SUPPLEMENTAL INFORMATION
LETHAL COVID-19 ASSOCIATES WITH RAAS-INDUCED INFLAMMATION FOR MULTIPLE ORGAN DAMAGE INCLUDING MEDIASTINAL LYMPH NODES

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Supplemental Materials and Methods

Human autopsy and nasopharyngeal samples collection and RNA Sequencing and Analysis. Nasopharyngeal specimens were collected from 216 SARS-CoV-2 -positive patients and 519 SARS-CoV-2 -negative patients, and autopsy heart, kidney, liver, lymph node, and lung samples were collected from 35-36 patients and 5-8 controls [1-3]. Tissue samples were provided by the Weill Cornell Medicine Department of Pathology. The Tissue Procurement Facility operates under Institutional Review Board (IRB) approved protocol and follows guidelines set by the Health Insurance Portability and Accountability Act. Experiments using samples from human subjects were conducted in accordance with local regulations and with the approval of the IRB at the Weill Cornell Medicine. The autopsy samples were collected under protocol 20–04021814. Autopsy consent was obtained from the families of the patients. The subdivision of autopsy subjects into "high viral load" and "low viral load" on "admission" was determined from the nasopharyngeal swab samples from COVID-19 patients at the time of infection and hospital visit. The viral loads were assessed with a qRT-PCR cycle threshold (Ct) value of SARS-CoV-2 primers, with Ct of less than or equal to 18 being assigned to "high-viral load" label and Ct between 18 and 40 being assigned to "low viral load" classes. Ct values above 40 were classified as negative. The generation and processing of these tissues and RNA sequencing have been previously reported in Guarnieri et al,[4]. RNAseq data was processed as described by Butler et al.[5] and Park et al.[1]. DESeq2[6] was utilized to generate the differential gene expression data.

Collection and RNA sequencing of whole blood samples from the EPICC Cohort. Whole blood specimens (PAXgene tube) were collected from the Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study. The full detail of this study is described in[7]. Briefly, the EPICC cohort study enrolls U.S. Military Health System (MHS) beneficiaries; eligibility criteria include a history of SARS-CoV-2 infection. Study procedures include collection of demographic and comorbidity data, COVID-19 vaccination data, acute COVID-19 illness clinical data, blood specimens, and other biospecimens. The EPICC study was approved by the Uniformed Services University Institutional Review Board (IDCRP-085) and all study participants provided consent when enrolled in the study. This study was conducted following good clinical practice and according to the Declaration of Helsinki guidelines.

Whole blood used for these RNAseq analyses was collected from 221 participants enrolled during 2020 and 2021 at eight Military Treatment Facilities (MTFs) in the United States: Alexander T. Augusta Military Medical Center, Brooke Army Medical Center, Madigan Army Medical Center, Naval Medical Center Portsmouth, Naval Medical Center San Diego, Tripler Army Medical Center, Walter Reed National Military Medical Center, and the William Beaumont Army Medical Center[7].

Whole blood transcriptomic data was derived from collected whole blood PAXgene specimens as follows: Whole blood-derived total RNA was used as input at 200-600 ng for library preparation using the TruSeq Stranded Total RNA with Ribo-Zero Globin and IDT for Illumina - TruSeq RNA UD Indexes (96 indexes, 96 samples). Sequencing libraries were evaluated for size distribution using an Agilent Fragment Analyzer and for yield by qPCR using the Roche Light Cycler II 480 and Kapa Library Quantification Kit for Illumina Platforms. Sequencing libraries were pooled and used as input for sequencing on the NovaSeq 6000 Platform on a NovaSeq 6000 S4 Reagent Kit v1.5 (200 cycles). Raw sequencing data was demultiplexed to FASTQ and processed for mapping and read counts by STAR within the seqEngine workflow. Differential Gene Expression (DGE) was determined using DESeq2 with a filter for genes with at least 10 or higher counts per million (CPM) in at least 10 samples. The fold-change, t-score, and p-adjusted values were utilized from the DESeq2 output for all downstream analyses.

SARS-CoV-2 model and RNA-sequencing of hamster samples. The generation and processing of hamster tissue and RNA samples were performed as described in Frere et al,[8]. Briefly, hamsters were infected by intranasal inoculation with SARS-CoV-2WA, and lung, kidney, heart, and brain (olfactory bulb, striatum, cerebellum) samples were collected at the maximum lung viral titer 3 DPI. To approximate likely human nasopharyngeal infection progression, we analyzed gene expression profiles in the hamster tissues at 3DPI.

SARS-CoV-2 model, and RNA-sequencing of C57BL/6 and BALB/c mice treated with or without baricitinib

or tofacitinib. Mouse experiments were conducted as previously described[25]. Mice were housed in the UNC ABSL3 facility on a 12:12 light cycle using autoclaved cages (Tecniplast, EM500), irradiated Bed-o-Cob (ScottPharma, Bed-o-Cob 4RB), ad libitum irradiated chow (LabDiet, PicoLab Select Rodent 50 IF/6F 5V5R), and autoclaved water bottles. Animals used in this study included female 16-week-old C57BL/6J (B6) (The Jackson Laboratory stock 000664) or 10-12-week-old BALB/cAnNHsd (BALB/c) (Envigo order code 047) mice, purchased directly from vendors.

Mice were infected following light sedation, using 50 mg/kg ketamine and 15 mg/kg xylazine, by intranasal inoculation with 10^4 pfu SARS-CoV-2 MA10 diluted in 50 µL PBS or PBS alone (mock infection). Blinded treatment groups for mice were used throughout the study to limit investigator subjectivity. 24 hours post infection mice were dosed with baricitinib 10 mg/kg or tofacitinib 50 mg/kg. 7 days post-infection mice were euthanized by an overdose of isoflurane anesthetic and lung tissues were collected for subsequent processing.

BALB/c or C57BL/6 mice were infected by intranasal inoculation with 10^4 pfu SARS-CoV-2-MA10, and lung samples were collected at 4 DPI, after viral loads had peaked and declined. The generation and processing of the BALB/c or C57BL/6 lung tissue samples was performed as described in Guarnieri et al,[4]. BALB/c or C57BL/6 mice were infected by intranasal inoculation with 10^4 pfu SARS-CoV-2-MA10, and lung samples were collected at 4 DPI, after viral loads had peaked and declined. To approximate midway between the human nasopharyngeal and autopsy viral titers, we analyzed gene expression profiles in hamster tissues at 4 DPI.

RNA from inferior mouse lung lobes was extracted using TRIzol Reagent (ThermoFisher Scientific), followed by overnight precipitation at -20°C, and quantified using a NanoDrop spectrophotometer (ThermoFisher Scientific). Ribosomal RNA from 1000 ng total extracted RNA was depleted using a NEBNext rRNA Depletion Kit (Human/Mouse/Rat; New England Biolabs Inc.). The remaining RNA was used to produce the sequencing libraries using the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (New England Biolabs Inc.) with AMPure XP (Beckman Coulter Life Sciences) for all bead cleanup steps. The libraries were sequenced on a NovaSeq 6000 System, using a NovaSeq 6000 SP Reagent Kit v1.5 (Illumina).

Analysis combining sample RNA-seq data. To combine the results from the autopsy, nasopharyngeal swab, hamster, mice, PBMCS, miR-2392 mimics, and whole blood RNA-seq data, we utilized the t-score values from the DESeq2 analysis. Heatmaps were displayed using pheatmap (version 1.0.12). Circular heatmaps were produced in R (version 4.1.0) using the Complex Heatmap (version 2.9.4) and circlize (version 0.4.12) packages.

Gene Set Enrichment Analysis (GSEA). Pathway analysis was conducted as previously described in Guarnieri et al,[4] utilizing fast Gene Set Enrichment Analysis (fGSEA)[9] on custom-made Gene Set files (available in **Table S2**). Using fGSEA, all samples were compared to controls, and the ranked list of genes was defined by the t-score statistics. The statistical significance was determined by 1000 permutations of the gene sets and a cutoff of FDR < 0.25 was used throughout the paper as recommended by GSEA instructions[10]. Lollipop plots were made using R (version 4.2.1) using ggplot2 package (ver 3.4.2).

Data Analysis Methods for Figures 1A and 1B.

All analyses were performed in R v4.3.1.

1. Regression Analysis on Viral Load: **Sample Filtering**: Samples were excluded from analysis if their total human sequence read count was less than 10e06. Number of subjects passing requirements: 486. **Viral gene count background estimation**: Viral sequence counts were found to have a direct relationship with PCR levels. From that analysis, we determined that the background (false positive rate) of SARS-CoV-2 virus sequences in non-infected individuals was approximately 100 reads per sample. We replaced all '0' reads in our viral sample counts from uninfected individuals with a random integer between 1-100. Viral count data was log-transformed. **DE analysis**: We model human gene expression counts vs. log-transformed SARS-CoV-2 gene expression counts as described above. We first filtered for all human genes with at least 100 reads total across the 486 samples. Analyses were performed in R v4.3.1. Using Bioconductor packages DESeq2 v1.36.0[6], sva v3.44.0 (https://doi.org/doi:10.18129/B9.bioc.sva) and apeglm v 1.18.0[11], we fit a model of viral sequence counts vs. human gene expression. Using sva, we employed two surrogate variables with the viral count model. We then used apeglm to shrink the effect sizes and decrease the number of false positive associations. We utilized the EnhancedVolcano package v1.14.0 to represent the resulting data, shown in Figure 1a.

2. Individual subject pathway analysis (z-score analysis) methodology: **Sample filtering**: Samples were excluded from analysis if their total human sequence read count was less than 10e06. Number of subjects passing requirements: 486. Subject counts used in this analysis were grouped by viral PCR categories; High: n = 48, Medium: n = 79, Low: n = 35, None: n = 324. **Batch Correction**: The ComBat_seq function in sva package v3.44.0 (https://doi.org/doi:10.18129/B9.bioc.sva) was employed for batch correction versus the plateID (see metadata). **Generation of z-scores**: Gene expression from nasal swabs on individuals with positive results for PCR-detectable SARS-CoV-2 virus ("High", "Medium", "Low") were compared to the group of negative result individuals ("None"). Each gene expression vector from a positive PCR subject was individually transformed into a gene expression z-score vector by individual comparison specifically with the "None" group gene expression vectors. Each "None" subject's gene expression z-score vector was similarly calculated vs. the rest of the "None" group's gene expression vectors. Z-scores in the vectors therefore represent each gene's expression deviation vs. that gene from the "None" group. The resulting gene expression z-score matrix was used to generate single-subject GSEA analyses. **Subject gene set enrichment analyses (GSEA)**: For each subject, the gene expression z-score vector is ranked from the most positive to the most negative z-score. Each subject's gene expression z-score vector was used as input into the R package fgsea (fast gene set enrichment analysis) v 1.22.0[9]. To measure the relative enrichment of gene sets for each individual subject based on the z-score rankings, we input each subject's z-score vector into the fgsea package. The MSigDB pathway database version 7.5.1 (doi: https://davislaboratory.github.io/msigdb) was employed as gene sets in the fgsea analysis, specifically the Hallmarks (H) and computational pathways (c2.cp) pathway sets. Results are shown in Figure 1c and in supplementary data.

Figure S1.

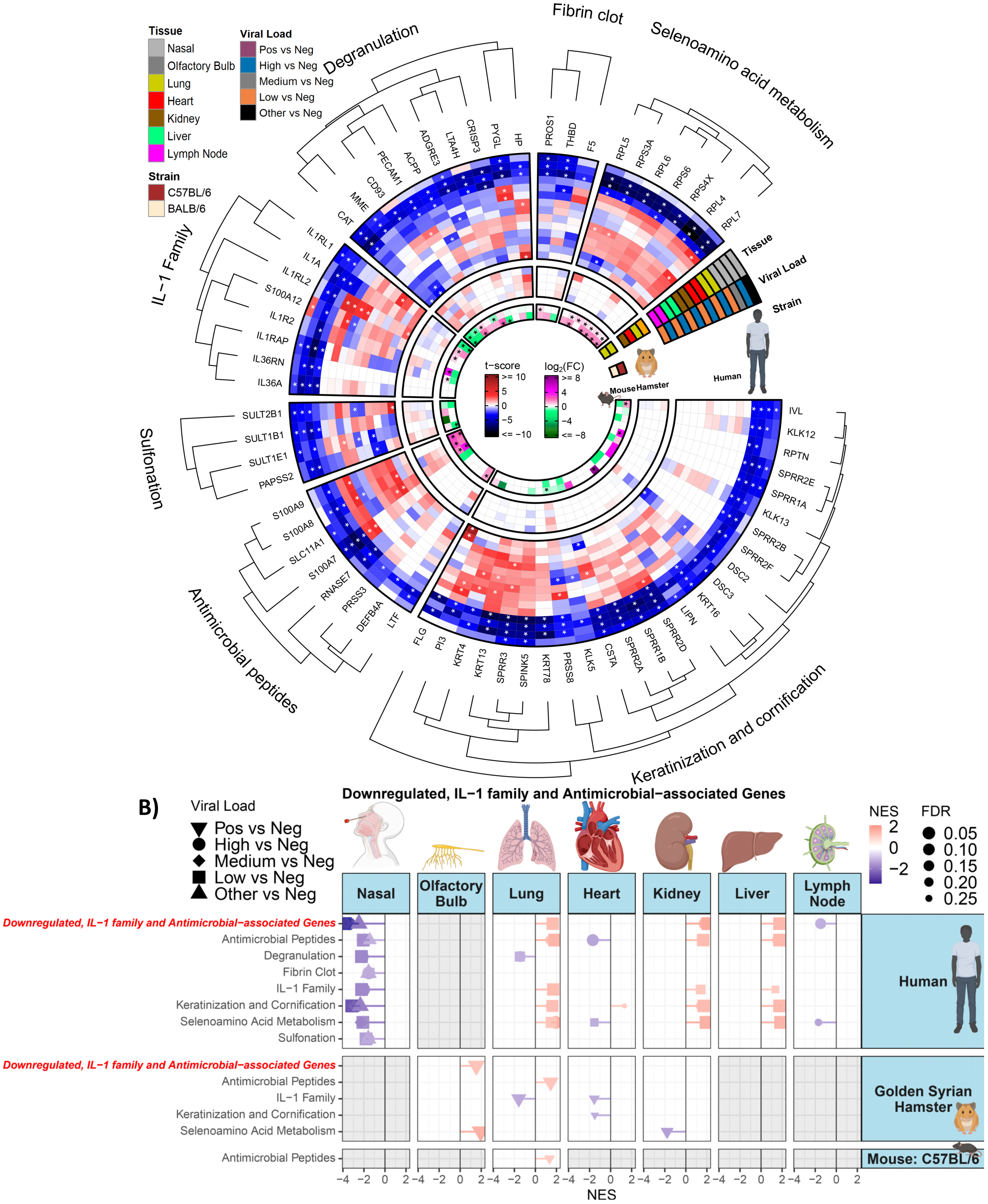

Fig. S1: Differentially regulated downregulated genes of interest in infected rodent samples and human autopsy tissues from COVID-19 patients. A) Circular heatmap displaying the t-score statistics for specific downregulated genes of interest, comparing SARS-CoV-2 infected hamster tissues, viral load versus negative patient nasopharyngeal and autopsy tissue samples, and log$_2$-foldchange (FC) for SARS-CoV-2 infected C57BL/6 and BALB/c mouse lungs. **B)** Lollipop plots for statistically significant changes in downregulated genes of interest sets determined by fGSEA for SARS-CoV-2 positive nasopharyngeal, autopsy, and rodent tissues, ranked by NES, nominal enrichment score.

Figure S2.

