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Article

The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

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A recent genetic association study[1] identified a gene cluster on chromosome 3 as a risk locus for respiratory failure upon SARS-CoV-2 infection. A new study[2] comprising 3,199 hospitalized COVID-19 patients and controls finds that this is the major genetic risk factor for severe SARS-CoV-2 infection and hospitalization (COVID-19 Host Genetics Initiative). Here, we show that the risk is conferred by a genomic segment of ~50 kb that is inherited from Neanderthals and is carried by ~50% of people in South Asia and ~16% of people in Europe today.

The SARS-CoV-2 pandemic has caused considerable morbidity and mortality, claiming the lives of a million people to date[3]. The clinical manifestations of the disease caused by the virus, COVID-19, vary widely in severity, ranging from no or mild symptoms to rapid progression to respiratory failure[4]. Early in the pandemic, it became clear that advanced age is a major risk factor, as well as male sex and some co-morbidities[5]. These risk factors, however, do not fully explain why some have no or mild symptoms while others become seriously ill. Thus, genetic risk factors may play a role. An early study[1] identified two genomic regions associated with severe COVID-19: one region on chromosome 3 containing six genes and one region on chromosome 9 that determines ABO blood groups. Recently, a new dataset was released from the COVID-19 Host Genetics Initiative where the region on chromosome 3 is the only region significantly associated with severe COVID-19 at the genome-wide level (Fig. 1a). The risk variant in this region confers an odds ratio for requiring hospitalization of 1.6 (95% confidence interval (CI): 1.42-1.79, Extended Data Figure 1).

The genetic variants which are most associated with severe COVID-19 on chromosome 3 (chr3: 45,859,651-45,909,024, *hg19*) are all in high linkage disequilibrium (LD), *i.e.* they are all strongly associated with each other in the population (r^2>0.98), and span 49.4 thousand bases (kb) (Fig. 1b). This "core" haplotype is furthermore in weaker LD with longer haplotypes of up to 333.8 kb (r^2>0.32) (Extended Data Fig. 2). Some such long haplotypes have entered the human population by gene flow from Neanderthals or Denisovans, extinct hominins that contributed genetic variants to the ancestors of present-day humans some 40,000 to 60,000 years ago[6,7]. We therefore investigated whether the haplotype may have come from Neanderthals or Denisovans.

The index variants of the two studies[1,2] are in high LD (r^2>0.98) in non-African populations (Extended Data Figure 3). We found the risk alleles of both these variants to be present in a homozygous form in the genome of the *Vindija 33.19* Neanderthal, a ~50,000-old-old Neanderthal from Croatia in southern Europe[8]. Of the 13 single nucleotides polymorphisms constituting the core haplotype, 11 occur in a homozygous form in the *Vindija 33.19* Neanderthal (Fig. 1b). Three of these variants occur in the "Altai"[9] as well as in the *Chagyrskaya 8*[10] Neanderthals, both of whom come from the Altai Mountains in southern Siberia and are ~120,000 and ~50,000 years old, respectively (Extended Data Table 1) while none occurs in the Denisovan genome[11]. In the 333.8 kb-haplotype, the alleles associated with risk for severe COVID-19 similarly match alleles in the *Vindija 33.19* Neanderthal genome (Fig. 1b). Thus, the risk haplotype is similar to the corresponding genomic region in the Neanderthal from Croatia and less similar to the Neanderthals from Siberia.

We next investigated whether the core 49.4 kb-haplotype might be inherited by both Neanderthals and present-day people from the common ancestors of the two groups that lived about half a million years ago[9]. The longer a present-day human haplotype shared with Neanderthals is, the less likely it is to originate from the common ancestor, because recombination in each generations will tend to break up haplotypes into smaller segments. Assuming a generational time of 29 years[12], the local recombination rate[13] (0.53 cM/Mb), a split between Neanderthals and modern humans of 550,000 years[9], and interbreeding between the two groups ~50,000 years ago, and using a published equation[14], we exclude that the Neanderthal-like haplotype derives from the common ancestor (p = 0.0009). For the 333.8 kb-long Neanderthal-like haplotype, the probability of an origin from the common ancestral population is even lower (p = 1.6e-26). The risk haplotype thus entered the modern human population from Neanderthals. This is in agreement with several previous studies, which have identified gene flow from Neanderthals in this chromosomal region[15–21] (Extended Data Table 2). The close relationship of the risk haplotype to the *Vindija 33.19* Neanderthal is compatible with this Neanderthal being closer to the majority of the Neanderthals who contributed DNA to present-day people than the other two Neanderthals[10].

