

Cite as: Q. Zhang *et al.*, *Science*
10.1126/science.abd4570 (2020).

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

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Clinical outcome upon infection with SARS-CoV-2 ranges from silent infection to lethal COVID-19. We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally define LOF variants in 23 patients (3.5%), aged 17 to 77 years, underlying autosomal recessive or dominant deficiencies. We show that human fibroblasts with mutations affecting this pathway are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

SARS-CoV-2 has already claimed at least 800,000 lives, has been detected in at least 20 million people, and has probably infected at least another 200 million. The clinical manifestations range from silent infection to lethal disease, with an infection-fatality rate of 0.1% to 0.9%. Three epidemiological factors increase the risk of severity: increasing age, decade-by-decade, after the age of 50 years, being male and various underlying medical conditions (1). However, even taking these factors into account, there is immense interindividual clinical variability in each demographic category considered. Following on from our human genetic studies of other severe infectious diseases (2, 3), we established the COVID Human Genetic Effort (<https://www.covidhge.com>) to test the general hypothesis that life-threatening COVID-19 may be caused, in some patients, by monogenic inborn errors of immunity to SARS-CoV-2, with incomplete or complete penetrance (4). We enrolled 659 patients (74.5% men and 25.5% women, 13.9% of whom died) of various ancestries, aged between one month and 99 years (Fig. 1A). These patients were hospitalized for life-threatening pneumonia due to SARS-CoV-2 (critical COVID-19). We sequenced their whole genome ($N = 364$) or exome ($N = 295$), and principal component analysis (PCA) on these data confirmed their ancestries (Fig. 1B).

Candidate variants at thirteen human loci that govern immunity to influenza virus

We first tested the specific hypothesis that inborn errors of TLR3- and IRF7-dependent type I interferon (IFN) immunity, which underlie life-threatening influenza pneumonia, may also underlie life-threatening COVID-19 pneumonia (5) (Fig. 2). We considered three loci previously shown to be mutated in patients with critical influenza pneumonia: *TLR3* (6), *IRF7* (7), and *IRF9* (8). We also considered 10 loci mutated in patients with other viral illnesses but directly connected to the three core genes conferring influenza susceptibility: *TICAM1/TRIF* (9), *UNC93B1* (10), *TRAF3* (11), *TBK1* (12), *IRF3* (13) and *NEMO/IKBK* (14) in the TLR3-dependent type I IFN induction pathway, and *IFNAR1* (15), *IFNAR2* (16), *STAT1* (17), and *STAT2* (18) in the IRF7- and IRF9-dependent type I IFN amplification pathway. We collected both mono- and biallelic non-synonymous variants with a minor allele frequency (MAF) < 0.001 at all 13 loci. Twelve of the thirteen candidate loci are autosomal, while *NEMO* is X-linked. For the latter gene, we considered only a recessive model (19). Autosomal dominant (AD) inheritance has not been proven for six of the 12 autosomal loci (*UNC93B1*, *IRF7*, *IFNAR1*, *IFNAR2*, *STAT2*, *IRF9*), but we nevertheless considered heterozygous variants, because none of the patients enrolled had been hospitalized for critical viral infections before COVID-19, raising the possibility that any underlying genetic defects they might have display a lower penetrance for influenza and other viral illnesses than for COVID-19, which is triggered by a more virulent virus.

Enrichment of variants predicted to be loss-of-function at the influenza susceptibility loci

We found four unrelated patients with biallelic variants of *IRF7* or *IFNAR1* (Table 1 and table S1). We also found 113

