

Genetic mechanisms of critical illness in COVID-19

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Host-mediated lung inflammation is present¹, and drives mortality², in the critical illness caused by coronavirus disease 2019 (COVID-19). Host genetic variants associated with critical illness may identify mechanistic targets for therapeutic development³. Here we report the results of the GenOMICC (Genetics Of Mortality In Critical Care) genome-wide association study in 2,244 critically ill patients with COVID-19 from 208 UK intensive care units. We have identified and replicated the following new genome-wide significant associations: on chromosome 12q24.13 (rs10735079, $P=1.65 \times 10^{-8}$) in a gene cluster that encodes antiviral restriction enzyme activators (*OAS1*, *OAS2* and *OAS3*); on chromosome 19p13.2 (rs74956615, $P=2.3 \times 10^{-8}$) near the gene that encodes tyrosine kinase 2 (*TYK2*); on chromosome 19p13.3 (rs2109069, $P=3.98 \times 10^{-12}$) within the gene that encodes dipeptidyl peptidase 9 (*DPP9*); and on chromosome 21q22.1 (rs2236757, $P=4.99 \times 10^{-8}$) in the interferon receptor gene *IFNAR2*. We identified potential targets for repurposing of licensed medications: using Mendelian randomization, we found evidence that low expression of *IFNAR2*, or high expression of *TYK2*, are associated with life-threatening disease; and transcriptome-wide association in lung tissue revealed that high expression of the monocyte–macrophage chemotactic receptor *CCR2* is associated with severe COVID-19. Our results identify robust genetic signals relating to key host antiviral defence mechanisms and mediators of inflammatory organ damage in COVID-19. Both mechanisms may be amenable to targeted treatment with existing drugs. However, large-scale randomized clinical trials will be essential before any change to clinical practice.

As critical illness in patients with COVID-19 is caused, in part, by inflammatory injuries that affect the lungs and lung blood vessels⁴, there are at least two distinct biological components to the mortality risk: susceptibility to viral infection and propensity to develop harmful pulmonary inflammation. Susceptibility to life-threatening infections⁴ and immune-mediated diseases are both strongly heritable. In particular, susceptibility to respiratory viruses⁵ such as influenza⁶ is heritable and known to be associated with specific genetic variants⁷. In the case of COVID-19, one genetic locus—on chromosome 3p21.31—has been repeatedly associated with hospitalization^{8,9}. As with other virus-associated diseases¹⁰, there are several examples of loss-of-function variants affecting essential immune processes that lead to severe disease in young people, such as *TLR7*¹¹ and some genes implicated in type I interferon signalling, including the receptor subunit *IFNAR2*¹². Genome-wide studies have the potential to reveal previously undescribed molecular mechanisms of critical illness in patients with COVID-19, which may provide therapeutic targets to modulate the host immune response to promote survival³.

Strong evidence indicates that critical illness caused by COVID-19 is qualitatively different from mild or moderate disease, even among hospitalized patients. There are multiple distinct disease phenotypes with differing patterns of symptoms¹³ and marked differential responses to immunosuppressive therapy². In patients without respiratory failure, there is a trend indicating that treatment with corticosteroids is harmful, whereas among patients with critical respiratory failure, there is

a substantial benefit². On this basis, we consider patients with critical COVID-19 respiratory failure to have a distinct pathophysiology.

In the UK, the group of patients admitted to critical care is relatively homogeneous, with profound hypoxaemic respiratory failure being the archetypal presentation¹⁴. The active disease process in these patients is markedly responsive to corticosteroid therapy¹⁵ and is characterized by pulmonary inflammation including diffuse alveolar damage, influx of monocytes and macrophages, mononuclear cell pulmonary artery vasculitis and microthrombus formation^{1,16}.

Host-directed therapies have long been an aim for the treatment of the severe disease caused by respiratory viruses¹⁷. Identification of genetic loci associated with susceptibility to COVID-19 may lead to specific targets for the development or repurposing of drugs³.

The GenOMICC (Genetics Of Mortality In Critical Care, <https://genomicc.org/>) study has been recruiting patients with critical illness syndromes, including influenza, sepsis and emerging infections, for 5 years. To better understand the host mechanisms that lead to life-threatening disease in patients with COVID-19, we performed a genome-wide association study (GWAS) comparing critically ill patients with COVID-19 with controls from population genetic studies in the UK.

Characteristics of participants

Critically ill cases were recruited through the GenOMICC study in 208 UK intensive care units and hospitalized cases were recruited through

Table 1 | Lead variants from independent genome-wide significant regions

SNP	Chr.: pos.	Risk	Alt.	RAF _{gcc}	RAF _{ukb}	OR	CI	P _{gcc.ukb}	P _{gcc.gs}	P _{gcc.100k}	Locus
rs73064425	3: 45,901,089	T	C	0.15	0.07	2.1	1.88–2.45	4.8 × 10 ⁻³⁰	2.9 × 10 ⁻²⁷	3.6 × 10 ⁻³²	LZTFL1
rs9380142	6: 29,798,794	A	G	0.74	0.69	1.3	1.18–1.43	3.2 × 10 ⁻⁸	0.00091	1.8 × 10 ⁻⁸	HLA-G
rs143334143	6: 31,121,426	A	G	0.12	0.07	1.8	1.61–2.13	8.8 × 10 ⁻¹⁸	2.6 × 10 ⁻²⁴	5.8 × 10 ⁻¹⁸	CCHCR1
rs3131294	6: 32,180,146	G	A	0.9	0.86	1.5	1.28–1.66	2.8 × 10 ⁻⁸	1.3 × 10 ⁻¹⁰	2.3 × 10 ⁻⁸	NOTCH4
rs10735079	12: 113,380,008	A	G	0.68	0.63	1.3	1.18–1.42	1.6 × 10 ⁻⁸	2.8 × 10 ⁻⁹	4.7 × 10 ⁻⁶	OAS1–OAS3
rs2109069	19: 4,719,443	A	G	0.38	0.32	1.4	1.25–1.48	4 × 10 ⁻¹²	4.5 × 10 ⁻⁷	2.4 × 10 ⁻⁸	DPP9
rs74956615	19: 10,427,721	A	T	0.079	0.05	1.6	1.35–1.87	2.3 × 10 ⁻⁸	2.2 × 10 ⁻¹³	3.9 × 10 ⁻⁶	TYK2
rs2236757	21: 34,624,917	A	G	0.34	0.28	1.3	1.17–1.41	5 × 10 ⁻⁸	8.9 × 10 ⁻⁵	8.3 × 10 ⁻⁷	IFNAR2

As this is a meta-analysis of all available data, external replication cannot be attempted, so SNPs are included if they meet a more stringent P-value threshold of $P < 10^{-8}$. SNP, the strongest SNP in the locus. Chr.: pos., chromosome and position of the top SNP (build 37); Risk, risk allele; Alt., alternative allele; RAF, risk allele frequency; OR, effect size (odds ratio) of the risk allele in the GenOMICC European analysis; CI, 95% confidence interval for the odds ratio in the GenOMICC European cohort; P, P value; Locus, gene nearest to the top SNP. Subscript identifiers indicate the cohorts used for cases (gcc, GenOMICC European cohort) and controls (ukb, UK Biobank; gs, Generation Scotland; 100k, 100,000 Genomes Project).

the International Severe Acute Respiratory Infection Consortium (ISARIC) Coronavirus Clinical Characterization Consortium (4C) study.

DNA was extracted from whole blood and array-based genome-wide genotypes of good quality were obtained for 2,734 unique individuals (Methods). Genetic ancestry was inferred using principal component analyses and individuals from the 1000 Genomes Project were included as population references (Methods). After quality control and matching to ancestry groups, 2,244 individuals were included in the GWAS for analysis. Clinical and demographic features of these cases are shown in Extended Data Table 1. Additional clinical details for a subset of 1,069 cases for whom additional data were available are presented in Supplementary Figs. 7–13 and Supplementary Table 2. Cases were representative of critically ill patients with COVID-19 in the UK population¹⁴. Imputation in this multi-ancestry cohort was performed using the TOPMed reference panel.

Ancestry-matched control individuals were selected from the large population-based cohort of UK Biobank (five controls were included for each case). Controls with a known positive COVID-19 test were excluded. The inevitable presence of individuals in the control group, who may exhibit the critical illness phenotype if exposed to SARS-CoV-2 is expected to bias any associations towards the null hypothesis. GWAS was carried out separately for each ancestry group using logistic regression in PLINK and accounting for age, sex, deprivation decile based on the individual's residential postal code and principal components of ancestry. In addition to several standard filters to minimize spurious associations (Methods), whole-genome sequencing analysis of a subset of 1,613 cases was used to filter out variants that are likely to have been badly called or imputed; 83,937 out of the 4,469,187 imputed variants that passed other quality-control filters after GWAS were thus removed. There was a high level of residual inflation in the South Asian and East Asian ancestry groups, rendering results in these subgroups unreliable (Extended Data Fig. 1, Supplementary Fig. 4). The largest ancestry group contained 1,676 individuals of European descent; this group was used for the primary analyses presented below.

GWAS results

In the primary analysis (cases of European descent from GenOMICC versus controls from the UK Biobank), after linkage-disequilibrium-based clumping, 15 independent association signals were genome-wide significant at $P < 5 \times 10^{-8}$ (Supplementary Fig. 1). Eight of these signals were successfully validated in GWAS analyses using two independent population genetic studies (100,000 Genomes Project and Generation Scotland: Scottish Family Health Study, hereafter Generation Scotland) as controls (Table 1) and were therefore taken forward for replication. A sex-specific GWAS among this group found no sex-specific associations (Supplementary Table 1). A trans-ethnic meta-analysis did not reveal any additional associations (Supplementary Fig. 3).

Replication

As no study of critical illness in patients with COVID-19 of sufficient size is available, replication was carried out in a meta-analysis of data from 2,415 hospitalized patients with COVID-19 and 477,741 population controls from the COVID-19 Host Genetics Initiative (HGI, individuals of mixed ancestry from which cases and controls of the UK Biobank were excluded) and 1,128 cases and 679,531 controls of European ancestry from the 'broad respiratory phenotype' study of 23andMe Inc, which includes cases that were reported as having been placed on a ventilator, administered oxygen or having had pneumonia compared with control individuals who did not report COVID-19-positive tests. In addition to the locus on chromosome 3 that has previously been reported (rs73064425, odds ratio = 2.14, discovery $P = 4.77 \times 10^{-30}$), we found robust replication for previously undescribed associations in four loci from GenOMICC: a locus on chromosome 12 in the OAS gene cluster (rs10735079, odds ratio = 1.3, discovery $P = 1.65 \times 10^{-8}$), near TYK2 on chromosome 19 (rs74956615, odds ratio = 1.6, discovery $P = 2.3 \times 10^{-8}$), in DPP9 on chromosome 19 (rs2109069, odds ratio = 1.36, discovery $P = 3.98 \times 10^{-12}$) and a locus on chromosome 21, which contains the gene IFNAR2 (rs2236757, odds ratio = 1.28, discovery $P = 4.99 \times 10^{-8}$) (Fig. 1, Extended Data Table 2).

