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Supplemental information

Pan-ancestry exome-wide association analyses of COVID-19 outcomes in 586,157 individuals

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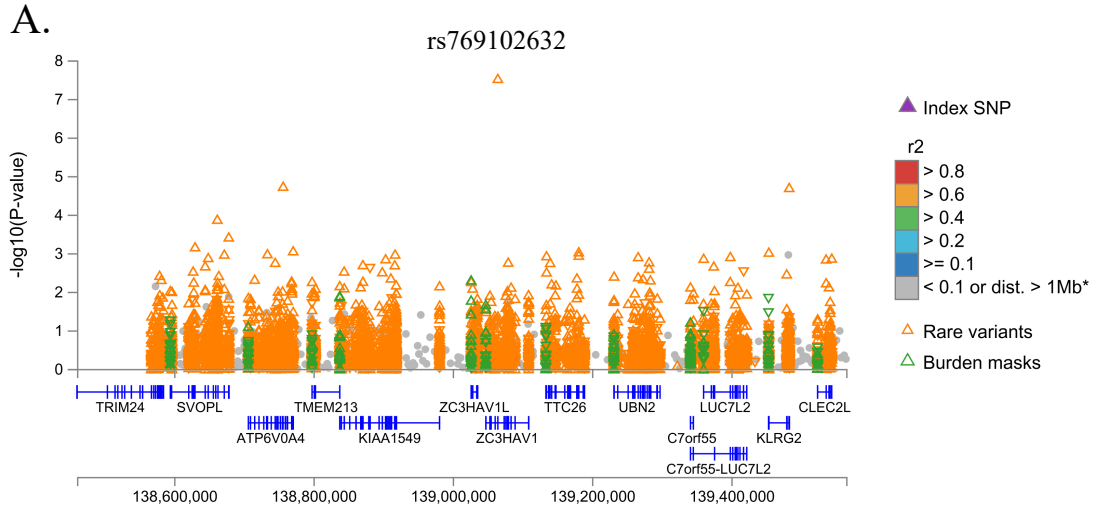
SUPPLEMENTARY FIGURES

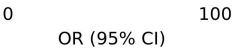
Figure S1: Association of a rare missense variant in *ZC3HAV1* and COVID-19.

A.



B.

STUDY	N CASES RR|RA|AA	N CONTROLS RR|RA|AA	OR [95% CI]	PVALUE	AAF
UKB_Freeze_450_AFR	578|3|0	8178|2|0	27.928 [4.444,175.515]	3.8e-04	0.00029
UKB_Freeze_450_EUR	13372|4|0	393040|6|0	25.956 [5.8,116.159]	2.1e-05	1e-05
META	**13950|7|0**	**401218|8|0**	**26.725 [8.366,85.377]**	**2.9e-08**	**2e-05**



Association between an ultra-rare missense variant in *ZC3HAV1* (rs769102632:A) and higher risk of COVID-19. (A) Regional association plot centered on rs769102632. Orange triangles: individual rare variants (MAF<0.5%). Green squares: burden tests. Grey circles: individual common variants (MAF>0.5%). (B) Forest plot showing association in the two individual datasets included in the meta-analysis of this variant.

SUPPLEMENTARY TABLES

Tables S1 to S8 are provided in a separate Excel document.

Table S1. Demographics and clinical characteristics of study participants.

Table S2. Breakdown of COVID-19 status across the four studies included in the analysis.

Table S3. Definitions used for the seven COVID-19 phenotypes analyzed.

Table S4. Genomic inflation factor (λ_{GC}) observed in the analysis of exome sequence variants for each of the eight phenotypes tested.

Table S5. No carriers of the rare rare missense variant rs769102632 in *ZC3HAV1* were observed in an additional 6,223 individuals with COVID-19.

Table S6. Nominally-significant associations (P<0.05) among 14,050 burden tests performed across 281 genes located in 15 susceptibility loci identified by the COVID-19 Host Genetics Initiative.

Table S7. Results from burden association tests for 13 genes related to interferon signaling and recently reported to contain rare (MAF<0.1%), deleterious variants in patients with severe COVID-19.

Table S8. Results from burden association tests for an additional 32 genes that are involved in the etiology of SARS-CoV-2, encode therapeutic targets or have been implicated in other immune or infectious diseases through GWAS.

SUPPLEMENTARY METHODS

Participating Studies

Geisinger Health System (GHS). The GHS MyCode Community Health Initiative study has been described previously [1]. Briefly, the GHS study is a health system-based cohort from central and eastern Pennsylvania (USA) with ongoing recruitment since 2006. A subset of 144,182 MyCode participants sequenced as part of the GHS-Regeneron Genetics Center DiscovEHR partnership were included in this study. All subjects consented to participation and the analysis was approved by the Geisinger Institutional Review Board under project number 2006-0258. Information on COVID-19 outcomes were obtained through GHS's COVID-19 registry. Patients were identified as eligible for the registry based on relevant lab results and ICD-10 diagnosis codes; patient charts were then reviewed to confirm COVID-19 diagnoses. The registry contains data on outcomes, comorbidities, medications, supplemental oxygen use and ICU admissions.