A Neanderthal haplotype present in the genomes of people living today is expected to be more similar to a Neanderthal genome than to other haplotypes in the current human population. To investigate the relationships of the 49.4 kb-haplotype to Neanderthal and to other human haplotypes we analysed all 5,008 haplotypes in the 1000 Genomes Project[22] for this genomic region. We included all positions which are called in the Neanderthal genomes and excluded variants found on only one chromosome and haplotypes seen only once in the 1000 Genomes data. This resulted in 253 present-day haplotypes containing 450 variable positions. Fig. 2 shows a phylogeny relating such haplotypes found more than 10 times (see Extended Data Fig. 4 for all haplotypes). We find that all risk haplotypes associated with severe COVID-19 form a clade with the three high-coverage Neanderthal genomes. Within this clade, they are most closely related to the *Vindija 33.19* Neanderthal.

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Among the individuals in the 1000 Genomes Project, the Neanderthal-derived haplotypes are almost completely absent in Africa, consistent with that gene flow from Neanderthals into African populations was limited and probably indirect[20]. The Neanderthal core haplotype occurs in South Asia at a frequency of 30%, in Europa at 8%, among admixed Americans at 4% and at lower frequencies in East Asia (Fig. 3)[23]. The highest frequency occurs in Bangladesh, where more than half the population (63%) carries at least one copy of the Neanderthal risk haplotype and 13% is homozygous for the haplotype. The Neanderthal haplotype may thus be a substantial contributor to COVID-19 risk in certain populations besides other risk factors, most notably advanced age. In apparent agreement with this, individuals of Bangladeshi origin in the UK have about two times higher risk to die from COVID-19 than the general population (hazard ratio 95% CI: 1.7-2.4)[24].

It is striking that the Neanderthal risk haplotype occurs at a frequency of 30% in South Asia whereas it is almost absent in East Asia (Fig. 3). This extent of difference in allele frequencies between South and East Asia is unusual ($p = 0.006$, Extended Data Fig. 5) and indicates that it may have been affected by selection in the past. Indeed, previous work has suggested that the Neanderthal haplotype has been positively selected in Bangladesh[25]. At this point, we can only speculate about the reason for this, one possibility being protection against other pathogens. It is also possible that the haplotype has decreased in frequency in East Asia due to negative selection, perhaps from corona viruses or other pathogens. In any event, the COVID-19 risk haplotype on chromosome 3 is similar to some other Neanderthal and Denisovan genetic variants that have reached high frequencies in certain populations[14,26–28], but it is now under negative selection due to the SARS-CoV-2 pandemic.

It is currently not known what feature in the Neanderthal-derived region confers risk for severe COVID-19 and if the effects of any such feature is specific to SARS-CoV-2, to other coronaviruses or to other pathogens. Once the functional feature is elucidated, it may be possible to speculate about the susceptibility of Neanderthals to relevant pathogens. However, with respect to the current pandemic, it is clear that gene flow from Neanderthals has tragic consequences.

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/s41586-020-2818-3.

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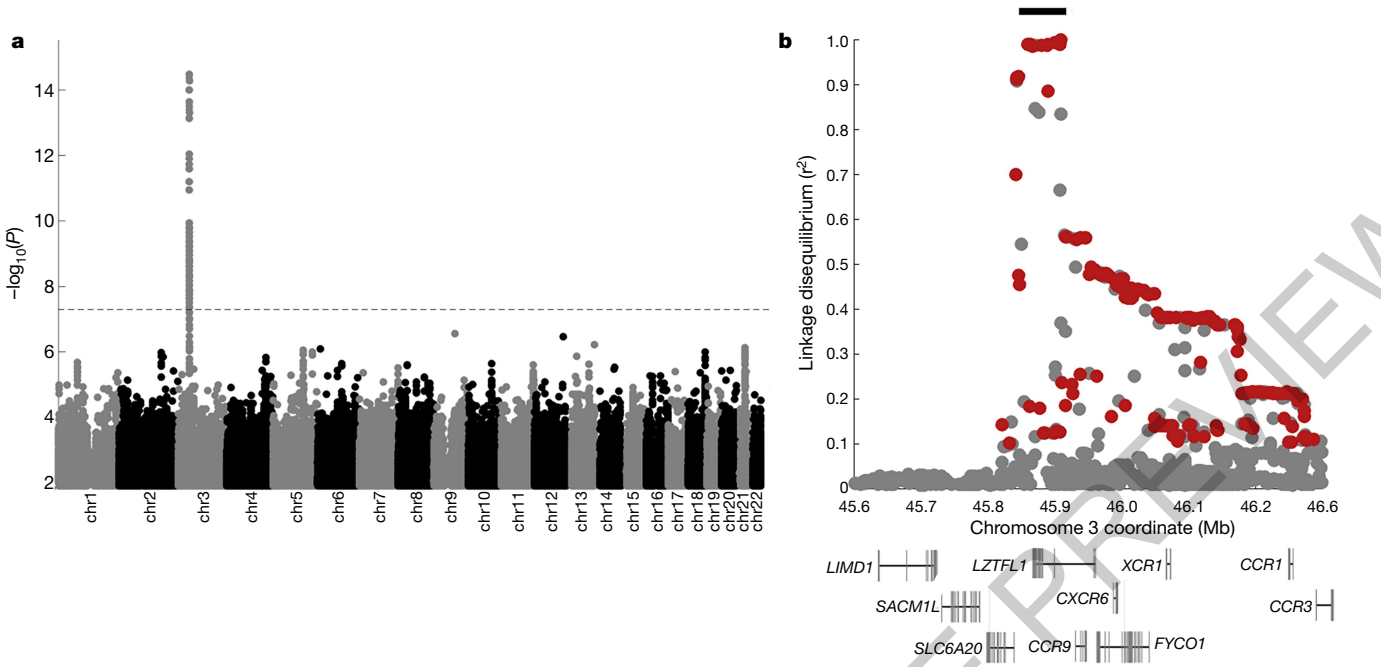

