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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

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
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ 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.