Penn Medicine BioBank (PMBB) study. PMBB study participants are recruited through the University of Pennsylvania Health System, which enrolls participants during hospital or clinic visits. After providing consent, participants donate blood or tissue and allow access to EHR information[2]. The PMBB COVID-19 registry consists of patients who have positive qPCR testing for SARS-COV-2. We then used electronic health records to classify COVID-19 patients into hospitalized and severe (ventilation or death) categories and the study was approved by the University of Pennsylvania Institutional Review Board (protocol #813913).

UK Biobank (UKB) study. 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[3]. 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 8 March 2021 data refresh and excluded from the analysis 28,547 individuals with a death registry event prior to 2020. The study was approved by the research ethics committee under approval number 11/NW/0382.

COVID-19 phenotypes used for genetic association analyses

We grouped participants from each study into three broad COVID-19 disease categories (**Table S2**): (i) positive – those with a positive qPCR or serology test for SARS-CoV-2, or a COVID-19-related ICD10 code (U07), hospitalization or death; (ii) negative – those with only negative qPCR or serology test results for SARS-CoV-2 and no COVID-19-related ICD10 code (U07), hospitalization or death; and (iii) unknown – those with no qPCR or serology test results 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 seven COVID-19-related phenotypes for genetic association analyses, as detailed in **Table S3**.

Array genotyping

Genotyping was performed on one of four SNP array types: Illumina OmniExpress Exome array (OMNI; 59345 samples from GHS), Illumina Global Screening Array (GSA; PMBB and 82,527 samples from GHS), Applied Biosystems UK BiLEVE Axiom Array (49,950 samples from UKB), or Applied Biosystems UK Biobank Axiom Array (438,427 samples from UKB). We retained variants with a minor allele frequency (MAF) >1%, <10% missingness, Hardy-Weinberg equilibrium test *P*-value>10^{-15}. Array data were then used: (i) to define ancestry subsets; and (ii) as part of the exome-wide association analyses carried out in REGENIE (see below).

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 [IDT]) 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 either (i) a slightly modified version of IDT's xGen probe library (for UKB, PMBB and 81,620 samples of GHS); or (ii) NimbleGen VCRome (58,856 samples of GHS). 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: (i) for UKB samples – 75 bp paired-end reads with two 10 base pair index reads on the Illumina NovaSeq 6000 platform using S2 or S4 flow cells; (ii) for GHS samples captured with VCRome – 75 bp paired-end reads with two 8 bp index reads on the Illumina HiSeq 2500; (iii) for GHS captured with IDT – two 8 bp index reads on the Illumina HiSeq 2500 or two 10 bp index reads on the Illumina NovaSeq 6000 on S4 flow cells; (iv) for UPENN-PMBB – two 10 bp index reads on the Illumina NovaSeq 6000 on 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. [4]. 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 (DP) less than seven and indel genotypes with read depth less than ten 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 (AB) greater than the cutoff (AB ³ 0.15 for SNVs and AB ³ 0.20 for indels).

Identification of low-quality variants from exome-sequencing using machine learning. Briefly, in each study, 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 (UKB and GHS); (iv) variant loadings on 20 principal components derived

from the analysis of variants with a MAF<1%; (v) transmitted singletons. The model was then trained on up to 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 performed a grid search with 5-fold cross-validation on the training set to identify the hyperparameters that return the highest accuracy during cross-validation, which are then applied to the test set to confirm accuracy. This approach identified as low-quality a total of 7 million variants in the UKB study (86% in the buffer region), 7.2 million across the two GHS datasets (IDT and VCRome; 84% in the buffer region) and 1.1 million in the PMBB study (88% in the buffer region). These variants were removed from analysis in the respective studies.

Gene burden masks. Briefly, for each gene region as defined by Ensembl [5], 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"). Variants were annotated using SnpEff 4.3[6] and the most severe consequence for each variant was chosen, considering complete protein-coding transcripts for each gene. The following variants were considered to be pLoF variants: frameshift-causing indels, variants affecting splice acceptor and donor sites, variants leading to stop gain, stop loss and start loss. The five missense deleterious algorithms used were SIFT [7], PolyPhen2 (HDIV), PolyPhen2 (HVAR) [8], LRT [9], and MutationTaster [10]. 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 each study were performed using the genome-wide Firth logistic regression test implemented in REGENIE [11]. In this implementation, Firth's approach is applied when the p-value from 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.

