Genetic association analysis of SARS-CoV-2 infection in 455,838 UK Biobank participants

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ABSTRACT

Background. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes Coronavirus disease-19 (COVID-19), a respiratory illness with influenza-like symptoms that can result in hospitalization or death. We investigated human genetic determinants of COVID-19 risk and severity in 455,838 UK Biobank participants, including 2,003 with COVID-19.

Methods. We defined eight COVID-19 phenotypes (including risks of infection, hospitalization and severe disease) and tested these for association with imputed and exome sequencing variants.

Results. We replicated prior COVID-19 genetic associations with common variants in the 3p21.31 (in *LZTFL1*) and 9q34.2 (in *ABO*) loci. The 3p21.31 locus (rs11385942) was associated with disease severity amongst COVID-19 cases (OR=2.2, $P=3\text{x}10^{-5}$), but not risk of SARS-CoV-2 infection without hospitalization (OR=0.89, $P=0.25$). We identified two loci associated with risk of infection at $P<5\text{x}10^{-8}$, including a missense variant that tags the ε4 haplotype in *APOE* (rs429358; OR=1.29, $P=9\text{x}10^{-9}$). The association with rs429358 was attenuated after adjusting for cardiovascular disease and Alzheimer's disease status (OR=1.15, $P=0.005$). Analyses of rare coding variants identified no significant associations overall, either exome-wide or with (i) 14 genes related to interferon signaling and reported to contain rare deleterious variants in severe COVID-19 patients; (ii) 36 genes located in the 3p21.31 and 9q34.2 GWAS risk loci; and (iii) 31 additional genes of immunologic relevance and/or therapeutic potential.

Conclusions. Our analyses corroborate the association with the 3p21.31 locus and highlight that there are no rare protein-coding variant associations with effect sizes detectable at current sample sizes. Our full analysis results are publicly available, providing a substrate for meta-analysis with results from other sequenced COVID-19 cases as they become available. Association results are available at https://rgc-covid19.regeneron.com .

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China in late 2019 [1] and causes coronavirus disease 2019 (COVID-19) [2]. COVID-19 symptoms range from flu-like symptoms such as fever, cough and headaches to respiratory failure, acute immune responses and death [3]. It is estimated that most infected individuals display few, if any, symptoms [4, 5]. As of October 2020, SARS-CoV-2 has been reported in >41 million individuals and to be associated with >1.1 million deaths worldwide. Known risk factors include male sex, older age, ancestry, obesity, cardiovascular and kidney disease, chronic obstructive pulmonary disease (COPD) and dementia [6-9], among others.

Studying host genetic variation among individuals infected with SARS-CoV-2 holds the potential to identify mechanisms that influence disease severity and outcomes. Akin to *IFNGR1*, *STAT1, TLR7* and other genetic immune deficiencies that predispose to early-onset severe infections [10-15], this information may help identify individuals at high risk of SARS-CoV-2 infection who should be prioritized for disease prevention strategies, including vaccination or monoclonal antibody treatments [16, 17]. Further, understanding host mechanisms that provide protection from SARS-CoV-2 infection or that modulate disease severity might guide the development of treatment efforts, in the same way that *CCR5* variation and HIV infection [18], or *FUT2* variation and infection by certain strains of norovirus [19], helped identify therapeutic strategies and targets for these diseases.

Since the start of the SARS-CoV-2 pandemic, host genetic analysis of common genetic variation among SARS-CoV-2 patients identified two genome-wide significant loci, one at 3p21.31 spanning at least six genes (including *SLC6A20* and *LZTFL1*) and a second at 9q34.2 in the *ABO* locus [20, 21]. The first locus has been consistently replicated in additional studies [21,

22], while the association at the *ABO* locus remains contentious. In addition to these genome-wide association studies (GWAS), two studies suggest that rare deleterious variants in genes related to interferon signaling may be implicated in more extreme clinical outcomes [14, 23]. However, to date, there has been no assessment of the contribution of rare genetic variation to COVID-19 disease susceptibility or severity through large population-based exome-wide association analyses.

To identify rare coding variants associated with COVID-19 susceptibility and severity, we evaluated clinical data derived from quantitative polymerase chain reaction (qPCR) tests for SARS-CoV-2, together with anonymized electronic health records and death registry data for both COVID-19 patients and other individuals in the UK Biobank study. We first analyzed imputed data for 455,838 individuals (2,003 with COVID-19), including a deep dive into the unequivocal 3p21.31 locus as a positive control, to calibrate our susceptibility and severity phenotypes with those used in other COVID-19 GWAS. We then analyzed exome sequencing data for a subset of 424,183 individuals (1,865 with COVID-19) to investigate disease associations with individual rare variants and rare variant-aggregated gene-burden tests. In addition to an agnostic exome-wide search for genetic risk factors, we also focused on 81 specific genes of interest (i) with a known role in interferon signaling and recently observed to contain rare deleterious variants in patients with severe COVID-19 [14, 23]; (ii) near two common risk variants for COVID-19 identified by GWAS [20]; or (iii) of immunologic relevance and/or therapeutic potential.

This study represents the largest exome-sequencing study of COVID-19 performed to date. Expanded analyses, particularly among individuals disproportionally affected by SARS-CoV-2, are essential to help identify human genetic determinants of disease risk and identify therapeutic avenues for the treatment of COVID-19.

METHODS

Study participants

We studied the host genetics of SARS-CoV-2 infection in participants of the UK Biobank study, which took place between 2006 and 2010 and includes approximately 500,000 adults aged 40-69 at recruitment [24]. In collaboration with UK health authorities, the UK Biobank has made available regular updates on COVID-19 status for all participants, including results from four main data types: qPCR test for SARS-CoV-2, anonymized electronic health records, primary care and death registry data. We report results based on the 12 September 2020 data refresh and excluded from the analysis 28,547 individuals with a death registry event prior to 2020.

COVID-19 phenotypes used for genetic association analyses

Using the data types outlined above, we grouped UK Biobank participants into three broad COVID-19 disease categories (**Table 1**): (i) positive – those with a positive qPCR test for SARS-CoV-2 or a COVID-19-related ICD10 code (U07), hospitalization or death; (ii) negative – those with only negative qPCR test results for SARS-CoV-2 and no COVID-19-related ICD10 code (U07), hospitalization or death; and (iii) unknown – those with no qPCR test result and no COVID-19-related ICD10 code (U07), hospitalization or death. We then used these broad COVID-19 disease categories, in addition to hospitalization and disease severity information, to create eight COVID-19-related phenotypes for genetic association analyses, as detailed in **Table 2**.

Array genotyping and imputation

DNA samples from participants of the UK Biobank study were genotyped as described previously

[24] using the Applied Biosystems UK BiLEVE Axiom Array (N=49,950) or the closely related Applied Biosystems UK Biobank Axiom Array (N=438,427). Genotype data for variants not included in the arrays were then inferred using three reference panels (Haplotype Reference Consortium, UK10K and 1000 Genomes Project phase 3) as described previously [24].

Exome sequencing

Sample Preparation and Sequencing. Genomic DNA samples normalized to approximately 16 ng/ul were transferred to the Regeneron Genetics Center from the UK Biobank in 0.5ml 2D matrix tubes (Thermo Fisher Scientific) and stored in an automated sample biobank (LiCONiC Instruments) at -80°C prior to sample preparation. Exome capture was completed using a high-throughput, fully-automated approach developed at the Regeneron Genetics Center. Briefly, DNA libraries were created by enzymatically shearing 100ng of genomic DNA to a mean fragment size of 200 base pairs using a custom NEBNext Ultra II FS DNA library prep kit (New England Biolabs) and a common Y-shaped adapter (Integrated DNA Technologies) was ligated to all DNA libraries. Unique, asymmetric 10 base pair barcodes were added to the DNA fragment during library amplification with KAPA HiFi polymerase (KAPA Biosystems) to facilitate multiplexed exome capture and sequencing. Equal amounts of sample were pooled prior to overnight exome capture, approximately 16 hours, with a slightly modified version of IDT's xGen probe library; supplemental probes were added to capture regions of the genome well-covered by a previous capture reagent (NimbleGen VCRome), but poorly covered by the standard xGen probes (design bed file available by request). Captured fragments were bound to streptavidin-coupled Dynabeads (Thermo Fisher Scientific) and non-specific DNA fragments removed through a series of stringent washes using the xGen Hybridization and Wash kit according to the manufacturer's recommended

protocol (Integrated DNA Technologies). The captured DNA was PCR amplified with KAPA HiFi and quantified by qPCR with a KAPA Library Quantification Kit (KAPA Biosystems). The multiplexed samples were pooled and then sequenced using 75 base pair paired-end reads with two 10 base pair index reads on the Illumina NovaSeq 6000 platform using S2 or S4 flow cells.

Variant calling and quality control. Sample read mapping and variant calling, aggregation and quality control were performed via the SPB protocol described in Van Hout et al. [25] (https://www.ukbiobank.ac.uk/wp-content/uploads/2019/08/UKB-50k-Exome-Sequencing-Data-Release-July-2019-FAQs.pdf). Briefly, for each sample, NovaSeq WES reads are mapped with BWA MEM to the hg38 reference genome. Small variants are identified with WeCall and reported as per-sample gVCFs. These gVCFs are aggregated with GLnexus into a joint-genotyped, multi-sample VCF (pVCF). SNV genotypes with read depth less than seven (DP < 7) and indel genotypes with read depth less than ten (DP < 10) are changed to no-call genotypes. After the application of the DP genotype filter, a variant-level allele balance filter is applied, retaining only variants that meet either of the following criteria: (i) at least one homozygous variant carrier or (ii) at least one heterozygous variant carrier with an allele balance greater than the cutoff (AB >= 0.15 for SNVs and AB >= 0.20 for indels).

Identification of low-quality variants from exome-sequencing using machine learning. Briefly, we defined a set of positive control and negative control variants based on: (i) concordance in genotype calls between array and exome sequencing data; (ii) mendelian inconsistencies in the exome sequencing data; (iii) differences in allele frequencies between exome sequencing batches; (iv) variant loadings on 20 principal components derived from the analysis of variants with a

MAF<1%. The model was then trained on 30 available WeCall/GLnexus site quality metrics, including, for example, allele balance and depth of coverage. We split the data into training (80%) and test (20%) sets. We then performed a grid search with 5-fold cross-validation on the training set and applied the model with highest accuracy to the test set. Out of 15 million variants in the exome target region, 1 million (6.5%) were identified as low-quality and excluded from the analysis. Similarly, we identified and removed 6 million out of 21 million variants (28.6%) in the buffer region.

Gene burden masks. Briefly, for each gene region as defined by Ensembl [26], genotype information from multiple rare coding variants was collapsed into a single burden genotype, such that individuals who were: (i) homozygous reference (Ref) for all variants in that gene were considered homozygous (RefRef); (ii) heterozygous for at least one variant in that gene were considered heterozygous (RefAlt); (iii) and only individuals that carried two copies of the alternative allele (Alt) of the same variant were considered homozygous for the alternative allele (AltAlt). We did not phase rare variants; compound heterozygotes, if present, were considered heterozygous (RefAlt). We did this separately for four classes of variants: (i) predicted loss of function (pLoF), which we refer to as an "M1" burden mask; (ii) pLoF or missense ("M2"); (iii) pLoF or missense variants predicted to be deleterious by 5/5 prediction algorithms ("M3"); (iv) pLoF or missense variants predicted to be deleterious by 1/5 prediction algorithms ("M4"). The five missense deleterious algorithms used were SIFT [27], PolyPhen2 (HDIV), PolyPhen2 (HVAR) [28], LRT [29], and MutationTaster [30]. For each gene, and for each of these four groups, we considered five separate burden masks, based on the frequency of the alternative allele of the variants that were screened in that group: <1%, <0.1%, <0.01%, <0.001% and singletons

only. Each burden mask was then tested for association with the same approach used for individual variants (see below).

Genetic association analyses

Association analyses in the UK Biobank study were performed using the Firth logistic regression test implemented in REGENIE [31], separately for variants derived from array-based imputation and exome sequencing. In this test, Firth's approach is applied when the p-value from the standard logistic regression score test is below 0.05. As the Firth penalty (*i.e.* Jeffrey's invariant prior) corresponds to a data augmentation procedure where each observation is split into a case and a control with different weights, it can handle variants with no minor alleles among cases. With no covariates, this corresponds to adding 0.5 in every cell of a 2x2 table of allele counts versus case-control status.

We included in step 1 of REGENIE (*i.e.* prediction of individual trait values based on the genetic data) variants that were directly genotyped, had a minor allele frequency (MAF) >1%, <10% missingness, Hardy-Weinberg equilibrium test *P*-value>10^{-15} and after linkage-disequilibrium (LD) pruning (1000 variant windows, 100 sliding windows and r^2<0.9). The association model used in step 2 of REGENIE included as covariates age, age^2, sex, age-by-sex, age^2-by-sex, and the first 10 ancestry-informative principle components (PCs) released by the UK Biobank. For the analysis of exome variants, we also included as covariates an indicator for exome sequencing batch and 20 PCs derived from the analysis of exome variants with a MAF between $2.6x10^{-5}$ (roughly corresponding to a minor allele count [MAC] of 20) and 1%. We did this because previous studies have found that PCs derived from common variants do not adequately correct for fine-scale population structure [32, 33].

For imputed variants, we retained association results for variants with both an imputation information score ≥0.3 and MAC ≥5, and either (i) MAF>0.5% or (ii) a protein-altering consequence (*i.e.* pLOF, missense or splice variants). For exome sequencing variants, we retained association results for variants with a MAC≥5. Association analyses were performed separately for three different ancestries defined based on the array data (African [AFR], European [EUR] and South Asian [SAS]), with results subsequently combined across ancestries using an inverse variance-weighed fixed-effects meta-analysis.