Three variants, all in a region of chromosome 6 for which population stratification is difficult to control (the major histocompatibility complex) did not replicate (Extended Data Table 2, Supplementary Fig. 2). Further studies will be required to determine whether these associations are real.

To increase power for exploratory analyses, inverse-variance meta-analysis was performed between critically ill patients of European descent from GenOMICC ($n = 1,676$ cases, $n = 8,380$ controls), hospitalized patients with COVID-19 versus population controls (B2, version 2) without UK Biobank participants from the HGI ($n = 2,415$ cases, $n = 477,741$ controls) and the participants with the broad respiratory phenotype from 23andMe ($n = 1,128$ cases, $n = 679,531$ controls). This revealed one additional (unreplicated) locus in CCHCR1 at genome-wide significance (using a more-stringent threshold of $P < 10^{-8}$ because of the absence of replication opportunities for the meta-analysis) (Table 2).

Mendelian randomization

Mendelian randomization provides evidence for a causal relationship between an exposure variable and an outcome, given a set of well-characterized assumptions¹⁸. We used two-sample summary-data Mendelian randomization to assess the evidence in support of causal effects of RNA expression (Genotype-Tissue expression (GTEx) v.7, whole blood) of various genes on the odds of patients becoming critically ill due to COVID-19.

We specified an a priori list of target genes that relate to the mechanism of action of many host-targeted drugs that have been proposed for

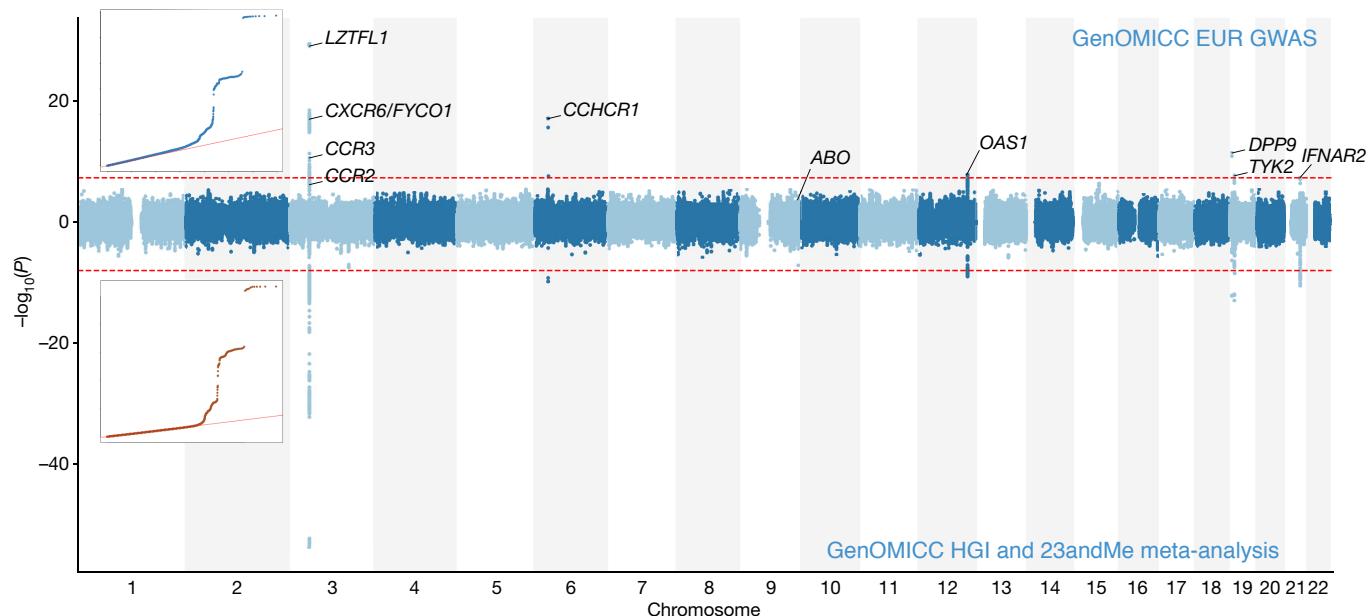


Fig. 1 | Discovery GWAS and meta-analysis results. Miami plot showing the P values for the GenOMICC GWAS in individuals of European ancestry after validation (top) and meta-analysis including patients from the COVID-19 HGI and 23andMe (bottom). Uncorrected P values from GWAS analysis are shown. Top, the red horizontal line indicates genome-wide significance for common variants at $-\log_{10}(5 \times 10^{-8})$. Bottom, the red horizontal line indicates a

more-stringent genome-wide significance threshold for meta-analysis variants at $-\log_{10}(1 \times 10^{-8})$. Insets, quantile–quantile (QQ) plots of observed versus expected P values that show genomic inflation (λ) for each analysis: GenOMICC European cohort, $\lambda=1.099$; GenOMICC HGI–23andMe meta-analysis, $\lambda=1.017$. Full QQ plots are shown in Extended Data Fig. 1.

the treatment of patients with COVID-19 (Supplementary Table 3). Seven of these targets had a suitable locally acting expression quantitative trait locus (eQTL) in GTEx (v.7). Of these, *IFNAR2* remained significant after Bonferroni correction for multiple testing for seven tests ($\beta=-1.49$, s.e. = 0.52, $P=0.0043$) (Supplementary Table 4). There was equivocal evidence of heterogeneity (HEIDI¹⁹ $P=0.015$), indicating that the effect of this variant on critical illness in COVID-19 may be mediated through another mechanism, which may lead to an under- or overestimation of the effect of *IFNAR2* expression on the risk of critical illness in COVID-19.

We next performed transcriptome-wide Mendelian randomization to quantify support for unselected genes as potential therapeutic targets. Instruments (genetic variants that affect gene expression) were available for 4,614 unique Ensembl gene IDs. No genes were statistically significant after correcting for multiple comparisons in this analysis (4,614 tests). After conservative filtering for heterogeneity (HEIDI $P>0.05$), the smallest Mendelian randomization $P=0.00049$ was associated with a variant on chromosome 19: 10,466,123 that affects expression of *TYK2*. Nine other genes with nominally significant Mendelian randomization P values ($P<0.0051$) were also taken forward for further analysis (Supplementary Table 5).

To replicate these findings, we tested for external evidence using a separate eQTL data set (eQTLgen)²⁰ and GWAS (HGI B2, excluding UK Biobank participants). Mendelian randomization signals with consistent directions of effect were significant for *IFNAR2* ($P=7.5 \times 10^{-4}$) and *TYK2* ($P=5.5 \times 10^{-5}$) (Supplementary Table 6).

Transcriptome-wide association study

We performed a transcriptome-wide association study (TWAS)^{21,22} to link GWAS results to tissue-specific gene expression data by inferring gene expression from known genetic variants that are associated with transcript abundance (eQTL). For this analysis, we used GTEx v.8 data for two disease-relevant tissues chosen a priori: whole blood and lung samples (Fig. 2). We selected genes with $P<0.05$ in these tissues and performed a combined meta-TWAS analysis²³, incorporating eQTL data

from other tissues in GTEx, to optimize power to detect differences in predicted expression in lung or blood.

We discovered five genes with genome-wide significant differences in predicted expression compared to control individuals (Supplementary Table 7). This included four genes with differential predicted expression in lung tissue (three on chromosome 3, *CCR2*, *CCR3* and *CXCR6*; and one on chromosome 5, *MTA2B*) (Supplementary Tables 8–10).

We used meta-analysis by information content (MAIC)²⁴ to put these results in the context of existing biological knowledge about host–virus interactions associated with COVID-19. We combined the top 2,000 genes in metaTWAS with previous systematically compiled experimental evidence implicating human genes in SARS-CoV-2 replication and host response. MAIC derives a data-driven weighting for each gene from a range of experimental data sources in the form of gene lists, and outperforms other approaches to providing a composite of multiple lists²⁴. We found that the GenOMICC TWAS results had greater overlap with results from transcriptomic, proteomic and CRISPR studies of host genes implicated in COVID-19 than any other data source (Extended Data Fig. 2).

Genetic correlations

We used a high-definition likelihood method²⁵ to provide an initial estimate of heritability based on single-nucleotide polymorphisms (SNPs) (that is, the proportion of phenotypic variance captured by additive effects at common SNPs) for severe COVID-19, which was found to be 0.065 (s.e. = 0.019). We were not able to detect a significant signal for heritability in two additional analyses: first, using controls from the 100,000 Genomes Project (in which matching to the cases from GenOMICC is less close, which may limit heritability estimation) and second, in a smaller GWAS in which some cases from GenOMICC were compared with controls from the UK Biobank, using matched data for body-mass index and age where possible. This second analysis was less powerful because of the lack of close matches for many cases ($n=1,260$ cases, $n=6,300$ controls) (Supplementary Fig. 14). Including

Table 2 | Meta-analysis of overlapping SNPs between GenOMICC, HGI and 23andMe studies

SNP	Chr.: pos.	Risk	Alt.	OR _{gcc}	CI _{gcc}	P _{gcc}	OR _{meta}	CI _{meta}	P _{meta}	Locus
rs71325088	3: 45,862,952	C	T	2.1	1.87–2.43	9.3 × 10 ⁻³⁰	1.9	1.73–2	2.5 × 10 ⁻⁵⁴	LZTFL1
rs143334143	6: 31,121,426	A	G	1.8	1.61–2.13	8.8 × 10 ⁻¹⁸	1.3	1.27–1.48	1.5 × 10 ⁻¹⁰	CCHCR1
rs6489867	12: 113,363,550	T	C	1.3	1.15–1.37	6.9 × 10 ⁻⁷	1.2	1.14–1.25	9.7 × 10 ⁻¹⁰	OAS1–OAS3
rs2109069	19: 4,719,443	A	G	1.4	1.25–1.48	4 × 10 ⁻¹²	1.2	1.19–1.31	7 × 10 ⁻¹³	DPP9
rs11085727	19: 10,466,123	T	C	1.3	1.17–1.4	1.3 × 10 ⁻⁷	1.2	1.18–1.31	1.2 × 10 ⁻¹³	TYK2
rs13050728	21: 34,615,210	T	C	1.3	1.15–1.38	3 × 10 ⁻⁷	1.2	1.16–1.28	5.1 × 10 ⁻¹²	IFNAR2

gcc, GenOMICC European study compared with UK Biobank; meta, combined meta-analysis of all three studies for individuals of European ancestry: GenOMICC ($n = 1,676$ cases, $n = 8,380$ controls), HGI ($n = 2,415$ cases, $n = 477,741$ controls) and 23andMe ($n = 1,128$ cases, $n = 679,531$ controls).

rare variants in future analyses, which have larger numbers of cases of COVID-19, will provide a more comprehensive estimate of heritability. We also tested for genetic correlations with other traits—that is, the degree to which the underlying genetic components are shared with severe COVID-19. Using the high-definition likelihood method, we identified significant negative genetic correlations with educational attainment and intelligence. Significant positive genetic correlations were detected for a number of adiposity phenotypes including body-mass index and leg fat (Supplementary Fig. 19).