Fig. 1 | Genetic variants associated with severe COVID-19. A) Manhattan plot of a genome-wide association study of 3,199 hospitalized COVID-19 patients and 897,488 population controls. Dashed line indicates genome wide significance (p = 5e-8, *i.e.*, threshold corresponding to Bonferroni correction for one million independent variants for a two-sided z-test). Data modified from the COVID-19 Host Genetics Initiative[2] (https://www.covid19hg.org/). **B**) Linkage disequilibrium between the index risk variant (rs35044562) and genetic variants in the 1000 Genomes Project. Red marks genetic variants where alleles are correlated to the risk variant (r^2>0.1) and the risk alleles match the *Vindija 33.19* Neanderthal genome. The core Neanderthal haplotype (r^2>0.98) is indicated by a black bar. Note that some individuals carry longer Neanderthal-like haplotypes. The *x*-axis gives *hg19* coordinates.

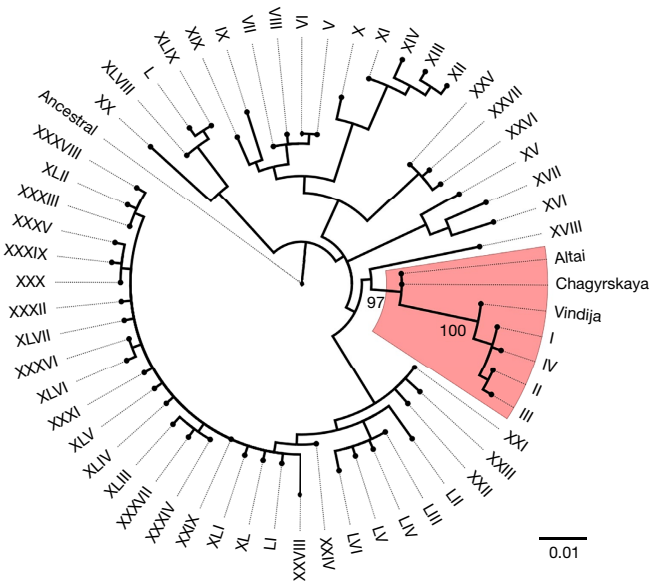

Fig. 2 | Phylogeny relating DNA sequences covering the core Neanderthal haplotype in 1000 Genomes individuals and Neanderthals. The coloured area indicates haplotypes that carry the risk allele at rs35044562, *i.e.* the risk haplotypes for severe COVID-19. Arabic numbers indicate bootstrap support (100 replicates). The phylogeny is rooted with the inferred ancestral sequence of present-day humans. The three Neanderthal genomes carry no heterozygous positions in this region.

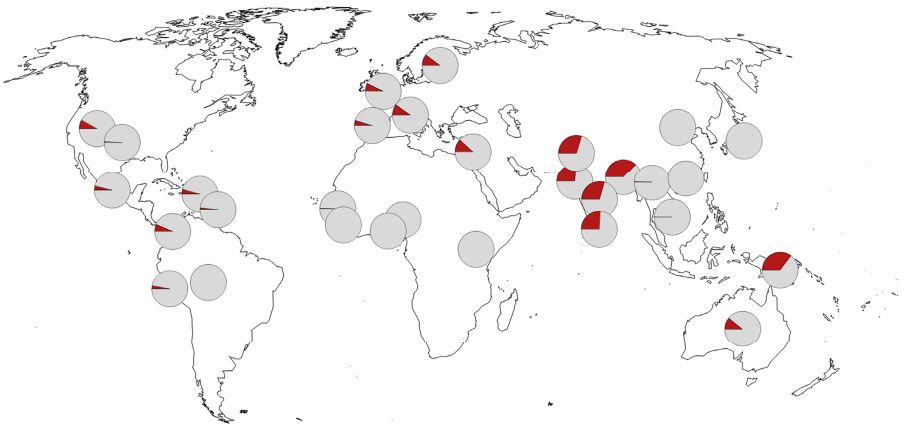

Fig. 3 | Geographic distribution of the Neanderthal core haplotype conferring risk for severe COVID-19. Pie charts indicate minor allele frequency at rs35044562. Frequency data from the 1000 Genomes Project[22]. Map source data from OpenStreetMap[23].