Results availability

All genotype-phenotype association results reported in this study are available for browsing using the RGC's COVID-19 Results Browser (https://rgc-covid19.regeneron.com). Data access and use is limited to research purposes in accordance with the Terms of Use (https://rgc-covid19.regeneron.com/terms-of-use). The COVID-19 Results Browser provides a user-friendly interface to explore genetic association results, enabling users to query summary statistics across multiple cohorts and association studies using genes, variants or phenotypes of interest. Results are displayed in an interactive tabular view ordered by p-value – enabling filtering, sorting, grouping and viewing additional statistics – with link outs to individual GWAS reports, including interactive Manhattan and QQ plots. LocusZoom views of LD information surrounding variants of interest are also available, with LD calculated using the respective source genetic datasets.

The data resource supporting the COVID-19 Results Browser is built using a processed version of the raw association analysis outputs. Using the RGC's data engineering toolkit based in Apache Spark and Project Glow (https://projectglow.io/), association results are annotated, enriched and partitioned into a distributed, columnar data store using Apache Parquet. Processed

Parquet files are registered with AWS Athena, enabling efficient, scalable queries on unfiltered association result datasets. Additionally, “filtered” views of associations significant at a threshold of p-value < 0.001 are stored in AWS RDS Aurora databases for low latency queries to service primary views of top associations. APIs into RDS and Athena are managed behind the scenes such that results with a p-value>0.001 are pulled from Athena as needed.

RESULTS

Demographics and health characteristics of study participants

Among 473,977 participants of the UK Biobank study who were alive in January 2020, 2,118 were COVID-19 positive, 16,331 were COVID-19 negative and 455,528 had unknown COVID-19 status (**Table 1**). Relative to participants who were COVID-19 negative or unknown (**Table 1**), COVID-19 positive individuals were more likely to be male, to have African or South Asian ancestry and to have cardiovascular or respiratory co-morbidities (**Table 3**). These co-morbidities were also observed in analyses stratified by ancestry group (**Table 4**).

Genome-wide association study (GWAS) of imputed variants

We performed ancestry-specific GWAS for eight COVID-19-related phenotypes, using imputed variants available for a subset of 455,838 individuals (**Table 5**). These phenotypes captured a spectrum of disease severity, from COVID-19 cases who did not require hospitalization to those with severe disease (respiratory support or death). Association results are publicly available at https://rgc-covid19.regeneron.com and main findings summarized below. The genomic inflation factor (λ_{GC}) was close to 1 for most analyses (**Supplementary Table 1**).

Association with variants reported in previous COVID-19 GWAS. Recently, Ellinghaus et al. [20] performed a GWAS comparing 1,610 cases with a PCR-positive test for SARS-CoV-2 and respiratory failure, against 2,205 controls with unknown SARS-CoV-2 status (mostly blood donors), all from Spain or Italy. Two loci reached genome-wide significance in that study: (i) 3p21.31, near the *LZTFL1* gene (rs11385942, OR=1.77 for the GA allele; 95% CI=1.48-2.11;

P=1.1x10^{-10}); and (ii) 9q34.2, near the *ABO* gene (rs657152, OR=1.39 for the A allele; 95% CI=1.20-1.47; P=4.9x10^{-8}) [20]. Both loci were recently replicated in a larger GWAS [21], with the former also replicated in a GWAS of severe COVID-19 patients in the UK [22]. We found a nominally significant and directionally consistent association with both variants in the European-specific analysis of the phenotype COVID-19 positive vs. COVID-19 negative or unknown (**Figure 1**). For the 3p21.31 locus (**Figure 1A**), we observed the largest effect with risks of hospitalization (OR=1.69; 95% CI=1.25-2.28; P=6x10^{-4}) and severe disease (OR=2.29; 95% CI=1.56-3.35; P=2x10^{-5}) amongst COVID-19 cases. In contrast, there was no association with the phenotype COVID-19 positive and not hospitalized vs. COVID-19 negative or unknown (OR=0.87; 95% CI=0.71-1.08; P=0.21). These results suggest that variants in this 3p21.31 locus influence COVID-19 severity and not risk of SARS-CoV-2 infection.

Significant associations with common variants in ancestry-specific GWAS. Across the eight phenotypes tested, we identified two loci with an association P<5x10^{-8}, both found in the European-specific analysis of the phenotype COVID-19 positive (N=1,797) vs. COVID-19 negative or unknown (N=434,038). The first locus was on chromosome 19q13.32; the lead variant was rs429358 (MAF=15%, OR=1.29, CI=1.18-1.40, P=8.9x10^{-9}), a common missense variant (Cys130Arg) that tags the epsilon (ε) 4 haplotype in *APOE* (**Figure 2A)**. This variant has established associations with both Alzheimer's disease (AD) and coronary artery disease (CAD). In addition, AD and CAD are known risk factors associated with COVID-19, and we observed an enrichment of both diseases amongst COVID-19 positive individuals (**Supplementary Table 2**). Therefore, we tested if the association between the *APOE* locus and susceptibility to COVID-19 could be confounded by AD or CAD case-control status. When both diseases were added as

covariates to the model, we found that the association with rs429358 was significantly attenuated (OR=1.15; 95% CI=1.04-1.26; *P*=0.005). These results suggest that the association between rs429358 in *APOE* and COVID-19 risk likely arose because of the enrichment of AD and CAD amongst COVID-19 cases.

The second locus was on chromosome 19p13.11, also associated with the phenotype COVID-19 positive vs. COVID-19 negative or unknown. The lead variant was rs117336466 (MAF=0.9%; OR=2.16, 95% CI=1.64-2.85, $P=4.5\text{x}10^{-8}$), located in the first intron of *TMEM161A* (**Figure 2B**). This variant was not associated with risks of hospitalization (OR=0.60, 95% CI=0.33-1.09, *P*=0.094) or severe disease (OR=0.58, 95% CI=0.27-1.24, *P*=0.161) amongst COVID-19 positive cases.

Genome-wide significant associations in trans-ancestry meta-analysis. Seven of the eight phenotypes were tested in two or more ancestries. For these, we combined results across ancestries using a fixed-effects meta-analysis, but no new loci were identified at $P<5\text{x}10^{-8}$.

Exome-wide association study of sequenced variants

We tested the association between the same eight COVID-19-related phenotypes and exome sequencing variants available for a subset of 424,183 individuals from the UKB study. We tested both single variants and a burden of rare variants in protein-coding genes (see Methods).

Exome-wide association results. The λ_{GC} for common variants (MAF>0.5%) was close to 1 for most analyses (**Supplementary Table 3**), while for rare variants (MAF<0.5%) we observed a considerable deflation of test statistics, caused by a large proportion of variants having a MAC of

0 in cases (*e.g.* 89% of variants in the European-only analysis of COVID-19 positive and hospitalized [N=1,065] vs. COVID-19 negative or unknown [N=403,700]). Overall, when considering both trans- and single-ancestry association analyses, we did not identify any associations with rare coding variants at a $P<5x10^{-8}$.

Association results for 14 genes in the anti-viral interferon signaling pathway. Two recent exome sequencing studies of COVID-19 suggested that rare deleterious variants in 14 genes related to interferon signaling may be implicated in more extreme clinical outcomes [14, 23]. Given our larger sample size, we examined whether there was any evidence for association between the COVID-19 hospitalization phenotype (1,184 cases vs. 422,318 controls) and a burden of rare (MAF<0.1%) pLoF variants (M1 burden test) or pLoF plus deleterious missense variants (M3 burden test) in these 14 genes. We found no nominal significant associations ($P<0.05$) with any of the 14 genes (**Table 6**). Further, these results were unchanged when testing COVID-19 severe cases (N=471), or when restricting the burden tests to include variants with a MAF<1% or singleton variants (**Supplementary Table 4**). Therefore, in our analysis of the UK Biobank data, we found no evidence for an association between the 14 specific interferon signaling genes and COVID-19 outcomes.

Association results for 36 genes located in two risk loci for COVID-19 identified by Ellinghaus et al. [20]. Associations with rare protein-coding variants might help pinpoint target genes of common risk variants identified in GWAS of COVID-19. To address this possibility, we focused on 36 protein-coding genes located within 500 kb of the two common risk variants identified by Ellinghaus et al. [20]: rs11385942 (locus 3p21.31) and rs657152 (locus 9q34.2). Of the 72 gene

burden tests performed (36 genes x 2 burden tests, considering variants with MAF<1%), four had a nominal significant association (**Supplementary Table 5**), including two protective (*CCR9* and *TSC1*) and two predisposing (*SARDH* and *XCR1*) associations. However, these associations did not remain significant after correcting for the number of tests performed (all with $P>0.05/72=0.0007$).

Association results for 31 additional genes of interest. Lastly, we performed the same analysis for 31 genes that are involved in the etiology of SARS-CoV-2 infection (*e.g. ACE2, TMPRSS2*), encode therapeutic targets (*e.g. IL6R, JAK2*) or have been implicated in other immune or infectious diseases through GWAS (*e.g. IL33*). After correcting for multiple testing, there were also no significant associations with a burden of rare deleterious variants for this group of genes (**Supplementary Table 6**).

DISCUSSION

Eleven months since the first reported cases of "pneumonia of unknown cause" to the World Health Organization and six months since the declaration of the COVID-19 pandemic [34], >41 million individuals have been infected with SARS-CoV-2 worldwide. Epidemiological studies have identified groups of individuals at high risk for severe disease, clinical complications and death [8, 9, 35-38]. More recently, studies focusing on host genetics have begun to identify common variants that contribute to heterogeneity in COVID-19 risk and severity [20-22].

Our analysis of COVID-19 in the UK Biobank indicates that, consistent with observational studies in the same UK participants [35, 37], COVID-19-related hospitalizations and deaths skew towards older, male individuals of non-European ancestry. Hypertension, obesity, CAD, type-2 diabetes and dementia are among the most frequently reported COVID-19 disease comorbidities [8, 9, 35]. Similarly, after adjusting for age, we observed a 1.7-fold enrichment in both cardiovascular disease and Alzheimer's disease among COVID-19 cases in the UK Biobank study.

Previous GWAS reported an association between risk of SARS-CoV-2 infection and common variants in the 3p21.31 locus [20-22]. We confirmed this association and further showed that this locus affects disease severity but not (or less so) risk of infection. We note, as have others, that the lead variant rs35652899 is in high LD with a lead expression quantitative trait locus (eQTL) for *SCL6A20* in lung tissue [39]. The *SLC6A20* gene encodes SIT1, a proline transporter expressed in the small intestine, lung, and kidney [40]. SIT1 expression and function is increased via interaction with angiotensin-converting enzyme 2 (ACE2), which is the SARS-CoV-2 receptor [41]. One intriguing hypothesis is that increased expression of *SLC6A20* in the gastrointestinal tract, lung or kidney might promote viral uptake, thus leading to increased risk of severe disease due to pathology in these tissues. Other candidate genes in the region include *LZTFL1*, which

366 encodes a cytoplasmic ciliary transport protein with expression in the lung and implicated in
367 recessive ciliopathies with renal dysfunction as one feature, *CXCR6* and *CCR9*, chemokine
368 receptors which mediate trafficking of T lymphocytes to the lung and GI tract, respectively, and
369 *XCR1* on plasmacytoid dendritic cells, which mediates antigen cross presentation, potentially
370 implicating dysregulation of immune cell trafficking and function in severe COVID-19, but further
371 work is required to attribute the purported biological mechanisms of these genes with SARS-CoV-
372 2 infection and disease progression of COVID-19.

373 Ellinghaus et al. [20] first reported an association between common variants in the *ABO*
374 locus and risk of SARS-CoV-2 infection. Furthermore, ABO blood groups have been associated
375 with severe COVID-19 [42, 43], with blood group A being associated with increased disease risk.
376 These observations raise the possibility that genes in the *ABO* locus play a role in COVID-19
377 susceptibility. However, genetic associations at the *ABO* locus can be confounded by population
378 stratification [44, 45]. Furthermore, the analysis reported by Ellinghaus et al [20] used blood
379 donors (which skew toward type O) as controls, which might have biased the association results
380 at the *ABO* locus. As such, it is important to determine if the association with the *ABO* locus is
381 reproducible in independent studies. First, we found no difference in representation of blood types
382 among COVID-19 cases and controls (not shown). Second, although we did observe a directionally
383 consistent and nominally significant association between risk of infection and the published lead
384 variant, when we combined results from the UK Biobank with those from the discovery cohort
385 [20], the association with this variant did not reach genome-wide significance (not shown). Third,
386 we found no evidence for an association between this locus and disease severity. Therefore, it
387 remains unclear whether variants in the *ABO* locus represent bona fide risk factors for COVID-19.

In our GWAS of imputed variants, we identified a genome-wide significant association between risk of SARS-CoV-2 infection and a variant that tags the ε4 haplotype in *APOE*. Common variants in *APOE* have been previously associated with SARS-CoV-2 infection, independent of CAD, dementia and other comorbidities [46]. However, in contrast to these findings, we found that the association with *APOE* was significantly attenuated after adjusting for AD and CAD. Similar results were obtained after conditioning on AD alone (not shown). This suggests that the observed association between risk of SARS-CoV-2 infection and *APOE* in our analysis of the UK Biobank was, at least partly, confounded with AD status.

We also identified a putative new association between common variants on chromosome 19p13.11 and risk of SARS-CoV-2 infection. However, this locus was not associated with increased risks of hospitalization or severe disease amongst COVID-19 positive individuals. Replication in independent studies is required to validate the association between 19p13.11 and risk of SARS-CoV-2 infection.

Lastly, we analyzed exome sequence data for a subset of 424,183 individuals in the UK Biobank to test the association between COVID-19 phenotypes and rare variants not captured by array genotyping or imputation. We found no associations at a $P<5x10^{-8}$ with pLoF variants, missense variants or in gene-burden analyses. We then concentrated on 81 genes of interest, including 14 genes related to interferon signaling [14, 23], 36 genes in two GWAS loci [20] and 31 additional genes of immunologic relevance and/or therapeutic potential. After correcting for the number of tests performed, there were no significant associations between the COVID-19 hospitalization phenotype and a burden of rare deleterious variants in any of these genes. We are expanding our analysis of exome sequence data to include additional studies and will update results accordingly.