Consistent with GWAS results from other infectious and inflammatory diseases, there was a significant enrichment of strongly associated variants in promoters and enhancers²⁶, particularly those identified by the ExAC study as under strong evolutionary selection²⁷ (Supplementary Fig. 18). The strongest tissue-type enrichment was in spleen (which may reflect enrichment in immune cells), followed by pancreas (Supplementary Fig. 20).

Discussion

We have discovered and replicated significant genetic associations that are associated with life-threatening COVID-19 (Fig. 1). Our focus on critical illness increases the probability that some of these associations relate to the later, immune-mediated phase of COVID-19 associated with respiratory failure that requires invasive mechanical ventilation². Notably, the GWAS approach is unbiased and genome-wide, enabling the discovery of previously undescribed pathophysiological mechanisms. Because genetic variation can be used to draw a causal inference, genetic evidence in support of a therapeutic target substantially improves the probability of successful drug development²⁸. In particular, Mendelian randomization occupies a unique position in the hierarchy of clinical evidence²⁹.

Patients admitted to intensive care units in the UK during the first wave of COVID-19 were, on average, younger and less burdened by comorbid illnesses than the hospitalized population¹⁴. The population studied here was defined by their propensity to critical respiratory failure due to COVID-19. GenOMICC recruited in 208 intensive care units (covering >95% of the capacity of intensive care units in the UK), ensuring that a broad spread across the genetic ancestry of patients from the UK was included (Extended Data Fig. 3).

For external replication, the nearest comparison is the analysis of hospitalized patients versus population controls in the COVID-19 HGI, and the broad respiratory phenotype dataset from 23andMe, which have been generously shared with the international community. We have also immediately made full summary statistics from GenOMICC data openly available at <https://genomicc.org/data/>.

Despite the differences in case definitions, new associations from our study of critical illness replicate robustly in combined data from studies of hospitalized cases of COVID-19 (Extended Data Table 2). Separately, the Mendelian randomization results that suggest a causal role for *IFNAR2* and *TYK2* are also statistically significant in confirmatory analyses. Our findings reveal that critical illness in COVID-19 is related

to at least two biological mechanisms: innate antiviral defences, which are known to be important early in disease (*IFNAR2* and *OAS* genes), and host-driven inflammatory lung injury, which is a key mechanism of late, life-threatening COVID-19 (*DPP9*, *TYK2* and *CCR2*)².

Interferons are canonical mediators of antiviral signalling in the host and stimulate release of many essential components of the early host response to viral infection³⁰. Consistent with a beneficial role for type I interferons, increased expression of the interferon receptor subunit *IFNAR2* reduced the odds of severe COVID-19 with Mendelian randomization discovery $P = 0.0043$ (seven tests); replication $P = 7.5 \times 10^{-4}$ (one test). Within the assumptions of Mendelian randomization, this represents evidence for a protective role of *IFNAR2* in COVID-19. Rare loss-of-function mutations in *IFNAR2* are associated with severe COVID-19¹² and many other viral diseases^{31,32}. This suggests that administration of interferon may reduce the probability of critical illness in COVID-19, but our evidence cannot distinguish when during disease progression of COVID-19 such a treatment may be effective. Exogenous interferon treatment did not reduce mortality in hospitalized patients in a large-scale clinical trial³³, suggesting that this genetic effect may be mediated during the early phase of disease when the viral load is high.

The variant rs10735079 (chromosome 12, $P = 1.65 \times 10^{-8}$) lies in the interferon-inducible oligoadenylate synthetase (OAS) gene cluster (*OAS1*, *OAS2* and *OAS3*) (Fig. 1). Our TWAS detected significant associations with predicted expression of *OAS3* (Fig. 2). *OAS1* variants were implicated in susceptibility to SARS-CoV in candidate gene association studies in Vietnam³⁴ and China³⁵. These genes encode enzymes that produce a host antiviral mediator (2',5'-oligoadenylate (2-5A)) that activates an effector enzyme, RNase L. RNase L degrades double-stranded RNA³⁶, a replication intermediate of coronaviruses³⁷. The betacoronaviruses OC43 and MHV make viral phosphodiesterases that cleave 2-5A³⁸, but SARS-CoV-2 is not known to have this ability. The OAS genes therefore also provide a potential therapeutic target: endogenous phosphodiesterase 12 (PDE-12) activity degrades 2-5A. Therapeutic PDE-12 inhibitors are available and augment OAS-mediated antiviral activity³⁹.

The association on chromosome 19p13.3 (rs2109069, $P = 3.98 \times 10^{-12}$) is an intronic variant in the gene that encodes dipeptidyl peptidase 9 (*DPP9*). Variants in this locus are associated with idiopathic pulmonary fibrosis⁴⁰. *DPP9* encodes a serine protease that has diverse intracellular functions, including the cleavage of the key antiviral signalling mediator CXCL10⁴¹, and key roles in antigen presentation⁴² and inflammasome activation⁴³.

As opportunities for therapeutic intervention, particularly experimental therapy, are more abundant in later, more-severe cases of disease, it is important that our results also reveal genes that may act to drive inflammatory organ injury. *TYK2* is one of four gene targets for JAK inhibitors such as baricitinib⁴⁴, one of the nine candidate drugs that we used in the creation of our *a priori* target list (Supplementary Table 3). The association between *TYK2* expression and critical illness was also confirmed in an external dataset (Table 2).

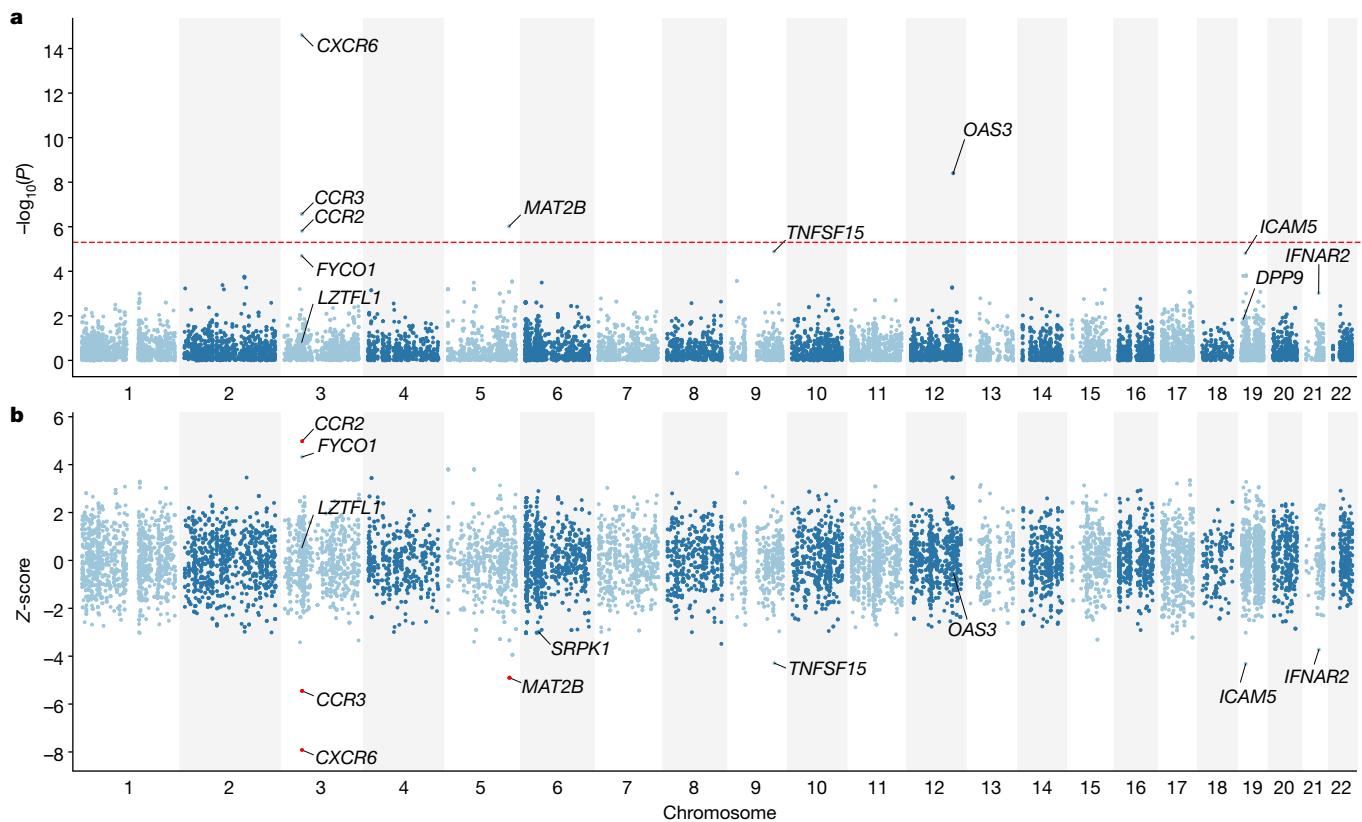


Fig. 2 | Summary of TWAS results. **a**, Gene-level Manhattan plot showing raw P -value results from meta-TWAS analysis across tissues (see Methods). The red horizontal line shows gene-level genome-wide significance at $-\log_{10}(5 \times 10^{-6})$.

b, Z-scores showing the direction of effect for the genotype-inferred expression of transcripts that encode protein-coding genes in lung tissue (GTEx v.8). Red circles indicate genes with genome-wide significance at $P < 5 \times 10^{-6}$.

We replicate the association at chromosome 3p21.31 that has previously been described⁸. The extremely small P value at this locus ($P = 4.77 \times 10^{-30}$) may reflect the large size of our study, and our focus on extreme severity, as we see a larger effect size in the GenOMICC dataset than in the replication studies (Extended Data Fig. 4). A number of genes in this locus could plausibly explain an association. Our systematic review and meta-analysis of experimental data on infections with betacoronaviruses from other sources provides moderate biological support for *FYCO1*, although this additional information comes mostly from *in vitro* model systems⁴⁵. Our TWAS results show that variants in this region confer genome-wide significant differences in predicted expression of *CXCR6*, *CCR2* and *CCR3* (Fig. 2a); it is likely that at least one of these genes is an important mediator of critical illness in patients with COVID-19.

Association with critical illness for genotype-inferred *CCR2* (CC-chemokine receptor 2) expression is particularly strong in lung tissue (Fig. 2b). *CCR2* promotes chemotaxis of monocytes and macrophages towards sites of inflammation, and there is increased expression of the canonical ligand for *CCR2* (monocyte chemoattractant protein (MCP-1)), in bronchoalveolar lavage fluid from the lungs of patients with COVID-19 during mechanical ventilation⁴⁶. Concentrations of circulating MCP-1 are associated with more-severe disease⁴⁷. Anti-*CCR2* monoclonal antibody therapy for the treatment of rheumatoid arthritis is safe⁴⁸.