In the UKB study, we included in step 1 of REGENIE (*i.e.* prediction of individual trait values based on the genetic data) array variants with a minor allele frequency (MAF) >1%, <10% missingness, Hardy-Weinberg equilibrium test *P*-value>10^{-15} and linkage-disequilibrium (LD) pruning (1000 variant windows, 100 variant sliding windows and r^2<0.9). In the GHS and PMBB studies we instead used exome (not array) variants in step 1. We did this in the GHS study because two different exome capture technologies (IDT and VCRome) were used to sequence the GHS samples, and so it was important to capture in step 1 of REGENIE any differences in exome sequencing performance between IDT and VCRome. For the PMBB study, array data were not yet available for about 40K samples, and so we used exome data for step 1 to maximize the sample size available for analysis. We excluded from step 1 any SNPs with high inter-chromosomal LD, in the major histo-compatibility (MHC) region, or in regions of low complexity.

The association model used in step 2 of REGENIE included as covariates (i) age, age^2, sex, age-by-sex and age^2-by-sex; (ii) 10 ancestry-informative principal components (PCs) derived from the analysis of a set of LD-pruned (50 variant windows, 5 variant sliding windows and r^2<0.5) common variants from the array (imputed for the GHS study; exome for PMBB) data generated separately for each ancestry; (iii) an indicator for exome sequencing batch (GHS: two IDT batches, one VCRome batch; UKB: six IDT batches); and (iv) 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% also generated separately for each ancestry. We corrected for PCs built from rare variants because previous studies demonstrated PCs derived from common variants do not adequately correct for fine-scale population structure [12, 13].

Within each study, association analyses were performed separately for different continental ancestries defined based on the array data: African (AFR), Admixed American (AMR), European (EUR) and South Asian (SAS). We determined continental ancestries by projecting each sample onto reference principal components calculated from the HapMap3 reference panel. Briefly, we merged our samples with HapMap3 samples and kept only SNPs in common between the two datasets. We further excluded SNPs with MAF<10%, genotype missingness >5% or Hardy-Weinberg Equilibrium test p-value < 10^{-5}. We calculated PCs for the HapMap3 samples and projected each of our samples onto those PCs. To assign a continental ancestry group to each non-HapMap3 sample, we trained a kernel density estimator (KDE) using the HapMap3 PCs and used the KDEs to calculate the likelihood of a given sample belonging to each of the five continental ancestry groups. When the likelihood for a given ancestry group was >0.3, the sample was assigned to that ancestry group. When two ancestry groups had a likelihood >0.3, we arbitrarily assigned AFR over EUR (N_{GHS} = 36 [0.9%], N_{UKB} = 56 [0.6%], $N_{UPENN\text{-}PMBB}$ = 7 [0.1%]), AMR over EUR (N_{GHS} = 455 [22.5%], N_{UKB} = 436 [47.8%], $N_{UPENN\text{-}PMBB}$ = 138 [23.5%]), AMR over EAS (N_{GHS} = 2 [0.05%], N_{UKB} = 2 [0.2%], $N_{UPENN\text{-}PMBB}$ = 1 [0.2%]), SAS over EUR (N_{GHS} = 32 [7.8%], N_{UKB} = 592 [9.6%], $N_{UPENN\text{-}PMBB}$ = 36 [6.3%]), and AMR over AFR (N_{GHS} = 192 [9.5%], N_{UKB} = 51 [5.6%], $N_{UPENN\text{-}PMBB}$ = 77 [13.1%]). Samples were excluded from analysis if no ancestry likelihoods were >0.3, or if more than three ancestry likelihoods were > 0.3 (N_{GHS} = 821, N_{UKB} = 1205, $N_{UPENN\text{-}PMBB}$ = 384).

Results were subsequently meta-analyzed across studies and ancestries using an inverse variance-weighed fixed-effects meta-analysis.

Frequency of *ZC3HAV1* rare missense variant in COVID-19 cases from independent studies

To help understand if the association between COVID-19 risk and rs769102632 in *ZC3HAV1* was likely to be a true-positive association, we determine its frequency in 6,223 cases from three additional studies.

