{snp}
FAM3D†	0.17	0.016	4.82×10^{-24}	6
GOLM1†	0.24	0.026	2.43×10^{-20}	3
ICAM5†	-0.17	0.022	8.30×10^{-14}	8
QSOX2	0.12	0.017	1.26×10^{-13}	12
ABO†	0.1	0.014	2.51×10^{-13}	16
CD209†	0.13	0.018	2.53×10^{-12}	8
ICAM1†	0.069	0.01	3.05×10^{-11}	15
SELE†	-0.095	0.015	1.42×10^{-10}	8
CREB3L4	0.15	0.025	1.12×10^{-9}	4
PDGFRL†	0.071	0.013	1.98×10^{-8}	16
ICAM5†	-0.098	0.018	2.72×10^{-8}	6
MPO	-0.14	0.038	2.67×10^{-4}	4
TLR4.LY96†	-0.082	0.024	7.32×10^{-4}	5
ADAMTS13	0.092	0.027	8.19×10^{-4}	5
MBL2	-0.042	0.013	1.34×10^{-3}	15

Proteins significantly linked to COVID-19 severity (false discovery rate (FDR) < 0.05). Exposure: protein name; b: effect-size estimate of the protein on COVID-19 severity from GSMR; se: standard-error of b; p: p-value of the GSMR result; N: Number of independent SNPs included in the analysis. †: indicates proteins with GSMR evidence previously presented in Kousathanas et al.².

Extended Data Table 2 | Replication table

chr.pos.b38	rsid	Gene	SCGG	GenOMICC1	HGI1	GenOMICC2	HGI2	GenOMICC3
			Jul-2020	Aug-2020	May-2021	Sep-2021	Nov-2021	March-2022
1:9067157	rs2478868	SLC2A5						✓
1:64948270	rs12046291	JAK1						✓
1:77501822	rs71658797	AK5						✓
1:155066988	rs114301457	EFNA4				✓		✓
1:155175305	rs7528026	TRIM46				✓		✓
1:155197995	rs41264915	THBS3	✓			✓	✓	✓
1:155278322	rs11264349	HGN3					✓	✓
2:60480453	rs1123573	BCL11A				✓		✓
3:45796521	rs2271616	SLC6A20			✓	✓	✓	✓
3:45818159	rs17713054*	LZTF1	✓	✓	✓	✓	✓	✓
3:45873093	rs35482426	LZTF1	✓	✓	✓	✓	✓	✓
3:101790631	rs11706494	NXPE3						✓
3:146522652	rs343314	PLSCR1				✓		✓
4:25446871	rs7664615	ANAPC4						✓
4:105673359	rs72670002	ARHGEF38						✓
4:167824478	rs1073165	.						✓
5:132422622	rs2269821	IRF1-AS1				✓		✓
6:31153455	rs111837807	CCHCR1		✓	✓		✓	✓
6:31571991	rs2071590	LTA						✓
6:32702687	rs2858305	HLA-DQA1				✓		✓
6:41522644	rs41435745	FOXP4			✓		✓	✓
7:75623396	rs1179620	HIP1						✓
7:100032719	rs2897075	ZKSCAN1						✓
8:60532539	rs13276831	RAB2A						✓
9:21206606	rs28368148	IFNA10				✓		✓
9:33425186	rs60840586	AQP3						✓
9:133271182	rs879055593	ABO	✓		✓		✓	✓
10:79946568	rs721917	SFTPD					✓	✓
11:1219991	rs35705950	MUC5B					✓	✓
11:34482745	rs61882275	ELF5				✓	✓	✓
12:112919637	rs2660	OAS1		✓	✓		✓	✓
12:132481571	rs11614702	FBRSL1				✓	✓	✓
13:112881427	rs12585036	ATP11A				✓		✓
16:89196249	rs117169628	SLC22A31				✓	✓	✓
17:40003082	rs12941811	PSMD3						✓
17:46085231	rs8080583	KANSL1			✓		✓	✓
17:49863303	rs77534576	TAC4			✓		✓	✓
19:4717660	rs12610495	DPP9		✓	✓	✓	✓	✓
19:10352442	rs34536443	TYK2		✓	✓		✓	✓
19:10414696	rs142770866	PDE4A			✓			✓
19:48702915	rs516246	FUT2				✓		✓
19:50374423	rs35463555	NRIH2					✓	✓
20:6489447	rs2326788	CASC20						✓
21:33229937	rs188401375	IFNAR2		✓	✓	✓	✓	✓
21:33237639	rs9636867	IFNAR2		✓	✓	✓	✓	✓
21:33287378	rs8178521	IL10RB				✓	✓	✓
21:33980963	rs76608815	ATP5PO				✓		✓
21:41479527	rs915823	TMPRSS2						✓
23:15523993	rs35697037	ACE2					✓	✓

Each report of genome-wide significant associations with severe COVID-19 is shown, with associations that were first reported by the GenOMICC consortium are highlighted in blue.