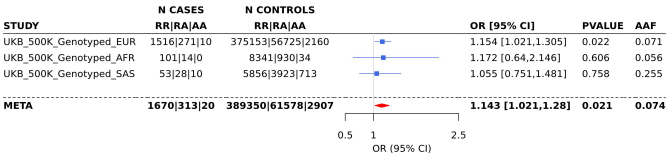
411

412 At the outset of the pandemic, testing for SARS-CoV-2 was restricted to symptomatic individuals
413 and often performed exclusively at inpatient/outpatient care sites. Thus, this current analysis is
414 likely weighted toward cases with demonstrable COVID-19 symptoms or clinical presentation.
415 Broader analysis of seropositive individuals who were asymptomatic or had infections mild
416 enough to resolve at home will be critical to identify genetic factors that might protect from severe
417 disease, particularly among high-risk groups with comorbidities. Regardless, further genetic
418 studies across ancestry groups will shed more light on human genetic risk factors associated with
419 susceptibility to SARS-CoV-2 and may point to pathways and approaches for the treatment of
420 COVID-19.

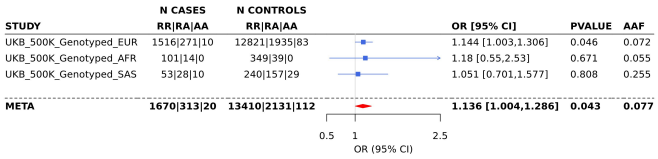
FIGURES

A. Locus 3p21.31 (rs11385942:GA, near the *LZTFL1* gene)

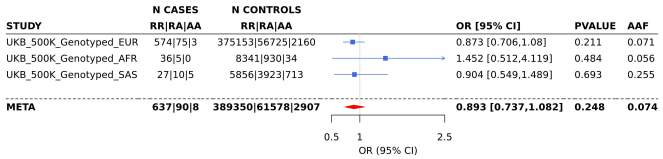
Covid-19 positive
vs.
Covid-19 negative or unknown



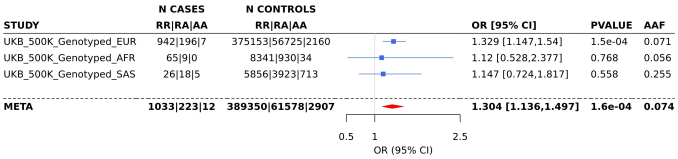
Covid-19 positive
vs.
Covid-19 negative



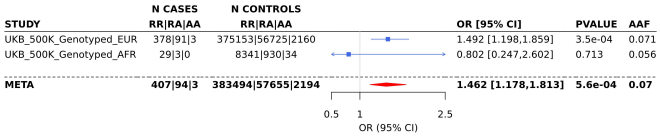
Covid-19 positive and not hospitalized
vs.
Covid-19 negative or unknown



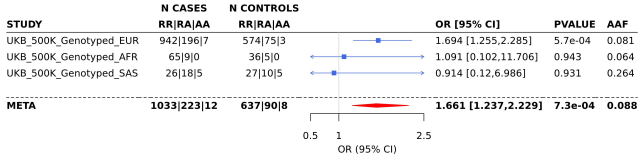
Covid-19 positive and hospitalized
vs.
Covid-19 negative or unknown



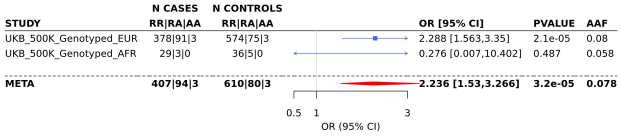
Covid-19 positive and severe
vs.
Covid-19 negative or unknown



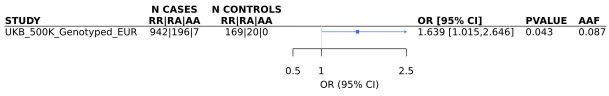
Covid-19 positive and hospitalized
vs.
Covid-19 positive and not hospitalized



Covid-19 positive and severe
vs.
Covid-19 positive and not hospitalized



Covid-19 positive and hospitalized
vs.
Covid-19 positive, not hospitalized, comorbidities and age>60



B. Locus 9q34.2 (rs8176719:TC, in the *ABO* gene)

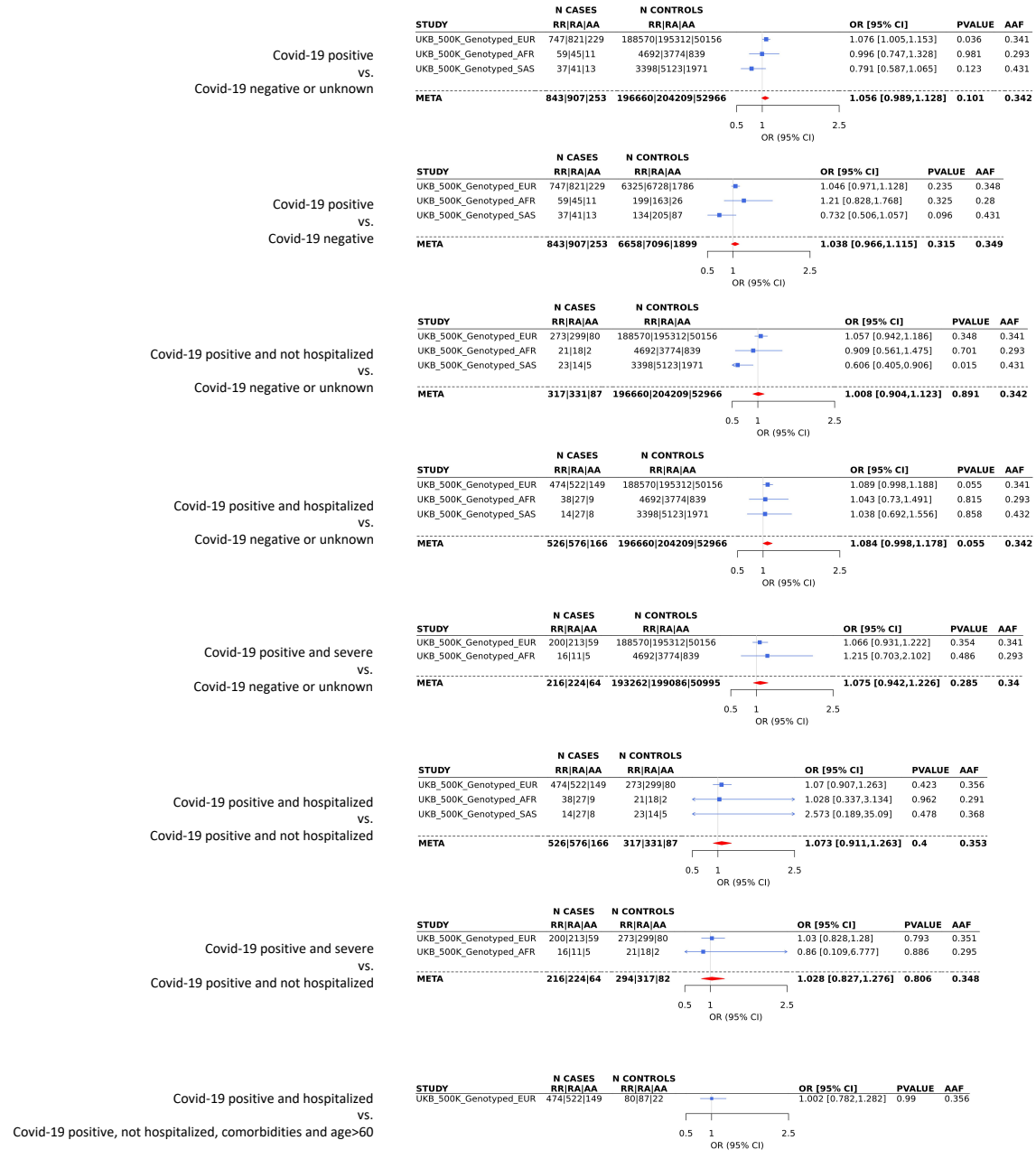
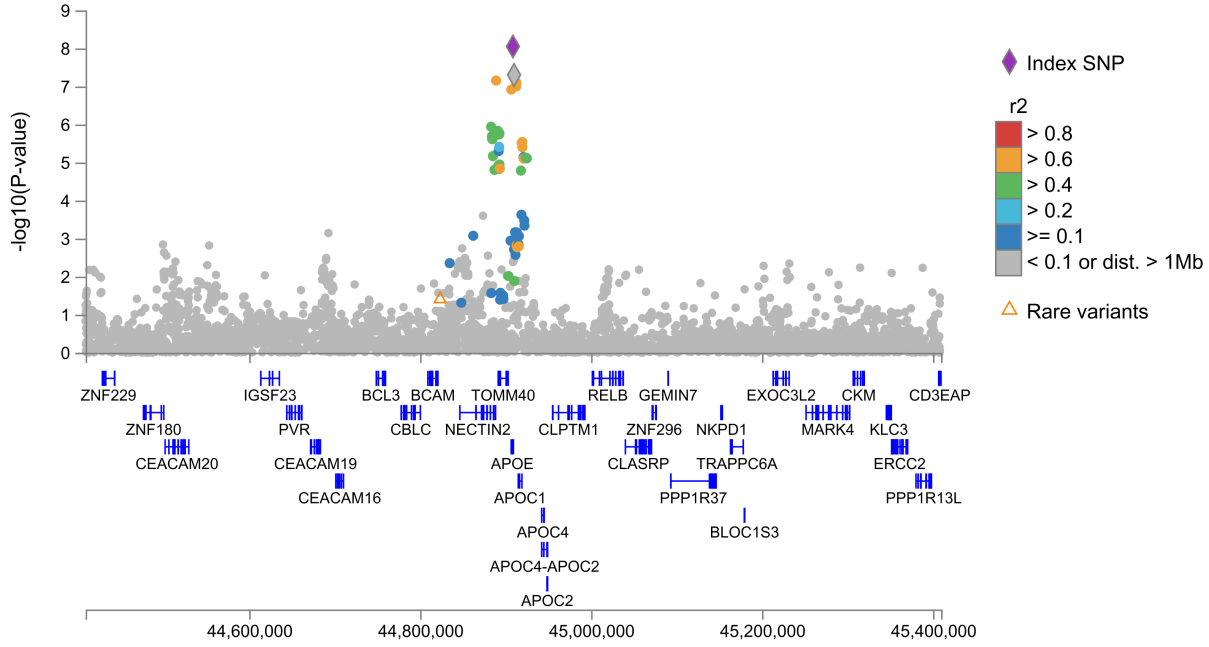


Figure 1. Results in the UKB for variants in two loci reported recently by Ellinghaus et al. [20] to associate with risk of hospitalization with severe COVID-19. For the chromosome 9 locus, we used rs8176719 as a proxy (r^2=0.94) for the lead variant reported by Ellinghaus et al. (rs657152).

A. Locus 19q13.32 (rs429358 in *APOE*)



B. Locus 19p13.11 (rs117336466 in *TMEM161A*)

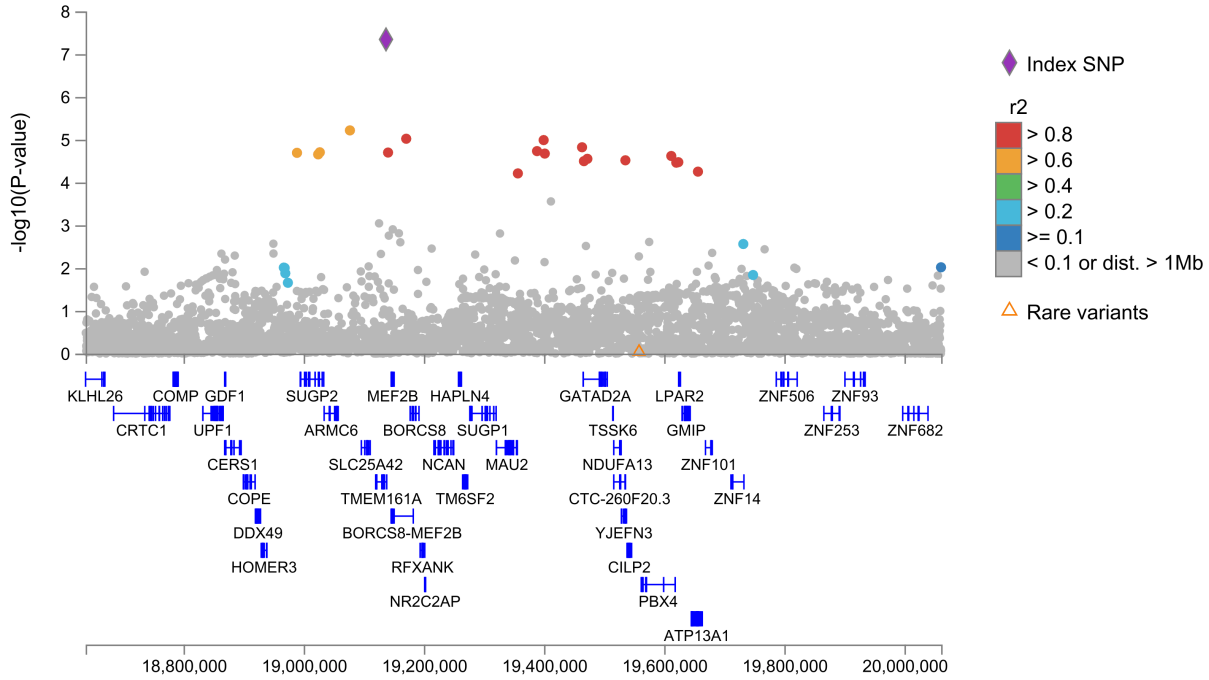


Figure 2. Regional association results for the three loci with common variants associated with COVID-19 phenotypes at $P<5x10^{-8}$. (A) *APOE* locus (lead variant rs429358), associated with COVID-19 positive vs. COVID-19 negative or unknown. (B) *TMEM161A* locus (lead variant rs117336466), associated with COVID-19 positive vs. COVID-19 negative or unknown. The lead variant in each locus is shown by the purple diamond. Linkage disequilibrium (LD) in these figures was estimated using genetic data from European individuals of the HapMap3 project.