patients carrying 113 monoallelic variants at 12 loci: *TLR3* ($N = 7$ patients/7 variants), *UNC93B1* ($N = 10/9$), *TICAM1* ($N = 17/15$), *TRAF3* ($N = 6/6$), *TBK1* ($N = 12/11$), *IRF3* ($N = 5/5$), *IRF7* ($N = 20/13$), *IFNAR1* ($N = 14/13$), *IFNAR2* ($N = 17/15$), *STAT1* ($N = 4/4$), *STAT2* ($N = 11/11$), and *IRF9* ($N = 4/4$). We detected no copy number variation (CNV) for these 13 genes. Remarkably, one of these variants has been reported in patients with life-threatening influenza pneumonia (*TLR3* p.Pro554Ser) (6, 20), and another was shown to be both deleterious and dominant-negative (*IFNAR1* p.Pro335del) (21). Nine of the 118 biallelic or monoallelic variants were predicted to be loss-of-function (pLOF), whereas the remaining 109 were missense or in-frame indels (table S1). In a sample of 534 controls with asymptomatic or mild SARS-CoV-2 infection, we found only one heterozygous pLOF variation with a MAF < 0.001 at the 13 loci (*IRF7* p.Leu99fs). A PCA-adjusted burden test on the 12 autosomal loci revealed significant enrichment in pLOF variants in patients relative to controls ($p = 0.01$, OR = 8.28 [1.04–65.64, 95%CI]) under an AD mode of inheritance. The same analysis performed on synonymous variants with a MAF < 0.001 was not significant ($p = 0.19$), indicating that our ethnicity-adjusted burden test was well calibrated.

Experimentally deleterious alleles at the influenza susceptibility loci in 3.5% of the patients

We tested 113 of these 118 variants experimentally in ad hoc overexpression systems. We found that 24 variants of eight genes were deleterious (including all the pLOF variants), as they were loss-of-expression (LOE), LOF, or severely hypomorphic (HYPO): *TLR3* ($N = 4$ variants), *UNC93B1* ($N = 1$), *TICAM1* ($N = 3$), *TBK1* ($N = 2$), *IRF3* ($N = 2$), *IRF7* ($N = 8$), *IFNAR1* ($N = 3$), and *IFNAR2* ($N = 1$) (table S1, Fig. 3, and figs. S1 to S8). Consistently, heterozygous LOF variants of *IRF3* and *IRF7* were reported in single patients with life-threatening influenza pneumonia (22, 23). The remaining 89 variants tested were biochemically neutral. Twenty-three patients carried these 24 deleterious variants, resulting in four autosomal recessive (AR) deficiencies (homozygosity or compound heterozygosity for *IRF7*, homozygosity for *IFNAR1*) and 19 AD deficiencies. These 23 patients did not carry candidate variants at the other 417 loci known to underlie inborn errors of immunity (table S2) (24–26). These findings suggest that at least 23 (3.5%) unrelated patients of the 659 patients tested suffered from a deficiency at one of eight loci among the 13 tested: four patients with a known AR disorder (*IRF7*, *IFNAR1*) (7, 15), eleven with a known AD disorder (*TLR3*, *TICAM1*, *TBK1*, *IRF3*) (6, 9, 12, 13, 20), and eight with a previously unknown AD genetic disorder (*UNC93B1*, *IRF7*, *IFNAR1*, *IFNAR2*).

Impaired TLR3- and IRF7-dependent type I immunity in the patients' cells in vitro

We tested cells from patients with selected genotypes. We showed that PHA-driven T-cell blasts (PHA-T cells) from

patients with AR or AD IRF7 deficiency had low levels of IRF7 expression (Fig. 4A). We then isolated circulating plasmacytoid dendritic cells (pDCs) from a patient with AR IRF7 deficiency (fig. S9A) (7). These cells were present in normal proportions (fig. S9B), but they did not produce any detectable type I or III IFNs in response to SARS-CoV-2, as analyzed by cytometric bead array (CBA), ELISA, and RNA-seq (Fig. 4, B and C). We also showed that PHA-T cells from a patient with AR IFNAR1 deficiency had impaired IFNAR1 expression and responses to IFN- α 2 or - β , and that the patient's SV40-transformed fibroblast (SV40-Fib cells) did not respond to IFN- α 2 and - β (Fig. 5). We then infected TLR3^{-/-}, TLR3^{+/-}, IRF7^{-/-}, IRF7^{-/-} rescued with wild-type IRF7, IFNAR1^{-/-}, and IFNAR1^{-/-} rescued with wild-type IFNAR1 SV40-Fib cells previously transduced with ACE2 and TMPRSS2. SARS-CoV-2 infection levels were higher in mutant cells than in cells from healthy donors, and transduction of wild-type *IRF7* or *IFNAR1* rescued their defects (Fig. 6). Collectively, these findings showed that AR IRF7 deficiency impaired the production of type I IFN by pDCs stimulated with SARS-CoV-2, whereas AR and AD deficiencies of TLR3, or AR deficiency of IFNAR1 impaired fibroblast-intrinsic type I IFN immunity to SARS-CoV2. They also suggest that heterozygosity for LOF variations at the other five mutated loci also underlie life-threatening COVID-19.