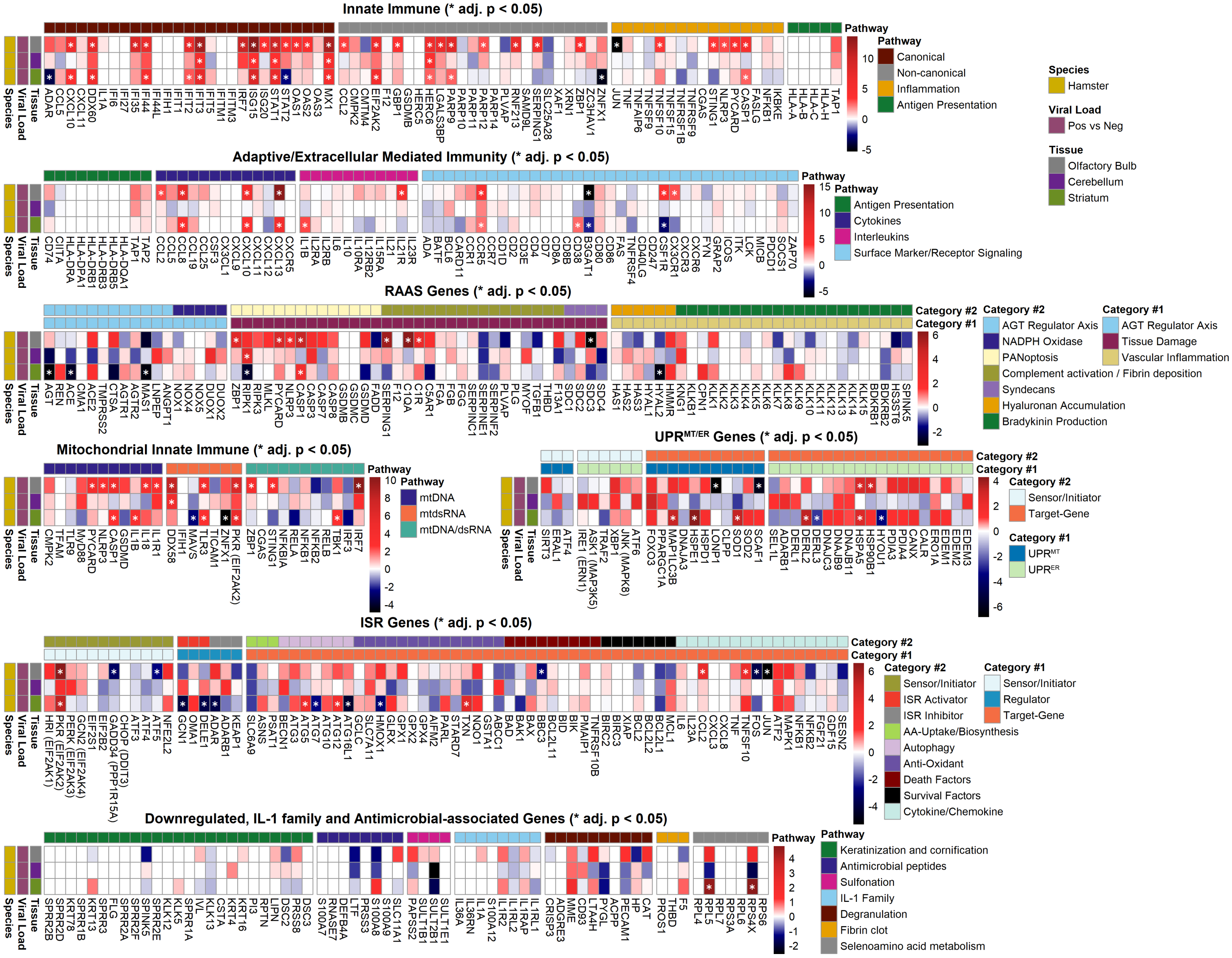

Fig. S2: Differentially regulated immune genes in SARS-CoV-2 infected hamster olfactory bulb, cerebellum, and striatum. Linear heatmap displaying the t-score statistics for innate immune genes of interest, comparing SARS-CoV-2 infected hamster tissues

Figure S3.

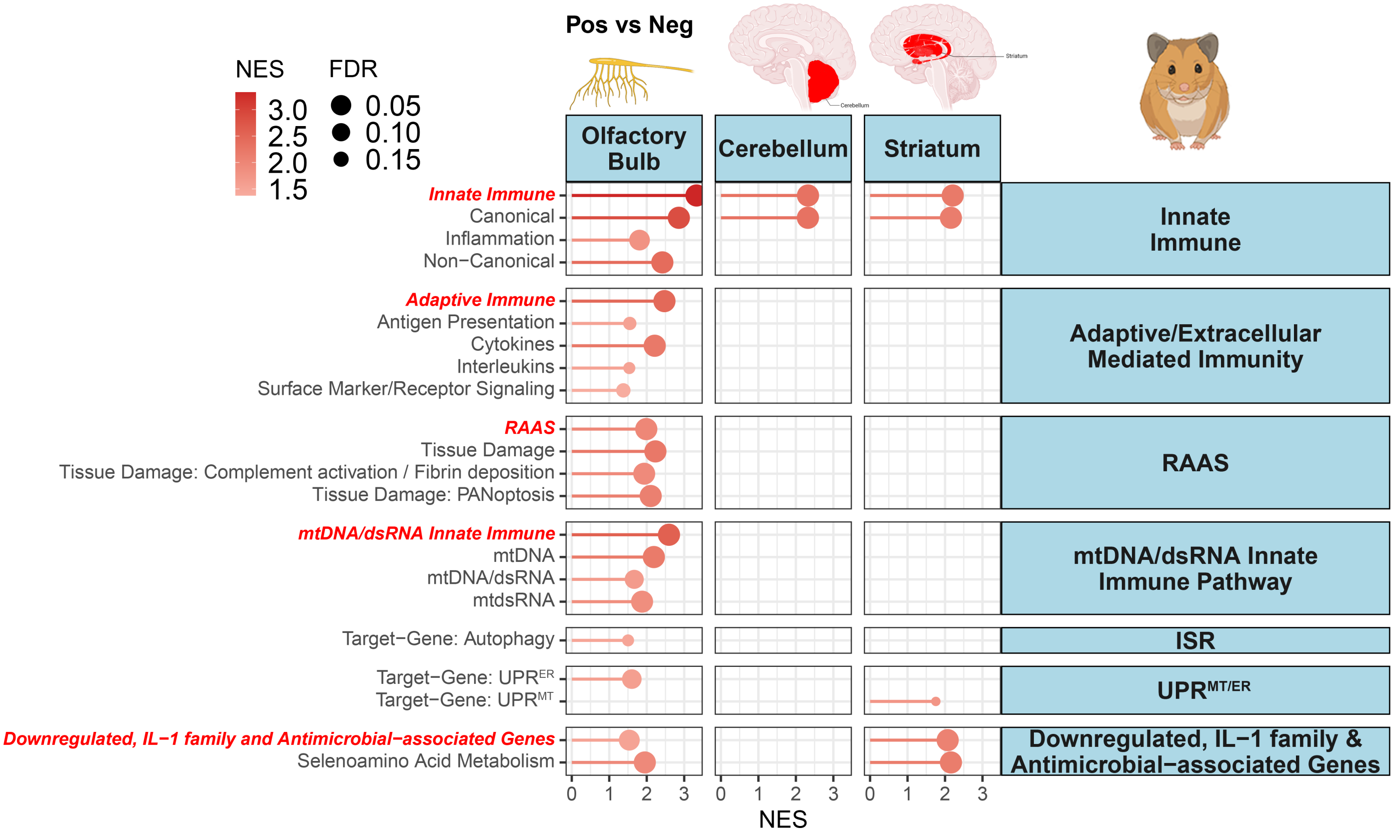

Fig. S3: Lollipop plots for statistically significant changes in innate immune gene sets determined by fGSEA for SARS-CoV-2 positive hamster tissues. Ranked by NES, nominal enrichment score.

Figure S4.

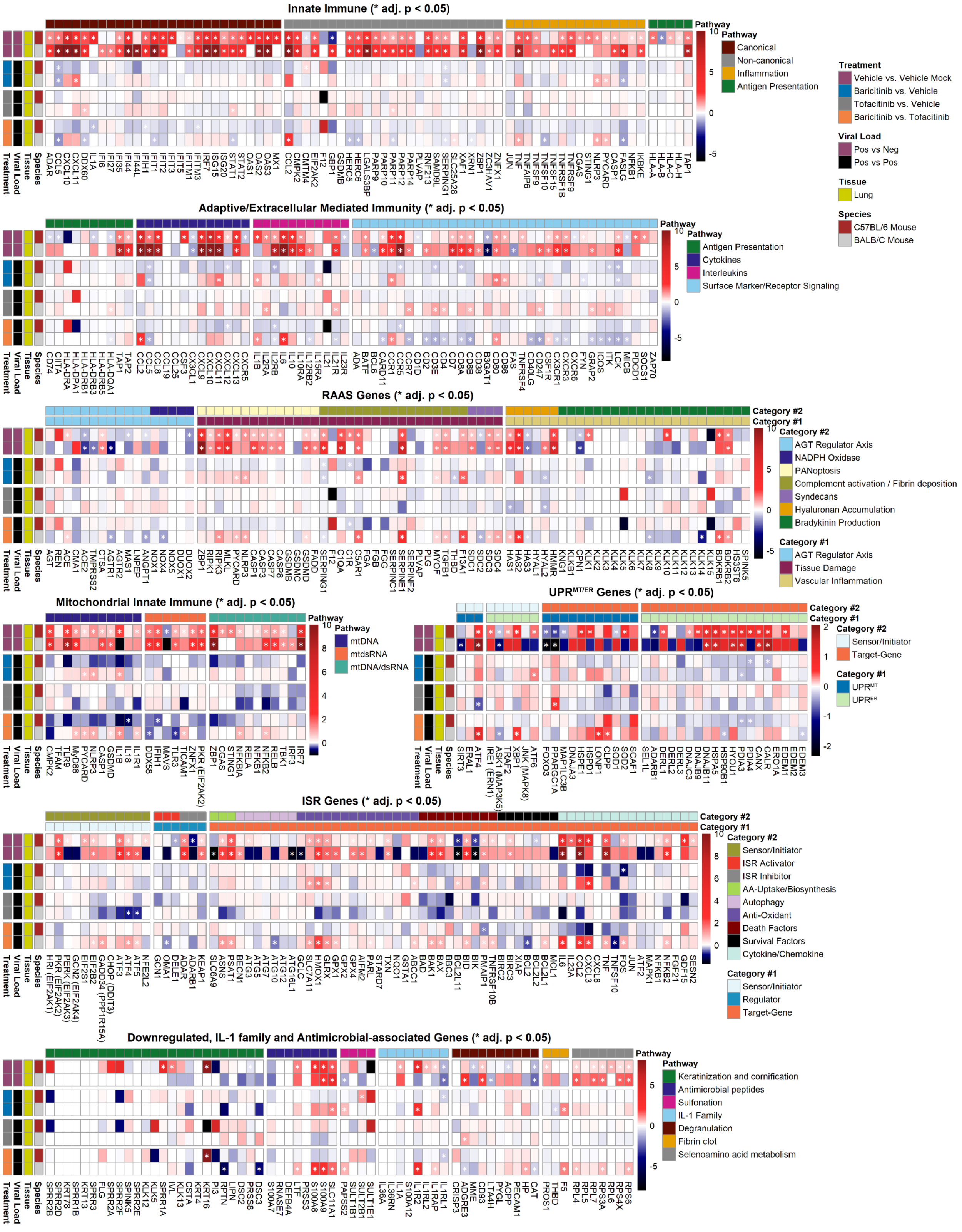

Fig. S4: Differentially regulated immune genes in SARS-CoV-2 infected C57BL/6 and BALB/c mouse lungs treated with or without baricitinib or tofacitinib. Linear heatmap displaying the t-score statistics for innate immune genes of interest, comparing SARS-CoV-2 infected mouse lungs treated with or without baricitinib or tofacitinib.

Figure S5.

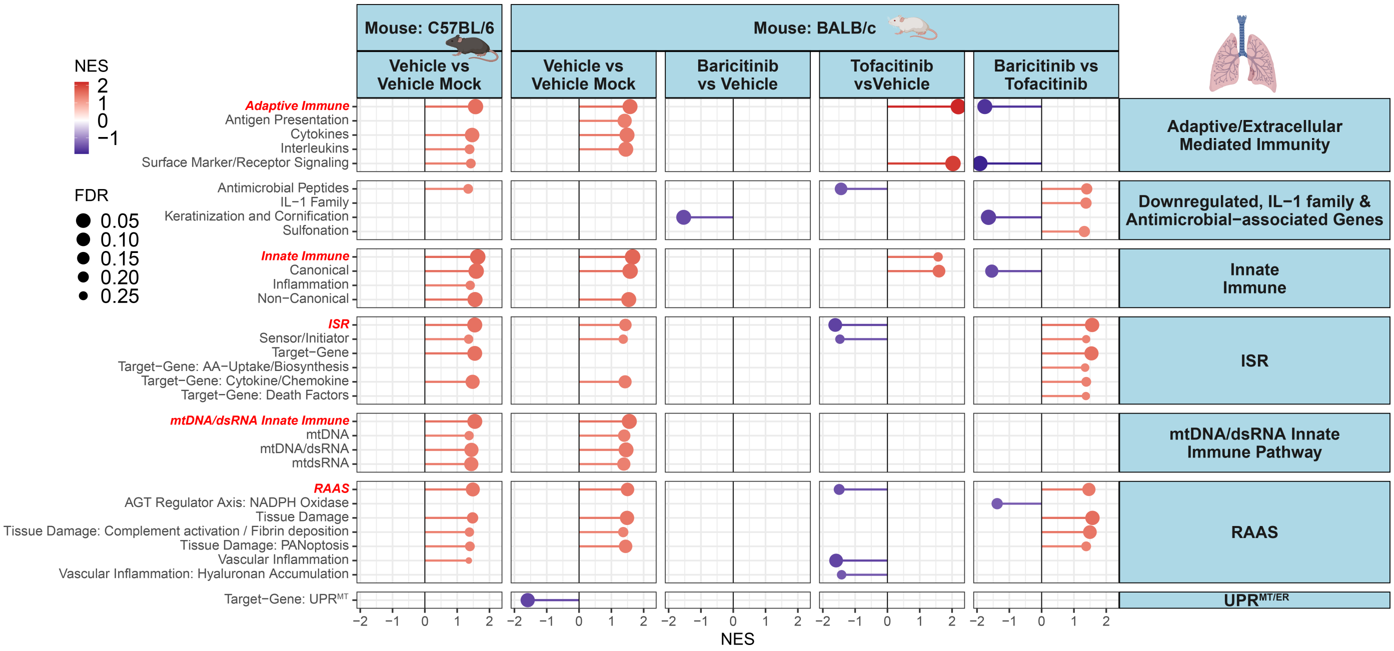

Fig. S5: Lollipop plots for statistically significant changes in innate immune gene sets determined by fGSEA for SARS-CoV-2 positive mouse lungs treated with or without baricitinib or tofacitinib. Ranked by NES, nominal enrichment score.

Figure S6.