TABLES

Table 1. Breakdown of COVID-19 status in participants of the UK Biobank study as of September 12, 2020.

COVID-19 status	Positive PCR for SARS-CoV-2	ICD10 U07 diagnosis	COVID-19-related death	Negative PCR test for SARS-CoV-2	N
Positive	Yes	Yes	Yes	-	251
	Yes	Yes	-	-	642
	Yes	-	Yes	-	42
	Yes	-	-	-	777
	-	Yes	Yes	-	16
	-	Yes	-	-	92
	-	-	Yes	-	122
	-	Yes	Yes	Yes	15
	-	Yes	-	Yes	150
	-	-	Yes	Yes	11
					Total = 2118
Negative	-	-	-	Yes	16331
Unknown	-	-	-	-	455528

Table 2. Criteria used to define COVID-19 phenotypes for genetic association analysis.

Phenotype	Case/ control group	COVID-19 status	Hospitalized	Severe disease*
COVID-19 positive vs. COVID-19 negative or unknown	Cases	Positive	-	-
	Controls	Negative or unknown	No or NA	No or NA
COVID-19 positive vs. COVID-19 negative	Cases	Positive	-	-
	Controls	Negative	No or NA	No or NA
COVID-19 positive and not hospitalized vs. COVID-19 negative or unknown	Cases	Positive	No	No
	Controls	Negative or unknown	No or NA	No or NA
COVID-19 positive and hospitalized vs. COVID-19 negative or unknown	Cases	Positive	Yes (or death**)	-
	Controls	Negative or unknown	No or NA	No or NA
COVID-19 positive and severe vs. COVID-19 negative or unknown	Cases	Positive	-	Yes
	Controls	Negative or unknown	No or NA	No or NA
COVID-19 positive and hospitalized vs. COVID-19 positive and not hospitalized	Cases	Positive	Yes (or death**)	-
	Controls	Positive	No	No
COVID-19 positive and severe vs. COVID-19 positive and not hospitalized	Cases	Positive	-	Yes
	Controls	Positive	No	No
COVID-19 positive and hospitalized vs. COVID-19 positive, not hospitalized, comorbidities and age>60	Cases	Positive	Yes (or death**)	-
	Controls	Positive with co-morbidities and age>60	No	No

* Severe disease: respiratory support (oxygen, ventilation) or death. ** A total of 175 individuals had a record of death due to COVID-19 but had no record of hospitalization. These individuals were included as cases. A hyphen ("-") indicates that the variable (*i.e.* Hospitalized and Severe Disease) was not considered as inclusion criteria.

453 **Table 3.** Demographics for participants of the UK Biobank study included in the analysis.

Demographic and clinical characteristics	**COVID-19 positive**	**COVID-19 negative**	**COVID-19 unknown**
N	2118	16331	455528
Female, n (%)	995 (46.9)	8547 (52.3)	252361 (55.4)
Median age at assessment, years (95% CI)	59 (51,67)	60 (53-66)	57 (50, 63)
Median body mass index, kg/m^2 (95% CI)	28 (24, 31)	27 (24, 30)	26 (23, 29)
Median C-reactive protein levels (95% CI)	1.6 (0.35, 2.9)	1.5 (0.3, 2.7)	1.3 (0.3, 0.3)
Number of current/past smokers, n (%)	1098 (51.8)	8228 (50.3)	199923 (43.9)
Median number of inpatient ICD10 3D codes (95% CI)	12 (3, 21)	12 (3, 20)	8 (2, 14)
Median Townsend deprivation index (95% CI)	-1.14 (-3.7, 1.46)	-1.9 (-4.2, 0.4)	-2.17 (-4.2, -0.12)
Ancestry			
African, n (%)	115 (5.4)	388 (2.4)	8921 (1.9)
East Asian, n (%)	17 (0.8)	65 (0.4)	2213 (0.4)
South Asian, n (%)	92 (4.3)	428 (2.6)	10125 (2.2)
European, n (%)	1798 (84.9)	14864 (91.0)	420007 (92.2)
Co-morbidities			
Hypertension, n (%)	1169 (55.2)	8917 (54.6)	200277 (43.9)
Coronary Disease, n (%)	229 (10.8)	1743 (10.6)	26015 (5.7)
Heart Failure, n (%)	100 (4.7)	563 (3.4)	5317 (1.1)
Type 2 Diabetes, n (%)	320 (15.1)	2013 (12.3)	30581 (6.7)
Chronic kidney disease, n (%)	92 (4.3)	573 (3.5)	6615 (1.4)
Asthma, n (%)	340 (16.0)	2895 (17.7)	64315 (14.1)
COPD, n (%)	159 (7.5)	1042 (6.4)	10661 (2.3)
Alzheimer's disease, n (%)	42 (1.9)	69 (0.42)	359 (0.07)

454

455 **Table 4.** Prevalence of co-morbidities, stratified by ancestry.

Disease	COVID-19 positive			Covid-19 negative or unknown
	All	Hospitalized*	Not hospitalized	
African ancestry				
Total N	115	74	41	9309
Hypertension, n (%)	76 (66.1)	51 (68.9)	25 (60.9)	4561 (48.9)
Coronary Disease, n (%)	5 (4.4)	4 (5.4)	1 (2.4)	329 (3.5)
Heart Failure, n (%)	6 (5.2)	6 (8.1)	0	98 (1.1)
Type 2 Diabetes, n (%)	31 (26.9)	26 (35.1)	5 (12.2)	1325 (14.2)
Chronic kidney disease, n (%)	4 (3.4)	4 (5.4)	0	179 (1.9)
Asthma, n (%)	16 (13.9)	10 (13.5)	6 (14.6)	1332 (14.3)
COPD, n (%)	3 (2.6)	3 (4.1)	0	98 (1.1)
Alzheimer's disease, n (%)	0	0	0	7 (0.07)
European ancestry				
Total N	1798	1145	653	434871
Hypertension, n (%)	993 (55.2)	704 (61.4)	289 (44.2)	191906 (44.1)
Coronary Disease, n (%)	205 (11.4)	166 (14.5)	39 (5.9)	25512 (5.8)
Heart Failure, n (%)	85 (4.7)	75 (6.5)	10 (1.5)	5396 (1.2)
Type 2 Diabetes, n (%)	267 (14.8)	211 (18.4)	56 (8.5)	27611 (6.3)
Chronic kidney disease, n (%)	78 (4.3)	64 (5.6)	14 (2.1)	6563 (1.5)
Asthma, n (%)	295 (16.4)	189 (16.5)	106 (16.2)	61755 (14.2)
COPD, n (%)	151 (8.4)	131 (11.4)	20 (3.1)	10949 (2.5)
Alzheimer's disease, n (%)	41 (2.3)	26 (2.7)	15 (2.3)	385 (0.08)
South Asian ancestry				
Total N	92	50	42	10553
Hypertension, n (%)	47 (51.1)	26 (52)	21 (50)	5149 (48.7)
Coronary Disease, n (%)	10 (10.8)	6 (12)	4 (9.5)	994 (9.4)
Heart Failure, n (%)	5 (5.4)	3 (6)	2 (4.7)	167 (1.6)
Type 2 Diabetes, n (%)	25 (27.1)	16 (32)	9 (21.4)	2308 (21.9)
Chronic kidney disease, n (%)	6 (6.5)	6 (12)	0	202 (1.9)
Asthma, n (%)	17 (18.4)	10 (20)	7 (16.6)	1691 (16.0)
COPD, n (%)	3 (3.2)	2 (4)	1 (2.3)	185 (1.7)
Alzheimer's disease, n (%)	0	0	0	9 (0.08)

456 *A total of 175 individuals had a record of death due to COVID-19 but had no record of hospitalization. These individuals were

457 included in the "Hospitalized" group in this analysis.

Table 5. Case-control sample size for eight COVID-19-related phenotypes tested in genetic association analyses in the UK Biobank study.

Phenotype	Ancestry	N cases		N controls	
		Imputed	Exome	Imputed	Exome
COVID-19 positive vs. COVID-19 negative or unknown	Combined	2003	1865	453,835	422,318
	AFR	115	110	9305	8599
	EUR	1797	1673	434,038	404,300
	SAS	91	82	10,492	9419
COVID-19 positive vs. COVID-19 negative	Combined	2003	1865	15,653	14,519
	AFR	115	110	388	361
	EUR	1797	1673	14,839	13,765
	SAS	91	82	426	393
COVID-19 positive and not hospitalized vs. COVID-19 negative or unknown	Combined	734	681	453,835	422,318
	AFR	41	39	9305	8599
	EUR	652	605	434,038	404,300
	SAS	42	37	10,492	9419
COVID-19 positive and hospitalized vs. COVID-19 negative or unknown	Combined	1268	1184	453,835	422,318
	AFR	74	71	9305	8599
	EUR	1145	1068	434,038	404,300
	SAS	49	45	10,492	9419
COVID-19 positive and severe vs. COVID-19 negative or unknown	Combined	-	471	443,343	412,899
	AFR	32	32	9305	8599
	EUR	-	439	434,038	404,300
COVID-19 positive and hospitalized vs. COVID-19 positive and not hospitalized	Combined	1268	1068	735	605
	AFR	74	-	41	-
	EUR	1145	1068	652	605
	SAS	49	-	42	-
COVID-19 positive and severe vs. COVID-19 positive and not hospitalized	Combined	504	439	693	605
	AFR	32	-	41	-
	EUR	472	439	652	605
COVID-19 positive and hospitalized vs. COVID-19 positive, not hospitalized, comorbidities and age>60	EUR	1145	1068	189	174

SAS case and control sample sizes for both severe COVID-19 sample sizes fell below the minimum case threshold to properly analyze. Dashes (-) in cells indicate the sample sizes were also too small for analysis.

Table 6. Association between the phenotype COVID-19 positive and hospitalized (N=1,184) vs COVID-19 negative or unknown (N=422,318) and 14 genes related to interferon signaling that were recently reported to contain rare (MAF<0.1%), deleterious variants in patients with severe COVID-19 [14, 23].

Gene	Burden test	Odds Ratio [95% CI]	P-value	Cases RR|RA|AA	Controls RR|RA|AA	AAF
STAT2	M3	2.34 (1.0, 5.5)	0.050	1176|8|0	421086|1231|1	1.47E-03
UNC93B1	M3	2.07 (0.93, 4.58)	0.073	1177|7|0	420917|1401|0	1.66E-03
IRF7	M3	2.15 (0.8, 5.74)	0.129	1179|5|0	421275|1043|0	1.24E-03
IFNAR1	M3	0.37 (0.08, 1.68)	0.195	1184|0|0	421811|507|0	5.99E-04
UNC93B1	M1	3.4 (0.43, 26.93)	0.247	1066|2|0	403926|374|0	4.64E-04
IRF7	M1	2.07 (0.6, 7.12)	0.247	1181|3|0	421674|644|0	7.64E-04
TLR7	M3	0.52 (0.15, 1.77)	0.297	1184|0|0	421856|334|128	6.97E-04
IFNAR1	M1	0.37 (0.04, 3.77)	0.404	1139|0|0	412664|235|0	2.84E-04
TLR3	M1	0.37 (0.02, 6.06)	0.488	1184|0|0	422141|177|0	2.09E-04
STAT1	M3	0.37 (0.02, 7.77)	0.520	1184|0|0	422137|181|0	2.14E-04
STAT2	M1	0.36 (0.01, 8.76)	0.529	1068|0|0	404195|105|0	1.30E-04
TRAF3	M3	0.37 (0.01, 10.13)	0.553	1139|0|0	412750|149|0	1.80E-04
IRF3	M1	1.5 (0.29, 7.66)	0.625	1182|2|0	422001|317|0	3.77E-04
TICAM1	M1	0.37 (0.0, 28.86)	0.652	1068|0|0	404205|95|0	1.17E-04
TICAM1	M3	0.37 (0.0, 28.86)	0.652	1068|0|0	404205|95|0	1.17E-04
TBK1	M1	0.36 (0.0, 31.85)	0.658	1068|0|0	404231|69|0	8.51E-05
IKBKG	M3	0.43 (0.0, 64.35)	0.744	1113|0|0	413640|70|9	1.06E-04
STAT1	M1	0.37 (0.0, 375.39)	0.776	1068|0|0	404268|32|0	3.95E-05
TBK1	M3	0.84 (0.24, 2.97)	0.787	1182|2|0	421450|867|1	1.03E-03
TLR3	M3	0.9 (0.39, 2.06)	0.803	1179|5|0	420322|1995|1	2.36E-03
IRF9	M1	0.37 (0.0, 1526.67)	0.813	1068|0|0	404275|25|0	3.08E-05
IRF9	M3	0.37 (0.0, 1526.67)	0.813	1068|0|0	404275|25|0	3.08E-05
IKBKG	M1	0.49 (0.0, 369.27)	0.834	1113|0|0	413679|31|9	5.91E-05
TRAF3	M1	0.37 (0.0, 10210.6)	0.847	1068|0|0	404284|16|0	1.97E-05
TLR7	M1	0.51 (0.0, 617.09)	0.851	1068|0|0	404282|12|6	2.96E-05
IRF3	M3	1.12 (0.26, 4.83)	0.874	1182|2|0	421885|433|0	5.14E-04
IFNAR2	M1	1.04 (0.14, 7.7)	0.968	1183|1|0	421965|353|0	4.18E-04
IFNAR2	M3	1.01 (0.14, 7.18)	0.996	1183|1|0	421949|369|0	4.37E-04

RR: individuals who were homozygote for the reference allele for all variants included in the burden test. RA: individuals who were heterozygote for at least one variant included in the burden test. AA: individuals who were homozygote for the alternative allele for at least one variant included in the burden test. The genes *TLR7* and *IKBKG* are located on the X chromosome; individuals counted as homozygote for the alternative allele include hemizygous males.