Impaired production of type I IFNs in the patients in vivo

We tested whether these genotypes impaired the production of type I IFN in vivo, during the course of SARS-CoV-2 infection. We measured the levels of the 13 types of IFN- α in the blood of patients during the acute phase of COVID-19. We found that 10 of the 23 patients with mutations for whom samples were available (one with AR IRF7 deficiency, four with AD IRF7 deficiency, one with AD TLR3 deficiency, two with AD TBK1 deficiency, one with AR IFNAR1 deficiency, and one with AD TICAM1 deficiency) had serum IFN- α levels below 1 pg/mL (Fig. 7). By contrast, previously published cohorts of patients hospitalized with unexplained, severe COVID-19 had various serum IFN- α levels, significantly higher than our 10 patients (one-way ANOVA, $p = 1.4 \times 10^{-7}$; Fig. 7) (27, 28). Importantly, another 29 patients from our cohort displaying auto-Abs against type I IFNs, reported in an accompanying paper, had undetectable levels of serum IFN- α (29). Moreover, none of the 23 patients with LOF mutations of the eight genes had detectable auto-Abs against type I IFNs (29), strongly suggesting that the two mechanisms of disease are similar, but independent. Strikingly, excluding patients with auto-Abs against type I IFN from the burden test of pLOF variants at the 12 autosomal loci strengthened the association signal ($p = 0.007$, OR = 8.97 [1.13–71.09, 95%CI]).

Inborn errors of TLR3- and IRF7-dependent type I immunity underlie critical COVID-19

Collectively, our data suggest that at least 23 of the 659 patients with life-threatening COVID-19 pneumonia studied have known (six disorders) or new (four disorders) genetic

defects at eight loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs. This discovery reveals the essential role of both the dsRNA sensor TLR3 and type I IFN cell-intrinsic immunity in the control of SARS-CoV-2 infection in the lungs, consistent with their previously documented roles in pulmonary immunity to influenza virus (5–8). Strikingly, these genotypes were silent until infection with SARS-CoV-2. The most thought-provoking examples are the AR deficiencies of IRF7 and IFNAR1. AR IRF7 deficiency was diagnosed in two individuals aged 49 and 50 years, and AR IFNAR1 deficiency was diagnosed in two individuals aged 26 and 38 years, with no prior history of life-threatening infections (Table 1). One patient with IRF7 deficiency tested was seropositive for several common viruses, including various influenza A and B viruses (figs. S10 and S11). These genetic defects therefore display incomplete penetrance for influenza respiratory distress, and only manifested clinically upon infection with the more virulent SARS-CoV-2.

Conclusion

The AR form of IFNAR1 deficiency highlights the importance of type I IFN production, relative to type III IFN, the production of which is also impaired by defects of TLR3, IRF7, and IRF9 (5). This conclusion is also supported by our accompanying report of neutralizing auto-antibodies against type I, but not type III IFNs, in other patients with life-threatening COVID-19 pneumonia (29). Inborn errors of TLR3- and IRF7-dependent type I IFN immunity at eight loci were found in as many as 23 patients (3.5%) of various ages (17 to 77 years) and ancestries (various nationalities, from Asia, Europe, Latin America and the Middle East), and in patients of both sexes (Table 1). Our findings suggest that there may be mutations in other type I IFN-related genes in other patients with life-threatening COVID-19 pneumonia. They also suggest that the administration of type I IFN may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection.