Methods

Linkage disequilibrium was calculated using LDlink 4.1[29] and alleles were compared to the archaic genomes[8–11] using tabix[30] (HTSlib 1.10). Haplotypes were constructed from the phase 3 release of the 1000 Genomes Project[22] as described. Phylogenies were estimated with phyML 3.3[31] using the Hasegawa-Kishino-Yano-85[32] substitution model with a gamma shape parameter and the proportion of invariant sites estimated from the data. The probability of observing a haplotype of a certain length or longer due to incomplete lineage sorting was calculated as described[14]. The inferred ancestral states at variable positions among present-day humans were taken from Ensembl[33]. The distribution of frequency differences between East and South Asia of Neanderthal haplotypes was computed by filtering diagnostic Neanderthal variants (fixed positions in the three high-coverage Neanderthal genomes and the Neanderthal allele missing in 108 Yoruba individuals) using a published introgression map[20], followed by pruning using PLINK1.90[34] (r^2 cut-off 0.5 in a sliding window of 100 variants) and allele frequency assessment in the 1000 Genomes Project. Maps displaying allele frequencies and LD in different populations were made using Mathematica 11.0 (Wolfram Research, Inc., Champaign, IL) and OpenStreetMap data.

For the meta-analysis carried out by the COVID-19 Host Genetics Initiative[2], participants were consented and ethical approvals were obtained (https://www.covid19hg.org/partners/). The eight studies contributing to the meta analysis of hospitalization versus population controls are: Genetic modifiers for COVID-19 related illness 'BelCovid' (Université Libre de Bruxelles, Belgium), Genetic determinants of COVID-19 complications in the Brazilian population 'BRACOVID' (University of Sao Paulo, Brazil), deCODE (deCODE genetics, Iceland), FinnGen (Institute for Molecular Medicine Finland, Finland), GEN-COVID (University of Siena, Italy), Genes & Health (Queen Mary University of London, UK), COVID19-Host(a)ge (Kiel University and University Hospitals of Oslo and Schleswig-Holstein, Germany/Norway) and the UK Biobank (Stockport, UK).

Reporting summary

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

Data availability

The summary statistics of the genetic association study supporting the finding of this study are available from the COVID-19 Host Genetics Initiative (round 3, ANA_B2_V2: hospitalized covid vs. population, https://www.covid19hg.org/). The genomes used are available from the 1000 Genomes Project (phase 3 release, https://www.internationalgenome.org/) and the Max Planck Institute for Evolutionary Anthropology (Chagyrskaya, Altai, and Vindija 33.19, http://cdna.eva.mpg.de/neandertal/). The ancestral alleles are available at Ensembl (release 100, https://www.ensembl.org/). Map data copyrighted OpenStreetMap contributors and available from https://www.openstreetmap.org.

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Author contributions H.Z. performed the haplotype analysis. H.Z. and S.P. jointly wrote the manuscript.

Competing interests The authors declare no competing interests.