* M1: burden of rare (MAF<0.1%) pLoF variants. M3: burden of rare (MAF<0.1%) pLoF or missense variants that are predicted to be deleterious by 5 out of 5 algorithms.

SUPPLEMENTARY TABLES

Supplementary Tables 1 to 6 are provided in a separate document.

Supplementary Table 1. Genomic inflation factor (λ_{GC}) observed in the analysis of imputed variants for each of the eight phenotypes tested.

Supplementary Table 2. Association between COVID-19 phenotypes and both cardiovascular disease and Alzheimer's disease.

Supplementary Table 3. Genomic inflation factor (λ_{GC}) observed in the analysis of exome sequence variants for each of the eight phenotypes tested.

Supplementary Table 4. Results from burden association tests for 14 genes related to interferon signaling and recently reported to contain rare (MAF<0.1%), deleterious variants in patients with severe COVID-19 [14, 23].

Supplementary Table 5. Association between the phenotype COVID-19 positive and hospitalized (N=1,184) vs COVID-19 negative or unknown (N=422,318) and 36 genes located in two loci identified in a previous GWAS of severe COVID-19 [20].

Supplementary Table 6. Association between the phenotype COVID-19 positive and hospitalized (N=1,184) vs COVID-19 negative or unknown (N=422,318) and 31 genes that are

501 involved in the etiology of SARS-CoV-2, encode therapeutic targets or have been implicated in
502 other immune or infectious diseases through GWAS.

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Supplementary Table 1

Phenotype	Ancestry	N cases	N controls	Imputed variants with MAF>0.5%	
				N variants	Lambda GC
COVID19 positive hospitalized vs COVID19 negative or unknown	SAS	49	10492	12205268	1.049
COVID19 positive hospitalized vs COVID19 negative or unknown	AFR	74	9305	20334378	1.024
COVID19 positive hospitalized vs COVID19 negative or unknown	EUR	1145	434038	11528346	1.01
COVID19 positive hospitalized vs COVID19 negative or unknown	meta	1268	453835	23159148	1.032
COVID19 positive hospitalized vs COVID19 positive not hospitalized	SAS	49	42	8525763	0.243
COVID19 positive hospitalized vs COVID19 positive not hospitalized	AFR	74	41	13652965	0.389
COVID19 positive hospitalized vs COVID19 positive not hospitalized	EUR	1145	652	11342582	1.067
COVID19 positive hospitalized vs COVID19 positive not hospitalized	meta	1268	735	17154252	0.725
COVID19 positive hospitalized vs COVID19 positive not hospitalized comorbidites age60	EUR	1145	189	11308346	1.018
COVID19 positive not hospitalized vs COVID19 negative or unknown	AFR	41	9305	20332658	1.075
COVID19 positive not hospitalized vs COVID19 negative or unknown	SAS	42	10492	12205070	1.04
COVID19 positive not hospitalized vs COVID19 negative or unknown	EUR	652	434038	11528296	1.008
COVID19 positive not hospitalized vs COVID19 negative or unknown	meta	735	453835	23147019	1.078
COVID19 positive severe vs COVID19 negative or unknown	AFR	32	9305	20332141	1.039
COVID19 positive severe vs COVID19 negative or unknown	EUR	472	434038	11528272	1.014
COVID19 positive severe vs COVID19 negative or unknown	meta	504	443343	22036364	1.056
COVID19 positive severe vs COVID19 positive not hospitalized	AFR	32	41	11643990	0.491
COVID19 positive severe vs COVID19 positive not hospitalized	EUR	472	652	11285446	1.013
COVID19 positive severe vs COVID19 positive not hospitalized	meta	504	693	15273231	0.817
COVID19 positive vs COVID19 negative	SAS	91	426	11784544	0.865
COVID19 positive vs COVID19 negative	AFR	115	388	19599852	0.92
COVID19 positive vs COVID19 negative	EUR	1797	14839	11467751	1.038
COVID19 positive vs COVID19 negative	meta	2003	15653	22379507	0.979
COVID19 positive vs COVID19 negative or unknown	SAS	91	10492	12206295	1.001
COVID19 positive vs COVID19 negative or unknown	AFR	115	9305	20336000	1.011
COVID19 positive vs COVID19 negative or unknown	EUR	1797	434038	11528361	1.009
COVID19 positive vs COVID19 negative or unknown	meta	2003	453835	23145587	1.01

Supplementary Table 2

Phenotype	Association* with cardiovascular disease		Association with Alzheimer's disease	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
COVID19 positive vs COVID19 negative or unknown	1.58 (1.34, 1.84)	1.45e-8	1.83 (1.31, 2.51)	1.67E-68
COVID19 positive vs COVID19 negative	1.00 (0.85, 1.18)	1.00	5.91 (3.94, 8.78)	2.62E-18
COVID19 positive hospitalized vs COVID19 positive not hospitalized	1.37 (0.92, 2.07)	0.13	3.85 (1.98, 7.67)	0.005
COVID19 positive severe vs COVID19 positive not hospitalized	1.26 (0.79, 2.03)	0.23	0.55 (0.26, 1.18)	0.122

* Association tested in individuals of European ancestry, using logistic regression with age and sex included as covariates.

Supplementary Table 3

Phenotype	Ancestry	N cases	N controls	Exome-sequencing variants with MAF<0.5%			Exome-sequencing variants with MAF<0.5% & MAC>25			Exome-sequencing variants with MAF>0.5%		
				N variants	Proportion of variants with MAC=0 in cases	Lambda GC	N variants	Proportion of variants with MAC=0 in cases	Lambda GC	N variants	Proportion of variants with MAC=0 in cases	Lambda GC
COVID19 positive hospitalized vs COVID19 negative or unknown	SAS	45	9419	811706	0.910	0.131	226976	0.796	0.522	227627	0.281	1.186
COVID19 positive hospitalized vs COVID19 negative or unknown	AFR	71	8599	819509	0.847	0.246	251004	0.684	0.726	380172	0.140	0.968
COVID19 positive hospitalized vs COVID19 negative or unknown	EUR	1068	404300	6461813	0.886	0.078	2091112	0.705	0.367	166346	0.000	1.015
COVID19 positive hospitalized vs COVID19 negative or unknown	meta	1184	422318	7080202	0.861	0.087	2389804	0.650	0.416	202088	0.051	1.036
COVID19 positive hospitalized vs COVID19 positive not hospitalized	EUR	1068	605	154530	0.002	1.095	NA	NA	NA	169209	0.000	1.059
COVID19 positive hospitalized vs COVID19 positive not hospitalized comorbidites age60	EUR	1068	174	114895	0.000	1.149	NA	NA	NA	168029	0.000	0.985
COVID19 positive not hospitalized vs COVID19 negative or unknown	SAS	37	9419	811487	0.924	0.094	226975	0.827	0.385	227471	0.323	1.066
COVID19 positive not hospitalized vs COVID19 negative or unknown	AFR	39	8599	818751	0.906	0.121	250834	0.806	0.421	379594	0.262	0.999
COVID19 positive not hospitalized vs COVID19 negative or unknown	EUR	605	404300	6457502	0.920	0.043	2089442	0.785	0.216	166339	0.000	1.019
COVID19 positive not hospitalized vs COVID19 negative or unknown	meta	681	422318	7075150	0.897	0.049	2387898	0.733	0.258	201946	0.080	1.014
COVID19 positive severe vs COVID19 negative or unknown	AFR	32	8599	818418	0.922	0.091	250759	0.836	0.289	379404	0.309	0.801
COVID19 positive severe vs COVID19 negative or unknown	EUR	439	404300	6455980	0.936	0.029	2088734	0.825	0.151	166348	0.001	0.981
COVID19 positive severe vs COVID19 negative or unknown	meta	471	412899	6792129	0.916	0.033	2291013	0.778	0.175	196510	0.078	0.916
COVID19 positive severe vs COVID19 positive not hospitalized	EUR	439	605	93086	0.033	1.017	NA	NA	NA	167697	0.000	0.994
COVID19 positive vs COVID19 negative	SAS	82	393	NA	NA	NA	NA	NA	NA	239636	0.138	0.901
COVID19 positive vs COVID19 negative	AFR	110	361	NA	NA	NA	NA	NA	NA	392416	0.063	0.803
COVID19 positive vs COVID19 negative	EUR	1673	13765	733544	0.251	1.264	233347	0.012	1.06	166548	0.000	1.055
COVID19 positive vs COVID19 negative	meta	1865	14519	724098	0.234	1.232	259084	0.009	1.008	368390	0.051	0.923
COVID19 positive vs COVID19 negative or unknown	SAS	82	9419	814482	0.847	0.243	228572	0.664	0.892	226863	0.146	1.13
COVID19 positive vs COVID19 negative or unknown	AFR	110	8599	822896	0.778	0.384	253263	0.559	1.115	379071	0.072	1.016
COVID19 positive vs COVID19 negative or unknown	EUR	1673	404300	6467227	0.851	0.122	2093385	0.627	0.541	166343	0.000	1.014
COVID19 positive vs COVID19 negative or unknown	meta	1865	422318	7087889	0.822	0.138	2393361	0.569	0.612	201731	0.030	1.028

Supplementary Table 4

Trait	Gene	Burden test	MAF	Odds Ratio [95% CI]	P-value	Cases_RR|RA|AA	Controls_RR|RA|AA	AAF
COVID19 hospitalized vs COVID19 negative or unknown	*UNC93B1*	M1	<0.1%	3.4 (0.43, 26.93)	0.247	1066|2|0	403926|374|0	4.64E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IRF7*	M1	<0.1%	2.07 (0.6, 7.12)	0.247	1181|3|0	421674|644|0	7.64E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR1*	M1	<0.1%	0.37 (0.04, 3.77)	0.404	1139|0|0	412664|235|0	2.84E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TLR3*	M1	<0.1%	0.37 (0.02, 6.06)	0.488	1184|0|0	422141|177|0	2.09E-04
COVID19 hospitalized vs COVID19 negative or unknown	*STAT2*	M1	<0.1%	0.36 (0.01, 8.76)	0.529	1068|0|0	404195|105|0	1.30E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IRF3*	M1	<0.1%	1.5 (0.29, 7.66)	0.625	1182|2|0	422001|317|0	3.77E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TICAM1*	M1	<0.1%	0.37 (0.0, 28.86)	0.652	1068|0|0	404205|95|0	1.17E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TBK1*	M1	<0.1%	0.36 (0.0, 31.85)	0.658	1068|0|0	404231|69|0	8.51E-05
COVID19 hospitalized vs COVID19 negative or unknown	*STAT1*	M1	<0.1%	0.37 (0.0, 375.39)	0.776	1068|0|0	404268|32|0	3.95E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF9*	M1	<0.1%	0.37 (0.0, 1526.67)	0.813	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IKBKG*	M1	<0.1%	0.49 (0.0, 369.27)	0.834	1113|0|0	413679|31|9	5.91E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TRAF3*	M1	<0.1%	0.37 (0.0, 10210.6)	0.847	1068|0|0	404284|16|0	1.97E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TLR7*	M1	<0.1%	0.51 (0.0, 617.09)	0.851	1068|0|0	404282|12|6	2.96E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR2*	M1	<0.1%	1.04 (0.14, 7.7)	0.968	1183|1|0	421965|353|0	4.18E-04
COVID19 hospitalized vs COVID19 negative or unknown	*UNC93B1*	M1	<1%	3.4 (0.43, 26.93)	0.247	1066|2|0	403926|374|0	4.64E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IRF7*	M1	<1%	2.07 (0.6, 7.12)	0.247	1181|3|0	421674|644|0	7.64E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR1*	M1	<1%	0.37 (0.04, 3.77)	0.404	1139|0|0	412664|235|0	2.84E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TLR3*	M1	<1%	0.37 (0.02, 6.06)	0.488	1184|0|0	422141|177|0	2.09E-04
COVID19 hospitalized vs COVID19 negative or unknown	*STAT2*	M1	<1%	0.36 (0.01, 8.76)	0.529	1068|0|0	404195|105|0	1.30E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IRF3*	M1	<1%	1.5 (0.29, 7.66)	0.625	1182|2|0	422001|317|0	3.77E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TICAM1*	M1	<1%	0.37 (0.0, 28.86)	0.652	1068|0|0	404205|95|0	1.17E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TBK1*	M1	<1%	0.36 (0.0, 31.85)	0.658	1068|0|0	404231|69|0	8.51E-05
COVID19 hospitalized vs COVID19 negative or unknown	*STAT1*	M1	<1%	0.37 (0.0, 375.39)	0.776	1068|0|0	404268|32|0	3.95E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF9*	M1	<1%	0.37 (0.0, 1526.67)	0.813	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IKBKG*	M1	<1%	0.49 (0.0, 369.27)	0.834	1113|0|0	413679|31|9	5.91E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TRAF3*	M1	<1%	0.37 (0.0, 10210.6)	0.847	1068|0|0	404284|16|0	1.97E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TLR7*	M1	<1%	0.51 (0.0, 617.09)	0.851	1068|0|0	404282|12|6	2.96E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR2*	M1	<1%	1.04 (0.14, 7.7)	0.968	1183|1|0	421965|353|0	4.18E-04
COVID19 hospitalized vs COVID19 negative or unknown	*STAT2*	M1	singleton	0.35 (0.0, 41.68)	0.667	1068|0|0	404264|36|0	4.44E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR1*	M1	singleton	0.36 (0.0, 130.87)	0.737	1068|0|0	404263|37|0	4.56E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF3*	M1	singleton	0.36 (0.0, 906.29)	0.800	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*STAT1*	M1	singleton	0.37 (0.0, 1209.03)	0.808	1068|0|0	404278|22|0	2.71E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TBK1*	M1	singleton	0.37 (0.0, 1270.15)	0.809	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF7*	M1	singleton	0.37 (0.0, 1462.08)	0.812	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR2*	M1	singleton	0.37 (0.0, 2890.71)	0.826	1068|0|0	404282|18|0	2.22E-05
COVID19 hospitalized vs COVID19 negative or unknown	*UNC93B1*	M1	singleton	0.37 (0.0, 4121.4)	0.833	1068|0|0	404277|23|0	2.84E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TLR3*	M1	singleton	0.37 (0.0, 12612.3)	0.851	1068|0|0	404280|20|0	2.47E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TICAM1*	M1	singleton	0.37 (0.0, 15492.2)	0.853	1068|0|0	404281|19|0	2.34E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TLR7*	M1	singleton	0.46 (0.0, 10772.3)	0.881	1068|0|0	404287|9|4	2.10E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF9*	M1	singleton	0.37 (0.0, 259766.0)	0.884	1068|0|0	404289|11|0	1.36E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TRAF3*	M1	singleton	0.37 (0.0, 365138.0)	0.887	1068|0|0	404290|10|0	1.23E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IKBKG*	M1	singleton	0.47 (0.0, 3665200.0)	0.925	1068|0|0	404293|6|1	9.87E-06