The *ABO* locus was also previously associated with COVID-19⁸, but did not reach genome-wide significance in the GenOMICC cohort of critically ill patients with COVID-19. Notably, there is a signal close to genome-wide significance at this locus in the combined meta-analysis (Fig. 1), suggesting that this variant may be associated with susceptibility to COVID-19, but not critical illness (Extended Data Fig. 4).

Analysis of shared heritability highlights a positive correlation with adiposity. This does not confirm a causal relationship, as a number

of biases may affect this analysis. Two effects are likely to be present: first, increased body-mass index and lower socio-economic status are strong risk factors for severe COVID-19⁴⁴, and second, UK Biobank participants are disproportionately drawn from social groups in which obesity is underrepresented compared with the general population⁴⁹.

Because of the urgency of completing and reporting this study, we have included controls from population genetic studies with systematic differences in population structure, demographics and comorbid diseases, who were genotyped using different technologies compared with the cases that we report. Residual confounding is reflected in the genomic inflation ($\lambda_{0.5}$) value of 1.099 for the primary analysis (Extended Data Fig. 1). We mitigated the consequent risk of false-positive associations driven by genotyping errors by genotyping the majority of our participants using two different methods (microarray and whole-genome sequencing analyses), and by verifying significant associations using two additional control groups (the 100,000 Genomes Project and Generation Scotland). The success of these mitigations is demonstrated by robust replication of our sentinel SNPs in external studies. Our meta-analysis, combining GenOMICC with multiple additional sources of genome-wide associations, has a $\lambda_{0.5} = 1.017$ (Extended Data Fig. 1).

There is an urgent need to extend these findings through further studies. Our MAIC results show that highly ranked genes in the GenOMICC dataset are more likely to be implicated in COVID-19 in other studies (Extended Data Fig. 2). We continue to recruit to the GenOMICC study, in the expectation that additional associations exist and can be detected with larger numbers of cases of COVID-19. Future studies using whole-genome sequencing will search the rarer end of the allele frequency spectrum for variants that increase susceptibility to COVID-19. Effect sizes are likely to be greater in the GenOMICC study because the cohort is strongly enriched for immediately life-threatening disease in patients who are either receiving invasive mechanical ventilation,

or considered by the treating physicians to be at high risk of requiring mechanical support.

We have discovered new and highly plausible genetic associations with critical illness in COVID-19. Some of these associations lead directly to potential therapeutic approaches to augment interferon signalling, antagonize monocyte activation and infiltration into the lungs, or specifically target harmful inflammatory pathways. Although this adds substantially to the biological rationale that underpins specific therapeutic approaches, each treatment must be tested in large-scale clinical trials before entering clinical practice.

Online content

Any methods, additional references, Nature Research 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/s41586-020-03065-y>.

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Methods

Data reporting

No statistical methods were used to predetermine sample size. The experiments were not randomized and the investigators were not blinded to allocation during experiments and outcome assessment.

Recruitment of cases

In total, 2,636 patients who were recruited to the GenOMICC study (<https://genomicc.org/>) had confirmed COVID-19 according to local clinical testing and were deemed, in the view of the treating clinician, to require continuous cardiorespiratory monitoring. In UK practice this kind of monitoring is undertaken in high-dependency or intensive care units. An additional 135 patients were recruited through ISARIC4C (<https://isaric4c.net/>)—these individuals had confirmed COVID-19 according to local clinical testing and were deemed to require hospital admission. Both studies were approved by the appropriate research ethics committees (Scotland, 15/SS/0110; England, Wales and Northern Ireland, 19/WM/0247). Current and previous versions of the study protocol are available at <https://genomicc.org/protocol/>. All participants gave informed consent.

Genotyping

DNA was extracted from whole blood using the Nucleon Kit (Cytiva) with the BACC3 protocol. DNA samples were resuspended in 1 ml TE buffer pH 7.5 (10 mM Tris-Cl pH 7.5, 1 mM EDTA pH 8.0). The DNA yield was measured using Qubit and normalized to 50 ng μ l⁻¹ before genotyping.

Genotyping was performed using the Illumina Global Screening Array v.3.0 + multi-disease bead chips (GSAMD-24v3-0-EA) and Infinium chemistry. In summary, this consists of three steps: (1) whole-genome amplification; (2) fragmentation followed by hybridization; and (3) single-base extension and staining. For each of the samples, 4 μ l of DNA normalized to 50 ng μ l⁻¹ was used. Each sample was interrogated on the arrays against 730,059 SNPs. The arrays were imaged on an Illumina iScan platform and genotypes were called automatically using GenomicStudio Analysis software v.2.0.3, GSAMD-24v3-0-EA_20034606_A1.bpm manifest and cluster file provided by the manufacturer.

In 1,667 cases, genotypes and imputed variants were confirmed with Illumina NovaSeq 6000 whole-genome sequencing (WGS). Samples were aligned to the human reference genome hg38 and variant called to GVCF stage on the DRAGEN pipeline (software v.01.01.269.3.2.22, hardware v.01.01.269) at Genomics England. Variants were genotyped with the GATK GenotypeGVCFs tool v.4.1.8.1⁵⁰, filtered to minimum depth 8 \times (95% sensitivity for heterozygous variant detection⁵¹), merged and annotated with allele frequency with bcftools v.1.10.2.

Quality control

Genotype calls were carefully examined within GenomeStudio using manufacturer's and published⁵² recommendations, after excluding samples with low initial call rate (<90%) and reclustering the data thereafter. In brief, X and Y marker calls were all visually inspected and curated if necessary, as were those calls of autosomal markers with minor allele frequency (MAF) > 1% that had a low Gentrain score, cluster separation and an excess or deficit of heterozygous calls. Genotype-based sex determination was performed in GenomeStudio and samples were excluded if they did not match the expectation based on clinical records. Five individuals with XYY genotypes were also detected and excluded for downstream GWAS analyses. Genotypes were exported, in Genome Reference Consortium human build 37 (GRCh37) and Illumina 'source' strand orientation, using the GenotypeStudio PLINK input report plugin v.2.1-4. A series of filtering steps was then applied using PLINK1.9, leaving 2,790 individuals and 479,095 variants for further analyses (after exclusion of samples with a call rate of <95%, selection of variants with call rate of >99% and MAF > 1% and the final selection of samples using a call rate of >97%).

Kinship

Kinship and ancestry inferences were calculated following the UK Biobank⁴⁹ and 1 Million Veteran Program⁵³. First, King 2.1⁵⁴ was used to find duplicate individuals who have been recruited by two different routes. The analysis flagged 56 duplicate pairs, from which one was removed according to genotyping quality (GenomeStudio p50GC score and/or individual call rate). This left a set of 2,734 unique individuals.

Regions of high linkage disequilibrium (LD) defined in the UK Biobank⁴⁹ were excluded from the analysis, as well as SNPs with MAF < 1% or missingness > 1%. King 2.1 was used to construct a relationship matrix up to the third degree using the King command --kinship --degree 3 and then the function largest_independent_vertex_set() from the igraph tool <http://igraph.sf.net> was used to create a first set of unrelated individuals. Principal component analysis (PCA) was conducted with gcta 1.9⁵⁵ in the set of unrelated individuals with pruned SNPs using a window of 1,000 markers, a step size of 80 markers and an r^2 threshold of 0.1. SNPs with large weights in PC1, PC2 or PC3 were removed, keeping at least two-thirds of the number of pruned SNPs to keep as an input for the next round of King 2.1. The second round of King 2.1 was run using the SNPs with low weights in PC1, PC2 and PC3 to avoid overestimating kinship in individuals of non-European ancestry. After this round 2,718 individuals were considered unrelated up to the third degree.

Genetic ancestry

Unrelated individuals from the 1,000 Genome Project dataset were calculated using the same procedure as described above, and both datasets were merged using the common SNPs. The merged genotyped data was pruned with PLINK using a window of 1,000 markers, a step size of 50 and a r^2 of 0.05, leaving 92,017 markers that were used to calculate the 20 first principal components with gcta 1.9. Ancestry for GenOMICC individuals was inferred using ADMIXTURE⁵⁶ populations defined in the 1000 Genomes Project. When one individual had a probability >80% of pertaining to one ancestry, then the individual was assigned to this ancestry, otherwise the individual was assigned to 'admixed' ancestry as in the 1 Million Veteran cohort⁵³. According to this criterion, there are 1,818 individuals of European ancestry, 190 individuals of African ancestry, 158 individuals of East Asian ancestry, 254 individuals of South Asian ancestry and 301 individuals with admixed ancestry (2 or more ancestries).

Imputation

Genotype files were converted to plus strand and SNPs with Hardy-Weinberg equilibrium (HWE) $P < 10^{-6}$ were removed. Imputation was calculated using the TOPMed reference panel⁵⁷ and results were given in the GRCh38 human reference genome and plus strand. The imputed dataset was filtered for monogenic and low imputation quality score ($r^2 < 0.4$) using BCFtools 1.9. To perform GWAS analyses, files in VCF format were further filtered for $r^2 > 0.9$ and converted to BGEM format using QCtools 1.3⁵⁸.

UK Biobank imputed variants with imputation score > 0.9 and overlapping our set of variants ($n = 5,981,137$) were extracted and merged with GenOMICC data into a single BGEM file containing cases and controls using QCtools 1.3.

GWAS

Related individuals to third degree were removed. In addition, 13 individuals with American ancestry were removed as the sample size provided insufficient power to perform a reliable GWAS analyses for this group. The final dataset includes 2,244 individuals. Using PCA to infer genetic ancestry, there were 1,676 individuals of European ancestry, 149 individuals of East Asian ancestry, 237 individuals of South Asian ancestry and 182 individuals of African ancestry (Extended Data Table 1). If age or deprivation status were missing for some individuals, the value

Article

was set to the mean of their ancestry. GWAS analyses were performed separately for each ancestry group.

Tests for association between case-control status and allele dosage at individual SNPs were performed by fitting logistic regression models using PLINK⁵⁹. Independent analyses were performed for each ethnic group. All models included sex, age, mean-centred age², deprivation score decile of residential postcode, and the first 10 genomic principal components as covariates.

Genomic principal components were computed on the combined sample of all UK Biobank and GenOMICC participants. Specifically, 456,750 genetic variants were identified that were shared between the variants contained in the called genotypes in the GenOMICC dataset and imputed UK Biobank genotypes, which had an imputation info score >0.95 and MAF >1%. After merging genotypes at these variants, variants were removed that had MAF <2.5%, a missingness rate >1.5%, showed departure from HWE $P < 10^{-50}$ or were within previously identified regions of high linkage disequilibrium within the UK Biobank. After LD pruning of the remaining variants to a maximum r^2 of 0.01 based on a 1,000-variant window moving in 50 variants steps, using the PLINK indep-pairwise command and yielding 13,782 SNPs, the leading 20 genomic principal components were computed using FlashPCA⁶⁰.