Methods

Patients

We included in this study 659 patients with life-threatening COVID-19 pneumonia defined as patients with pneumonia who developed critical disease, whether pulmonary with mechanical ventilation (CPAP, BIPAP, intubation, hi-flow oxygen), septic shock, or with any other organ damage requiring admission to the ICU. Patients who developed Kawasaki-like syndrome were excluded. The age of the patients ranged from 0.1–99 years, with a mean age of 51.8 years (SD 15.9 years), and 25.5% of the patients were female. As controls, we enrolled 534 individuals infected with SARS-CoV-2 (based on a positive PCR and/or serological test and/or the presence of typical symptoms such as anosmia/ageusia after exposure to a confirmed COVID-19 case) who remained asymptomatic or developed mild, self-healing, ambulatory disease.

Next-generation sequencing

Genomic DNA was extracted from whole blood. For the 1193 patients and controls included, the whole exome ($N = 687$) or whole genome ($N = 506$) was sequenced. We used the Genome Analysis Software Kit (GATK) (version 3.4-46 or 4) best-practice pipeline to analyze our WES data (30). We aligned the reads obtained with the human reference genome (hg19), using the maximum exact matches algorithm in the Burrows–Wheeler Aligner (BWA) (31). PCR duplicates were removed with Picard tools (picard.sourceforge.net). The GATK base quality score recalibrator was applied to correct sequencing artifacts.

All the variants were manually curated using IGV and confirmed to affect the main functional protein isoform by checking the protein sequence before inclusion in further analyses. The main functional protein isoforms are: TLR3 (NM_003265), UNC93B1 (NM_030930.4), TICAM1 (NM_182919), TRAF3 (NM_145725.2), TBK1 (NM_013254.4), IRF3 (NM_001571), IRF7 (NM_001572.5), IFNAR1 (NM_000629.3), IFNAR2 (NM_001289125.3), STAT1 (NM_007315.4), STAT2 (NM_005419.4), IRF9 (NM_006084.5). The analysis of IKBKG was customized to unmask the duplicated region in IKBKG using a specific pipeline previously described (32). We searched the NGS data for deletions in the 13 genes of interest, using both the HMZDelFinder (33) and CANOES (34) algorithms.

Statistical analysis

We performed an enrichment analysis on our cohort of 659 patients with life-threatening COVID-19 pneumonia and 534 SARS-CoV2 infected controls, focusing on 12 autosomal IFN-related genes. We considered variants that were pLOF, with a MAF lower than 0.001 (gnomAD v2.1.1) after experimentally demonstrating that all the pLOF variants seen in the cases were actually LOF. We compared the proportion of individuals carrying at least one pLOF variant of the 12 autosomal genes in cases and controls by means of logistic regression with the likelihood ratio test. We accounted for the ethnic heterogeneity of the cohorts by including the first three principal components of the PCA in the logistic regression model. PC adjustment is a common and efficient strategy for accounting for different ancestries of patients and controls in the study of rare variants (35–38). We checked that our adjusted burden test was well calibrated, by also performing an analysis of enrichment in rare (MAF < 0.001) synonymous variants of the 12 genes. PCA was performed with Plink v1.9 software on Whole-Exome and Whole-Genome Sequencing data and 1000 Genomes (1kG) Project phase 3 public database as reference, using 27,480 exonic variants with a minor allele frequency > 0.01 and a call rate > 0.99. The odds ratio was also estimated by logistic regression and adjusted for ethnic heterogeneity.

Reporter assays

Cell lines or SV40-Fib cells with known defects were transiently or stably transfected with wild-type, mutant variants, IFN- β or ISRE-firefly luciferase reporter, and pRL-TK-Renilla luciferase reporter. Reporter activity was measured with the Dual-Luciferase Reporter Assay System (Promega Corporation), according to the manufacturer's instructions. Firefly luciferase activity was normalized against Renilla luciferase activity and expressed as a

fold-change were calculated. TRAF3-deficient HEK293T cells were kindly provided by Dr. Maria Romanelli (39).