COVID19 hospitalized vs COVID19 negative or unknown	*STAT2*	M3	<0.1%	2.34 (1.0, 5.5)	0.050	1176|8|0	421086|1231|1	1.47E-03
COVID19 hospitalized vs COVID19 negative or unknown	*UNC93B1*	M3	<0.1%	2.07 (0.93, 4.58)	0.073	1177|7|0	420917|1401|0	1.66E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IRF7*	M3	<0.1%	2.15 (0.8, 5.74)	0.129	1179|5|0	421275|1043|0	1.24E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR1*	M3	<0.1%	0.37 (0.08, 1.68)	0.195	1184|0|0	421811|507|0	5.99E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TLR7*	M3	<0.1%	0.52 (0.15, 1.77)	0.297	1184|0|0	421856|334|128	6.97E-04
COVID19 hospitalized vs COVID19 negative or unknown	*STAT1*	M3	<0.1%	0.37 (0.02, 7.77)	0.520	1184|0|0	422137|181|0	2.14E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TRAF3*	M3	<0.1%	0.37 (0.01, 10.13)	0.553	1139|0|0	412750|149|0	1.80E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TICAM1*	M3	<0.1%	0.37 (0.0, 28.86)	0.652	1068|0|0	404205|95|0	1.17E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IKBKG*	M3	<0.1%	0.43 (0.0, 64.35)	0.744	1113|0|0	413640|70|9	1.06E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TBK1*	M3	<0.1%	0.84 (0.24, 2.97)	0.787	1182|2|0	421450|867|1	1.03E-03
COVID19 hospitalized vs COVID19 negative or unknown	*TLR3*	M3	<0.1%	0.9 (0.39, 2.06)	0.803	1179|5|0	420322|1995|1	2.36E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IRF9*	M3	<0.1%	0.37 (0.0, 1526.67)	0.813	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF3*	M3	<0.1%	1.12 (0.26, 4.83)	0.874	1182|2|0	421885|433|0	5.14E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR2*	M3	<0.1%	1.01 (0.14, 7.18)	0.996	1183|1|0	421949|369|0	4.37E-04
COVID19 hospitalized vs COVID19 negative or unknown	*STAT2*	M3	<1%	2.34 (1.0, 5.5)	0.050	1176|8|0	421086|1231|1	1.47E-03
COVID19 hospitalized vs COVID19 negative or unknown	*UNC93B1*	M3	<1%	2.07 (0.93, 4.58)	0.073	1177|7|0	420917|1401|0	1.66E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IRF7*	M3	<1%	2.15 (0.8, 5.74)	0.129	1179|5|0	421275|1043|0	1.24E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR1*	M3	<1%	0.37 (0.08, 1.68)	0.195	1184|0|0	421811|507|0	5.99E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TLR7*	M3	<1%	0.52 (0.15, 1.77)	0.297	1184|0|0	421856|334|128	6.97E-04
COVID19 hospitalized vs COVID19 negative or unknown	*STAT1*	M3	<1%	0.37 (0.02, 7.77)	0.520	1184|0|0	422137|181|0	2.14E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TRAF3*	M3	<1%	0.83 (0.37, 1.83)	0.641	1179|5|0	420135|2180|3	2.59E-03
COVID19 hospitalized vs COVID19 negative or unknown	*TICAM1*	M3	<1%	0.37 (0.0, 28.86)	0.652	1068|0|0	404205|95|0	1.17E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IKBKG*	M3	<1%	1.19 (0.49, 2.86)	0.701	1111|0|2	412710|725|284	1.56E-03
COVID19 hospitalized vs COVID19 negative or unknown	*TBK1*	M3	<1%	0.84 (0.24, 2.97)	0.787	1182|2|0	421450|867|1	1.03E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IRF9*	M3	<1%	0.37 (0.0, 1526.67)	0.813	1068|0|0	404275|25|0	3.08E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TLR3*	M3	<1%	1.06 (0.58, 1.95)	0.852	1173|11|0	418393|3923|2	4.65E-03
COVID19 hospitalized vs COVID19 negative or unknown	*IRF3*	M3	<1%	1.12 (0.26, 4.83)	0.874	1182|2|0	421885|433|0	5.14E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR2*	M3	<1%	1.01 (0.14, 7.18)	0.996	1183|1|0	421949|369|0	4.37E-04
COVID19 hospitalized vs COVID19 negative or unknown	*IRF7*	M3	singleton	10.73 (1.17, 98.56)	0.036	1112|1|0	413669|50|0	6.15E-05
COVID19 hospitalized vs COVID19 negative or unknown	*STAT2*	M3	singleton	13.21 (0.32, 540.76)	0.173	1138|1|0	412815|84|0	1.03E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TLR3*	M3	singleton	0.39 (0.02, 7.54)	0.534	1184|0|0	422191|126|1	1.51E-04
COVID19 hospitalized vs COVID19 negative or unknown	*TBK1*	M3	singleton	0.37 (0.0, 33.05)	0.661	1113|0|0	413641|78|0	9.40E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR1*	M3	singleton	0.36 (0.0, 44.54)	0.680	1068|0|0	404251|49|0	6.04E-05
COVID19 hospitalized vs COVID19 negative or unknown	*UNC93B1*	M3	singleton	0.38 (0.0, 54.31)	0.701	1139|0|0	412846|53|0	6.40E-05
COVID19 hospitalized vs COVID19 negative or unknown	*STAT1*	M3	singleton	0.37 (0.0, 79.88)	0.715	1068|0|0	404241|59|0	7.28E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TRAF3*	M3	singleton	0.37 (0.0, 102.87)	0.726	1068|0|0	404251|49|0	6.04E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TLR7*	M3	singleton	0.48 (0.01, 32.54)	0.732	1113|0|0	413659|44|16	9.16E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF3*	M3	singleton	0.36 (0.0, 283.42)	0.766	1068|0|0	404264|36|0	4.44E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IFNAR2*	M3	singleton	0.37 (0.0, 2142.19)	0.820	1068|0|0	404281|19|0	2.34E-05
COVID19 hospitalized vs COVID19 negative or unknown	*TICAM1*	M3	singleton	0.37 (0.0, 15492.2)	0.853	1068|0|0	404281|19|0	2.34E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IRF9*	M3	singleton	0.37 (0.0, 259766.0)	0.884	1068|0|0	404289|11|0	1.36E-05
COVID19 hospitalized vs COVID19 negative or unknown	*IKBKG*	M3	singleton	0.46 (0.0, 1739110.0)	0.919	1068|0|0	404292|7|1	1.11E-05
COVID19 severe vs COVID19 negative or unknown	*IRF7*	M1	<0.1%	5.86 (0.59, 58.04)	0.131	469|2|0	412274|625|0	7.58E-04
COVID19 severe vs COVID19 negative or unknown	*UNC93B1*	M1	<0.1%	5.62 (0.22, 140.44)	0.293	438|1|0	403926|374|0	4.63E-04

COVID19 severe vs COVID19 negative or unknown	*IRF3*	M1	<0.1%	2.54 (0.18, 36.42)	0.493	470|1|0	412595|304|0	3.69E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR1*	M1	<0.1%	0.38 (0.02, 6.61)	0.507	471|0|0	412664|235|0	2.84E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR2*	M1	<0.1%	0.39 (0.02, 9.81)	0.567	471|0|0	412567|332|0	4.02E-04
COVID19 severe vs COVID19 negative or unknown	*TLR3*	M1	<0.1%	0.39 (0.0, 38.11)	0.685	471|0|0	412730|169|0	2.04E-04
COVID19 severe vs COVID19 negative or unknown	*TICAM1*	M1	<0.1%	0.37 (0.0, 87.63)	0.719	439|0|0	404205|95|0	1.17E-04
COVID19 severe vs COVID19 negative or unknown	*STAT2*	M1	<0.1%	0.38 (0.0, 119.7)	0.741	439|0|0	404195|105|0	1.30E-04
COVID19 severe vs COVID19 negative or unknown	*TBK1*	M1	<0.1%	0.37 (0.0, 467.39)	0.787	439|0|0	404231|69|0	8.52E-05
COVID19 severe vs COVID19 negative or unknown	*IRF9*	M1	<0.1%	0.37 (0.0, 12583.2)	0.850	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*STAT1*	M1	<0.1%	0.38 (0.0, 76425.5)	0.877	439|0|0	404268|32|0	3.95E-05
COVID19 severe vs COVID19 negative or unknown	*IKBKG*	M1	<0.1%	0.53 (0.0, 10828.2)	0.901	439|0|0	404264|28|8	5.44E-05
COVID19 severe vs COVID19 negative or unknown	*TRAF3*	M1	<0.1%	0.39 (0.0, 17442200.0)	0.916	439|0|0	404284|16|0	1.98E-05
COVID19 severe vs COVID19 negative or unknown	*TLR7*	M1	<0.1%	0.48 (0.0, 4388880.0)	0.928	439|0|0	404282|12|6	2.96E-05
COVID19 severe vs COVID19 negative or unknown	*IRF7*	M1	<1%	5.86 (0.59, 58.04)	0.131	469|2|0	412274|625|0	7.58E-04
COVID19 severe vs COVID19 negative or unknown	*UNC93B1*	M1	<1%	5.62 (0.22, 140.44)	0.293	438|1|0	403926|374|0	4.63E-04
COVID19 severe vs COVID19 negative or unknown	*IRF3*	M1	<1%	2.54 (0.18, 36.42)	0.493	470|1|0	412595|304|0	3.69E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR1*	M1	<1%	0.38 (0.02, 6.61)	0.507	471|0|0	412664|235|0	2.84E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR2*	M1	<1%	0.39 (0.02, 9.81)	0.567	471|0|0	412567|332|0	4.02E-04
COVID19 severe vs COVID19 negative or unknown	*TLR3*	M1	<1%	0.39 (0.0, 38.11)	0.685	471|0|0	412730|169|0	2.04E-04
COVID19 severe vs COVID19 negative or unknown	*TICAM1*	M1	<1%	0.37 (0.0, 87.63)	0.719	439|0|0	404205|95|0	1.17E-04
COVID19 severe vs COVID19 negative or unknown	*STAT2*	M1	<1%	0.38 (0.0, 119.7)	0.741	439|0|0	404195|105|0	1.30E-04
COVID19 severe vs COVID19 negative or unknown	*TBK1*	M1	<1%	0.37 (0.0, 467.39)	0.787	439|0|0	404231|69|0	8.52E-05
COVID19 severe vs COVID19 negative or unknown	*IRF9*	M1	<1%	0.37 (0.0, 12583.2)	0.850	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*STAT1*	M1	<1%	0.38 (0.0, 76425.5)	0.877	439|0|0	404268|32|0	3.95E-05
COVID19 severe vs COVID19 negative or unknown	*IKBKG*	M1	<1%	0.53 (0.0, 10828.2)	0.901	439|0|0	404264|28|8	5.44E-05
COVID19 severe vs COVID19 negative or unknown	*TRAF3*	M1	<1%	0.39 (0.0, 17442200.0)	0.916	439|0|0	404284|16|0	1.98E-05
COVID19 severe vs COVID19 negative or unknown	*TLR7*	M1	<1%	0.48 (0.0, 4388880.0)	0.928	439|0|0	404282|12|6	2.96E-05
COVID19 severe vs COVID19 negative or unknown	*IFNAR1*	M1	singleton	0.35 (0.0, 107.82)	0.721	439|0|0	404263|37|0	4.57E-05
COVID19 severe vs COVID19 negative or unknown	*STAT2*	M1	singleton	0.39 (0.0, 8163.05)	0.852	439|0|0	404264|36|0	4.45E-05
COVID19 severe vs COVID19 negative or unknown	*IRF3*	M1	singleton	0.38 (0.0, 32058.1)	0.869	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*TBK1*	M1	singleton	0.37 (0.0, 113347.0)	0.879	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*TLR3*	M1	singleton	0.37 (0.0, 192196.0)	0.883	439|0|0	404280|20|0	2.47E-05
COVID19 severe vs COVID19 negative or unknown	*STAT1*	M1	singleton	0.38 (0.0, 394545.0)	0.890	439|0|0	404278|22|0	2.72E-05
COVID19 severe vs COVID19 negative or unknown	*IRF7*	M1	singleton	0.39 (0.0, 2889130.0)	0.908	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*UNC93B1*	M1	singleton	0.39 (0.0, 5432760.0)	0.910	439|0|0	404277|23|0	2.84E-05
COVID19 severe vs COVID19 negative or unknown	*TICAM1*	M1	singleton	0.38 (0.0, 38323600.0)	0.919	439|0|0	404281|19|0	2.35E-05
COVID19 severe vs COVID19 negative or unknown	*TRAF3*	M1	singleton	0.39 (0.0, 75538800.0)	0.922	439|0|0	404290|10|0	1.24E-05
COVID19 severe vs COVID19 negative or unknown	*IFNAR2*	M1	singleton	0.42 (0.0, 33281000.0)	0.926	439|0|0	404282|18|0	2.22E-05
COVID19 severe vs COVID19 negative or unknown	*IKBKG*	M1	singleton	0.55 (0.0, 608045.0)	0.934	439|0|0	404293|6|1	9.88E-06
COVID19 severe vs COVID19 negative or unknown	*TLR7*	M1	singleton	0.47 (0.0, 31879200.0)	0.934	439|0|0	404287|9|4	2.10E-05
COVID19 severe vs COVID19 negative or unknown	*IRF9*	M1	singleton	0.38 (0.0, 41264800000.0)	0.940	439|0|0	404289|11|0	1.36E-05
COVID19 severe vs COVID19 negative or unknown	*UNC93B1*	M3	<0.1%	3.23 (1.19, 8.76)	0.022	466|5|0	411529|1370|0	1.66E-03
COVID19 severe vs COVID19 negative or unknown	*IRF7*	M3	<0.1%	5.79 (1.24, 26.97)	0.025	468|3|0	411884|1015|0	1.23E-03
COVID19 severe vs COVID19 negative or unknown	*TBK1*	M3	<0.1%	2.86 (0.4, 20.49)	0.295	469|2|0	412056|843|0	1.02E-03
COVID19 severe vs COVID19 negative or unknown	*STAT2*	M3	<0.1%	2.18 (0.41, 11.57)	0.362	468|3|0	411688|1210|1	1.47E-03