GWAS results for individuals of European ancestry were filtered for MAF > 0.01, HWE $P > 10^{-50}$ and genotyping rate >0.99. An extra filter was added to avoid bias for using a different genotyping method and imputation panel between controls and cases. This could not be controlled for using regression because all cases and all controls were genotyped using different methods. MAFs for each ancestry were compared between UK Biobank European controls and gnomAD hg38 non-Finnish European individuals downloaded in August 2020⁶¹. SNPs were removed from the GWAS results following two rules: (1) In SNPs with MAF >10% in gnomAD, an absolute difference in MAF of 5% between gnomAD and UK Biobank controls; (2) in SNPs with MAF <10% in gnomAD, a difference in MAF of >25% between UK Biobank controls and gnomAD. GWAS analyses of individuals of non-European ancestries were filtered for a MAF in UK Biobank controls corresponding to the same ancestry >5% and then for the SNPs that passed quality control in the European GWAS. To calculate differences between UK Biobank European individuals and gnomAD allele frequencies, gnomAD allele frequencies for individuals of non-Finnish European descent were used, as European UK Biobank controls are mainly non-Finnish.

Filtered GWAS analyses for each ancestry, containing a total of around 4.7 million SNPs, were combined in a trans-ethnic meta-analysis using METAL⁶² standard error mode and controlling for population stratification (genomic control on). The nearest genes were defined using the SNP2GENE function in FUMA v.1.3.6⁶³, using LD $r^2 > 0.6$ and UK Biobank release 2 reference panel.

A sex-specific GWAS within European individuals was performed using 1,180 cases of unrelated men and 496 cases of unrelated women and 5 UK Biobank random control individuals matched by sex and ancestry for each case. Tests for association between case-control status and allele dosage at individual SNPs were performed by fitting a logistic regression model with PLINK. Age, mean age squared, deprivation decile of residential postcode and the first 10 principal components were added as covariates in the models.

Deprivation score. The UK Data Service provides measures of deprivation based on census data and generated per postcode. The latest version of the deprivation scores were published in 2017 and are based on the 2011 census. As only partial postcodes were available for most samples we were unable to use these indices directly. However, we generated an approximation to the scores by calculating an average weighted by population count across the top-level postcode areas.

The initial input file was part of the aggregated census data identified by in the 2011 Census aggregate⁸⁵ and the postcode data were downloaded from <http://s3-eu-west-1.amazonaws.com/statistics>.

digitalresources.jisc.ac.uk/dkan/files/Postcode_Counts_and_Deprivation_Ranks/postcodes.zip.

Population count and deprivation score for each published postcode were extracted and the weighted average score was calculated for each top-level postcode. We further categorized each top-level postcode score into decile and quintile bins for more coarse-grained analyses.

WGS. WGSgVCF files were obtained for the 1,667 individuals for whom we had WGS data. Variants overlapping the positions of the imputed variants were called using GATK and variants with depth <8× (the minimum depth for which 95% coverage can be expected) were filtered. Individual VCF files were joined in a multi-sample VCF file for comparison with imputed variants. We used 1,613 of the 1,667 individuals in the final GWAS. Samples were filtered and variants were annotated using bcftools 1.9. VCF files obtained from imputation were processed in an identical manner. Alternative allele frequencies were calculated with PLINK 2.0⁶⁴ for both WGS and imputed data.

Controls

UK Biobank. UK Biobank participants were considered as potential controls if they were not identified by the UK Biobank as outliers based on either genotyping missingness rate or heterogeneity, and their sex inferred from the genotypes matched their self-reported sex. For these individuals, information on sex (UKBID 31), age, ancestry and residential postcode deprivation score decile was computed. Specifically, age was computed as age on 1 April 2020 based on the participant's birth month (UKBID 34) and year (UKBID 52). The first part of the residential postcode of participants was computed based on the participant's home location (UKBID 22702 and 22704) and mapped to a deprivation score decile as described above for GenOMICC participants. Ancestry was inferred as described above for GenOMICC participants.

After excluding participants who had received PCR tests for COVID-19, based on information downloaded from the UK Biobank in August 2020, five individuals with matching inferred ancestry were sampled for each GenOMICC participant as controls. After sampling each control, individuals related up to the third degree were removed from the pool of potential further controls. An additional analysis with more stringent matching on individual characteristics was also performed (Supplementary Information, 'Matched controls').

The 100,000 Genomes Project. Following ethical approval (14/EE/1112 and 13/EE/032), consenting participants from the 100,000 Genomes Project with a broad range of rare diseases, cancers and infection were enrolled by 13 regional NHS Genomic Medicine Centres across England and in Northern Ireland, Scotland and Wales and whole blood was drawn for DNA extraction. After quality assurance, WGS at 125 or 150 base pairs was performed by Illumina Laboratory Services on either HiSeq 2500 or HiSeq X sequencers in the Genomics England Sequencing Centre, followed by detection of small variants (single-nucleotide variants and small insertions or deletions) using Starling.

Tests for association between cases and control status were performed by running mixed model association tests using SAIGE (v.0.39). In total, 1,675 individuals from the GenOMICC study and 45,875 unrelated participants of European ancestry were included. Genomic principal components were calculated for the combined dataset of GenOMICC participants and WGS data from the 100,000 Genomes Project. PCA was performed with GCTA software using approximately 30,000 SNPs selected with MAF > 0.005 and after LD pruning ($r^2 < 0.1$ with a window size of 500 kb). Fitting of the null logistic mixed model was performed using the SNPs used for PCA and included age, sex, squared age, age × sex and the first 20 genomic principal components as covariates.

Tests for association using SAIGE were performed after filtering variants in the WGS dataset for genotype quality and MAF ≥ 0.05 . GWAS-specific quality filtering was performed to include variants

with minor allele count ≥ 20 for each phenotype, differential missingness between cases and controls ($P < 1 \times 10^{-5}$) and departure from HWE ($P < 1 \times 10^{-5}$).

Generation Scotland. The Generation Scotland: Scottish Family Health Study is a population-based cohort of 24,084 participants sampled from five regional centres across Scotland⁶⁵. A large subset of participants were genotyped using either Illumina HumanOmniExpressExome-8v1_A or v1-2, and 20,032 passed quality control criteria that have previously been described^{66,67}. Genotype imputation using the TOPMed reference panel was recently performed (freeze 5b) using Minimac4 v.1.0 on the University of Michigan server (<https://imputationserver.sph.umich.edu>)⁶⁸. Imputation data from 7,689 unrelated (genomic sharing identical-by-descent estimated to be $< 5\%$ using PLINK1.9) participants were used as control genotypes in a GWAS using GenOMICC cases of European ancestry, for quality control purpose of associated variants. GWAS was performed in a logistic regression framework implemented in the *glm* function of PLINK 2 (<https://www.cog-genomics.org/plink/2.0/>), adjusting for age, sex and the first 10 principal components of European ancestry. These coordinates were obtained from projection to the principal component space of the European population samples of the 1000 Genomes Project using KING v.2.2.5⁴ and a LD-pruned subset of target genotyped markers that passed quality control and intersecting with the reference populations.

Validation

Clumped hits in discovery GWAS analyses were validated using controls from Generation Scotland and the 100,000 Genomes Project. To consider a hit validated, the direction of effect should be the same in all three GWAS datasets and the *P* value in both Generation Scotland and the 100,000 Genomes Project had to be $P < 0.05/n_{\text{validations}}$, where $n_{\text{validations}}$ is the number of significant independent loci in our analysis at the discovery threshold of $P < 5 \times 10^{-8}$.

Replication

Loci in GenOMICC individuals of European ancestry were defined using the clump function of PLINK 1.9⁶⁴ and clumping parameters $r^2 = 0.1$, $P = 5 \times 10^{-8}$ and $P_2 = 0.01$; distance to the nearest gene was calculated using ENSEMBL GRCh37 gene annotation.

No GWAS has been reported of critical illness or mortality in COVID-19. As a surrogate, to provide some replication for our findings, replication analyses were performed using HGI build 37, version 2 (July 2020) B2 (hospitalized patients with COVID-19 versus the population) GWAS. Summary statistics were used from the full analysis, including all cohorts and GWAS without UK Biobank, to avoid sample overlap. The replication *P* value was set to 6.25×10^{-4} ($0.05/8$, where 8 is the number of loci significant in the discovery analysis).

Genome-wide meta-analysis

Meta-analysis of the GenOMICC, HGI and 23andMe datasets was performed using fixed-effect inverse-variance meta-analysis in METAL⁶², with correction for genomic control on. The 23andMe study comprises cases and controls from an European genetic ancestry group. The HGI B2 analysis is a trans-ancestry meta-analysis, with the great majority of cases being multi-ethnic European (European and Finnish), with 238 cases of non-European ancestry (176 individuals of admixed American descent from the BRACOVID study and 62 individuals of South Asian ancestry from the GNH study).

Post-GWAS analyses

TWAS and Meta-TWAS. We performed transcriptome-wide association using the MetaXcan framework²³ and the GTEx v.8 eQTL MASHR-M models (<http://predictdb.org/>). To increase SNP coverage to perform TWAS, GWAS summary statistics for European ancestry were first imputed using the fizi⁶⁹ impute function (<https://github.com/bogdanlab/fizi>),

the European population from the 1000 Genomes Project as LD reference and 30% as minimum proportion of SNPs for a region (-min-prop 0.3). Then, imputed GWAS results were harmonized, lifted over to hg38 and linked to the 1000 Genomes Project reference panel using GWAS tools (<https://github.com/hakyimlab/summary-gwas-imputation/wiki/GWAS-Harmonization-And-Imputation>).

Imputed and harmonized GWAS summary statistics were used to perform TWAS for whole-blood samples (Supplementary Fig. 16) and lung tissues (Fig. 2) in GTEx v.8 with the S-PrediXcan function. Resulting *P* values were corrected using the Bonferroni correction to find significant gene associations. To overcome the limitations of sample size in GTEx v.8 lung tissues and whole-blood samples, we performed a meta-TWAS prioritizing genes with small *P* values in these tissues and using GTEx v.8 gene expression in all tissues and S-Multixcan⁷⁰.

Mendelian randomization. Mendelian randomization¹⁹ based on two-sample summary data was performed using the results of GenOMICC and GTEx v.7⁷¹ (using SMR/HEIDI pre-prepared data from <https://cnsgenomics.com/software/smr/#DataResource>), with Generation Scotland^{65,72} forming a LD reference. GenOMICC results from individuals of European ancestry were used as the outcome; and GTEx (v.7) whole-blood expression results as the exposure. Additional data pertaining to GTEx v.7 were downloaded from GTEx: <https://gtex-portal.org/> (accessed 20 February, 5 April and 4 July 2020), and SMR/HEIDI from <https://cnsgenomics.com/software/smr/> (accessed 3 July 2020). Analyses were conducted using Python v.3.7.3 and SMR/HEIDI v.1.03 (plots were made using SMR/HEIDI v.0.71). An LD reference was created using data from the population-based Generation Scotland cohort (used with permission; described previously⁶⁷): from a random set of 5,000 individuals, using PLINK v.1.9 (www.cog-genomics.org/plink/1.9/), a set of individuals with a genomic relatedness cut-off of < 0.01 was extracted; 2,778 individuals remained in the final set. All data used for the SMR/HEIDI analyses were limited to autosomal biallelic SNPs: 4,264,462 variants remained in the final merged dataset.