pDC activation by SARS-CoV-2 and cytokine production

pDCs from an IRF7^{-/-} patient and a healthy donor matched for age and sex were cultured in the presence of medium alone, influenza virus (Charles River, A/PR/8/34, 2 μ g/mL), or the SARS-CoV-2 primary strain 220_95 (GISAID accession ID: EPI_ISL_469284) at a multiplicity of infection (MOI) of 2. After 12 hours of culture, pDC supernatant was collected for cytokine quantification. IFN- α 2 levels were measured in BD cytometric bead arrays (CBAs), in accordance with the manufacturer's protocol, with a 20 pg/mL detection limit. IFN- λ 1 secretion was measured in an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, DuoSet DY7246), in accordance with the manufacturer's instructions.

SARS-CoV-2 infection in patient SV40-Fib

To make patients-derived fibroblasts permissive to SARS-CoV-2 infection, we delivered human ACE2 and TMPRSS2 cDNA to cells by lentivirus transduction using a modified SCRPSY vector (GenBank: KT368137.1). SARS-CoV-2, strain USA-WA1/2020, was obtained from BEI Resources. ACE2/TMPRSS2-transduced cells were either left untreated or treated with 500 U/ml IFN- β (PBL Assay Science, cat. #11415-1) four hours prior to infection. Cells were infected with SARS-CoV-2 (MOI = 0.5) for one hour at 37°C. After 24 hours of infection, cells were fixed and taken out of the BSL3 for staining.

After fixation, cells were stained with SARS-CoV-2 and ACE2 primary antibodies (0.5 μ g/ml and 1 μ g/ml, respectively). Primary antibodies: SARS-CoV-2, human monoclonal anti-Spike-SARS-CoV-2 C121 (40); ACE2, mouse monoclonal Alexa Fluor 488-conjugated Antibody (R&D systems, cat. # FAB9332G-100UG). Images were acquired with an ImageXpress Micro XLS microscope (Molecular Devices) using the 4X objective. The MetaXpress software (Molecular Devices) produced single cell mean fluorescence intensity (MFI) values.

Data analysis on single cell MFI values was done in the R environment (v4.0.2). ACE2/TMPRSS2-transduced cells were classified ACE2 positive when the ACE2 log MFI was superior to the log mean MFI of mock-transduced cells plus 2.5 standard deviations. We excluded all wells with less than 150 ACE2-positive cells before SARS-CoV-2 scoring. ACE2-expressing cells were classified SARS-CoV-2 positive when the fluorescence intensity value was superior to the mean fluorescence intensity of mock-infected cells plus 4 standard deviations. The median SARS-CoV-2 MFI and percentage SARS-CoV-2 positive cells were calculated for each well (independent infection).

Single-molecule array (Simoa) IFN- α digital ELISA

Serum IFN- α concentrations were determined with Simoa technology, with reagents and procedures obtained from Quanterix Corporation (Quanterix SimoaTM IFN α Reagent Kit, Lexington, MA, USA). According to the manufacturer's instructions, the working dilutions were 1:2 for all sera, in working volumes of 170 μ L.

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ACKNOWLEDGMENTS

We thank the patients, their families, and healthy donors for placing their trust in us. We thank Y. Nemirovskaya, D. Papandrea, M. Woollet, D. Liu, C. Rivalain and C. Patissier for administrative assistance; and A. Adeleye, D. Bacikova, E. McGrath Martinez, A. R. Soltis, K. Dobbs, J. Danielson, H. Matthews, and S. Weber for technical and other assistance. We thank M. M. A. Ata and F. Al Ali for their contribution to VirScan experiments. We would like to thank Dr. Stephen Ellledge (Brigham and Women's Hospital and Harvard Medical School, Boston, MA) for kindly providing the VirScan phage library used in this study. We thank A. W. Ashbrook, the BSL3 manager of the Rice lab. We thank M. Lazzaro, Director of Immigration and Academic Appointments for his assistance. From JM lab, we thank W. Chung, K. Kiryluk, S. O'Byrne, D. Pendrick, J. Williamson, C. Andrews, and M. Disco. We thank Prof. Massimo Andreoni (Tor Vergata, Italy) for his clinical contribution. We thank Antonio Novelli (Bambino Gesù Hospital, Italy) for his collaboration. This study utilized the high-performance computational resources of the NIH HPC Biowulf cluster (<http://hpc.nih.gov>) and the Office of Cyber Infrastructure and Computational Biology (OCICB) High Performance Computing (HPC) cluster at the National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD. The opinions and assertions expressed herein are those of the authors and are not to be construed as reflecting the views of USUHS or the United States Department of Defense. **Funding:** We thank the