COVID19 severe vs COVID19 negative or unknown	*IFNAR1*	M3	<0.1%	0.37 (0.04, 3.29)	0.375	471|0|0	412408|491|0	5.94E-04
COVID19 severe vs COVID19 negative or unknown	*TLR3*	M3	<0.1%	0.58 (0.16, 2.06)	0.397	470|1|0	410946|1953|0	2.36E-03
COVID19 severe vs COVID19 negative or unknown	*TLR7*	M3	<0.1%	0.54 (0.08, 3.86)	0.541	471|0|0	412452|321|126	6.93E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR2*	M3	<0.1%	0.39 (0.02, 9.22)	0.559	471|0|0	412552|347|0	4.20E-04
COVID19 severe vs COVID19 negative or unknown	*IRF3*	M3	<0.1%	1.85 (0.16, 21.06)	0.618	470|1|0	412482|417|0	5.06E-04
COVID19 severe vs COVID19 negative or unknown	*STAT1*	M3	<0.1%	0.38 (0.0, 42.81)	0.690	471|0|0	412731|168|0	2.03E-04
COVID19 severe vs COVID19 negative or unknown	*TRAF3*	M3	<0.1%	0.38 (0.0, 72.6)	0.718	471|0|0	412750|149|0	1.80E-04
COVID19 severe vs COVID19 negative or unknown	*TICAM1*	M3	<0.1%	0.37 (0.0, 87.63)	0.719	439|0|0	404205|95|0	1.17E-04
COVID19 severe vs COVID19 negative or unknown	*IRF9*	M3	<0.1%	0.37 (0.0, 12583.2)	0.850	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*IKBKG*	M3	<0.1%	0.47 (0.0, 1170.45)	0.851	439|0|0	404226|66|8	1.01E-04
COVID19 severe vs COVID19 negative or unknown	*UNC93B1*	M3	<1%	3.23 (1.19, 8.76)	0.022	466|5|0	411529|1370|0	1.66E-03
COVID19 severe vs COVID19 negative or unknown	*IRF7*	M3	<1%	5.79 (1.24, 26.97)	0.025	468|3|0	411884|1015|0	1.23E-03
COVID19 severe vs COVID19 negative or unknown	*TBK1*	M3	<1%	2.86 (0.4, 20.49)	0.295	469|2|0	412056|843|0	1.02E-03
COVID19 severe vs COVID19 negative or unknown	*TRAF3*	M3	<1%	0.56 (0.16, 1.89)	0.346	470|1|0	410721|2175|3	2.64E-03
COVID19 severe vs COVID19 negative or unknown	*STAT2*	M3	<1%	2.18 (0.41, 11.57)	0.362	468|3|0	411688|1210|1	1.47E-03
COVID19 severe vs COVID19 negative or unknown	*IFNAR1*	M3	<1%	0.37 (0.04, 3.29)	0.375	471|0|0	412408|491|0	5.94E-04
COVID19 severe vs COVID19 negative or unknown	*TLR7*	M3	<1%	0.54 (0.08, 3.86)	0.541	471|0|0	412452|321|126	6.93E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR2*	M3	<1%	0.39 (0.02, 9.22)	0.559	471|0|0	412552|347|0	4.20E-04
COVID19 severe vs COVID19 negative or unknown	*IKBKG*	M3	<1%	1.46 (0.37, 5.74)	0.590	438|0|1	403298|719|283	1.59E-03
COVID19 severe vs COVID19 negative or unknown	*IRF3*	M3	<1%	1.85 (0.16, 21.06)	0.618	470|1|0	412482|417|0	5.06E-04
COVID19 severe vs COVID19 negative or unknown	*STAT1*	M3	<1%	0.38 (0.0, 42.81)	0.690	471|0|0	412731|168|0	2.03E-04
COVID19 severe vs COVID19 negative or unknown	*TICAM1*	M3	<1%	0.37 (0.0, 87.63)	0.719	439|0|0	404205|95|0	1.17E-04
COVID19 severe vs COVID19 negative or unknown	*IRF9*	M3	<1%	0.37 (0.0, 12583.2)	0.850	439|0|0	404275|25|0	3.09E-05
COVID19 severe vs COVID19 negative or unknown	*TLR3*	M3	<1%	0.94 (0.37, 2.39)	0.894	467|4|0	409028|3870|1	4.69E-03
COVID19 severe vs COVID19 negative or unknown	*TLR3*	M3	singleton	0.4 (0.01, 31.94)	0.684	471|0|0	412781|118|0	1.43E-04
COVID19 severe vs COVID19 negative or unknown	*IFNAR1*	M3	singleton	0.35 (0.0, 79.06)	0.706	439|0|0	404251|49|0	6.05E-05
COVID19 severe vs COVID19 negative or unknown	*TBK1*	M3	singleton	0.37 (0.0, 254.55)	0.765	439|0|0	404229|71|0	8.77E-05
COVID19 severe vs COVID19 negative or unknown	*STAT2*	M3	singleton	0.39 (0.0, 308.78)	0.784	471|0|0	412815|84|0	1.02E-04
COVID19 severe vs COVID19 negative or unknown	*UNC93B1*	M3	singleton	0.39 (0.0, 459.72)	0.792	471|0|0	412846|53|0	6.41E-05
COVID19 severe vs COVID19 negative or unknown	*TRAF3*	M3	singleton	0.38 (0.0, 2681.94)	0.831	439|0|0	404251|49|0	6.05E-05
COVID19 severe vs COVID19 negative or unknown	*TLR7*	M3	singleton	0.49 (0.0, 347.13)	0.833	439|0|0	404244|41|15	8.77E-05
COVID19 severe vs COVID19 negative or unknown	*STAT1*	M3	singleton	0.38 (0.0, 3424.18)	0.835	439|0|0	404241|59|0	7.29E-05
COVID19 severe vs COVID19 negative or unknown	*IRF3*	M3	singleton	0.38 (0.0, 11774.2)	0.856	439|0|0	404264|36|0	4.45E-05
COVID19 severe vs COVID19 negative or unknown	*IRF7*	M3	singleton	0.39 (0.0, 20568.7)	0.865	439|0|0	404256|44|0	5.44E-05
COVID19 severe vs COVID19 negative or unknown	*TICAM1*	M3	singleton	0.38 (0.0, 38323600.0)	0.919	439|0|0	404281|19|0	2.35E-05
COVID19 severe vs COVID19 negative or unknown	*IFNAR2*	M3	singleton	0.42 (0.0, 24062300.0)	0.924	439|0|0	404281|19|0	2.35E-05
COVID19 severe vs COVID19 negative or unknown	*IKBKG*	M3	singleton	0.55 (0.0, 485439.0)	0.932	439|0|0	404292|7|1	1.11E-05
COVID19 severe vs COVID19 negative or unknown	*IRF9*	M3	singleton	0.38 (0.0, 41264800000.0)	0.940	439|0|0	404289|11|0	1.36E-05

Supplementary Table 5

Gene	Chr	Start	End	Burden test	MAF	Odds Ratio [95% CI]	P-value	Cases RR|RA|AA	Controls RR|RA|AA	AAF
SARDH	9	133663888	133734173	M1	<1%	3.275[1.551,6.913]	1.90E-03	1174|10|0	421173|1144|1	0.00136
XCR1	3	46020945	46021947	M1	<1%	5.051[1.429,17.857]	1.20E-02	1136|3|0	412666|233|0	0.00028
CCR9	3	45894933	45901898	M3	<1%	0.272[0.095,0.778]	1.50E-02	1183|1|0	419533|2785|0	0.00329
TSC1	9	132896234	132928872	M3	<1%	0.464[0.232,0.928]	3.00E-02	1179|5|0	417754|4557|7	0.0054
LIMD1	3	45594879	45677059	M3	<1%	3.948[1.001,15.575]	5.00E-02	1180|4|0	421631|687|0	0.00082
DBH	9	133636371	133658447	M1	<1%	0.437[0.188,1.014]	5.40E-02	1183|1|0	420344|1974|0	0.00233
GBGT1	9	133153576	133162412	M3	<1%	1.322[0.966,1.811]	8.20E-02	1142|41|1	412304|9991|23	0.0119
LARS2	3	45394453	45547530	M3	<1%	1.433[0.944,2.174]	9.10E-02	1155|28|1	414329|7961|28	0.0095
SURF2	9	133356592	133361139	M3	<1%	0.366[0.103,1.298]	1.20E-01	1184|0|0	421546|772|0	0.00091
DBH	9	133636371	133658447	M3	<1%	0.807[0.599,1.086]	1.60E-01	1148|36|0	405914|16371|33	0.01945
XCR1	3	46020945	46021947	M3	<1%	2.865[0.662,12.389]	1.60E-01	1181|3|0	421826|492|0	0.00058
OBP2B	9	133205328	133209199	M1	<1%	1.413[0.846,2.358]	1.90E-01	1164|20|0	416980|5338|0	0.00633
OBP2B	9	133205328	133209199	M3	<1%	1.413[0.846,2.358]	1.90E-01	1164|20|0	416980|5338|0	0.00633
SURF2	9	133356592	133361139	M1	<1%	0.366[0.082,1.624]	1.90E-01	1184|0|0	421763|555|0	0.00066
FAM163B	9	133579021	133580223	M3	<1%	1.979[0.694,5.643]	2.00E-01	1172|12|0	418235|4083|0	0.00483
GTF3C5	9	133031011	133057980	M3	<1%	1.686[0.716,3.968]	2.30E-01	1176|8|0	420353|1965|0	0.00233
GFI1B	9	132986678	132991050	M3	<1%	0.660[0.331,1.317]	2.40E-01	1179|5|0	419558|2758|2	0.00327
SARDH	9	133663888	133734173	M3	<1%	1.309[0.800,2.143]	2.80E-01	1163|21|0	416816|5500|2	0.00652
SURF1	9	133351912	133356453	M1	<1%	1.849[0.605,5.646]	2.80E-01	1179|5|0	421108|1210|0	0.00143
MED22	9	133341504	133346662	M3	<1%	0.368[0.059,2.317]	2.90E-01	1184|0|0	421978|340|0	0.0004
GBGT1	9	133153576	133162412	M1	<1%	1.431[0.721,2.840]	3.10E-01	1174|9|1	419929|2384|5	0.00284
SLC6A20	3	45758436	45796419	M1	<1%	0.502[0.135,1.874]	3.10E-01	1184|0|0	421628|690|0	0.00081
SURF4	9	133363463	133375969	M3	<1%	0.367[0.051,2.633]	3.20E-01	1184|0|0	421942|375|1	0.00045
CACFD1	9	133460066	133468711	M3	<1%	0.610[0.227,1.639]	3.30E-01	1182|2|0	421046|1271|1	0.00151
SPACA9	9	132883947	132889968	M1	<1%	0.367[0.042,3.219]	3.70E-01	1184|0|0	422020|296|2	0.00035
REXO4	9	133406952	133417844	M1	<1%	2.089[0.352,12.391]	4.20E-01	1182|2|0	422069|249|0	0.0003
CCR9	3	45894933	45901898	M1	<1%	0.359[0.028,4.541]	4.30E-01	1113|0|0	413547|172|0	0.00021
LARS2	3	45394453	45547530	M1	<1%	0.363[0.030,4.462]	4.30E-01	1113|0|0	413453|266|0	0.00032
FYCO1	3	45921764	45984910	M1	<1%	1.571[0.495,4.981]	4.40E-01	1181|3|0	421446|872|0	0.00103
RPL7A	9	133348243	133351366	M3	<1%	0.367[0.028,4.763]	4.40E-01	1139|0|0	412723|176|0	0.00021
SPACA9	9	132883947	132889968	M3	<1%	0.662[0.227,1.926]	4.50E-01	1182|2|0	421070|1246|2	0.00148
RALGDS	9	133098586	133148980	M3	<1%	0.783[0.409,1.498]	4.60E-01	1177|7|0	419015|3297|6	0.00391
MED22	9	133341504	133346662	M1	<1%	0.364[0.020,6.688]	5.00E-01	1068|0|0	404151|149|0	0.00018
ADAMTSL2	9	133534740	133574864	M3	<1%	0.734[0.278,1.938]	5.30E-01	1181|3|0	421165|1146|7	0.00137
CXCR6	3	45946481	45947510	M1	<1%	0.365[0.016,8.492]	5.30E-01	1068|0|0	404133|167|0	0.00021
TSC1	9	132896234	132928872	M1	<1%	1.545[0.392,6.096]	5.30E-01	1181|3|0	421643|675|0	0.0008