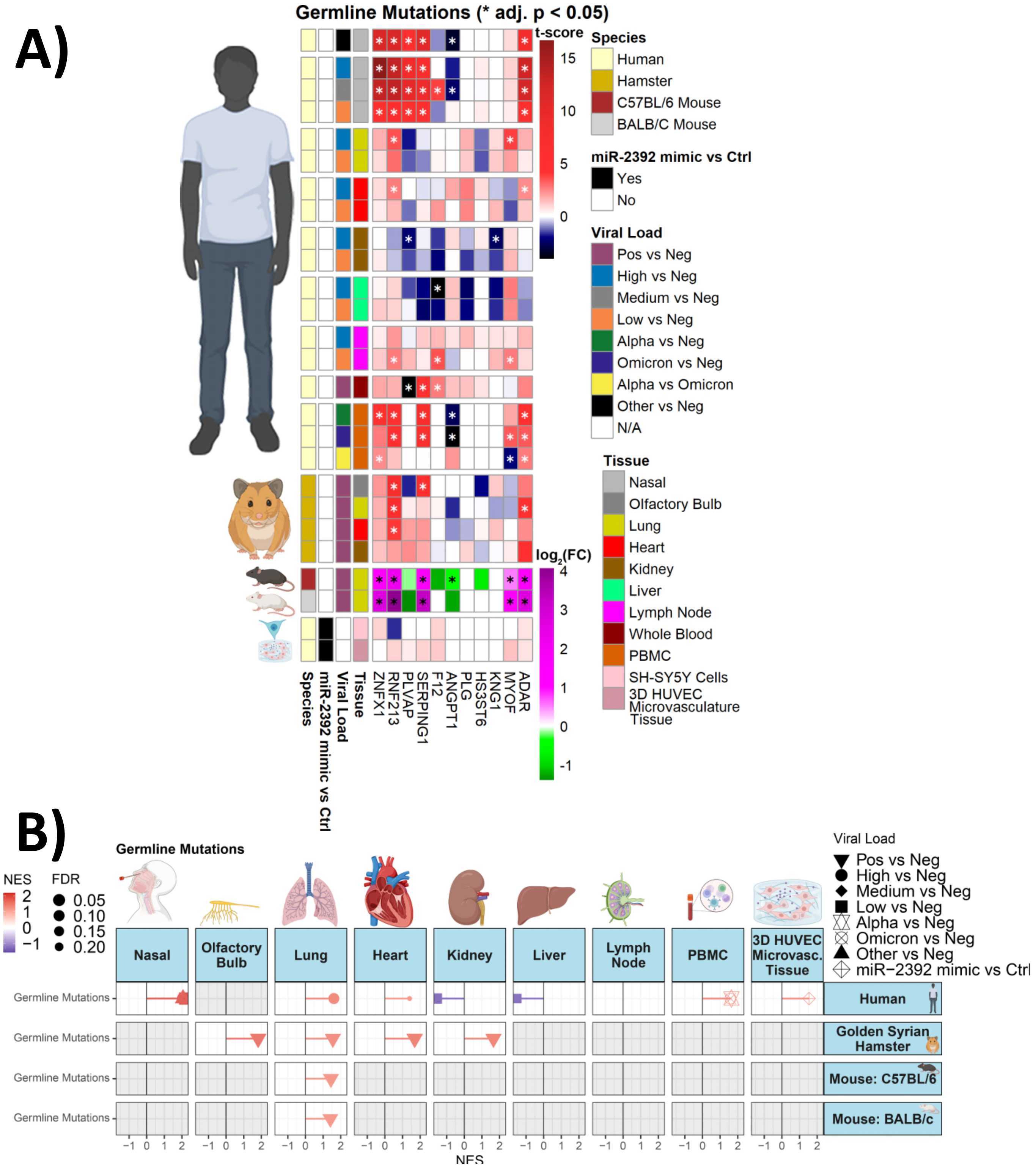

Fig. S6: Differentially regulated genes that have germline mutations in infected rodent samples and human autopsy and nasopharyngeal tissues from COVID-19 patients. Linear heatmap displaying the t-score statistics for genes that have germline mutations of interest, comparing SARS-CoV-2 infected hamster tissues, viral load versus negative patient nasopharyngeal and autopsy tissue samples, and $\log_2$-foldchange (FC) for SARS-CoV-2 infected C57BL/6 and BALB/c mouse lungs. **B)** Lollipop plots for statistically significant changes in germline mutation gene sets determined by fGSEA for SARS-CoV-2 positive nasopharyngeal, autopsy, and rodent tissues, ranked by NES, nominal enrichment score.

Figure S7.

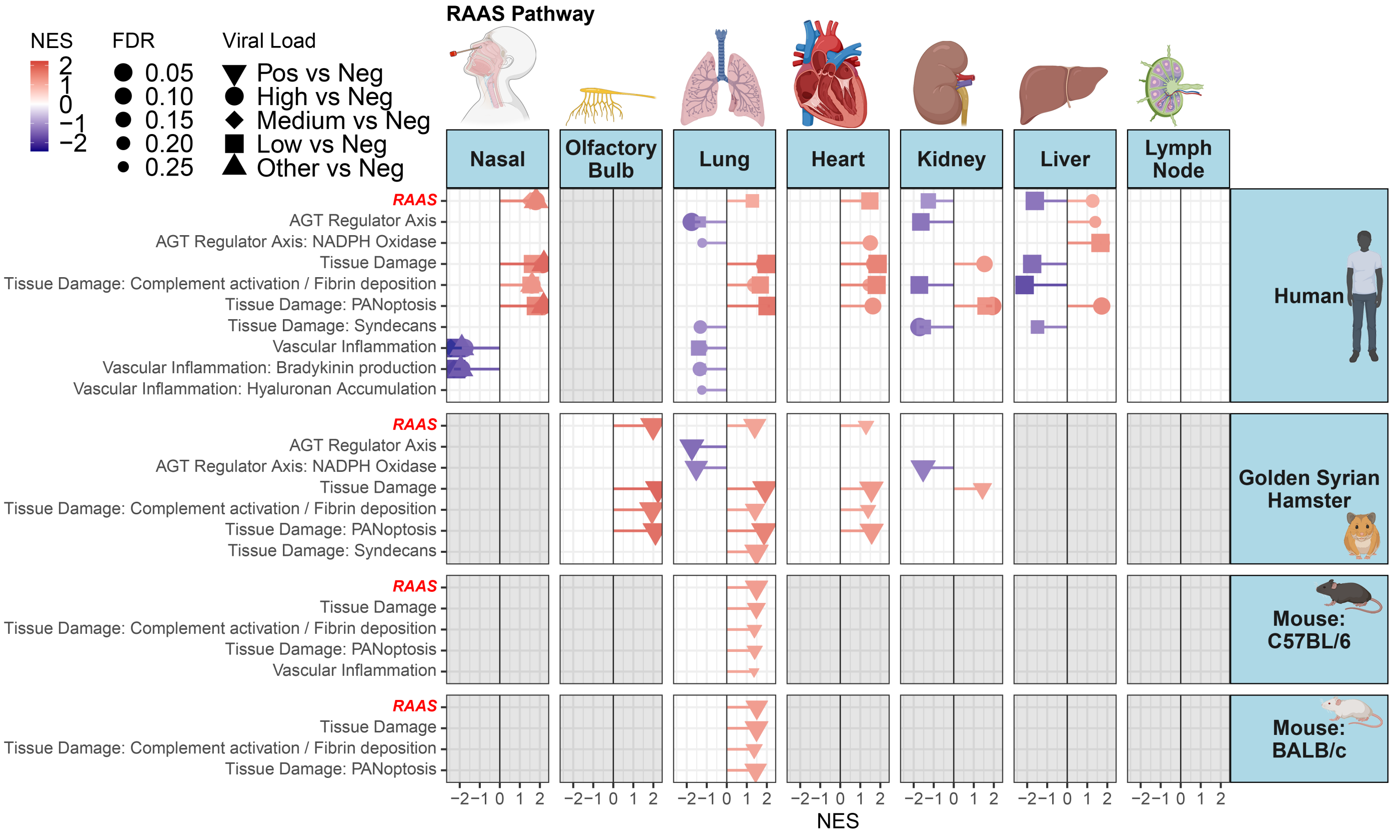

Fig. S7: Lollipop plots for statistically significant changes in RAAS gene sets determined by fGSEA in SARS-CoV-2 infected rodent samples and human autopsy and nasopharyngeal tissues from COVID-19 patients. Ranked by NES, nominal enrichment score.

Figure S8.

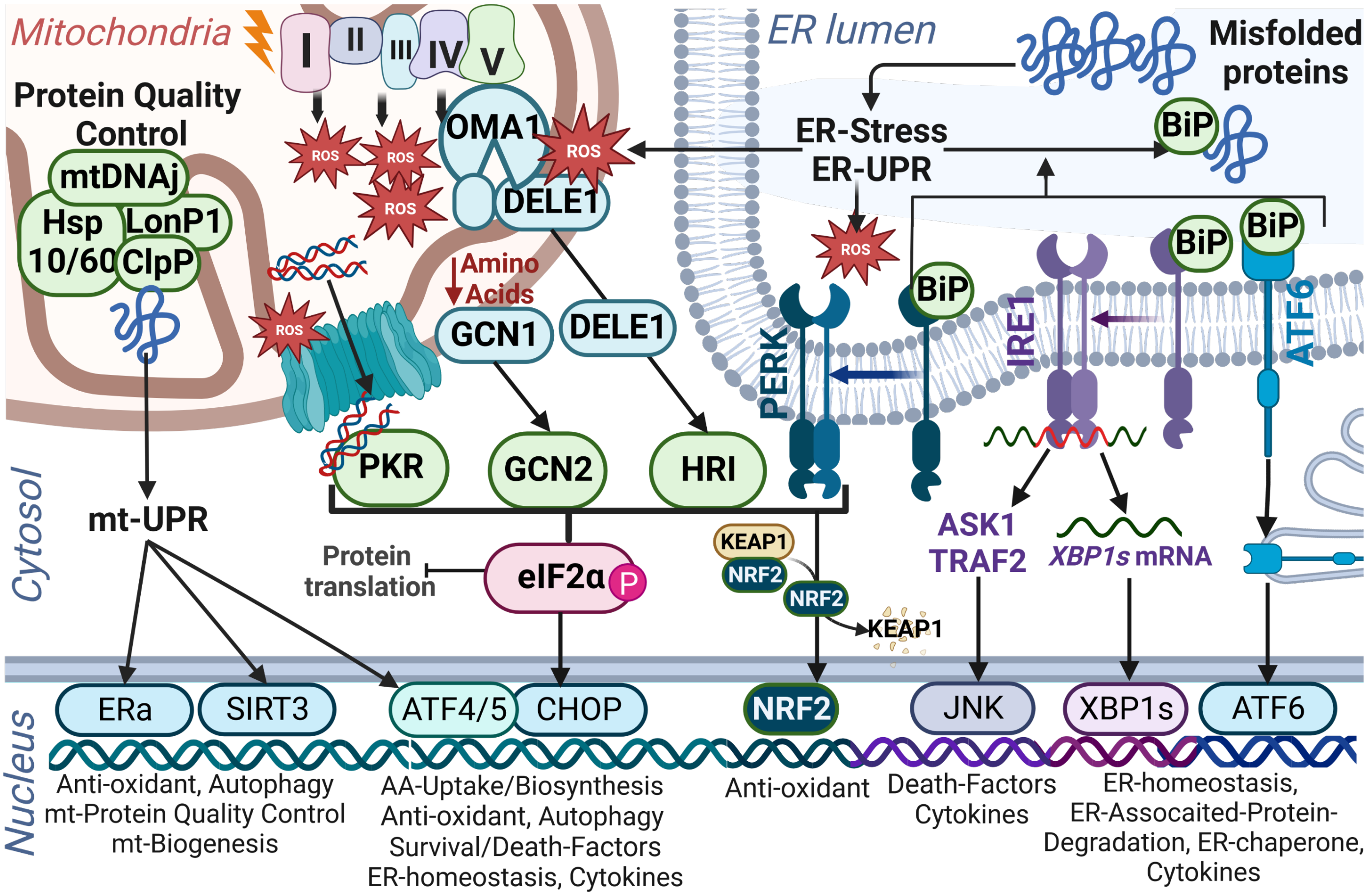

Fig. S8: Summary of key ISR, endoplasmic reticulum and mitochondrial UPR genes.

Figure S9.

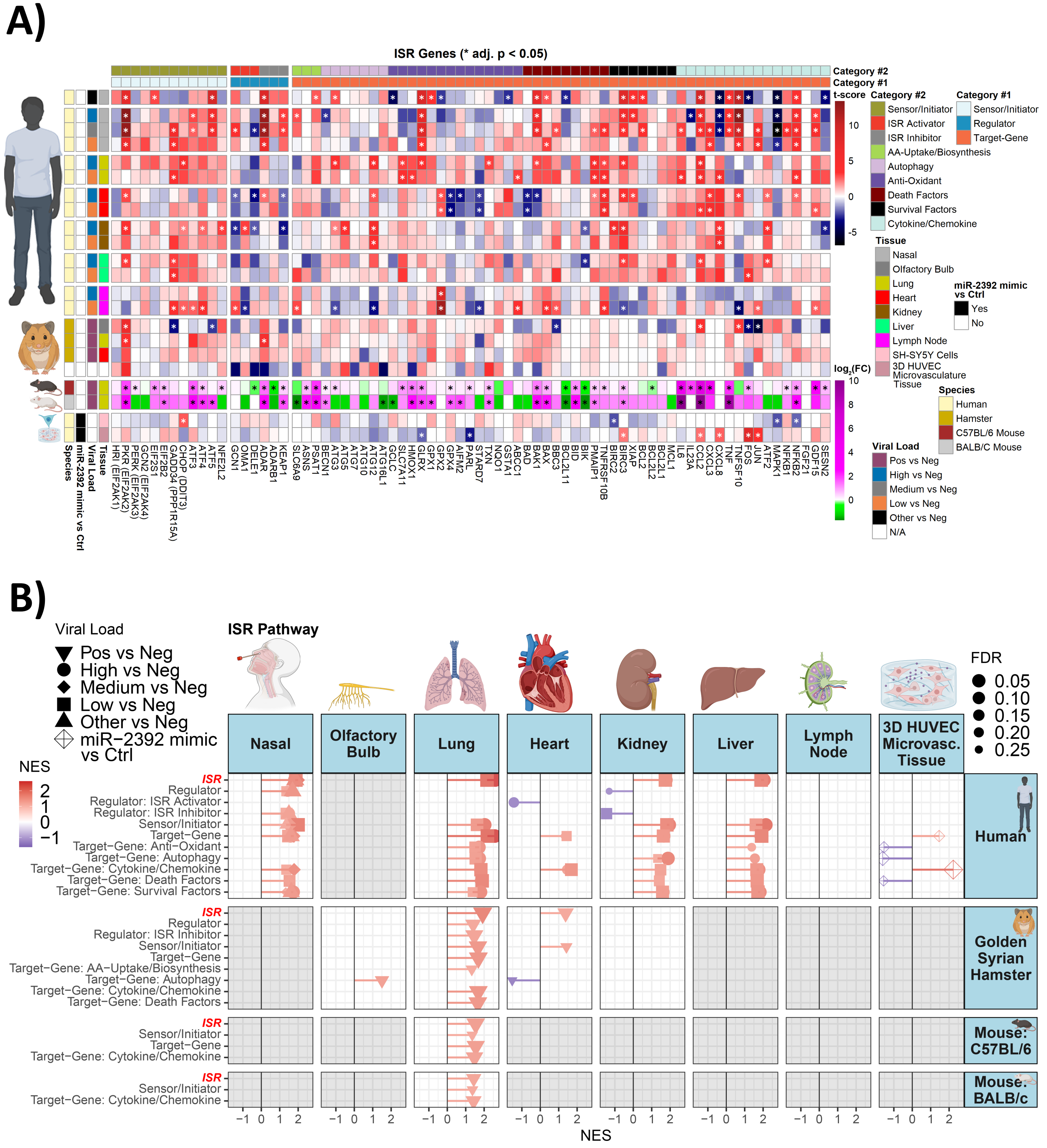

Fig. S9: Differentially regulated ISR genes in SARS-CoV-2 infected rodent samples and human autopsy and nasopharyngeal tissues from COVID-19 patients. A) Linear heatmap displaying the t-score statistics specific ISR gene sets, comparing SARS-CoV-2 infected hamster tissues, viral load versus negative patient nasopharyngeal and autopsy tissue samples, and log$_2$-foldchange (FC) for SARS-CoV-2 infected C57BL/6 and BALB/c mouse lungs. **B)** Lollipop plots for statistically significant changes in custom ISR gene sets determined by fGSEA for SARS-CoV-2 positive nasopharyngeal, autopsy, and rodent tissues, and miR-2392-expressing 3D-HUVEC-MT cells ranked by NES, nominal enrichment score.