generous donation from Fisher Center for Alzheimer's Research Foundation for our research. The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercatus Center at George Mason University, the Yale Center for Mendelian Genomics and the GSP Coordinating Center funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956), the French National Research Agency (ANR) under the "Investments for the Future" program (ANR-10-IAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBED), the French Foundation for Medical Research (FRM) (EQU201903007798), the FRM and ANR GENCOV project, ANRS-COV05, the Square Foundation, *Grandir - Fonds de solidarité pour l'enfance*, the SCOR Corporate Foundation for Science, Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Paris. The French COVID Cohort study group was sponsored by Inserm and supported by the REACTing consortium and by a grant from the French Ministry of Health (PHRC 20-0424). Regione Lombardia, Italy (project "Risposta immune in pazienti con COVID-19 e co-morbidità"), and the Intramural Research Program of the NIAID, NIH. The laboratory of Genomes & Cell Biology of Disease is supported by "Integrative Biology of Emerging Infectious Diseases" (grant no. ANR-10-LABX-62-IBED), the "Fondation pour la Recherche Médicale" (grant FRM - EQU202003010193), the "Agence Nationale de la Recherche" (ANR FLASH COVID project IDISCOVER cofounded by the "Fondation pour la Recherche Médicale"), University of Paris ("Plan de Soutien Covid-19": RACPL20FIR01-COVID-SOUL). IM is a senior clinical investigator with the FWO Vlaanderen; IM and LM are supported by FWO G0C8517N – G0B5120N. The VS team was supported by "Agence Nationale de la Recherche" (ANR-17-CE15-0003, ANR-17-CE15-0003-01), and by Université de Paris "PLAN D'URGENCE COVID19". LK was supported by a fellowship from the French Ministry of Research. VS-S is supported by a UKRI Future Leaders Fellowship (MR/S032304/1). SZA-M is supported by the Elite Journals Program at King Saud University through grant number PEJP-16-107. JM lab is supported by Columbia University COVID biobank and grant: UL1TR001873. Work in the Laboratory of Virology and Infectious Disease was supported by NIH grants P01AI138398-S1, 2U19AI111825, and R01AI091707-10S1, a George Mason University Fast Grant, and the G. Harold and Leila Y. Mathers Charitable Foundation. JLP is supported by a European Molecular Biology Organization Long-Term Fellowship (ALTF 380-2018). Work at the Neurometabolic Diseases Laboratory received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 824110 (EasiGenomics grant COVID-19/ PID12342) to A.P., and Roche and Illumina Covid Match Funds to M.G.. C.R.G. and colleagues are supported by Instituto de Salud Carlos III (COV20_01333 and COV20_01334), Spanish Ministry of Science and Innovation, with the funding of European Regional Development Fund-European Social Fund -FEDER-FSE; (RTC-2017-6471-1: AEI/FEDER, UE), and Cabildo Insular de Tenerife (CGIEU0000219140 and "Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19"). D.C.V. is supported by the Fonds de la recherche en santé du Québec clinician-scientist scholar program. Helen Su is adjunct faculty at the University of Pennsylvania. A-L.N. was supported by the Foundation Bettencourt Schueller. The Amsterdam UMC Covid-19 Biobank was funded by the Netherlands Organization for Health Research and Development (ZonMw, NWO-vici 91819627), The Corona Research Fund (Amsterdam UMC), Dr. J. C. Vaillantfonds, and Amsterdam UMC. Work on COVID-19 at the AG-S lab is partly supported by NIH supplements to grants U19AI135972, U19AI142733 and R35 HL135834, and to contract HHSN272201800048C, by a DoD supplement to grant W81XWH-20-1-0270, by DARPA project HR0011-19-2-0020, by CRIP (Center for Research on Influenza Pathogenesis), a NIAID funded Center of Excellence for Influenza Research and Surveillance (CEIRS, contract HHSN272201400008C), by an NIAID funded Collaborative Influenza Vaccine Innovation Center (SEM-CIVIC, contract 75N93019C00051) and by the generous support of the JPB Foundation, the Open Philanthropy Project (research grant 2020-215611(5384)) and anonymous donors. The Virscan analysis presented in fig. S11 was performed with financial support from Sidra Medicine. **Author contributions:** A.G., A.A., A.A.A., A.L.S., A-L.N., A.C., A.C., A.P., B.B., B.S.R., C.A., C.M., C.K., C.L., C.M.R., C.L.D., D.D., E.M., E.J., F.A., F.A-M., F.O., F.A., F.K., G.N., G.S., G.G., H-H.H., H.K.A.S., H.S., I.K.D.S., I.M., J.L.P., J.R., J.E.H., J.C., J.M., J.Y.,