SURF6	9	133331868	133336132	M1	<1%	2.245[0.160,31.471]	5.50E-01	1183|1|0	422127|191|0	0.00023
STKLD1	9	133376473	133405421	M3	<1%	1.311[0.533,3.225]	5.60E-01	1178|6|0	421189|1129|0	0.00134
SURF6	9	133331868	133336132	M3	<1%	1.248[0.583,2.670]	5.70E-01	1176|8|0	420485|1830|3	0.00218
LZTFL1	3	45826313	45913146	M3	<1%	1.653[0.285,9.596]	5.80E-01	1183|1|0	421959|358|1	0.00043
SACM1L	3	45689465	45743669	M1	<1%	0.364[0.009,14.779]	5.90E-01	1113|0|0	413629|90|0	0.00011
SLC2A6	9	133472020	133479059	M1	<1%	0.380[0.011,13.152]	5.90E-01	1184|0|0	422203|114|1	0.00014
LZTFL1	3	45826313	45913146	M1	<1%	0.366[0.007,19.657]	6.20E-01	1068|0|0	404207|93|0	0.00011
CACFD1	9	133460066	133468711	M1	<1%	1.813[0.151,21.747]	6.40E-01	1138|1|0	412759|140|0	0.00017
SURF4	9	133363463	133375969	M1	<1%	0.367[0.006,23.714]	6.40E-01	1113|0|0	413633|85|1	0.0001
ADAMTSL2	9	133534740	133574864	M1	<1%	0.788[0.284,2.183]	6.50E-01	1181|3|0	421298|1013|7	0.00122
CXCR6	3	45946481	45947510	M3	<1%	0.681[0.130,3.561]	6.50E-01	1184|0|0	421840|478|0	0.00056
CCR3	3	46264403	46266226	M1	<1%	0.748[0.195,2.877]	6.70E-01	1138|1|0	412584|313|2	0.00038
LIMD1	3	45594879	45677059	M1	<1%	0.365[0.003,45.783]	6.80E-01	1068|0|0	404238|62|0	0.00008
RPL7A	9	133348243	133351366	M1	<1%	0.363[0.003,43.151]	6.80E-01	1068|0|0	404244|56|0	0.00007
GFI1B	9	132986678	132991050	M1	<1%	0.336[0.001,89.947]	7.00E-01	1068|0|0	404258|42|0	0.00005
REXO4	9	133406952	133417844	M3	<1%	1.230[0.426,3.551]	7.00E-01	1180|4|0	421350|967|1	0.00115
TMEM8C	9	133514635	133524844	M1	<1%	0.366[0.002,57.057]	7.00E-01	1068|0|0	404234|66|0	0.00008
CEL	9	133061993	133071764	M1	<1%	0.893[0.498,1.604]	7.10E-01	1174|10|0	418298|4003|17	0.00478
SURF1	9	133351912	133356453	M3	<1%	1.171[0.493,2.779]	7.20E-01	1178|6|0	420402|1916|0	0.00227
FYCO1	3	45921764	45984910	M3	<1%	0.911[0.531,1.562]	7.30E-01	1174|10|0	418163|4152|3	0.00492
CCR3	3	46264403	46266226	M3	<1%	0.879[0.410,1.884]	7.40E-01	1179|5|0	420640|1670|8	0.002
SLC2A6	9	133472020	133479059	M3	<1%	0.810[0.235,2.788]	7.40E-01	1182|2|0	421405|912|1	0.00108
CCR1	3	46203245	46204313	M1	<1%	0.364[0.001,180.113]	7.50E-01	1068|0|0	404268|32|0	0.00004
GTF3C5	9	133031011	133057980	M1	<1%	1.440[0.151,13.777]	7.50E-01	1138|1|0	412579|320|0	0.00039
STKLD1	9	133376473	133405421	M1	<1%	1.180[0.346,4.021]	7.90E-01	1181|3|0	421593|725|0	0.00086
TMEM8C	9	133514635	133524844	M3	<1%	0.809[0.139,4.711]	8.10E-01	1183|1|0	421881|437|0	0.00052
ABO	9	133255601	133275189	M1	<1%	1.068[0.537,2.123]	8.50E-01	1175|9|0	419340|2972|6	0.00353
ABO	9	133255601	133275189	M3	<1%	1.068[0.537,2.123]	8.50E-01	1175|9|0	419340|2972|6	0.00353
FAM163B	9	133579021	133580223	M1	<1%	0.367[0.000,9326.220]	8.50E-01	1068|0|0	404280|20|0	0.00002
SACM1L	3	45689465	45743669	M3	<1%	0.905[0.221,3.707]	8.90E-01	1183|1|0	421716|601|1	0.00071
RALGDS	9	133098586	133148980	M1	<1%	1.135[0.150,8.607]	9.00E-01	1183|1|0	422081|237|0	0.00028
CCR1	3	46203245	46204313	M3	<1%	0.918[0.119,7.081]	9.30E-01	1184|0|0	422087|230|1	0.00027
ADAMTS13	9	133422443	133459180	M1	<1%	1.066[0.141,8.035]	9.50E-01	1183|1|0	421948|370|0	0.00044
ADAMTS13	9	133422443	133459180	M3	<1%	1.066[0.141,8.035]	9.50E-01	1183|1|0	421948|370|0	0.00044
CEL	9	133061993	133071764	M3	<1%	1.008[0.604,1.681]	9.80E-01	1169|15|0	417105|5195|18	0.00619
SLC6A20	3	45758436	45796419	M3	<1%	1.009[0.514,1.979]	9.80E-01	1176|8|0	419487|2829|2	0.00335

Supplementary Table 6

Gene	Burden test	MAF	Odds Ratio [95% CI]	P-value	Cases_RR|RA|AA	Controls_RR|RA|AA	AAF
IFNL3	M1	<1%	9.337[1.029,84.703]	4.70E-02	1067|1|0	404225|75|0	0.00009
IL1R1	M3	<1%	0.362[0.116,1.130]	8.00E-02	1184|0|0	421641|670|7	0.00081
IFNGR2	M1	<1%	36.697[0.546,2468.410]	9.30E-02	1067|1|0	404218|82|0	0.0001
IL1R1	M1	<1%	0.361[0.099,1.318]	1.20E-01	1113|0|0	413259|453|7	0.00056
IFNL3	M3	<1%	22.052[0.416,1169.220]	1.30E-01	1067|1|0	404204|96|0	0.00012
IL23R	M1	<1%	10.138[0.285,361.228]	2.00E-01	1067|1|0	404182|118|0	0.00015
IFNGR2	M3	<1%	9.590[0.277,331.923]	2.10E-01	1067|1|0	404186|114|0	0.00014
IL33	M1	<1%	1.378[0.782,2.428]	2.70E-01	1168|16|0	417441|4871|6	0.00578
IL33	M3	<1%	1.369[0.778,2.410]	2.80E-01	1168|16|0	417421|4891|6	0.00581
IL4R	M1	<1%	6.064[0.226,162.349]	2.80E-01	1112|1|0	413598|121|0	0.00015
JAK1	M1	<1%	2.459[0.458,13.211]	2.90E-01	1112|1|0	413552|165|2	0.0002
JAK1	M3	<1%	2.459[0.458,13.211]	2.90E-01	1112|1|0	413552|165|2	0.0002
IFNL1	M3	<1%	0.372[0.058,2.383]	3.00E-01	1184|0|0	421955|362|1	0.00043
JAK2	M3	<1%	0.667[0.312,1.427]	3.00E-01	1180|4|0	420200|2115|3	0.00251
IFNL1	M1	<1%	0.372[0.054,2.570]	3.20E-01	1184|0|0	421992|325|1	0.00039
IL4R	M3	<1%	4.130[0.195,87.362]	3.60E-01	1183|1|0	422191|127|0	0.00015
IL17A	M3	<1%	0.363[0.039,3.351]	3.70E-01	1068|0|0	404058|242|0	0.0003
IL1RAP	M1	<1%	3.522[0.184,67.305]	4.00E-01	1067|1|0	404112|188|0	0.00023
CCR5	M1	<1%	0.717[0.323,1.593]	4.10E-01	1180|4|0	420124|2190|4	0.0026
CCR5	M3	<1%	0.717[0.323,1.593]	4.10E-01	1180|4|0	420124|2190|4	0.0026
IL6R	M3	<1%	3.315[0.181,60.787]	4.20E-01	1183|1|0	422155|163|0	0.00019
IL17RA	M1	<1%	0.351[0.023,5.434]	4.50E-01	1139|0|0	412735|164|0	0.0002
IL23A	M3	<1%	0.365[0.026,5.109]	4.50E-01	1113|0|0	413516|202|1	0.00025
IL12B	M3	<1%	0.369[0.025,5.458]	4.70E-01	1184|0|0	422149|169|0	0.0002
IL17RC	M3	<1%	1.500[0.493,4.561]	4.70E-01	1182|2|0	421509|809|0	0.00096
IFNLR1	M3	<1%	0.364[0.021,6.424]	4.90E-01	1113|0|0	413565|154|0	0.00019
C5	M1	<1%	1.704[0.312,9.295]	5.40E-01	1182|2|0	421838|480|0	0.00057
IFNLR1	M1	<1%	0.365[0.014,9.500]	5.40E-01	1113|0|0	413589|130|0	0.00016
IL1B	M3	<1%	0.365[0.015,8.910]	5.40E-01	1113|0|0	413548|171|0	0.00021
IL7R	M1	<1%	1.401[0.479,4.099]	5.40E-01	1181|3|0	421398|920|0	0.00109
JAK2	M1	<1%	0.365[0.015,9.001]	5.40E-01	1113|0|0	413555|164|0	0.0002

IL23R	M3	<1%	0.844[0.478,1.491]	5.60E-01	1174|10|0	417706|4598|14	0.00547
IL17RC	M1	<1%	1.680[0.281,10.027]	5.70E-01	1183|1|0	421921|397|0	0.00047
IL1B	M1	<1%	0.365[0.011,11.836]	5.70E-01	1068|0|0	404159|141|0	0.00017
IL17RA	M3	<1%	1.138[0.719,1.800]	5.80E-01	1163|21|0	416094|6208|16	0.00739
IFNG	M3	<1%	0.366[0.009,14.565]	5.90E-01	1068|0|0	404182|118|0	0.00015
VEGFA	M3	<1%	0.714[0.210,2.430]	5.90E-01	1182|2|0	421474|843|1	0.001
IL12B	M1	<1%	0.365[0.008,17.252]	6.10E-01	1068|0|0	404216|84|0	0.0001
IL1A	M1	<1%	0.378[0.007,20.424]	6.30E-01	1139|0|0	412820|79|0	0.0001
IL6	M3	<1%	0.369[0.006,22.961]	6.40E-01	1139|0|0	412810|89|0	0.00011
IL6	M1	<1%	0.365[0.004,34.420]	6.60E-01	1068|0|0	404220|80|0	0.0001
IFNG	M1	<1%	0.366[0.004,36.506]	6.70E-01	1068|0|0	404226|74|0	0.00009
IL17A	M1	<1%	0.359[0.002,51.956]	6.90E-01	1068|0|0	404268|32|0	0.00004
IL6R	M1	<1%	0.366[0.003,51.222]	6.90E-01	1068|0|0	404226|74|0	0.00009
IFNB1	M3	<1%	0.852[0.345,2.105]	7.30E-01	1180|4|0	420490|1825|3	0.00217
IL1RAP	M3	<1%	1.335[0.262,6.813]	7.30E-01	1183|1|0	421841|477|0	0.00056
IL23A	M1	<1%	0.365[0.001,188.812]	7.50E-01	1068|0|0	404264|36|0	0.00004
PDCD1	M3	<1%	0.367[0.000,356.757]	7.80E-01	1068|0|0	404257|43|0	0.00005
CSF2	M3	<1%	0.365[0.000,585.209]	7.90E-01	1068|0|0	404273|27|0	0.00003
C5	M3	<1%	0.938[0.563,1.561]	8.00E-01	1170|14|0	418377|3927|14	0.00469
PDCD1	M1	<1%	0.366[0.000,1167.050]	8.10E-01	1068|0|0	404272|28|0	0.00003
IFNGR1	M1	<1%	1.265[0.146,10.971]	8.30E-01	1183|1|0	421995|323|0	0.00038
CSF2	M1	<1%	0.364[0.000,14751.000]	8.50E-01	1068|0|0	404293|7|0	0.00001
IL7R	M3	<1%	1.064[0.479,2.365]	8.80E-01	1179|5|0	420502|1816|0	0.00215
IFNGR1	M3	<1%	0.905[0.142,5.764]	9.20E-01	1183|1|0	421923|395|0	0.00047
VEGFA	M1	<1%	0.925[0.218,3.932]	9.20E-01	1182|2|0	421709|608|1	0.00072
TNF	M1	<1%	0.367[0.000,25493000000.000]	9.40E-01	1068|0|0	404295|5|0	0.00001
IFNL2	M3	<1%	0.945[0.141,6.332]	9.50E-01	1183|1|0	421977|341|0	0.0004
TNF	M3	<1%	0.937[0.141,6.239]	9.50E-01	1138|1|0	412431|468|0	0.00057
IFNB1	M1	<1%	1.017[0.377,2.749]	9.70E-01	1135|4|0	411413|1484|2	0.0018
IFNL2	M1	<1%	1.040[0.141,7.655]	9.70E-01	1183|1|0	422015|303|0	0.00036
IL1A	M3	<1%	0.967[0.151,6.205]	9.70E-01	1138|1|0	412626|272|1	0.00033