Significant (as per GTEx v.7; nominal *P* value below the nominal *P*-value threshold) local (distance to transcriptional start site < 1 Mb) eQTLs from GTEx v.7 whole-blood samples for protein-coding genes (as per GENCODE v.19) with a MAF > 0.01 (GTEx v.7 and GenOMICC) were considered to be potential instrumental variables. Per variant, we first selected the Ensembl gene ID with which the eQTL was most strongly associated followed by selecting the variant with which each Ensembl gene ID was most strongly associated. Instruments were available for 4,614 unique Ensembl gene IDs.

Results were assessed based on a list of genes selected a priori as of interest (Supplementary Table 3), and together as a whole. Replication of Bonferroni-corrected significant results was attempted for the results of COVID-19 HGI (<https://www.covid19hg.org/>) with the UK Biobank excluded (2 July 2020 data release) using the eQTLgen expression dataset²⁰. Hospitalized patients with COVID-19 versus population (ANA_B2_V2) was selected as the phenotype most similar to our own, and therefore the most appropriate to use as a replication cohort.

To further validate the analyses above, generalized summary-data Mendelian randomization (GSMR)⁷³ was performed using exposure data from <https://www.eqtlgen.org/index.html> (accessed 26 October 2020)²⁰ and the publicly available GenOMICC European data for TYK2 and IFNAR2 (Supplementary Fig. 15). GSMR was performed using GCTA v.1.92.1 beta6 Linux. Pleiotropic SNPs were filtered using HEIDI-outlier test (threshold = 0.01) and instrument SNPs were selected at a genome-wide significance level ($P_{\text{eQTL}} < 5 \times 10^{-8}$) using LD clumping (LD r^2 threshold = 0.05 and window size = 1 Mb). The imputed genotypes for 50,000 unrelated individuals (based on SNP-derived genomic relatedness < 0.05 using SNPs from HapMap 3) from the UK Biobank were used as the LD reference for clumping. GSMR accounts for remaining LD not removed by LD clumping.

Article

Genomic region plots. Genomic region plots were created using <https://github.com/Geeketics/LocusZooms> (Supplementary Figs. 5, 6).

Gene-level and pathway analyses. The gene-level burden of significance in the results of the European ancestry group was calculated using MAGMA v.1.08⁷⁴ (Supplementary Fig. 17). SNPs were annotated to genes by mapping based on genomic location. SNPs were assigned to a gene if the SNPs location was within 5 kb up- or down-stream of the gene region (defined as the transcription start site to transcription stop site). The MAGMA SNP-wise mean method was applied, which utilizes the sum of squared SNP Z-statistics as the test statistic. The European reference panel of the 1000 Genomes Project was used to estimate LD between SNPs.

Auxiliary files were downloaded from <https://ctg.cncr.nl/software/magma> on 1 September 2020. Gene location files for protein-coding genes were obtained from NCBI (<ftp.ncbi.nlm.nih.gov>) on 29 April 2015 (gene/DATA/GENE_INFO/Mammalia/Homo_sapiens.gene_info.gz) and 25 May 2016 (genomes/Homo_sapiens/ARCHIVE/ANNOTATION_RELEASE.105/mapview/seq_gene.md.gz).

The reference data files used to estimate LD are derived from Phase 3 of the 1000 Genomes Project.

Competitive gene set enrichment analysis was conducted in MAGMA using a regression model that accounts for gene–gene correlations to reduce bias resulting from clustering of functionally similar genes on the genome⁷⁴. Gene sets were queried from the databases KEGG 2019, Reactome 2016, GO Biological Process 2018, Biocarta 2016 and WikiPathways 2019. The Benjamini–Hochberg procedure was used to control false-discovery rate (<0.05).

MAIC. To put these results in the context of existing biological data about host genes in SARS-CoV-2 replication and response, we performed MAIC²⁴ analysis, which integrates gene-level results from the GenOMICC metaTWAS and an existing systematic review of host factors implicated in SARS-CoV-2 viral replication and host response in COVID-19⁴⁵.

We developed MAIC to evaluate and integrate gene-level data from diverse sources²⁴. Multiple in vitro and in vivo studies have identified key host genes that either directly interact with SARS-CoV-2, or define the host response to SARS-CoV-2. We have previously conducted a systematic review of these studies⁴⁵. To put the new associations from this GWAS into context, we performed a data-driven meta-analysis of gene-level results combined with pre-existing biological data using MAIC²⁴.

In brief, MAIC aggregates both ranked and unranked lists and performs better than other methods, particularly when presented with heterogeneous source data. The input to MAIC is a list of named genes. MAIC assigns a score to each gene according to how many source datasets have reported that gene, and then creates a data-driven weighting for each data source (usually an individual experiment) based on the scores of the genes that are highly ranked on that list. This procedure is performed iteratively until the scores and weightings converge on stable values. To prevent a single type of experiment from unduly biasing the results, input gene lists are assigned to categories, and a rule applied that only one weighting from each category can contribute to the score for any given gene.

Tissue and functional genomic enrichment. We downloaded the mean gene expression data summarized from RNA sequencing by the GTEx Project (<https://gtexportal.org/>). The GTEx v.7 dataset contains gene expression data of 19,791 genes in 48 human tissues. Gene expression values were normalized to numbers of transcripts per million reads. To measure the expression specificity of each gene in each tissue, each gene expression specificity was defined as the proportion of its expression in each tissue among all the tissues—that is, a value ranging

between 0 and 1. SNPs within the 10% most specifically expressed genes in each tissue were annotated for subsequent testing of heritability enrichment. For functional genomic enrichment analysis, we considered the inbuilt primary functional annotations v.2.2 provided in the ldsc software (<https://alkesgroup.broadinstitute.org/LDSCORE/>) to annotated the SNPs.

With the annotated SNPs, we used stratified LD score regression⁷⁵ to test whether any human tissue or specific functional genomic feature is associated with severe COVID-19. Our GWAS summary statistics were harmonized by the munge_sumstats.py procedure in ldsc. LD scores of HapMap3 SNPs (MHC region excluded) for gene annotations in each tissue were computed using a 1-cM window. The enrichment score was defined as the proportion of heritability captured by the annotated SNPs divided by the proportion of annotated SNPs.

Genetic correlations. We applied both the LD score regression⁷⁶ and high-definition likelihood²⁵ methods to evaluate the genetic correlations between severe COVID-19 and 818 GWAS-analysed phenotypes stored on LD-Hub⁷⁷. GWAS summary statistics were harmonized by the munge_sumstats.py procedure in the ldsc software. In the high-definition likelihood analysis, we estimated the SNP-based narrow-sense heritability for each phenotype, and for the 818 complex traits GWAS analyses, those with SNPs with less than 90% overlap with the high-definition likelihood reference panel were removed.

Genome build

Results are presented using Genome Reference Consortium human build 37. Imputed genotypes and WGS data were lifted over from Genome Reference Consortium Human Build 38 using Picard liftoverVCF mode from GATK 4.0, which is based on the UCSC liftover tool (chain file obtained from ftp://ftp.ensembl.org/pub/assembly_mapping/homo_sapiens/GRCh38_to_GRCh37.chain.gz)⁷⁸.

Reporting summary

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

Data availability

Full summary-level data that support the findings of this study are available from <https://genomicc.org/data>. Individual-level data can be analysed by qualified researchers in the ISARIC4C/GenOMICC data analysis platform by application at <https://genomicc.org/data>. The full GWAS summary statistics for the 23andMe discovery dataset are available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. More information and access to the data are provided at <https://research.23andMe.com/dataset-access/>.

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Competing interests The authors declare no competing interests.

Additional information

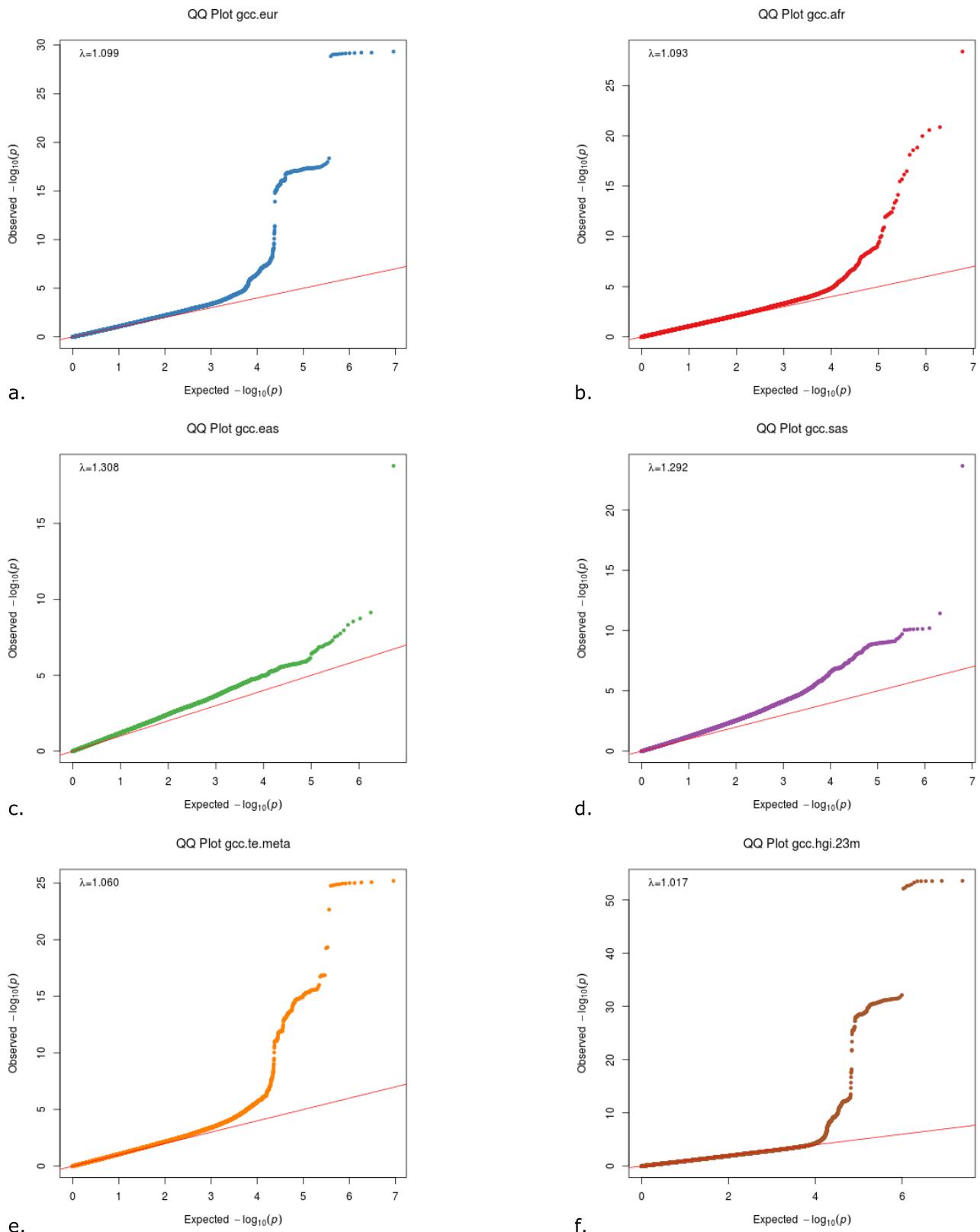
Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41586-020-03065-y>.