Additional information
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Correspondence and requests for materials should be addressed to H.Z. or S.P.
Peer review information *Nature* thanks Tobias Lenz, Yang Luo 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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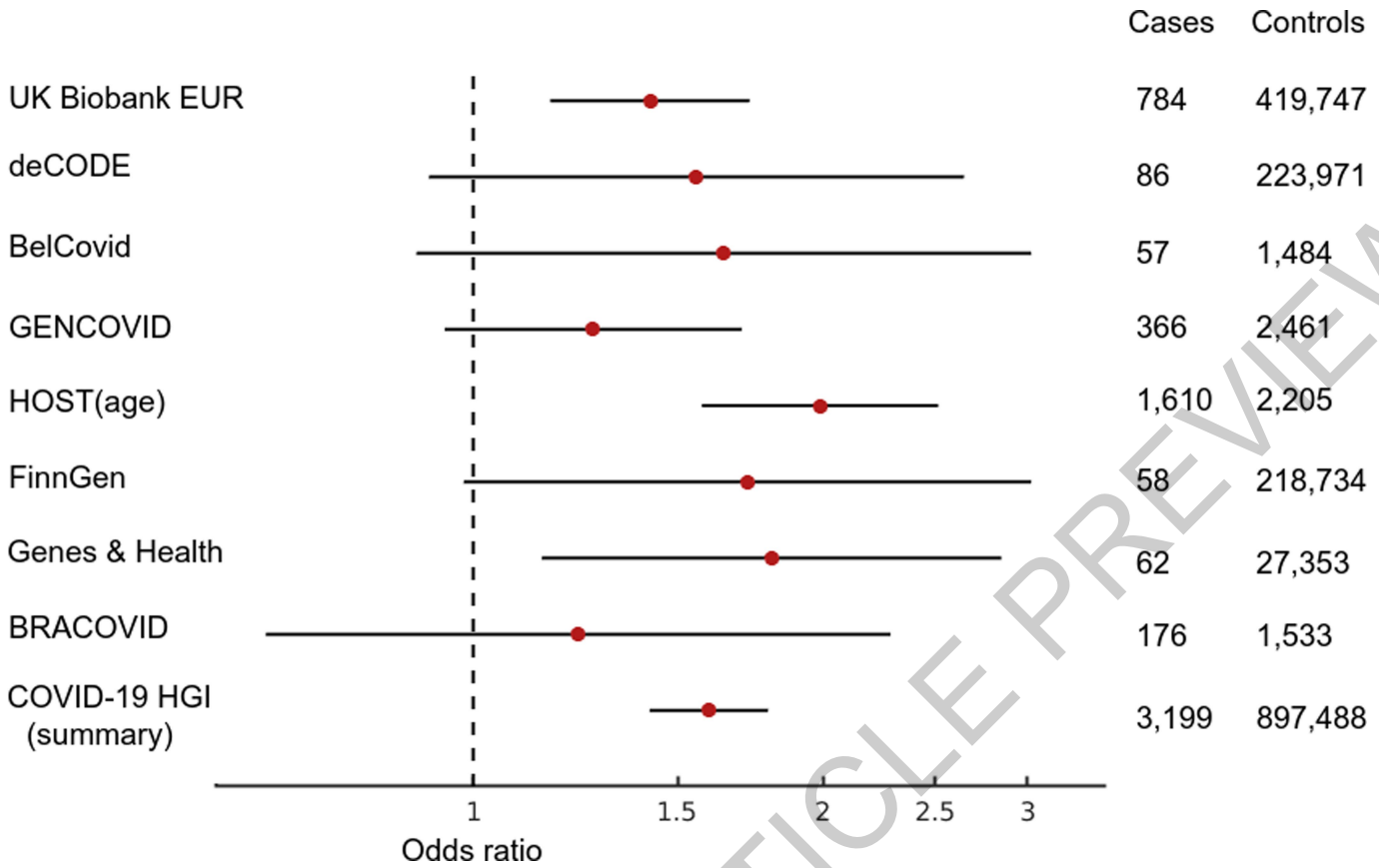
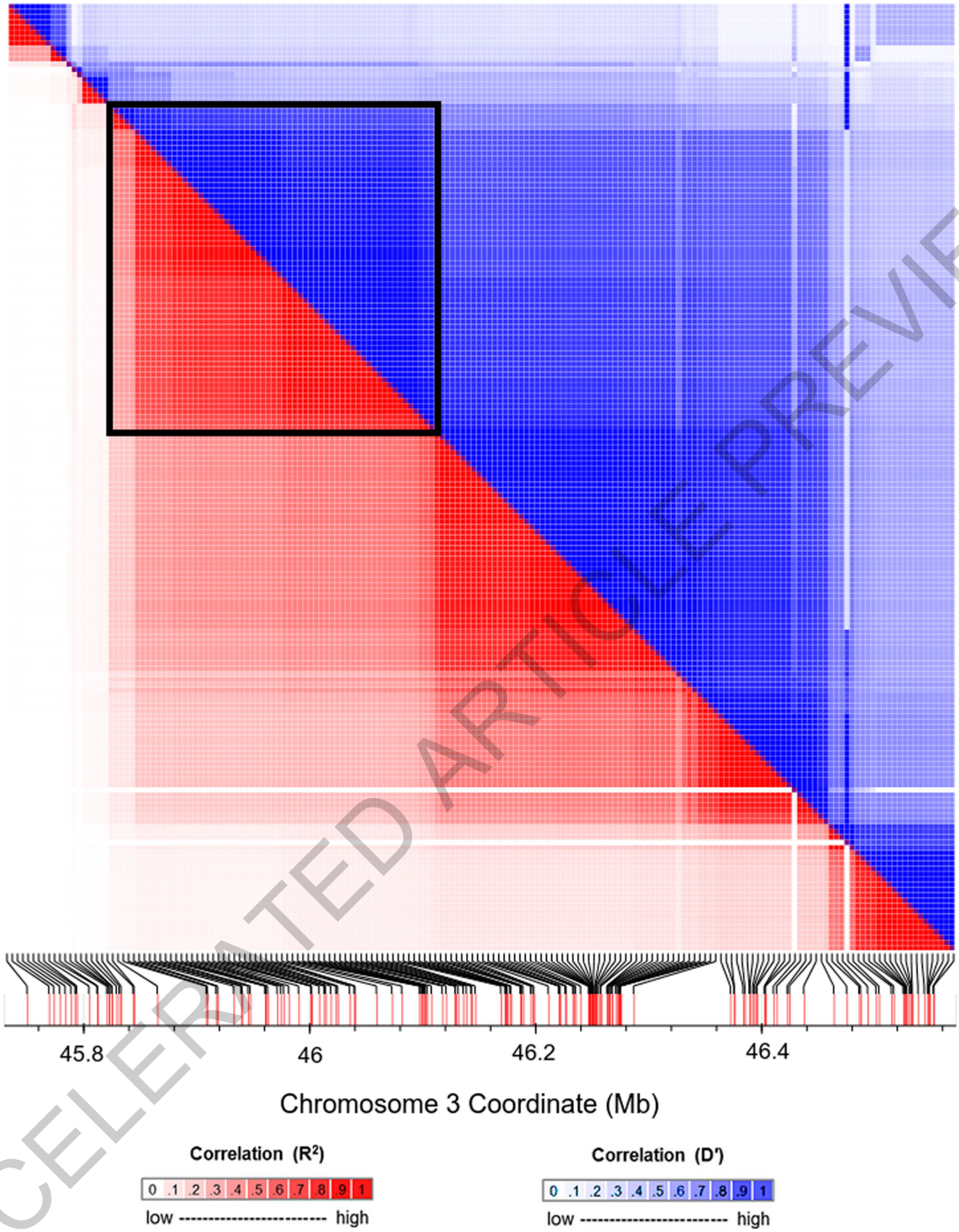
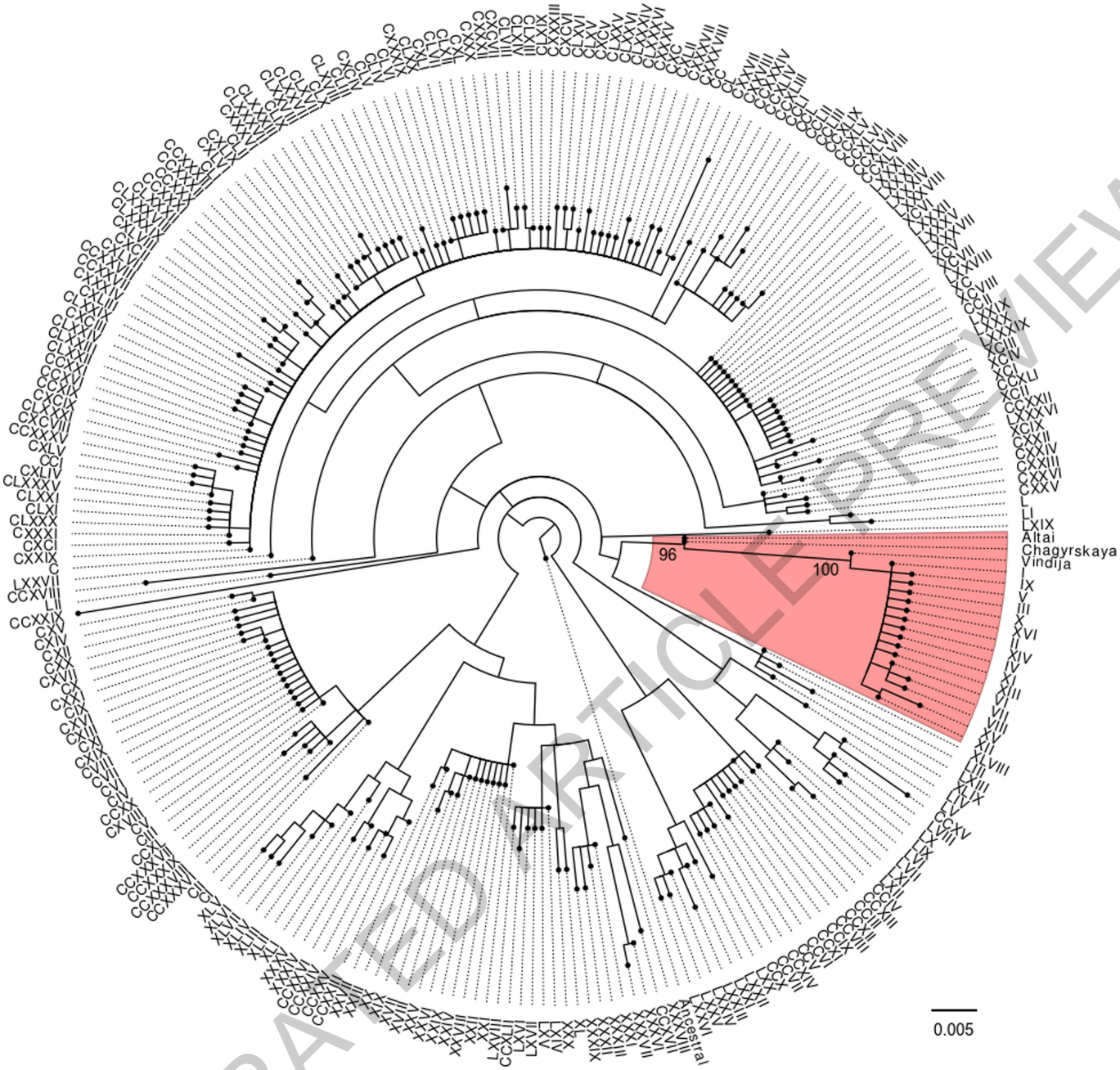