GenOMICC (n=4,851). Individuals with severe COVID-19 were ascertained as described previously[14]. DNA samples were then whole-genome sequenced on the Illumina NovaSeq 6000 platform, aligned to the human reference genome hg38 and variant called to GVCF stage on the

DRAGEN pipeline (software v01.011.269.3.2.22, hardware v01.011.269) at Genomics England. rs769102632 +/-50bp was genotyped with the GATK GenotypeGVCFs tool v4.1.8.1 and filtered to minimum depth 8X. Ancestry for individuals with array genotyping (n=2,048) was inferred using ADMIXTURE[15] populations defined in 1000 Genomes[16]. When one individual had a probability > 80% of pertaining to one ancestry, then the individual was assigned to this ancestry (n=1,837), otherwise the individual was considered to be of admixed ancestry (n=211), as performed in the Million veteran program [17]. Of the remaining samples (n=3,014), Somalier v0.2.12[18] was used to estimate ancestry from the whole-genome sequencing data: 2,606 samples could be confidently (³92.5% probability) assigned to a population, while the remaining 408 were assigned to admixed ancestry.

Columbia University COVID-19 biobank (n=1,152). This cohort has previously been described in detail[19]. Briefly, 1,152 COVID-19 patients that were treated for COVID-19 at the Columbia University Irving Medical Center were recruited to the Columbia University COVID-19 Biobank between March and May 2020. All patients had PCR-confirmed SARS-CoV-2 infection and the vast majority had severe COVID-19 requiring hospitalization. For all cases, exomes were captured with the IDT xGen Exome Research Panel V1.0 and sequenced on Illumina's NovaSeq 6000 platform with 150 bp paired-end reads according to standard protocols. All cases were processed with the same bioinformatic pipeline for variant calling. In brief, reads were aligned to human reference GRCh37 using DRAGEN and duplicates were marked with Picard. Variants were called according to the Genome Analysis Toolkit (GATK) Best Practices recommendations v3.66[20]. Finally, variants were annotated with ClinEff[6] and the IGM's in-house tool ATAV[21]. A centralized database was used to store variant and per site coverage data for all samples enabling well controlled analyses without the need of generating jointly called VCF files (see Ren et al. 2021 for details[21]). For each patient, we performed ancestry classification into one of the six major ancestry groups (European, African, Latin, East Asian, South Asian and Middle Eastern) using a neural network trained on a set of samples with known ancestry labels. We used a 50% probability cut-off to assign an ancestry label to each sample and labeled samples that did not reach 50% for any of the ancestral groups as "Admixed". We only included samples that had at least 90% of the consensus coding sequence (CCDS release 20[22]) covered at ≥ 10x and ≤ 3% contamination levels according to VerifyBamID[23]. Additionally, we removed samples with a discordance between self-declared and sequence-derived gender and samples with an

inferred relationship of second-degree or closer according to KING[24]. All cases had at least 10x coverage at the position of rs769102632.

Biobanque Québec Covid-19 (n=220). The Biobanque Québec COVID-19 (www.BQC19.ca) is a provincial biobank prospectively enrolling patients with suspected COVID-19, or COVID-19 confirmed through SARS-CoV-2 PCR testing and was previously described[19]. For this study, we used results from patients with available WGS data and who were recruited at the Jewish General Hospital (JGH) in Montreal. The JGH is a university affiliated hospital serving a large multi-ethnic adult population and the Québec government designated the JGH as the primary COVID-19 reference center early in the pandemic. In total, Biobanque Quebec contained 533 participants with WGS, including 62 cases of COVID-19 who required invasive ventilatory support (BiPAP, high flow oxygen, or endotracheal intubation) or died, 128 COVID-19 patients who were hospitalized but did not require invasive ventilatory support, 30 individuals with COVID-19 did not require hospitalization, and 313 SARS-CoV-2 PCR-negative participants. Using genetic PCAs derived from genome-wide genotyping, 76% of participants were of European ancestry, 9% were of African ancestry, 7% were of east Asian ancestry, and 5% were of south Asian ancestry. We performed WGS at a mean depth of 30x on all individuals using Illumina's Novaseq 6000 platform (Illumina, San Diego, CA, USA). Sequencing results were analyzed using the McGill Genome Center bioinformatics pipelines[25], in accordance with Genome Analysis Toolkit (GATK) best practices recommendations[20]. Reads were aligned to the GRCh38 reference genome. Variant quality control was performed using the variantRecalibrator and applyVQSR functions from GATK.

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SUPPLEMENTARY TEXT

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Contribution: J.A.K. and M.A.F. performed association analyses and led manuscript writing group. J.B. identified low-quality variants in exome sequence data using machine learning. L.G. and K.W. helped with visualization of association results. A.H.L., A.E.L., A.M. and D.S. prepared the analytical pipelines to perform association analyses. J.M. and J.M. developed and helped deploy REGENIE. S.M. and C.O'D. helped defined COVID-19 phenotypes. G.R.A. supervised all analyses. All authors contributed to and reviewed the final version of the manuscript.

Immune, Respiratory, and Infectious Disease Therapeutic Area Genetics

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Contribution: J.E.H. helped defined COVID-19 phenotypes, interpret association results and led the manuscript writing group.

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