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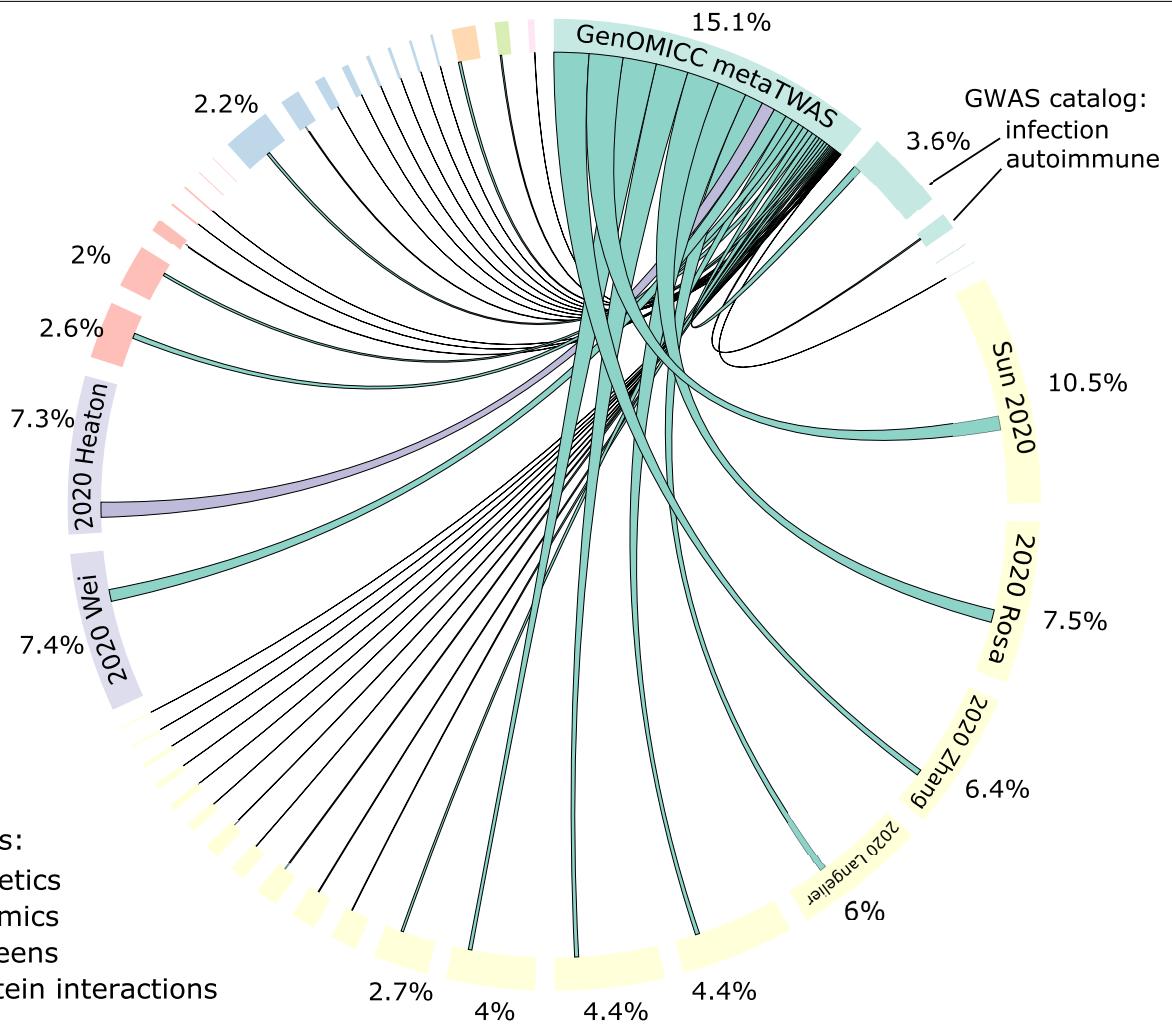
Reprints and permissions information is available at <http://www.nature.com/reprints>.

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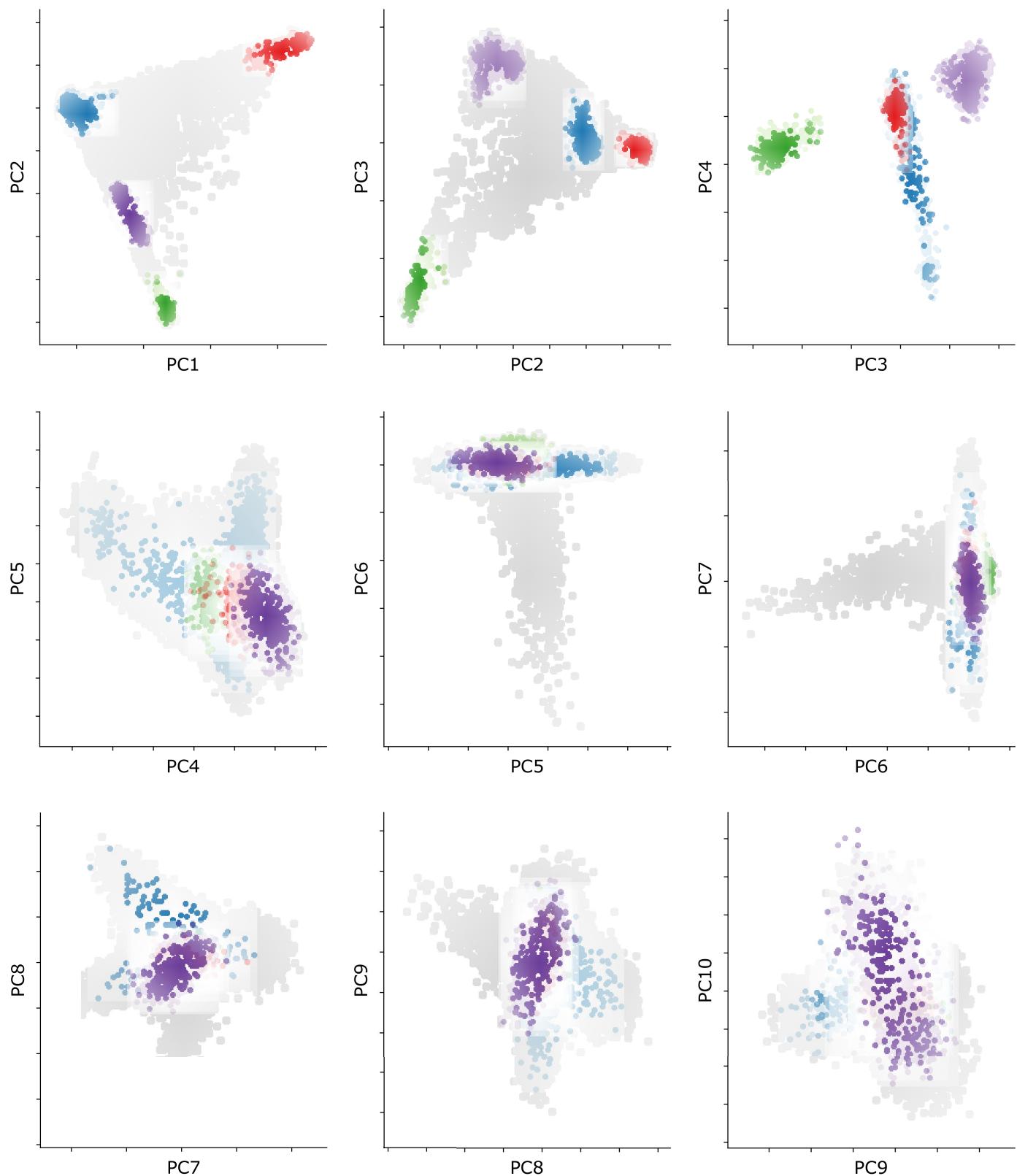
Extended Data Fig. 1 | QQ plots. a–f, Raw (uncorrected) P values are shown for each ancestry group in GenOMICC (European (a; gcc.eur); African (b; gcc.afr); East Asian (c; gcc.eas); South Asian (d; gcc.sas)) as well as a trans-ethnic meta-analysis (gcc.te.meta) and a meta-analysis comprising GenOMICC, HGI

and 23andMe data (gcc.hgi.23m). λ , genomic inflation value. Note that some residual inflation is evident in the primary analysis in GenOMICC European cohort. Repeating the analysis using more principal components (20 PCs) as covariates did not improve the inflation ($\lambda_{0.5} = 1.10$).