Figure S10.

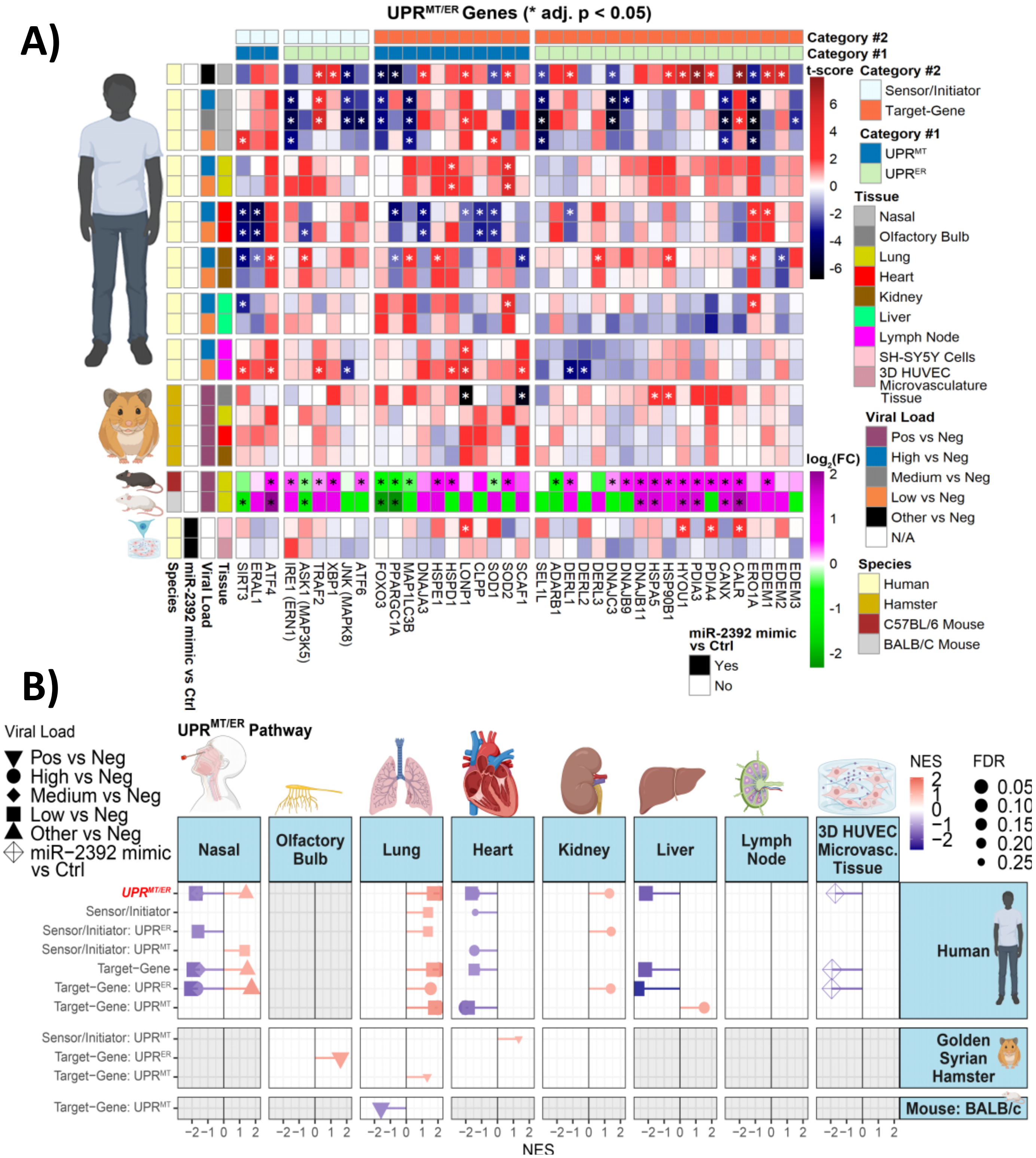

Fig. S10: Differentially regulated UPR$^{ER/MT}$ genes in SARS-CoV-2 infected rodent samples and human autopsy and nasopharyngeal tissues from COVID-19 patients. A) Linear heatmap displaying the t-score statistics specific UPR$^{ER/MT}$ gene sets, comparing SARS-CoV-2 infected hamster tissues, viral load versus negative patient nasopharyngeal and autopsy tissue samples, and log$_2$-foldchange (FC) for SARS-CoV-2 infected C57BL/6 and BALB/c mouse lungs. **B)** Lollipop plots for statistically significant changes in custom UPR$^{ER/MT}$ gene sets determined by fGSEA for SARS-CoV-2 positive nasopharyngeal, autopsy, and rodent tissues, and miR-2392-expressing 3D-HUVEC-MT cells ranked by NES, nominal enrichment score.

Figure S11.

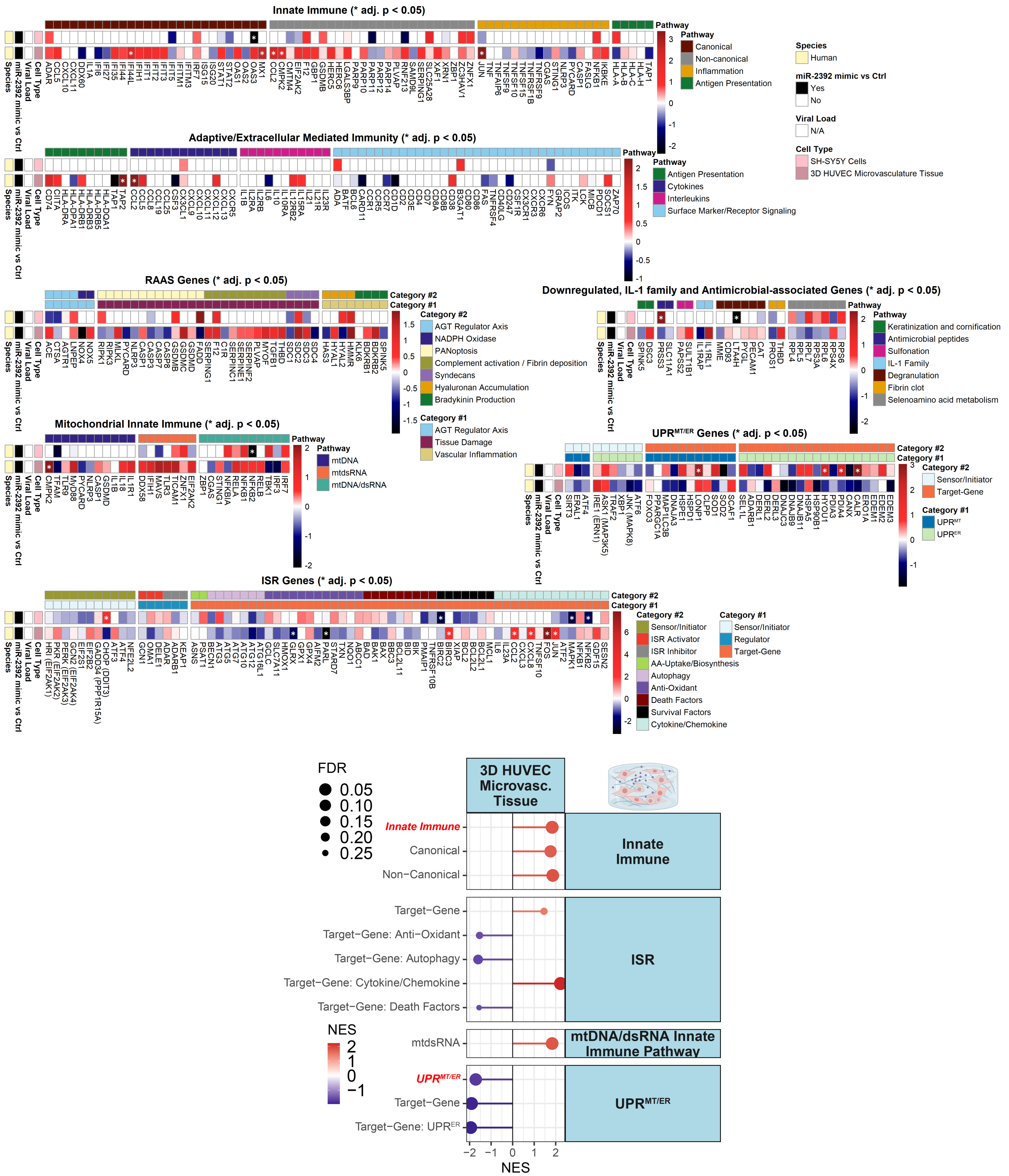

Fig. S11: Differentially regulated immune genes in miR-2392-expressing 3D-HUVEC-MT and SH-SY5Y cells. **A)** Linear heatmap displaying the t-score statistics for innate immune genes comparing miR-2392-expressing 3D-HUVEC-MT cells. **B)** Lollipop plots for statistically significant changes in innate immune gene sets determined by miR-2392-expressing 3D-HUVEC-MT cells, ranked by NES, nominal enrichment score.

Figure S12.

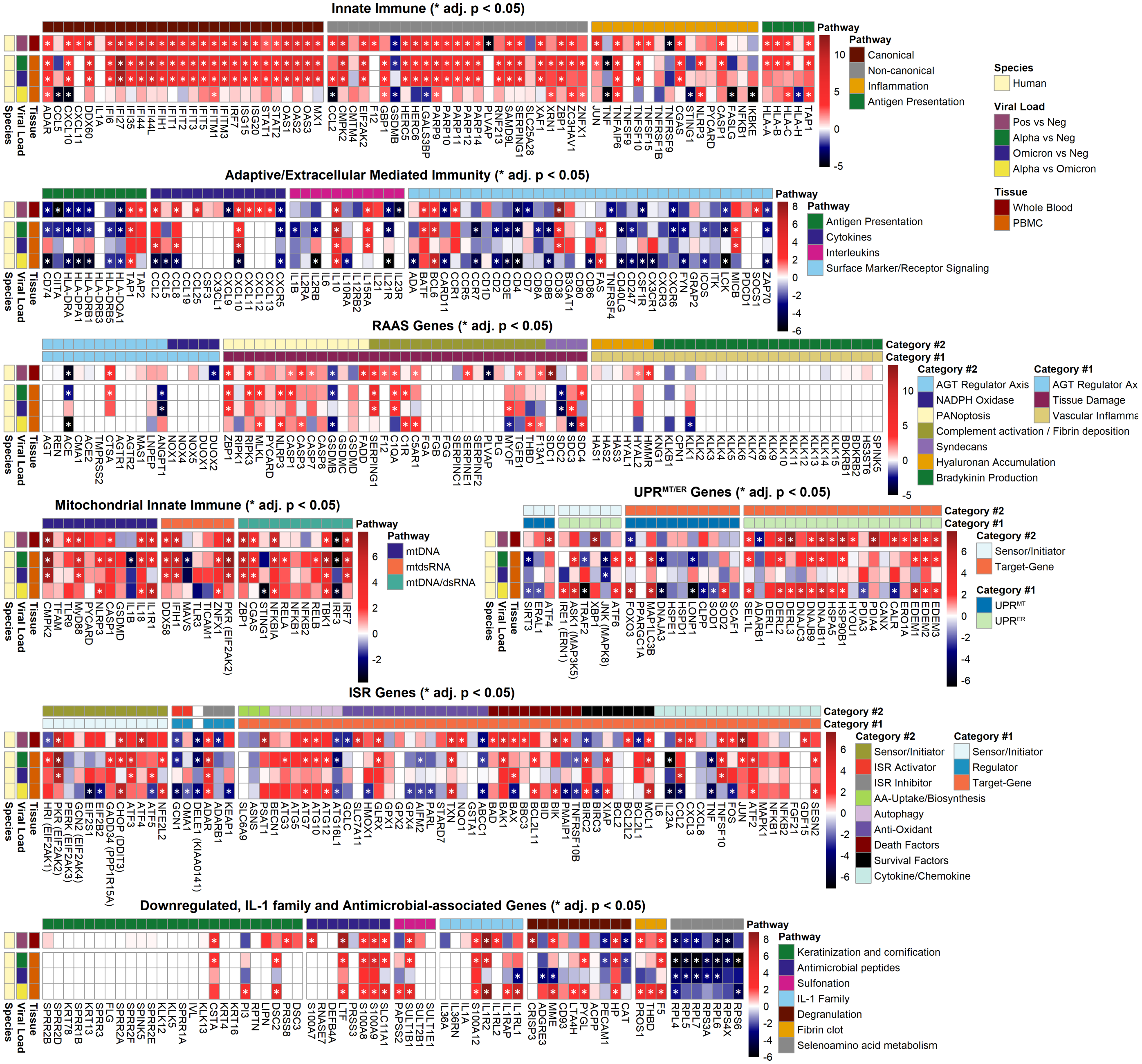

Fig. S12: Differentially regulated immune genes in PBMCs and whole blood samples collected individuals with early and later SARS-CoV-2 variants. Linear heatmap displaying the t-score statistics for innate immune genes comparing PBMCs and whole blood samples collected from SARS-CoV-2 infected individuals.

Table. S1. SARS-CoV-2 Viral Load of Human Nasopharyngeal, Autopsy, Rodent and PBMCs Samples.

STAGE	Hamster Lungs PFU Log10 ($\bar{X}\pm\sigma_M$)				REF
ACUTE	DAY 1	7.4	±	0.2	12
	DAY 2	8.2	±	0.4	
	DAY 3	7.2	±	0.3	
	DAY 7	0	±	0	
	Hamster Tissues 3DPI TPM ($\bar{X}\pm\sigma_M$)				13
	Lung	2.3E+05	±	4.0E+04	
	Kidney	8	±	8	
	Heart	58	±	16	
	Olfactory Bulb	581	±	247	
	Cerebellum	428	±	220	
	Striatum	75	±	73	
EARLY	**Nasal Samples TPM ($\bar{X}\pm\sigma_M$)**				
	Nasal-High	1.0E+07	±	1.4E+06	
	Nasal-Medium	7.0E+05	±	1.6E+05	
	Nasal-Low	1.5E+04	±	1.0E+04	
	Other-Viral	18	±	5	
MID	**Mouse Lungs 4DPI PFU Log10 ($\bar{X}\pm\sigma_M$)**				
	C57BL/6	4.76	±	4.8	
	BALB/c	4.85	±	4.6	
LATE	**Autopsy Tissue TPM ($\bar{X}\pm\sigma_M$)**				
	Lung	1	±	1	
	Heart	1	±	1	
	Kidney	1	±	1	
	Liver	1	±	1	
	LymphNode	2	±	2	
	PBMCs TPM ($\bar{X}\pm\sigma_M$)				14
	PBMCs α-strain	0	±	0	
	PBMCs o-strain	0	±	0	

Table S2. Curated Immune Gene List

REF:[15]

INNATE IMMUNE GENES

Canonical:

ADAR (Adenosine Deaminase RNA Specific): Enzyme that converts adenosine to inosine in double-stranded RNA, which can impact RNA stability and function.

CCL5 (C-C Motif Chemokine Ligand 5): A chemokine involved in recruiting immune cells to sites of inflammation.

CXCL10 (C-X-C Motif Chemokine Ligand 10): Chemokine that attracts immune cells, particularly during infection or inflammation.

CXCL11 (C-X-C Motif Chemokine Ligand 11): Chemokine that recruits activated T cells to sites of infection or inflammation.

DDX60 (DEAD (Asp-Glu-Ala-Asp) Box Polypeptide 60): An RNA helicase involved in antiviral responses, recognizing viral RNA.

IFI27 (Interferon Alpha Inducible Protein 27): Protein induced by interferon, playing a role in antiviral defense.