Extended Data Fig. 1 | Odds ratios for hospitalization due to COVID-19 for cohorts contributing to the meta-analysis (round 3) of the COVID-19 Host Genetics Initiative (rs35044562). The odds ratio and the p-value for the summary effect are OR = 1.60 (95% CI: 1.42-1.79) and p = 3.1e-15 (two-sided z-test, n = 3,199 cases and 897,488 controls over 8 independent studies). Data are presented as odds ratios with 95% confidence intervals as error bars. HOST(age), UKBB, GENCOVID, deCODE and BelCovid use European population controls. BRACOVID, Genes & Health, and FinnGen use American, South Asian and Finnish population controls, respectively.

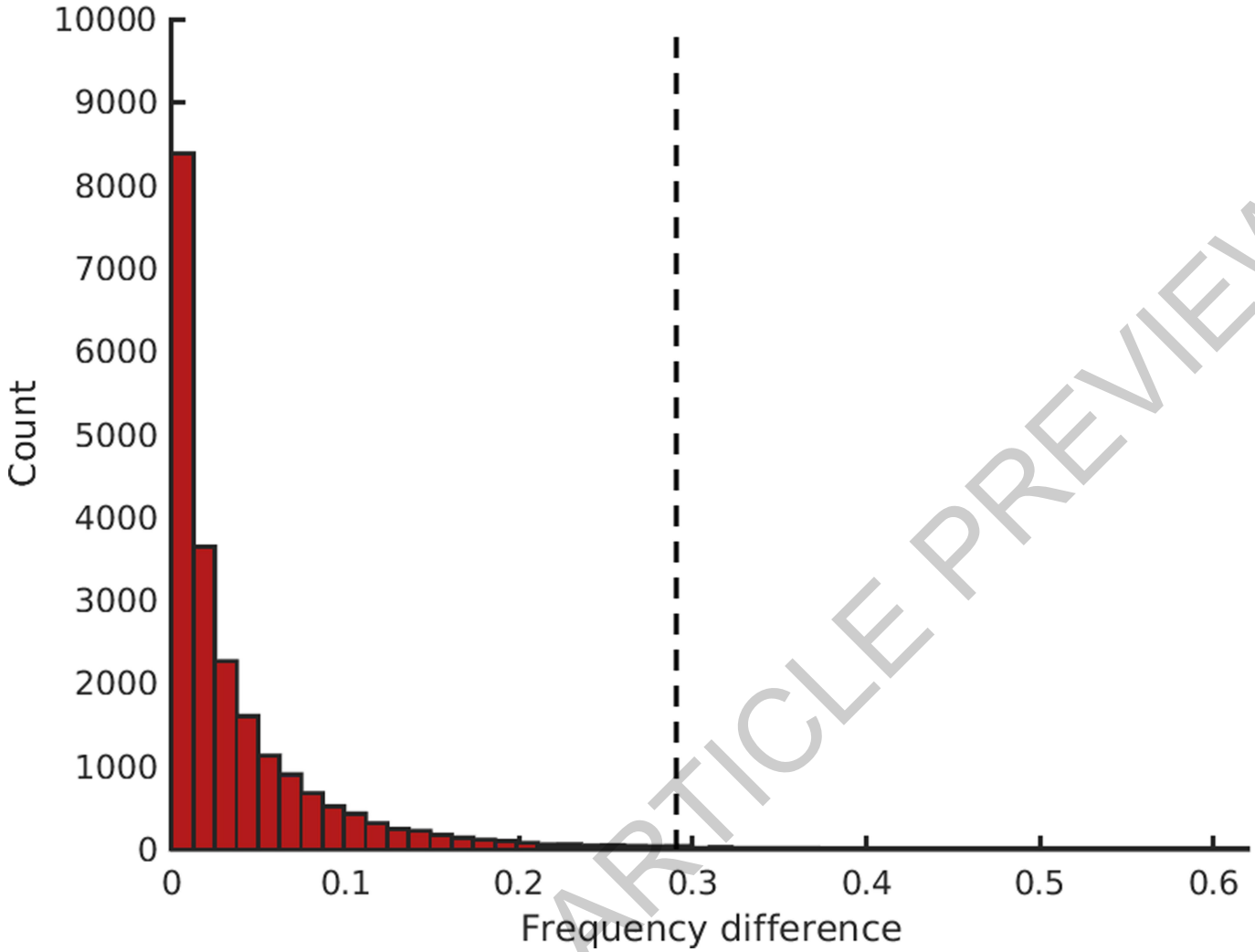


Extended Data Fig. 2 | Pairwise linkage disequilibrium between diagnostic Neanderthal variants. Heat map of LD between genetic variants where one allele is shared with three Neanderthal genomes and missing in 108 Yoruba individuals. The black box indicates a haplotype of 333.8 kb between rs17763537 and rs13068572 (chr3: 45,843,315-46,177,096). Red colours show r^2 and blue colours D′, as indicated.