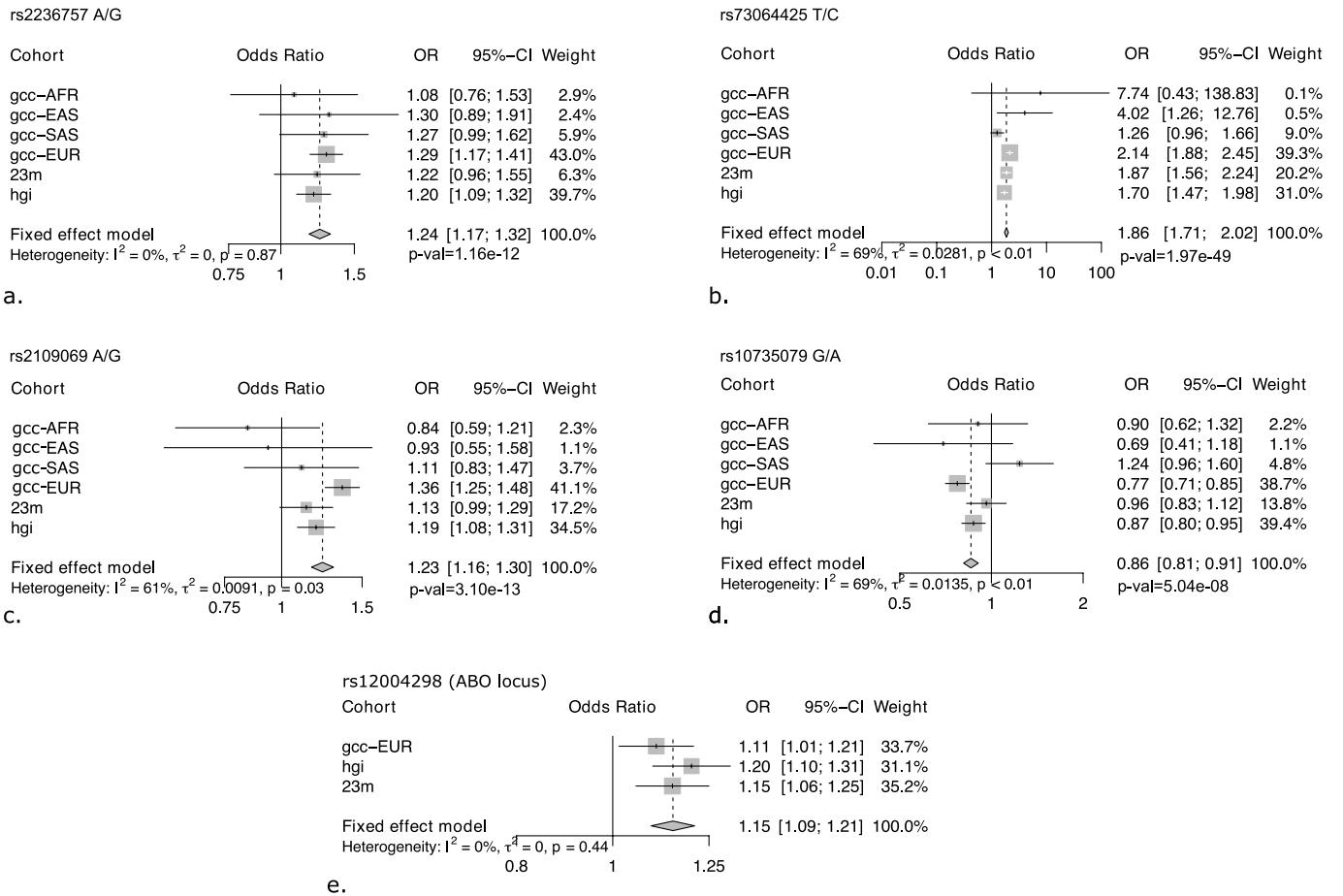
Extended Data Fig. 2 | MAIC shared information content. Representation of shared information content among data sources in the MAIC analysis. Each experiment or data source is represented by a block on the outer ring of the circle; the size of data source blocks is proportional to the summed information content of the input list—that is, the total contribution that this data source makes to the aggregate, calculated as the sum of the MAIC gene scores contributed by that list. Lines are coloured according to the dominant data source. Data sources within the same category share the same colour. The largest categories and data sources are labelled: Sun 2020⁷⁹, 2020 Rosa⁸⁰,

2020 Zhang⁸¹, 2020 Langelier⁸², 2020 Wei⁸³, 2020 Heaton⁸⁴. An interactive version of this figure is available at <https://baillielab.net/maic/covid>. To estimate the probability of the specific enrichment for GenOMICC metaTWAS, we randomly sampled genes from the baseline distribution of metaTWAS 1,000 times, re-running the MAIC with the same set of COVID-19 systematic review inputs, but substituting the randomly sampled input list for the GenOMICC metaTWAS results. Modelling a normal distribution based on these empirical results, we estimated that the probability of a MAIC enrichment with this strength arising by random chance is $P=4.2\times10^{-12}$.



Extended Data Fig. 3 | Genomic overlap among cases and controls. PCA plots show the distribution of all cases and controls for the first 10 principal components. Cases are shown as coloured circles: European (blue), African (red), East Asian (green) and South Asian (purple). Controls for each ancestry

group are shown as circles in a lighter shade of the colour for that ancestry group. The UK Biobank data (background population) are shown as light-grey circles.



Extended Data Fig. 4 | Effect sizes in ancestry groups within the GenOMICC study. **a–e**, Data are shown for the four replicated variants with genome-wide significant associations in GenOMICC (**a–d**) and the *ABO* locus (**e**). Forest plots display the effect size heterogeneity measures and *P* value (*p*) and meta-analysis estimates with 95% confidence interval (CI), and *P* value (*P*-val) under a fixed-effect model. The allele in bold is the reference allele for the reported effect (odds ratio). Sample sizes for the cases and controls analysed in

the four groups were: 1,092 individuals of African (AFR) ancestry, 894 individuals of East Asian (EAS) ancestry, 10,055 individuals of European (EUR) ancestry and 1,422 individuals of South Asian (SAS) ancestry within GenOMICC. HGI, COVID-19 HGI; 23m, 23andMe. Observed heterogeneity in the effect size may be owing to genuine differences between ancestry groups, the limited statistical power in smaller groups (evident from the broad confidence intervals) or residual confounding factors.

Article

Extended Data Table 1 | Baseline characteristics of the 2,244 included patients

Patient Characteristics	GenOMICC (n=2109)	ISARIC 4C (n=135)
		<i>missing data</i>
Female sex	624 (30%)	46 (34%)
Age (yrs, mean \pm SD)	57.3 \pm 12.1	57.3 \pm 2.9
European ancestry	1573 (75%)	103 (76%)
South Asian ancestry	219 (10%)	18 (13%)
African ancestry	174 (8%)	8 (6%)
East Asian ancestry	143 (7%)	6 (4%)
Significant comorbidity	396 (19%)	40 (30%)
Invasive ventilation	1557 (74%)	25 (19%)
Died (60 days)	459 (22%)	22 (16%)
		<i>missing data</i>

Ancestry groups were determined by principal component analysis (Extended Data Fig. 3). Significant comorbidity was defined as the presence of functionally limiting comorbid illness in GenOMICC, according to the assessment of the treating clinicians. In ISARIC4C, significant comorbidity refers to the presence of any chronic cardiac, lung, kidney or liver disease, cancer or dementia. Age is shown as mean \pm standard deviation (SD).

Extended Data Table 2 | Replication in external data

SNP	chr:pos(b37)	Risk	Alt	OR _{gcc.ukb}	P _{gcc.ukb}	OR _{hgi.23m}	P _{hgi.23m}	Locus
rs73064425	3:45901089	T	C	2.1	4.8 x 10 ⁻³⁰	1.7	1.5 x 10 ^{-28*}	<i>LZTFL1</i>
rs9380142	6:29798794	A	G	1.3	3.2 x 10 ⁻⁸	1	0.76	<i>HLA-G</i>
rs143334143	6:31121426	A	G	1.9	8.8 x 10 ⁻¹⁸	1.1	0.019	<i>CCHCR1</i>
rs3131294	6:32180146	G	A	1.5	2.8 x 10 ⁻⁸	0.99	0.91	<i>NOTCH4</i>
rs10735079	12:113380008	A	G	1.3	1.6 x 10 ⁻⁸	1.1	0.00082*	<i>OAS1/3</i>
rs2109069	19:4719443	A	G	1.4	4 x 10 ⁻¹²	1.1	5 x 10 ^{-5*}	<i>DPP9</i>
rs74956615	19:10427721	A	T	1.6	2.3 x 10 ⁻⁸	1.4	2 x 10 ^{-6*}	<i>TYK2</i>
rs2236757	21:34624917	A	G	1.3	5 x 10 ⁻⁸	1.2	4.1 x 10 ^{-5*}	<i>IFNAR2</i>

Alt, alternative allele; chr:pos, chromosome:position; locus, gene nearest to the top SNP; OR, effect size (odds ratio) of the risk allele; P, P value; Risk, risk allele. Subscript identifiers show the data source: gcc.ukb, GenOMICC study, European ancestry, comparison with UK Biobank; hgi.23m, COVID-19 HGI and 23andMe meta-analysis, used for replication. Bonferroni significant values with external replication are indicated with an asterisk.

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- 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
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- 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
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

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
Data analysis	GenomeStudio v2.03, DRAGEN v0.1.11.269.3.2.22, GATK 4.1.8.1, Plink 1.9, Plink 2.0, King 2.1, R v3.6, python v3.7, GATK 4.0, USC liftover, GCTA v1.92 ,SAIGE v0.39, metal, MAGMAv1.08, BCFTools 1.9, QCtools 1.3, FlashPCA2, admixture, FUMA v1.3.6, SMR/HEIDI v1.03, MetaXcan (git commit 0b7c10d633d3d7bfe794e4f35bd8190356bb2514), MiniMac4 v1.0,

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Full summary-level data in support of the findings of this study are available for download from [<https://genomicc.org/data>]. Individual level data can be analysed by qualified researchers in the ISARIC 4C/GenOMICC data analysis platform by application at [<https://genomicc.org/data>].

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.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	n=2244 critically ill Covid-19 patients, n=11220 random controls matched by ancestry from UK Biobank. The sample size was determined pragmatically by the number of cases recruited during the first wave of the outbreak in the UK. Adequate statistical power was determined by the detection of significant associations, and is confirmed by replication in external studies.
Data exclusions	Patients of mixed genetic ancestry, and from ancestry groups with small numbers of cases (such as North American Indian) defined using principal components analysis, were excluded because we were not able to match adequate controls for these individuals.
Replication	Replicated main findings using 2415 hospitalised Covid-19 patients and 477741 population controls from Covid19 Host genetics initiative and 1128 Covid19 cases and 679531 population controls from 23andme Inc "broad respiratory" phenotype. 3 variants did not replicate; all are in the MHC region, which is both highly sensitive to population stratification (potentially causing spurious associations) and commonly associated with infectious and immune disease.
Randomization	Not relevant to the study. There wasn't any allocation to experimental groups
Blinding	Blinding was not used in this study because the exposure (genotype) and outcome (ICU admission) are objective. Confounding was controlled by the use of covariates: age, sex, deprivation score and genetic ancestry (principal components).

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

- | | |
|-------------------------------------|-------------------------------|
| n/a | Involved in the study |
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| <input checked="" type="checkbox"/> | Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | Animals and other organisms |
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Methods

- | | |
|-------------------------------------|------------------------|
| n/a | Involved in the study |
| <input checked="" type="checkbox"/> | ChIP-seq |
| <input checked="" type="checkbox"/> | Flow cytometry |
| <input checked="" type="checkbox"/> | MRI-based neuroimaging |

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics 1574 males, 670 females. 1176 European ancestry, 227 South Asian ancestry, 182 African ancestry, 149 East Asian ancestry. Mean age is 57.3 years

Recruitment

Critically-ill cases were recruited through the GenOMICC study in 208 UK Intensive Care Units and hospitalised cases through the International Severe Acute Respiratory Infection Consortium (ISARIC) Coronavirus Clinical Characterisation Consortium (4C) study. Genomicc patients ha confirmed Covid-19 according to local clinical testing and were deemed by the treating physician to require continuous cardiorespiratory monitoring in intensive care units. ISARIC4C individuals had confirmed Covid-19 and were deemed to require hospital admission. Since this outcome is determined by clinicians it is unlikely to be affected by self-selection bias.

Ethics oversight

Research ethics committees (Scotland 15/SS/0110, England, Wales and Northern Ireland: 19/WM/0247. Current and previous versions of the study protocol are available at genomicc.org/protocol. All participants gave informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.