IFI35 (Interferon-Induced Protein 35): Protein involved in the regulation of antiviral responses.

IFI44 (Interferon-Induced Protein 44): Protein induced by interferon, contributing to antiviral responses.

IFI44L (Interferon-Induced Protein 44-Like): Protein similar to IFI44, involved in antiviral defense.

IFI6 (Interferon Alpha Inducible Protein 6): Protein involved in apoptosis and antiviral defense.

IFIH1 (Interferon-Induced with Helicase C Domain 1): Also known as MDA5, detects viral RNA and activates antiviral responses.

IFIT1 (Interferon-Induced Protein with Tetratricopeptide Repeats 1): Protein that binds viral RNA and inhibits viral replication.

IFIT2 (Interferon-Induced Protein with Tetratricopeptide Repeats 2): Similar to IFIT1, binds viral RNA and inhibits viral replication.

IFIT3 (Interferon-Induced Protein with Tetratricopeptide Repeats 3): Protein involved in antiviral responses and immune signaling.

IFIT5 (Interferon-Induced Protein with Tetratricopeptide Repeats 5): Protein that detects and binds viral RNA.

IFITM1 (Interferon-Induced Transmembrane Protein 1): Protein that inhibits viral entry into cells.

IFITM3 (Interferon-Induced Transmembrane Protein 3): Protein that inhibits viral entry and replication.

IL1A (Interleukin 1 Alpha): Cytokine involved in inflammatory responses and fever induction.

IRF7 (Interferon Regulatory Factor 7): Transcription factor that regulates type I interferon production.

ISG15 (Interferon-Stimulated Gene 15): Ubiquitin-like protein that modifies other proteins to enhance antiviral responses.

ISG20 (Interferon-Stimulated Gene 20): Exonuclease that degrades viral RNA.

MX1 (MX Dynamin-Like GTPase 1): GTPase involved in inhibiting viral replication.

OAS1 (2'-5'-Oligoadenylate Synthetase 1): Enzyme that synthesizes molecules activating RNase L to degrade viral RNA.

OAS2 (2'-5'-Oligoadenylate Synthetase 2): Similar to OAS1, synthesizes molecules activating RNase L.

OAS3 (2'-5'-Oligoadenylate Synthetase 3): Enzyme that enhances antiviral defense through RNase L activation.

PARP9 (Poly(ADP-Ribose) Polymerase Family Member 9): Protein involved in DNA repair and modulation of antiviral responses.

SAMD9L (Sterile Alpha Motif Domain Containing 9-Like): Protein involved in antiviral responses and cell proliferation regulation.

STAT1 (Signal Transducer and Activator of Transcription 1): Transcription factor activated by interferons, mediating antiviral responses.

STAT2 (Signal Transducer and Activator of Transcription 2): Transcription factor that forms a complex with STAT1 to mediate antiviral responses.

Non-Canonical:

CCL2 (C-C Motif Chemokine Ligand 2): Chemokine involved in recruiting monocytes to sites of inflammation.

CMPK2 (Cytidine/Uridine Monophosphate Kinase 2): Enzyme involved in nucleotide synthesis and innate immune responses.

CMTM4 (CKLF Like MARVEL Transmembrane Domain Containing 4): Protein with potential roles in immune cell signaling.

EIF2AK2 (Eukaryotic Translation Initiation Factor 2 Alpha Kinase 2): Also known as PKR, kinase activated by viral dsRNA, inhibiting protein synthesis to block viral replication.

GBP1 (Guanylate Binding Protein 1): GTPase involved in antimicrobial and antiviral responses.

GSDMB (Gasdermin B): Protein involved in pyroptosis, an inflammatory form of programmed cell death.

HERC5 (HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 5): E3 ligase involved in ISGylation, enhancing antiviral responses.

HERC6 (HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 6): Similar to HERC5, involved in ISGylation.

LGALS3BP (Galectin 3 Binding Protein): Protein involved in immune cell activation and adhesion.

PARP10 (Poly(ADP-Ribose) Polymerase Family Member 10): Enzyme involved in protein modification and potentially immune responses.

PARP11 (Poly(ADP-Ribose) Polymerase Family Member 11): Enzyme with roles in protein modification and possibly antiviral responses.

PARP12 (Poly(ADP-Ribose) Polymerase Family Member 12): Enzyme involved in antiviral responses.

PARP14 (Poly(ADP-Ribose) Polymerase Family Member 14): Protein involved in regulating immune responses and inflammation.

PLVAP (Plasmalemma Vesicle Associated Protein): Protein involved in vascular permeability and immune cell trafficking.

RNF213 (Ring Finger Protein 213): E3 ubiquitin ligase involved in immune responses and possibly in Moyamoya disease.

SERPING1 (Serpin Family G Member 1): Protein inhibiting complement activation, reducing inflammation.

SLC25A28 (Solute Carrier Family 25 Member 28): Mitochondrial iron transporter, potentially impacting immune responses.

XAF1 (XIAP Associated Factor 1): Protein promoting apoptosis and modulating immune responses.

ZBP1 (Z-DNA Binding Protein 1): Sensor of viral nucleic acids, activating antiviral responses.

ZC3HAV1 (Zinc Finger CCCH-Type Antiviral Protein 1): Protein with antiviral activity, possibly by inhibiting viral RNA.

ZNFX1 (Zinc Finger NFX1-Type Containing 1): Protein involved in recognizing viral RNA and activating immune responses.

Inflammation

CASP1 (Caspase 1): Enzyme that processes pro-inflammatory cytokines, playing a role in pyroptosis.

CGAS (Cyclic GMP-AMP Synthase): Enzyme that senses cytosolic DNA and activates type I interferon responses.

FASLG (Fas Ligand): Protein that induces apoptosis in Fas-expressing cells.

IKBKE (Inhibitor of Nuclear Factor Kappa B Kinase Subunit Epsilon): Kinase involved in activating NF-κB signaling.

JUN (Jun Proto-Oncogene, AP-1 Transcription Factor Subunit): Transcription factor involved in inflammatory responses.

NFKB1 (Nuclear Factor Kappa B Subunit 1): Subunit of NF-κB, a transcription factor regulating inflammation and immune responses.

NLRP3 (NLR Family Pyrin Domain Containing 3): Component of the inflammasome, activating caspase-1 and promoting inflammation.

PYCARD (PYD And CARD Domain Containing): Adapter protein involved in inflammasome assembly.

STING1 (Stimulator of Interferon Response CGAMP Interactor 1): Protein that senses cytosolic DNA and activates type I interferon responses.

TNF (Tumor Necrosis Factor): Cytokine involved in systemic inflammation and apoptosis.

TNFAIP6 (Tumor Necrosis Factor Alpha-Induced Protein 6): Protein involved in extracellular matrix remodeling and inflammation.

TNFRSF1B (TNF Receptor Superfamily Member 1B): Receptor for TNF, mediating inflammatory and immune responses.

TNFRSF9 (TNF Receptor Superfamily Member 9): Receptor involved in T cell activation and survival.

TNFSF9 (TNF Superfamily Member 9): Also known as 4-1BB ligand, involved in T cell co-stimulation.

TNFSF10 (TNF Superfamily Member 10): Also known as TRAIL, induces apoptosis in target cells.

TNFSF15 (TNF Superfamily Member 15): Cytokine involved in inflammation and endothelial cell apoptosis.

Antigen Presentation

HLA-A (Major Histocompatibility Complex, Class I, A): Gene encoding an MHC class I molecule involved in presenting peptides to T cells.

HLA-B (Major Histocompatibility Complex, Class I, B): Gene encoding an MHC class I molecule involved in presenting peptides to T cells.

HLA-C (Major Histocompatibility Complex, Class I, C): Gene encoding an MHC class I molecule involved in presenting peptides to T cells.

HLA-H (Major Histocompatibility Complex, Class I, H): Gene encoding a non-classical MHC class I molecule with roles in immune responses.

TAP1 (Transporter 1, ATP Binding Cassette Subfamily B Member): Protein involved in transporting peptides into the endoplasmic reticulum for MHC class I presentation.

DOWNREGULATED GENES OF INTEREST

Keratinization and Cornification:

CSTA (Cystatin A): Protein inhibiting proteases, involved in skin barrier function.
DSC2 (Desmocollin 2): Component of desmosomes, contributing to cell adhesion in the skin.
DSC3 (Desmocollin 3): Similar to DSC2, involved in cell adhesion.
FLG (Filaggrin): Protein involved in skin barrier formation and hydration.
IVL (Involucrin): Protein involved in the formation of the skin's cornified envelope.
KLK5 (Kallikrein Related Peptidase 5): Serine protease involved in skin barrier function and desquamation.
KLK12 (Kallikrein Related Peptidase 12): Serine protease involved in skin desquamation.
KLK13 (Kallikrein Related Peptidase 13): Similar to KLK12, involved in skin desquamation.
KRT4 (Keratin 4): Similar to KRT13, found in epithelial cells.
KRT13 (Keratin 13): Intermediate filament protein in epithelial cells.
KRT16 (Keratin 16): Intermediate filament protein involved in the integrity of epithelial cells.
KRT78 (Keratin 78): Intermediate filament protein with roles in epithelial cell structure.
LIPN (Lipase Family Member N): Enzyme potentially involved in lipid metabolism in the skin.
PI3 (Peptidase Inhibitor 3, Skin-Derived): Protein inhibiting proteases, contributing to skin barrier function.
PRSS8 (Protease, Serine 8): Serine protease involved in epidermal homeostasis.
RPTN (Repetin): Protein involved in skin barrier function.
SPINK5 (Serine Peptidase Inhibitor Kazal Type 5): Protease inhibitor involved in skin barrier function.
SPRR1A (Small Proline Rich Protein 1A): Protein involved in the formation of the cornified envelope in the skin.
SPRR1B (Small Proline Rich Protein 1B): Similar to SPRR1A, involved in the cornified envelope formation.
SPRR2A (Small Proline Rich Protein 2A): Protein contributing to the cornified envelope in the skin.
SPRR2B (Small Proline Rich Protein 2B): Similar to SPRR2A, involved in skin barrier formation.
SPRR2D (Small Proline Rich Protein 2D): Similar to SPRR2A, involved in skin barrier function.
SPRR2E (Small Proline Rich Protein 2E): Similar to SPRR2A, involved in skin barrier function.
SPRR2F (Small Proline Rich Protein 2F): Similar to SPRR2A, involved in skin barrier function.
SPRR3 (Small Proline Rich Protein 3): Protein contributing to skin barrier function.

Antimicrobial Peptides:

DEFB4A (Defensin Beta 4A): Antimicrobial peptide involved in the defense against bacteria.
LTF (Lactotransferrin): Protein with antimicrobial properties, found in secretions like milk and saliva.
PRSS3 (Protease, Serine 3): Serine protease involved in immune responses.
RNASE7 (Ribonuclease A Family Member 7): Antimicrobial peptide with ribonuclease activity.
S100A7 (S100 Calcium Binding Protein A7): Protein involved in immune responses and antimicrobial activity.
S100A8 (S100 Calcium Binding Protein A8): Protein involved in inflammation and immune responses.
S100A9 (S100 Calcium Binding Protein A9): Protein similar to S100A8, involved in immune responses.
SLC11A1 (Solute Carrier Family 11 Member 1): Protein involved in transporting divalent metal ions, impacting antimicrobial responses.

Sulfonation:

PAPSS2 (3'-Phosphoadenosine 5'-Phosphosulfate Synthase 2): Enzyme involved in the synthesis of active sulfate, important for sulfonation reactions.
SULT1B1 (Sulfotransferase Family 1B Member 1): Enzyme involved in the sulfonation of hormones and xenobiotics.
SULT1E1 (Sulfotransferase Family 1E Member 1): Enzyme involved in estrogen metabolism through sulfonation.
SULT2B1 (Sulfotransferase Family 2B Member 1): Enzyme involved in the sulfonation of steroids and other molecules.

IL-1 Family:

IL1A (Interleukin 1 Alpha): Cytokine involved in inflammatory responses and fever induction.
IL1R2 (Interleukin 1 Receptor Type 2): Decoy receptor that regulates IL-1 signaling by binding IL-1 without eliciting a response.
IL1RAP (Interleukin 1 Receptor Accessory Protein): Co-receptor that enhances IL-1 signaling.
IL1RL1 (Interleukin 1 Receptor Like 1): Receptor for IL-33, involved in inflammatory responses.
IL1RL2 (Interleukin 1 Receptor Like 2): Receptor involved in immune and inflammatory responses.
IL36A (Interleukin 36 Alpha): Cytokine involved in inflammatory responses.
IL36RN (Interleukin 36 Receptor Antagonist): Protein that inhibits IL-36 signaling, reducing inflammation.
S100A12 (S100 Calcium Binding Protein A12): Protein involved in inflammatory responses.

Degranulation:

ACPP (Acid Phosphatase, Prostate): Enzyme involved in hydrolyzing phosphate esters, potentially impacting immune responses.

ADGRE3 (Adhesion G Protein-Coupled Receptor E3): Receptor involved in immune cell adhesion and signaling. *CAT* (Catalase): Enzyme that degrades hydrogen peroxide, reducing oxidative stress.

CD93 (CD93 Molecule): Protein involved in cell adhesion and phagocytosis.

CRISP3 (Cysteine-Rich Secretory Protein 3): Protein involved in immune responses and inflammation.

HP (Haptoglobin): Protein that binds free hemoglobin, reducing oxidative stress.

LTA4H (Leukotriene A4 Hydrolase): Enzyme involved in leukotriene biosynthesis, impacting inflammation. *MME* (Membrane Metalloendopeptidase): Enzyme involved in degrading bioactive peptides, impacting immune responses.

PECAM1 (Platelet And Endothelial Cell Adhesion Molecule 1): Protein involved in leukocyte transmigration and immune responses. *PYGL* (Glycogen Phosphorylase L): Enzyme involved in glycogen metabolism, potentially impacting immune responses.

Fibrin Clot:

F5 (Coagulation Factor V): Protein involved in blood coagulation.

PROS1 (Protein S): Protein that acts as a cofactor for protein C in inhibiting blood coagulation.

THBD (Thrombomodulin): Protein that modulates coagulation and inflammation.

Selenoamino Acid Metabolism:

RPL4 (Ribosomal Protein L4): Ribosomal protein involved in protein synthesis.

RPL5 (Ribosomal Protein L5): Ribosomal protein involved in protein synthesis.

RPL6 (Ribosomal Protein L6): Ribosomal protein involved in protein synthesis.

RPL7 (Ribosomal Protein L7): Ribosomal protein involved in protein synthesis.

RPS3A (Ribosomal Protein S3A): Ribosomal protein involved in protein synthesis.

RPS4X (Ribosomal Protein S4, X-Linked): Ribosomal protein involved in protein synthesis.

RPS6 (Ribosomal Protein S6): Ribosomal protein involved in protein synthesis.

EXTRACELLULAR IMMUNITY GENES

Antigen Presentation:

CD74 (Cluster of Differentiation 74): This gene encodes a protein that is involved in the regulation of antigen processing and presentation. It acts as a chaperone for MHC class II molecules and is crucial for the proper functioning of the immune system.

CIITA (Class II Major Histocompatibility Complex Transactivator): CIITA is a master regulator of MHC class II gene expression. It is essential for the activation of immune responses, particularly in antigen-presenting cells.

HLA-DPA1 (Major Histocompatibility Complex, Class II, DP Alpha 1): This gene encodes a protein that forms part of the HLA-DP molecule, which presents antigens to T cells, triggering an immune response.

HLA-DQA1 (Major Histocompatibility Complex, Class II, DQ Alpha 1): HLA-DQA1 encodes a component of the HLA-DQ molecule, involved in the presentation of peptides to immune cells.