Extended Data Fig. 3 | Linkage disequilibrium between the Ellinghaus *et al.* index variant (rs11385942) and the index variant of the COVID-19 Host Genetics Initiative (rs35044562). Shades of red indicate the extent of linkage disequilibrium (r^2) in the 1000 Genomes populations. Populations labelled with "n/a" are monomorphic for the protective allele of rs35044562. The Ellinghaus *et al.*[1] index variant does not have any genetic variants in LD (r^2>0.8) in African populations. Map source data from OpenStreetMap[23].



Extended Data Fig. 4 | Phylogeny of haplotypes in 1000 Genomes individuals and Neanderthals covering the genomic region of the core risk haplotype. The shaded area highlights a monophyletic group containing all present-day haplotypes carrying the risk allele at rs35044562 and the haplotypes of the three high-coverage Neanderthals. Arabic numbers show bootstrap support (100 replicates). The tree is rooted with the inferred ancestral human sequence.



Extended Data Fig. 5 | Frequency differences between South and East Asia for haplotypes introgressed from Neanderthals. The dashed line indicates the frequency difference for the Neanderthal haplotype conferring risk to severe COVID-19.

Extended Data Table 1 | Genetic variants in LD (r^2>0.98) with rs35044562 and the corresponding Neanderthal variants

Chr	Pos	rsid	LD with rs35044562	Ref	Alt/Risk	Vindija	Altai	Chagyrskaya
3	45909024	rs35044562	1.000	A	G	G	G	G
3	45901089	rs73064425	0.992	C	T	T	C	C
3	45899651	rs34326463	0.992	A	G	A	A	A
3	45908116	rs13081482	0.989	A	T	T	T	T
3	45880481	rs35508621	0.989	T	C	C	T	T
3	45864732	rs10490770	0.989	T	C	C	C	C
3	45862952	rs71325088	0.989	T	C	C	T	T
3	45861932	rs13078854	0.989	G	A	A	G	G
3	45859651	rs17713054	0.987	G	A	A	G	G
3	45871908	rs67959919	0.987	G	A	G	G	G
3	45888690	rs34288077	0.987	A	G	G	A	A
3	45889921	rs35081325	0.987	A	T	T	A	A
3	45867440	rs35624553	0.984	A	G	G	A	A

Data from the 1000 Genomes Project[22]. "Ref" gives the *hg19* alleles. The three Neanderthal genomes are homozygous at these positions.

Extended Data Table 2 | Previous studies that identified gene flow from Neanderthals at the core haplotype

Study	Chr	Start (Mb)	Stop (Mb)
This study	3	45.86	45.91
Sankararaman *et al.* 2014	3	45.84	46.89
Vernot *et al.* 2014	3	45.84	45.91
Vernot *et al.* 2016	3	45.21	46.33
Gittelman *et al.* 2016	3	45.84	46.17
Steinrücken *et al.* 2018	3	45.84	45.88
Skov *et al.* 2020	3	45.85	46.58
Chen *et al.* 2020	3	45.82	45.92

Table gives *hg19* coordinates for the previously identified[15–21] introgressed haplotypes.

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Reporting Summary

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n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒	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	No new data was produced in the present study.
Data analysis	LDlink 4.1 for linkage disequilibrium (LD), PhyML 3.3 for the maximum-likelihood phylogenies, tabix (HTSlib 1.10) for calling variants in the genomes. PLINK 1.90 for LD pruning. Mathematica 11.0 for creating maps. All software are publicly available and except Mathematica free of charge.

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

GWAS results (round 3, ANA_B2_V2): https://www.covid19hg.org/results/
Neandertal genomes (Altai, Vindija 33.19, Chagyrskaya): http://cdna.eva.mpg.de/neandertal/
1000 genomes project (phase 3 release): https://www.internationalgenome.org/
Ensembl (release 100): http://www.ensembl.org/

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	We used all available high-coverage Neandertal genomes (n=3). The sample size of the GWAS (3,199 cases and 897,488 controls) was limited by the data provided from the cohorts. We used all genomes in the phase 3 release (n=2504) of the 1000 genomes project.
Data exclusions	Sites which are not shared between any two individuals were excluded, since those positions in the genome are not informative for the phylogenetic relationship. This exclusion criterium was not pre-established.
Replication	The findings in our study are easily reproducible using publicly available genomes. The significance of the phylogenies was assessed using bootstrap: the identified haplotypes grouped with the Vindija Neandertal 100 times out of 100 bootstrap replicates. All eight cohorts contributing to the meta-analysis showed a positive correlation between the risk allele and hospitalization.
Randomization	We used all relevant public data at hand, hence we did not performed any randomization of a subsample or equivalent. The genetic association study is not the product of this manuscript, we have only interpreted the results in an evolutionary perspective. For the phylogenetic trees, however, we use the built-in random number generator of PhyML 3.3 to calculate the phylogenies. As stated above, all bootstrap replicates resulted in the same monophyletic group.
Blinding	We analysed publicly available meta statistics from a genetic association study of hospitalized COVID-19 patients. The nature of the underlying data (hospitalized COVID-19 patients) is such that blinding (of hospitalization and infection with SARS-CoV2) was not possible within ethical and practical constraints.

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