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- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- A description of all covariates tested
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- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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Software and code

Policy information about [availability of computer code](#)

Data collection

Illumina i-scan platform, GenomeStudio Analysis software v2.0.3, GSAMD-24v3-0-EA_20034606_A1.bpm manifest and cluster file provided by manufacturer for GenOMICC UK genotyping. Affymetrix Saub1 chip (Saudi Arabia) and Axiom Analysis suite 5.1.1.1 manifest and cluster file provided by manufacturer for GenOMICC Saudi Arabia. Other datasets were collected previously and Summary statistics used. In order to detect eQTLs, untreated primary monocytes were prepared from 174 healthy individuals of Northern European (British) ancestry recruited via the Oxford biobank. Poly-A RNA was paired-end 100bp sequenced in the Oxford Genome Centre using Illumina HiSeq-4000 machines (median = 47,735,438 reads per sample). Genotyping was performed with Illumina HumanOmniExpress with coverage of 733,202 separate markers.

Data analysis

GenomeStudio v2.03, Plink 1.9, Plink 2.0, King 2.1, R v3.6.3, python v3.7, GATK 4.0, USC liftover, GCTA v1.92, REGENIE v3.1.2, metal (2018-08-28), BCFtools 1.9, QCTools 1.3, FlashPCA2, admixture, 1.3.0 SMR/HEIDI v1.03, MetaXcan v0.6.5, MiniMac4 v1.0, MetaSubtract package v1.60, Rv4.1.0, FUSION (commit e1ba5f7), python v3.10, HISAT2, bamtools, picard v.1.105, verifyBAMID, samtools, SHAPEIT2, PBWT, vcftools v.0.1.12b, HTseq, Deseq2.

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- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Downloadable summary data are available through the GenOMICC data site <https://genomicc.org/data>. Summary statistics will be available without including 23andme summary statistics, except for the 10,000 most significant hits which will have full summary statistics available. The full GWAS summary statistics for the 23andMe discovery data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit <https://research.23andMe.com/dataset-access/> for more information and to apply to access the data.

All individual-level genotype and whole genome sequence data (for both academic and commercial uses) can be accessed through the UKRI/HDR UK Outbreak Data Analysis Platform <https://odap.ac.uk>. A restricted dataset for a subset of GenOMICC participants is also available through the Genomics England data service.

Monocyte RNA-seq data is available under the title "Monocyte gene expression data" within the Oxford University Research Archives. DOI: 10.5287/ora-ko7q2nq66 (<http://dx.doi.org/10.5287/ora-ko7q2nq66>)

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender

Sex was asked in the study, and then confirmed by genotype. When there was a discordance between self-reported sex and genotyped sex the sample was removed from the study.

Sex-specific analysis were performed for both males and females but did not give any significant results

Overall the study included 45472 cases from which ~40% are female. As data comes from summary statistics from other analysis, it has not been possible to calculate the exact number of females and males.

Population characteristics

Cases have tested positive for Covid-19 and needed hospitalisation or ICU admission. Controls come from different sources, people which experienced mild (non-hospitalised) Covid-19 or population controls from different Biobanks. In GenOMICC Brazil, mild cases were selected from serological studies of SARS-COV2 infection and PCR test results among health professionals and the general population. In GenOMICC Saudi Arabia, mild controls were selected after a positive PCR test. SCOURGE population controls were extracted from Spanish DNA Biobank and the GR@CE consortium. Participants in 23andme analysis provided informed consent and answered surveys online according to 23andme human subjects research protocol.

Untreated primary monocytes were prepared from 174 healthy individuals from British ancestry via the Oxford Biobank

Recruitment

Cases were recruited by different studies in hospitals. All participants gave informed consent. Mild controls were recruited on the basis of having experienced mild or asymptomatic Covid-19.

For GenOMICC UK and ISARIC4C population controls were used from UK Biobank (project 788), or 100,000 genomes from genomics england. SCOURGE project used controls from Spanish DNA Biobank and the GR@CE consortium

Ethics oversight

GenOMICC Scotland: Scotland A Research Ethics Committee 15/SS/0110.

GenOMICC England/Wales/Northern Ireland Coventry and Warwickshire Research Ethics Committee 19/WM/0247.

GenOMICC Brazil (BraCovid) National Research Ethics Committee (CONEP) and Ethics Committee for the Analysis of Research Projects at HC FMUSP (CAPPesq) 5025/20/054.

GenOMICC Saudi Arabia IRB at King Abdullah International Medical Research Center.

ISARIC4C England/Wales/Northern Ireland South Central Oxford C Research Ethics Committee 13/SC/0149.

ISARIC4C Scotland Scotland A Research Ethics Committee 20/SS/0028.

SCOURGE Galician Ethical Committee 2020/197.

23andme Ethical and Independent Review Services <http://www.eandireview.com>.

Covid-19 HGI Multiple ethics committees (<https://www.covid19hg.org/>).

Oxford biobank approved by South Central - Oxford C Research Ethics Committee, reference 18/SC/0588

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Life sciences study design

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Sample size	cases 45472, controls 2929541
Data exclusions	no exclusions
Replication	As we meta-analysed all public data available for Covid-19, to verify replicability of the findings we performed a heterogeneity test between studies, using a Cochran's Q-test
Randomization	Not relevant to the study
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Methods

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