HLA-DRA (Major Histocompatibility Complex, Class II, DR Alpha): This gene encodes the alpha chain of the HLA-DR molecule, playing a critical role in presenting extracellular antigens to helper T cells.

HLA-DRB1 (Major Histocompatibility Complex, Class II, DR Beta 1): HLA-DRB1 encodes the beta chain of the HLA-DR molecule, important for antigen presentation to CD4+ T cells.

HLA-DRB3 (Major Histocompatibility Complex, Class II, DR Beta 3): This gene is another variant of the beta chain of HLA-DR, contributing to immune diversity.

HLA-DRB5 (Major Histocompatibility Complex, Class II, DR Beta 5): Similar to HLA-DRB3, this gene encodes an alternative beta chain for the HLA-DR molecule.

TAP1 (Transporter 1, ATP Binding Cassette Subfamily B Member): TAP1 is involved in the transport of antigenic peptides into the endoplasmic reticulum, a critical step in MHC class I antigen presentation.

TAP2 (Transporter 2, ATP Binding Cassette Subfamily B Member): TAP2 works alongside TAP1 to transport peptides into the ER for loading onto MHC class I molecules.

Cytokines:

CCL19 (C-C Motif Chemokine Ligand 19): This cytokine is involved in immune cell trafficking and homing to lymphoid tissues, playing a role in adaptive immune responses.

CCL2 (C-C Motif Chemokine Ligand 2): Also known as MCP-1, it recruits monocytes, memory T cells, and dendritic cells to sites of inflammation.

CCL5 (C-C Motif Chemokine Ligand 5): Also known as RANTES, it attracts immune cells such as T cells, eosinophils, and basophils to inflammatory sites.

CCL8 (C-C Motif Chemokine Ligand 8): This chemokine is involved in the recruitment of various immune cells, including monocytes and T cells, to sites of inflammation.

CCL25 (C-C Motif Chemokine Ligand 25): This chemokine is important for the homing of lymphocytes to the gutassociated lymphoid tissue.

CSF3 (Colony Stimulating Factor 3): Also known as G-CSF, it stimulates the production and differentiation of granulocytes in the bone marrow.

CX3CL1 (C-X3-C Motif Chemokine Ligand 1): This chemokine exists in both membrane-bound and soluble forms, playing roles in adhesion and migration of leukocytes.

CXCL9 (C-X-C Motif Chemokine Ligand 9): Also known as MIG, it recruits T cells to sites of inflammation.

CXCL10 (C-X-C Motif Chemokine Ligand 10): Also known as IP-10, it recruits immune cells such as T cells to sites of infection and inflammation.

CXCL11 (C-X-C Motif Chemokine Ligand 11): This chemokine attracts activated T cells and plays a role in the inflammatory response.

CXCL12 (C-X-C Motif Chemokine Ligand 12): Also known as SDF-1, it is involved in hematopoiesis and acts as a chemoattractant for lymphocytes.

CXCL13 (C-X-C Motif Chemokine Ligand 13): This chemokine is important for the organization of B cells within lymphoid tissues.

Interleukins:

IL6 (Interleukin 6): A multifunctional cytokine that plays roles in inflammation, immune response, and hematopoiesis.

IL10 (Interleukin 10): This cytokine has anti-inflammatory properties and helps regulate immune responses by inhibiting the production of pro-inflammatory cytokines.

IL1B (Interleukin 1 Beta): A key pro-inflammatory cytokine, IL-1β is involved in the regulation of immune and inflammatory responses.

IL21R (Interleukin 21 Receptor): This gene encodes the receptor for IL-21, a cytokine that influences the function of T cells, B cells, and NK cells.

IL23R (Interleukin 23 Receptor): This gene encodes the receptor for IL-23, which is involved in the inflammatory response and the maintenance of Th17 cells.

IL2RA (Interleukin 2 Receptor Subunit Alpha): Also known as CD25, it is a component of the IL-2 receptor, crucial for T cell proliferation.

IL10RA (Interleukin 10 Receptor Subunit Alpha): This gene encodes the alpha subunit of the IL-10 receptor, which is essential for IL-10 signaling.

IL15RA (Interleukin 15 Receptor Subunit Alpha): This gene encodes the alpha subunit of the IL-15 receptor, which is involved in the proliferation and activation of NK cells and memory CD8+ T cells.

IL2RB (Interleukin 2 Receptor Subunit Beta): This gene encodes the beta subunit of the IL-2 receptor, which is necessary for high-affinity IL-2 binding and signaling.

IL12RB2 (Interleukin 12 Receptor Subunit Beta 2): This gene encodes a subunit of the IL-12 receptor, important for the differentiation of T cells into Th1 cells.

Surface Marker/Receptor Signaling:

ADA (Adenosine Deaminase): This enzyme is involved in purine metabolism and is crucial for the proper function of the immune system, particularly in T cell development and function.

CARD11 (Caspase Recruitment Domain Family Member 11): This gene encodes a protein that plays a key role in the activation of NF-κB signaling in lymphocytes.

CCR1 (C-C Motif Chemokine Receptor 1): This receptor binds to various chemokines and mediates the migration and activation of immune cells.

CCR5 (C-C Motif Chemokine Receptor 5): This receptor is involved in the recruitment of immune cells to sites of inflammation and is also known as a co-receptor for HIV entry into cells.

CCR7 (C-C Motif Chemokine Receptor 7): This receptor plays a critical role in the homing of T cells to lymphoid tissues.

CD1D (CD1d Molecule): This gene encodes a protein that presents lipid antigens to natural killer T (NKT) cells, playing a role in immune surveillance.

CD2 (CD2 Molecule): A cell adhesion molecule found on the surface of T cells and NK cells, involved in T cell activation and adhesion.

CD4 (CD4 Molecule): A co-receptor that enhances the sensitivity of T cells to antigens presented by MHC class II molecules.

CD7 (CD7 Molecule): A protein found on T cells and NK cells, involved in T cell activation and adhesion.

CD8A (CD8a Molecule): This gene encodes the alpha chain of the CD8 co-receptor, which enhances the interaction between T cells and antigen-presenting cells.

CD38 (CD38 Molecule): This protein is involved in cell adhesion, signal transduction, and calcium signaling in immune cells.

CD80 (CD80 Molecule): This protein provides a costimulatory signal necessary for T cell activation and survival.

CD86 (CD86 Molecule): Similar to CD80, it provides costimulatory signals that are essential for T cell activation and immune responses.
CD247 (CD247 Molecule): Also known as CD3ζ, it is a component of the T cell receptor (TCR) complex and is essential for TCR signaling.
CD3E (CD3e Molecule): Part of the TCR complex, CD3ε is crucial for T cell activation and signal transduction.
CD8B (CD8b Molecule): This gene encodes the beta chain of the CD8 co-receptor, important for the function of cytotoxic T cells.
CSF1R (Colony Stimulating Factor 1 Receptor): This receptor is involved in the regulation of the development, survival, and proliferation of macrophages.
CX3CR1 (C-X3-C Motif Chemokine Receptor 1): The receptor for CX3CL1, involved in the adhesion and migration of immune cells.
CXCR3 (C-X-C Motif Chemokine Receptor 3): This receptor is involved in the chemotactic migration of immune cells to sites of inflammation.
CXCR6 (C-X-C Motif Chemokine Receptor 6): A receptor for the chemokine CXCL16, involved in the recruitment of T cells to inflamed tissues.
FYN (FYN Proto-Oncogene, Src Family Tyrosine Kinase): This gene encodes a member of the Src family of tyrosine kinases, involved in T cell receptor signaling.
GRAP2 (GRB2-Related Adaptor Protein 2): This adaptor protein is involved in T cell receptor signaling and the activation of downstream signaling pathways.
ICOS (Inducible T Cell Costimulator): A protein that provides a costimulatory signal to T cells, enhancing their proliferation and survival.
ITK (IL2-Inducible T-Cell Kinase): This kinase is involved in T cell receptor signaling and the activation of T cells.
LCK (LCK Proto-Oncogene, Src Family Tyrosine Kinase): A member of the Src family of tyrosine kinases, crucial for T cell receptor signaling.
MICB (MHC Class I Polypeptide-Related Sequence B): This gene encodes a stress-induced ligand for NKG2D, an activating receptor on NK cells.
PDCD1 (Programmed Cell Death 1): Also known as PD-1, this inhibitory receptor plays a role in maintaining immune tolerance and preventing autoimmunity.
SOCS1 (Suppressor of Cytokine Signaling 1): This protein is involved in the negative regulation of cytokine signaling, maintaining immune homeostasis.
ZAP70 (Zeta Chain of T Cell Receptor Associated Protein Kinase 70): A tyrosine kinase involved in T cell receptor signaling, essential for T cell activation and development.

MITOCHONDRIAL INNATE IMMUNE

mtDNA/dsRNA Activated Genes:

mtDNA:

CASP1 (Caspase 1): Enzyme that cleaves pro-IL-1β to its active form, involved in inflammation.
CMPK2 (Cytidine/Uridine Monophosphate Kinase 2): Enzyme involved in nucleotide metabolism and immune responses.
GSDMD (Gasdermin D): Protein that forms pores in cell membranes, leading to pyroptosis.
IL18 (Interleukin 18): Cytokine involved in stimulating immune responses.
IL1B (Interleukin 1 Beta): Cytokine involved in inflammatory responses and fever induction.
IL1R1 (Interleukin 1 Receptor Type 1): Receptor for IL-1, involved in signaling inflammatory responses.
MYD88 (Myeloid Differentiation Primary Response 88): Adapter protein involved in TLR and IL-1 receptor signaling.
NLRP3 (NLR Family Pyrin Domain Containing 3): Component of the inflammasome, involved in activating inflammatory responses.
PYCARD (PYD And CARD Domain Containing): Adapter protein that recruits CASP1 to the inflammasome.
TFAM (Transcription Factor A, Mitochondrial): Protein involved in mitochondrial DNA replication and transcription.
TLR9 (Toll-Like Receptor 9): Receptor that recognizes unmethylated CpG DNA, triggering immune responses.

mtdsRNA:

DDX58 (DExD/H-Box Helicase 58): Helicase involved in recognizing viral RNA and activating immune responses.
EIF2AK2 (Eukaryotic Translation Initiation Factor 2 Alpha Kinase 2): Kinase involved in the stress response to viral infection.
IFIH1 (Interferon Induced With Helicase C Domain 1): Protein that recognizes viral RNA, activating immune responses.
MAVS (Mitochondrial Antiviral Signaling Protein): Adapter protein that mediates antiviral signaling.
TICAM1 (Toll-Like Receptor Adaptor Molecule 1): Adapter protein involved in TLR signaling.
TLR3 (Toll-Like Receptor 3): Receptor that recognizes double-stranded RNA, triggering immune responses.

ZNFX1 (Zinc Finger NFX1-Type Containing 1): Protein involved in recognizing viral RNA and activating immune responses.

mtDNA/dsRNA:

CGAS (Cyclic GMP-AMP Synthase): Enzyme that synthesizes cGAMP in response to cytosolic DNA, activating immune responses.

IRF3 (Interferon Regulatory Factor 3): Transcription factor involved in the antiviral response.

IRF7 (Interferon Regulatory Factor 7): Transcription factor involved in the antiviral response.

NFKB1 (Nuclear Factor Kappa B Subunit 1): Transcription factor involved in immune and inflammatory responses.

NFKB2 (Nuclear Factor Kappa B Subunit 2): Similar to NFKB1, involved in immune and inflammatory responses.

NFKBIA (NFKB Inhibitor Alpha): Protein that inhibits NFKB, regulating immune responses.

RELA (RELA Proto-Oncogene, NF-KB Subunit): Subunit of NFKB, involved in immune and inflammatory responses.

RELB (RELB Proto-Oncogene, NF-KB Subunit): Similar to RELA, involved in immune and inflammatory responses.

STING1 (Stimulator Of Interferon Response CGAMP Interactor 1): Protein involved in the cGAS-STING pathway, activating immune responses.

TBK1 (TANK Binding Kinase 1): Kinase involved in antiviral signaling and the activation of IRF3/7.

ZBP1 (Z-DNA Binding Protein 1): Protein that recognizes viral RNA and DNA, activating immune responses.

INTEGRATED STRESS RESPONSE (ISR)

Sensor/Initiator:

ATF3 **(Activating Transcription Factor 3):** Transcription factor involved in cellular stress responses, including DNA damage, oxidative stress, and endoplasmic reticulum stress.

ATF4 **(Activating Transcription Factor 4):** Key regulator of the integrated stress response, promotes the expression of genes involved in amino acid metabolism, redox reactions, and apoptosis.

ATF5 **(Activating Transcription Factor 5):** Plays a role in the cellular stress response, particularly in response to nutrient deprivation and hypoxia.

CHOP **(***DDIT3***; DNA Damage Inducible Transcript 3):** Mediates endoplasmic reticulum stress-induced apoptosis, involved in the cellular stress response.

EIF2B2 **(Eukaryotic Translation Initiation Factor 2B Subunit Beta):** A component of the EIF2B complex, involved in the initiation of protein synthesis and its regulation under stress conditions.

EIF2S1 **(Eukaryotic Translation Initiation Factor 2 Subunit Alpha):** Phosphorylation of EIF2S1 inhibits protein synthesis and activates the integrated stress response.

GADD34 **(***PPP1R15A***; Protein Phosphatase 1 Regulatory Subunit 15A):** Induced by stress, dephosphorylates EIF2S1, thus promoting recovery from stress.

GCN2 **(***EIF2AK4***; Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4):** Senses amino acid deprivation and phosphorylates EIF2S1, inhibiting translation initiation.

HRI **(***EIF2AK1***; Eukaryotic Translation Initiation Factor 2 Alpha Kinase 1):** Heme-regulated inhibitor that responds to heme deficiency by phosphorylating EIF2S1.

NFE2L2 **(Nuclear Factor, Erythroid 2 Like 2):** Activates the expression of antioxidant proteins to protect against oxidative damage.

PERK **(***EIF2AK3***; Eukaryotic Translation Initiation Factor 2 Alpha Kinase 3):** Mediates endoplasmic reticulum stress by phosphorylating EIF2S1, reducing global protein synthesis.

PKR **(***EIF2AK2***; Eukaryotic Translation Initiation Factor 2 Alpha Kinase 2):** Activated by viral infection, phosphorylates EIF2S1, leading to inhibition of protein synthesis.

Regulator:

ISR Activator:

DELE1 **(DAP3 Binding Cell Death Enhancer 1):** Activates the integrated stress response by promoting EIF2S1 phosphorylation.

GCN1 **(GCN1 Activator Of EIF2 Alpha Kinase):** Interacts with GCN2 to sense amino acid starvation and activate the ISR.

OMA1 **(OMA1 Zinc Metallopeptidase):** Regulates mitochondrial function and stress response.

ISR Inhibitor:

ADAR **(Adenosine Deaminase RNA Specific):** Modulates RNA stability and the stress response.

ADARB1 **(Adenosine Deaminase RNA Specific B1):** Similar to ADAR, involved in RNA editing and stress response modulation.

KEAP1 **(Kelch Like ECH Associated Protein 1):** Negatively regulates NFE2L2, controlling oxidative stress response.

Target-Gene:

AA-Uptake/Biosynthesis:

ASNS **(Asparagine Synthetase):** Involved in amino acid biosynthesis, particularly asparagine.

SLC6A9 **(Solute Carrier Family 6 Member 9):** Glycine transporter, involved in amino acid uptake.

PSAT1 **(Phosphoserine Aminotransferase 1):** Involved in serine biosynthesis.

Autophagy:

BECN1 **(Beclin 1):** Key regulator of autophagy initiation.

ATG3 **(Autophagy Related 3):** Conjugates with ATG8 to promote autophagy.

ATG5 **(Autophagy Related 5):** Essential for autophagosome formation.

ATG7 **(Autophagy Related 7):** E1-like enzyme required for autophagy.

ATG10 **(Autophagy Related 10):** Involved in autophagosome formation.

ATG12 **(Autophagy Related 12):** Conjugates with ATG5 to form a complex essential for autophagy.

Anti-Oxidant:

ABCC1 (ATP Binding Cassette Subfamily C Member 1): Involved in the transport of various molecules across membranes.

AIFM2 (Apoptosis Inducing Factor Mitochondria Associated 2): Plays a role in apoptosis and oxidative stress response.

GCLC (Glutamate-Cysteine Ligase Catalytic Subunit): Involved in the synthesis of glutathione, a key antioxidant.

GLRX (Glutaredoxin): Involved in redox reactions and maintaining cellular redox homeostasis.

GPX1 (Glutathione Peroxidase 1): Reduces hydrogen peroxide, protecting cells from oxidative damage.

GPX2 (Glutathione Peroxidase 2): Similar function to GPX1, protecting cells from oxidative damage.

GPX4 (Glutathione Peroxidase 4): Protects cells against lipid peroxidation.

GSTA1 (Glutathione S-Transferase Alpha 1): Involved in detoxification processes.

HMOX1 (Heme Oxygenase 1): Provides cytoprotection against oxidative stress.

NQO1 (NAD(P)H Quinone Dehydrogenase 1): Protects cells from oxidative stress by detoxifying quinones.

PARL (Presenilin Associated Rhomboid Like): Involved in mitochondrial homeostasis and apoptosis regulation.

SLC7A11 (Solute Carrier Family 7 Member 11): Cystine/glutamate transporter, crucial for glutathione synthesis.

STARD7 (StAR Related Lipid Transfer Domain Containing 7): Involved in lipid transport and metabolism.

TXN (Thioredoxin): Maintains cellular redox balance and protects against oxidative stress.

Death Factors:

BAD (BCL2 Associated Agonist Of Cell Death): Promotes apoptosis by binding and inhibiting anti-apoptotic proteins.

BAK1 (BCL2 Antagonist/Killer 1): Promotes apoptosis by permeabilizing the mitochondrial outer membrane.

BAX (BCL2 Associated X, Apoptosis Regulator): Similar to BAK1, promotes apoptosis.

BBC3 (BCL2 Binding Component 3): Induces apoptosis by inhibiting anti-apoptotic BCL2 proteins.

BCL2L11 (BCL2 Like 11): Promotes apoptosis by binding to and inhibiting anti-apoptotic BCL2 proteins.

BID (BH3 Interacting Domain Death Agonist): Facilitates mitochondrial outer membrane permeabilization.

BIK (BCL2 Interacting Killer): Induces apoptosis by inhibiting anti-apoptotic proteins.

PMAIP1 (Phorbol-12-Myristate-13-Acetate-Induced Protein 1): Promotes apoptosis by antagonizing anti-apoptotic proteins.

TNFRSF10B (TNF Receptor Superfamily Member 10b): Receptor for TRAIL, induces apoptosis.

Survival Factors:

BCL2 (BCL2 Apoptosis Regulator): Inhibits apoptosis, promoting cell survival.

BCL2L1 (BCL2 Like 1): Similar to BCL2, inhibits apoptosis.

BCL2L2 (BCL2 Like 2): Another anti-apoptotic member of the BCL2 family.

BIRC2 (Baculoviral IAP Repeat Containing 2): Inhibits apoptosis by binding and inhibiting caspases.

BIRC3 (Baculoviral IAP Repeat Containing 3): Similar to BIRC2, inhibits apoptosis.

MCL1 (MCL1 Apoptosis Regulator, BCL2 Family Member): Anti-apoptotic protein that promotes cell survival.

XIAP (X-Linked Inhibitor Of Apoptosis): Inhibits caspases, preventing apoptosis.

Cytokines/Chemokines:

ATF2 (Activating Transcription Factor 2): Regulates genes involved in stress responses, inflammation, and apoptosis.

CCL2 (C-C Motif Chemokine Ligand 2): Recruits monocytes, memory T cells, and dendritic cells to sites of inflammation.

CXCL3 (C-X-C Motif Chemokine Ligand 3): Involved in inflammatory responses and attracts neutrophils.

CXCL8 (C-X-C Motif Chemokine Ligand 8): Also known as IL-8, involved in the chemotaxis of neutrophils.

FGF21 (Fibroblast Growth Factor

FOS (Fos Proto-Oncogene, AP-1 Transcription Factor Subunit): Regulates cell proliferation, differentiation, and survival.

GDF15 (Growth Differentiation Factor 15): Involved in regulating inflammatory and apoptotic pathways.

IL23A (Interleukin 23 Subunit Alpha): Part of the cytokine IL-23, involved in inflammatory responses.

IL6 (Interleukin 6): Pro-inflammatory cytokine and anti-inflammatory myokine.
JUN (Jun Proto-Oncogene, AP-1 Transcription Factor Subunit): Regulates gene expression in response to stress.
MAPK1 (Mitogen-Activated Protein Kinase 1): Involved in signaling pathways that regulate cell growth, differentiation, and stress responses.
NFKB1 (Nuclear Factor Kappa B Subunit 1): Regulates genes involved in immune and inflammatory responses.
NFKB2 (Nuclear Factor Kappa B Subunit 2): Similar to NFKB1, involved in immune response regulation.
SESN2 (Sestrin 2): Protects cells from oxidative stress and regulates metabolism.
TNF (Tumor Necrosis Factor): Involved in systemic inflammation, stimulates the acute phase reaction.
TNFSF10 (TNF Superfamily Member 10): Also known as TRAIL, induces apoptosis in cancer cells.

UNFOLDED PROTEIN RESPONSE (UPR)

Endoplasmic Reticulum UPR (UPR^{ER}):

Sensor/Initiator:

ASK1 (MAP3K5) (Mitogen-Activated Protein Kinase Kinase Kinase 5): *ASK1* is involved in stress-induced apoptosis and is activated by oxidative stress and endoplasmic reticulum (ER) stress.
ATF6 (Activating Transcription Factor 6): *ATF6* is a key ER stress sensor that, upon activation, moves to the Golgi where it is processed to release its cytoplasmic domain, which acts as a transcription factor to upregulate UPR target genes.
IRE1 (ERN1) (Endoplasmic Reticulum To Nucleus Signaling 1): *IRE1* is an ER transmembrane sensor that activates UPR by splicing *XBP1* mRNA, leading to the production of an active transcription factor.
JNK (MAPK8) (Mitogen-Activated Protein Kinase 8): *JNK* is a stress-activated protein kinase that is involved in apoptosis and inflammatory responses.
TRAF2 (TNF Receptor-Associated Factor 2): *TRAF2* is involved in the activation of *JNK* and *NF-κB* pathways in response to ER stress.
XBP1 (X-Box Binding Protein 1): *XBP1* is a transcription factor activated by *IRE1* that regulates genes involved in protein folding, secretion, and degradation in the ER.

Target-Gene:

ASK1 (MAP3K5) (Mitogen-Activated Protein Kinase Kinase Kinase 5): Functions in stress-induced apoptosis and ER stress response.
ATF6 (Activating Transcription Factor 6): Involved in upregulating UPR target genes.
IRE1 (ERN1) (Endoplasmic Reticulum To Nucleus Signaling 1): Activates *XBP1* mRNA splicing.
JNK (MAPK8) (Mitogen-Activated Protein Kinase 8): Involved in apoptosis and inflammatory responses.
TRAF2 (TNF Receptor-Associated Factor 2): Activates *JNK* and *NF-κB* pathways.
XBP1 (X-Box Binding Protein 1): Regulates genes for protein folding, secretion, and degradation.

Mitochondrial UPR (UPRMT):

Sensor/Initiator:

ERAL1 (Era Like 12S Mitochondrial rRNA Chaperone 1): *ERAL1* is involved in mitochondrial ribosome biogenesis and the response to mitochondrial stress.
SIRT3 (Sirtuin 3): *SIRT3* is a mitochondrial deacetylase that regulates the mitochondrial UPR by deacetylating proteins involved in mitochondrial function and stress responses.

Target-Gene:

CLPP (Caseinolytic Mitochondrial Matrix Peptidase Proteolytic Subunit): *CLPP* is a mitochondrial protease that degrades misfolded proteins, helping to maintain mitochondrial protein homeostasis.
DNAJA3 (DnaJ Heat Shock Protein Family (Hsp40) Member A3): *DNAJA3* acts as a co-chaperone in the mitochondrial stress response, aiding in protein folding and degradation.
FOXO3 (Forkhead Box O3): *FOXO3* is a transcription factor that regulates genes involved in oxidative stress resistance, apoptosis, and mitochondrial biogenesis.
HSPD1 (Heat Shock Protein Family D (Hsp60) Member 1): *HSPD1* is a mitochondrial chaperone involved in protein folding and assembly within the mitochondria.
HSPE1 (Heat Shock Protein Family E (Hsp10) Member 1): *HSPE1* functions with *HSPD1* to assist in mitochondrial protein folding.
LONP1 (Lon Peptidase 1, Mitochondrial): *LONP1* is a mitochondrial protease involved in the degradation of damaged or misfolded proteins within the mitochondria.
MAP1LC3B (Microtubule Associated Protein 1 Light Chain 3 Beta): *MAP1LC3B* is involved in autophagy, including the removal of damaged mitochondria.
PPARGC1A (Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha): *PPARGC1A* is a transcriptional coactivator that regulates genes involved in energy metabolism and mitochondrial biogenesis.

SCAF1 (Splicing Factor 1): *SCAF1* is involved in RNA splicing and the regulation of mitochondrial gene expression.

SOD1 (Superoxide Dismutase 1): *SOD1* is an enzyme that protects the cell from oxidative damage by converting superoxide radicals into oxygen and hydrogen peroxide.

SOD2 (Superoxide Dismutase 2): *SOD2* is a mitochondrial enzyme that also converts superoxide radicals into less harmful molecules, protecting the mitochondria from oxidative stress.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

AGT Regulatory Axis:

AGT Regulatory Axis:

ACE **(Angiotensin I Converting Enzyme):** Converts angiotensin I to the active vasoconstrictor angiotensin II.

ACE2 **(Angiotensin Converting Enzyme 2):** Converts angiotensin II to angiotensin 1-7, which has vasodilatory effects.

AGT **(Angiotensinogen):** Precursor to angiotensin I, which is converted to angiotensin II, a key regulator of blood pressure.

AGTR1 **(Angiotensin II Receptor Type 1):** Mediates the major cardiovascular effects of angiotensin II.

AGTR2 **(Angiotensin II Receptor Type 2):** Mediates opposing effects to AGTR1, including vasodilation.

ANGPT1 **(Angiopoietin 1):** Plays a crucial role in blood vessel maturation and stability.

CMA1 **(Chymase 1):** Converts angiotensin I to angiotensin II independently of ACE.

CPA3 **(Carboxypeptidase A3):** Degrades angiotensin I to inactive peptides.

CTSA **(Cathepsin A):** Involved in the breakdown of angiotensin I.

MAS1 **(MAS1 Proto-Oncogene, G Protein-Coupled Receptor):** Receptor for angiotensin 1-7, promoting vasodilation and anti-inflammatory effects.

REN **(Renin):** Initiates the RAAS cascade by converting angiotensinogen to angiotensin I.

TMPRSS2 **(Transmembrane Serine Protease 2):** Facilitates viral entry into cells and activates components of the RAAS.

NADPH Oxidase:

DUOX1 **(Dual Oxidase 1):** Produces reactive oxygen species (ROS) involved in host defense and signaling.

DUOX2 **(Dual Oxidase 2):** Similar to DUOX1, involved in generating ROS for host defense.

NOX1 (NADPH Oxidase 1): Generates ROS that contribute to cellular signaling and host defense.

NOX4 (NADPH Oxidase 4): Produces ROS that play roles in cell differentiation, proliferation, and survival.

NOX5 (NADPH Oxidase 5): Generates ROS involved in cellular signaling processes.

Tissue Damage:

PANoptosis:

CASP3 **(Caspase 3):** Key executioner of apoptosis, involved in cellular breakdown.

CASP7 **(Caspase 7):** Works with CASP3 in the execution phase of apoptosis.

CASP8 **(Caspase 8):** Initiates apoptosis through the extrinsic pathway.

FADD **(Fas Associated via Death Domain):** Mediates apoptotic signaling through death receptors.

GSDMB **(Gasdermin B):** Involved in pyroptosis, a form of inflammatory cell death.

GSDMC **(Gasdermin C):** Similar to GSDMB, implicated in pyroptosis.

GSDMD **(Gasdermin D):** Central to the process of pyroptosis by forming pores in the cell membrane.

MLKL **(Mixed Lineage Kinase Domain Like Pseudokinase):** Key mediator of necroptosis, another form of programmed cell death.

RIPK1 **(Receptor Interacting Serine/Threonine Kinase 1):** Regulates necroptosis and apoptosis.

RIPK3 **(Receptor Interacting Serine/Threonine Kinase 3):** Works with RIPK1 in necroptosis.

ZBP1 **(Z-DNA Binding Protein 1):** Activates necroptosis and inflammasome responses.

Complement activation/Fibrin deposition:

C1QA (Complement C1q A Chain): Part of the C1 complex initiating the classical complement pathway.

C1R (Complement C1r): Works with C1s in the C1 complex to cleave C4 and C2 in the classical pathway.

C5AR1 (Complement C5a Receptor 1): Mediates the inflammatory effects of the complement component C5a.

F12 (Coagulation Factor XII): Initiates the contact activation pathway of blood coagulation.

F13A1 (Coagulation Factor XIII A Chain): Stabilizes fibrin clots by cross-linking fibrin.

FGA (Fibrinogen Alpha Chain): Precursor to fibrin, a major component of blood clots.

FGB (Fibrinogen Beta Chain): Works with FGA in fibrin formation.

FGG (Fibrinogen Gamma Chain): Completes the fibrinogen molecule, essential for clot formation.

MYOF (Myoferlin): Involved in membrane repair and vesicle trafficking.

PLG (Plasminogen): Precursor to plasmin, which degrades fibrin clots.

PLVAP (Plasmalemma Vesicle Associated Protein): Involved in the formation of endothelial diaphragms.

SERPINC1 (Serpin Family C Member 1, Antithrombin): Inhibits thrombin and other proteases in the coagulation system.

SERPINE1 (Serpin Family E Member 1, PAI-1): Inhibits tissue plasminogen activator (tPA) and urokinase, controlling fibrinolysis.

SERPINF2 (Serpin Family F Member 2, Alpha-2 Antiplasmin): Inhibits plasmin, controlling fibrinolysis.
SERPING1 (Serpin Family G Member 1, C1 Inhibitor): Inhibits the C1 complex in the classical complement pathway.
TGFB1 (Transforming Growth Factor Beta 1): Regulates inflammation and immune responses, also involved in tissue regeneration.
THBD (Thrombomodulin): Binds thrombin, leading to activation of protein C and anticoagulation.

Syndecans:

SDC1 (Syndecan 1): Involved in cell adhesion, migration, and proliferation. Acts as a co-receptor for growth factors.
SDC2 (Syndecan 2): Plays a role in cell signaling, angiogenesis, and wound healing. Important for maintaining endothelial barrier function.
SDC3 (Syndecan 3): Primarily expressed in the nervous system, involved in neural development and synaptic plasticity.
SDC4 (Syndecan 4): Functions in cell-matrix interactions, regulating cytoskeletal organization, and cell migration.

Vascular Inflammation:

Hyaluronan Accumulation:

HAS1 (Hyaluronan Synthase 1): Synthesizes hyaluronan, a component of the extracellular matrix.
HAS2 (Hyaluronan Synthase 2): Main enzyme for hyaluronan production during embryogenesis and tissue repair.
HAS3 (Hyaluronan Synthase 3): Contributes to hyaluronan synthesis, particularly in inflammation.
HMMR (Hyaluronan Mediated Motility Receptor): Binds hyaluronan, facilitating cell motility and proliferation.
HYAL1 (Hyaluronidase 1): Degrades hyaluronan, regulating its turnover.
HYAL2 (Hyaluronidase 2): Works with HYAL1 in hyaluronan degradation.

Bradykinin production:

BDKRB1 (Bradykinin Receptor B1): Mediates responses to bradykinin during inflammation.
BDKRB2 (Bradykinin Receptor B2): Constitutively active receptor mediating most effects of bradykinin.
CPN1 (Carboxypeptidase N Subunit 1): Degrades bradykinin, regulating its activity.
HS3ST6 (Heparan Sulfate-Glucosamine 3-Sulfotransferase 6): Involved in modifying heparan sulfate, which can affect bradykinin activity.
KLK1 (Kallikrein 1): Converts kininogen to bradykinin.
KLK2 (Kallikrein 2): Similar to KLK1, involved in kininogen processing.
KLK3 (Kallikrein 3, Prostate-Specific Antigen): Processes various substrates including kininogen.
KLK4 (Kallikrein 4): Involved in enamel formation, also processes kininogen.
KLK5 (Kallikrein 5): Processes skin-specific substrates, including kininogen.
KLK6 (Kallikrein 6): Degrades extracellular matrix components, involved in inflammation.
KLK7 (Kallikrein 7): Degrades corneodesmosomes in skin, processes kininogen.
KLK8 (Kallikrein 8): Involved in neural development and inflammation.
KLK9 (Kallikrein 9): Expressed in the skin, processes various substrates.
KLK10 (Kallikrein 10): Tumor suppressor, involved in processing kininogen.
KLK11 (Kallikrein 11): Expressed in the prostate, involved in kininogen processing.
KLK12 (Kallikrein 12): Broad protease activity, including kininogen processing.
KLK13 (Kallikrein 13): Expressed in skin and other tissues, processes kininogen.
KLK14 (Kallikrein 14): Involved in skin desquamation and kininogen processing.
KLK15 (Kallikrein 15): Less understood, implicated in various physiological processes.
KLKB1 (Kallikrein B1): Processes kininogen to release bradykinin.
KNG1 (Kininogen 1): Precursor to bradykinin, involved in blood coagulation and inflammation.
SPINK5 **(Serine Peptidase Inhibitor, Kazal Type 5):** Inhibits a range of serine proteases, playing a crucial role in skin barrier function and immunity. Mutations in *SPINK5* are associated with Netherton syndrome, characterized by skin inflammation, allergies, and a compromised skin barrier.

Table S3. Special Mention of Germline Mutations

Gene Symbol: ZNFX1
Germline Mutation: Reduced Expression Mutations
Disease: Aicardi–Goutières syndrome (AGS), when exposed to pathogens
Description/Function: Zinc Finger NFX1-Type Containing 1 (ZNFX1) encodes a zinc finger helicase involved in the innate immune response by recognizing viral double-stranded RNA (dsRNA) and transporting it to the outer mitochondrial membrane. This process activates interferon (IFN) signaling, which is crucial for antiviral defense. In individuals with AGS, exposure to pathogens leads to persistent IFN signaling, resulting in severe inflammatory responses and potentially fatal outcomes. AGS is characterized by early-onset neuroinflammation that resembles congenital viral infections.
REF:[16]

Gene Symbol: RNF213
Germline Mutation: c.14429G > A (p.Arg4810Lys) Polymorphism
Disease: MOYA-MOYA disease
Description/Function: Ring Finger Protein 213 (RNF213) encodes a protein with a RING finger domain that plays a role in the regulation of blood vessel formation and immune response. It inhibits the Wnt signaling pathway, leading to vessel regression, and is involved in antigen processing and presentation. Mutations in RNF213 are linked to MOYA-MOYA disease, a condition marked by the progressive narrowing of intracranial arteries. Symptoms include headaches, seizures, weakness or paralysis on one side of the body, vision problems, speech difficulties (aphasia), developmental delays, and involuntary movements.
REF:[17]

Gene Symbol: PLVAP
Germline Mutation: Reduced Expression Mutations
Disease: Protein losing enteropathy (PLE)
Description/Function: Plasmalemma Vesicle Associated Protein (PLVAP) is essential for maintaining the integrity of endothelial diaphragms that control vascular permeability. It ensures proper function of endothelial fenestrae, crucial for microvascular barrier function. In mice, loss of PLVAP causes severe fluid and protein leakage into tissues, leading to premature death from diarrhea and edema of the intestines, kidneys, and pancreas. Reduced expression of PLVAP in humans results in protein-losing enteropathy (PLE), characterized by diarrhea, tissue swelling (edema), fluid accumulation in the abdomen (ascites), pleural and pericardial effusions, low protein levels (hypoproteinemia), and severe malnutrition.
REF:[18,19]

Gene Symbol: SERPING1
Germline Mutation: Reduced Expression Mutations
Disease: Hereditary Angioedema (HAE)-C1-INH
Description/Function: Serpin Family G Member 1 (SERPING1) encodes C1-Inhibitor (C1-INH), a plasma protein that regulates the complement system and contact system pathways by inhibiting C1 complex, FXIIa, and FXIIf. Reduced expression of SERPING1 leads to uncontrolled activation of these pathways, resulting in excess production of bradykinin and complement components, causing Hereditary Angioedema (HAE). Symptoms include episodic swelling (edema), gastrointestinal distress, respiratory issues, non-itchy rashes, tingling skin, skin tightness, fatigue, irritability, and mood changes.
REF: [20,21]

Gene Symbol: F12
Germline Mutation: Overexpression Mutation

Disease: HAE-FXII
Description/Function: Coagulation Factor XII (F12) encodes a glycoprotein known as Factor XII (FXII), which initiates the intrinsic pathway of blood coagulation, fibrinolysis, and the generation of bradykinin. Overexpression mutations in F12 increase FXII activity, leading to excessive bradykinin production and Hereditary Angioedema (HAE), characterized by recurrent episodes of severe swelling (angioedema).
REF: [22,21]

Gene Symbol: ANGPT1
Germline Mutation: Reduced Expression Mutation
Disease: HAE
Description/Function: Angiopoietin 1 (ANGPT1) is a crucial regulator of angiogenesis, promoting blood vessel maturation and stability by binding to the TIE2 receptor on endothelial cells. Reduced expression mutations in ANGPT1 can lead to impaired vascular integrity and increased permeability, contributing to the rare occurrence of Hereditary Angioedema (HAE). Symptoms include episodic swelling due to increased vascular permeability.
REF:[22]

Gene Symbol: PLG
Germline Mutation: c.988A>G (p.Lys330Glu) Mutation
Disease: HAE
Description/Function: Plasminogen (PLG) encodes the precursor of plasmin, an enzyme that degrades fibrin in blood clots (fibrinolysis). The c.988A>G (p.Lys330Glu) mutation in PLG disrupts this function, leading to defective fibrinolysis and contributing to vascular leakage and Hereditary Angioedema (HAE). Patients with this mutation experience recurrent swelling episodes due to impaired regulation of fibrinolysis and increased vascular permeability.
REF:[21,23]

Gene Symbol: HS3ST6
Germline Mutation: c.430A>T (p.Thr144Ser) Polymorphism
Disease: HAE
Description/Function: Heparan Sulfate-Glucosamine 3-Sulfotransferase 6 (HS3ST6) is involved in the final steps of heparan sulfate biosynthesis, which is crucial for various biological processes including cell signaling and anticoagulation. The c.430A>T (p.Thr144Ser) polymorphism in HS3ST6 alters its activity, leading to increased vasculogenesis and activation of antithrombin, contributing to Hereditary Angioedema (HAE). This results in recurrent swelling episodes due to enhanced vascular permeability and coagulation defects.
REF:[22]

Gene Symbol: KNG1
Germline Mutation: Truncation Variant
Disease: HAE
Description/Function: Kininogen 1 (KNG1) mRNA translates into high molecular weight kininogen (HMWK) or low molecular weight kininogen (LMWK). These kininogens are precursors for kinins, which induce vasodilation and increased vascular permeability. Mutations in KNG1 favoring HMWK production lead to elevated bradykinin levels, resulting in excessive complement activation and Hereditary Angioedema (HAE). Symptoms include recurrent episodes of severe swelling due to increased vascular permeability.
REF: [24,20]

Gene Symbol: MYOF
Germline Mutation: Frameshift mutation
Disease: HAE
Description/Function: Myoferlin (MYOF) encodes a protein that associates with Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2), playing a role in endothelial cell proliferation and migration, crucial for angiogenesis and blood vessel repair. Frameshift mutations in MYOF lead to defective angiogenesis and are

associated with cardiomyopathy. These mutations can also cause Hereditary Angioedema (HAE) by promoting pathological angiogenesis and increased vascular permeability, leading to recurrent swelling episodes. **REF**: [22]

Table S4. Characteristics of EPICC participants included in analyses.

	Acute COVID (N=221)	Control (N=99)	Total (N=320)	*P value*[a]
Gender				< 0.01
Female	75 (33.9%)	53 (53.5%)	128 (40.0%)	
Male	146 (66.1%)	46 (46.5%)	192 (60.0%)	
Race				0.32
White	104 (47.1%)	52 (52.5%)	156 (48.8%)	
Hispanic or Latino	57 (25.8%)	19 (19.2%)	76 (23.8%)	
Black	34 (15.4%)	20 (20.2%)	54 (16.9%)	
Others	26 (11.8%)	8 (8.1%)	34 (10.6%)	
Age group				< 0.01
<18	0 (0.0%)	3 (3.0%)	3 (0.9%)	
18-44	98 (44.3%)	56 (56.6%)	154 (48.1%)	
45-64	83 (37.6%)	31 (31.3%)	114 (35.6%)	
65+	40 (18.1%)	9 (9.1%)	49 (15.3%)	
Charlson Comorbidity Index				0.24
0	109 (49.3%)	54 (54.5%)	163 (50.9%)	
1-2	58 (26.2%)	30 (30.3%)	88 (27.5%)	
3-4	29 (13.1%)	6 (6.1%)	35 (10.9%)	
>5	25 (11.3%)	9 (9.1%)	34 (10.6%)	
Severity				< 0.01
Hospitalized	100 (45.2%)	20 (20.2%)	120 (37.5%)	
Outpatient	121 (54.8%)	79 (79.8%)	200 (62.5%)	
Variants				
Pre Delta	186 (84.2%)	0	186 (84.2%)	
Delta period[b]	35 (15.8%)	0	35 (15.8%)	

[a] *n x k Fisher's Exact Test*

[b] *July 1st 2021 to December 31st 2021*

Table S5: Genotype of EPICC participants included in analyses.

	Acute COVID (N=221)	Control (N=99)	Total (N=320)
PANGOLIN			
B.1.2	16 (11.3%)	0	16 (11.3%)
B.1	12 (8.5%)	0	12 (8.5%)
B.1.243	7 (5.0%)	0	7 (5.0%)
B.1.369	7 (5.0%)	0	7 (5.0%)
B.1.1.7	6 (4.3%)	0	6 (4.3%)
AY.100	4 (2.8%)	0	4 (2.8%)
AY.103	3 (2.1%)	0	3 (2.1%)
AY.25	3 (2.1%)	0	3 (2.1%)
B.1.1.207	3 (2.1%)	0	3 (2.1%)
B.1.617.2	3 (2.1%)	0	3 (2.1%)
B.1.429	3 (2.1%)	0	3 (2.1%)
B.1.637	2 (1.4%)	0	2 (1.4%)
B.1.1.519	2 (1.4%)	0	2 (1.4%)
B.1.1.222	2 (1.4%)	0	2 (1.4%)
AY.3	2 (1.4%)	0	2 (1.4%)
AY.119	2 (1.4%)	0	2 (1.4%)
B.1.1	2 (1.4%)	0	2 (1.4%)
B.1.206	2 (1.4%)	0	2 (1.4%)
B.1.234	2 (1.4%)	0	2 (1.4%)
B.1.351	2 (1.4%)	0	2 (1.4%)
B.1.355	2 (1.4%)	0	2 (1.4%)
B.1.355,B.1.369	2 (1.4%)	0	2 (1.4%)
A.27	1 (0.7%)	0	1 (0.7%)
A.3	1 (0.7%)	0	1 (0.7%)
AY.103,AY.116	1 (0.7%)	0	1 (0.7%)
AY.103,AY.44	1 (0.7%)	0	1 (0.7%)
AY.103,B.1	1 (0.7%)	0	1 (0.7%)
AY.103,B.1.617.2	1 (0.7%)	0	1 (0.7%)
AY.110	1 (0.7%)	0	1 (0.7%)
AY.116	1 (0.7%)	0	1 (0.7%)
AY.117	1 (0.7%)	0	1 (0.7%)
AY.118	1 (0.7%)	0	1 (0.7%)
AY.118,B.1.617.2	1 (0.7%)	0	1 (0.7%)
AY.14,B.1.617.2	1 (0.7%)	0	1 (0.7%)
AY.25,B.1.617.2	1 (0.7%)	0	1 (0.7%)
AY.25.1	1 (0.7%)	0	1 (0.7%)
AY.25.1,B.1.617.2	1 (0.7%)	0	1 (0.7%)
AY.44	1 (0.7%)	0	1 (0.7%)
B.1,B.1.147,B.1.369	1 (0.7%)	0	1 (0.7%)
B.1,B.1.162	1 (0.7%)	0	1 (0.7%)
B.1,B.1.332	1 (0.7%)	0	1 (0.7%)

	Acute COVID (N=221)	Control (N=99)	Total (N=320)
B.1,B.1.336	1 (0.7%)	0	1 (0.7%)
B.1,B.1.428	1 (0.7%)	0	1 (0.7%)
B.1.1.148	1 (0.7%)	0	1 (0.7%)
B.1.1.291	1 (0.7%)	0	1 (0.7%)
B.1.1.304	1 (0.7%)	0	1 (0.7%)
B.1.1.318	1 (0.7%)	0	1 (0.7%)
B.1.1.339	1 (0.7%)	0	1 (0.7%)
B.1.1.380	1 (0.7%)	0	1 (0.7%)
B.1.1.432	1 (0.7%)	0	1 (0.7%)
B.1.1.7,B.1.2	1 (0.7%)	0	1 (0.7%)
B.1.110.3	1 (0.7%)	0	1 (0.7%)
B.1.110.3,B.1.369	1 (0.7%)	0	1 (0.7%)
B.1.126	1 (0.7%)	0	1 (0.7%)
B.1.139,B.1.2	1 (0.7%)	0	1 (0.7%)
B.1.2,B.1.333	1 (0.7%)	0	1 (0.7%)
B.1.2,B.1.369	1 (0.7%)	0	1 (0.7%)
B.1.233	1 (0.7%)	0	1 (0.7%)
B.1.236	1 (0.7%)	0	1 (0.7%)
B.1.240	1 (0.7%)	0	1 (0.7%)
B.1.292	1 (0.7%)	0	1 (0.7%)
B.1.298	1 (0.7%)	0	1 (0.7%)
B.1.367	1 (0.7%)	0	1 (0.7%)
B.1.400	1 (0.7%)	0	1 (0.7%)
B.1.427,B.1.429	1 (0.7%)	0	1 (0.7%)
B.1.427,B.1.637	1 (0.7%)	0	1 (0.7%)
B.1.480	1 (0.7%)	0	1 (0.7%)
B.1.556	1 (0.7%)	0	1 (0.7%)
B.1.561	1 (0.7%)	0	1 (0.7%)
B.1.565	1 (0.7%)	0	1 (0.7%)
B.1.595	1 (0.7%)	0	1 (0.7%)
B.1.605	1 (0.7%)	0	1 (0.7%)
P.1.13	1 (0.7%)	0	1 (0.7%)
Q.4	1 (0.7%)	0	1 (0.7%)
NA	80 (36.2%)	99 (100%)	179 (55.9%)

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