K.D., K.B., L.A., L.L-D., L.K., L.M., L.B-M., L.B., L.D.N., M.M-V., M.C., M.O., M.C., M.N., M.F.T., M.S., M.F.A., N.M., N.S., P.B., P.M., Q.Z., Q.Z., Q.P., R.L., R.Y., S.A.T., S.Z-A-M., S.H., S.K., S.H., S.B-D., T.K., T.M., T.M., V.S-S., V.S., V.B., W.S., X.D., Y.S., Z.L. either performed or supervised experiments, generated and analyzed data, and contributed to the manuscript. A.S., A.C.U., A.B., A.O., A.P., B.B., D.V.D.B., F.R., G.K., J.M., P.Z., S-Y.Z., T.L-V., Y.S., Y.Z. performed computational analysis. A.S., A.N.S., A.M-N., A.B., C.R., D.M., D.C.V., E.Q-R., F.H., I.M., I.V., J.B., J-C.G., L.R.B., L.R., L.I., M.D., P.B., P.S-P., P-E.M., R.H., R.C., S.K., S.P., T.O., Y.T-L., K.K., S.S., J.F., S.N.K. evaluated and recruited patients to COVID and/or control cohorts. Q.Z. P.B. A.C. E.J. L.A. S-Y.Z. and J-L.C. wrote the manuscript. All authors edited the manuscript. J-L.C. supervised the project. **Competing interests:** The authors declare no competing financial interest. Jean-Laurent Casanova is listed as an inventor on patent application US63/055, 155 filed by The Rockefeller University that encompasses aspects of this publication. Richard Lifton is a non-executive director of Roche and its subsidiary Genentech. **Data and materials availability:** Plasma, cells, and genomic DNA are available from Dr. Jean-Laurent Casanova/Dr. Donald Vinh under a material agreement with Rockefeller University/Research Institute-McGill University Health Centre. pSCRPSY_TMPRSS2-2A-NeoR_ACE2 and Huh-7.5 cells are available upon request from C. Rice under a material agreement with The Rockefeller University, or The Rockefeller University and Apath, LLC, respectively. Clinical data, DNA, and other patient samples are available from the Amsterdam UMC Covid-19 Biobank (Diederik van de Beek) under a material agreement with Amsterdam UMC. Material and reagents used are almost exclusively commercially available and non-proprietary. Requests for materials derived from human samples may be made available, subject to any underlying restrictions on such samples. Jean-Laurent Casanova can make material transfer agreements available through The Rockefeller University. Detailed genotype counts for all coding variants in the genes investigated in this manuscript are available at <https://doi.org/10.5061/dryad.8pk0p2nkk>. The WGS datasets used for the analyses including critical patients and asymptomatic controls described in this manuscript were deposited in dbGaP under **accession number** phs002245.v1.p1. All other data are available in manuscript or supplementary material. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S11

Tables S1 and S2

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MDAR Reproducibility Checklist

22 June 2020; accepted 16 September 2020

Published online 24 September 2020

10.1126/science.abd4570

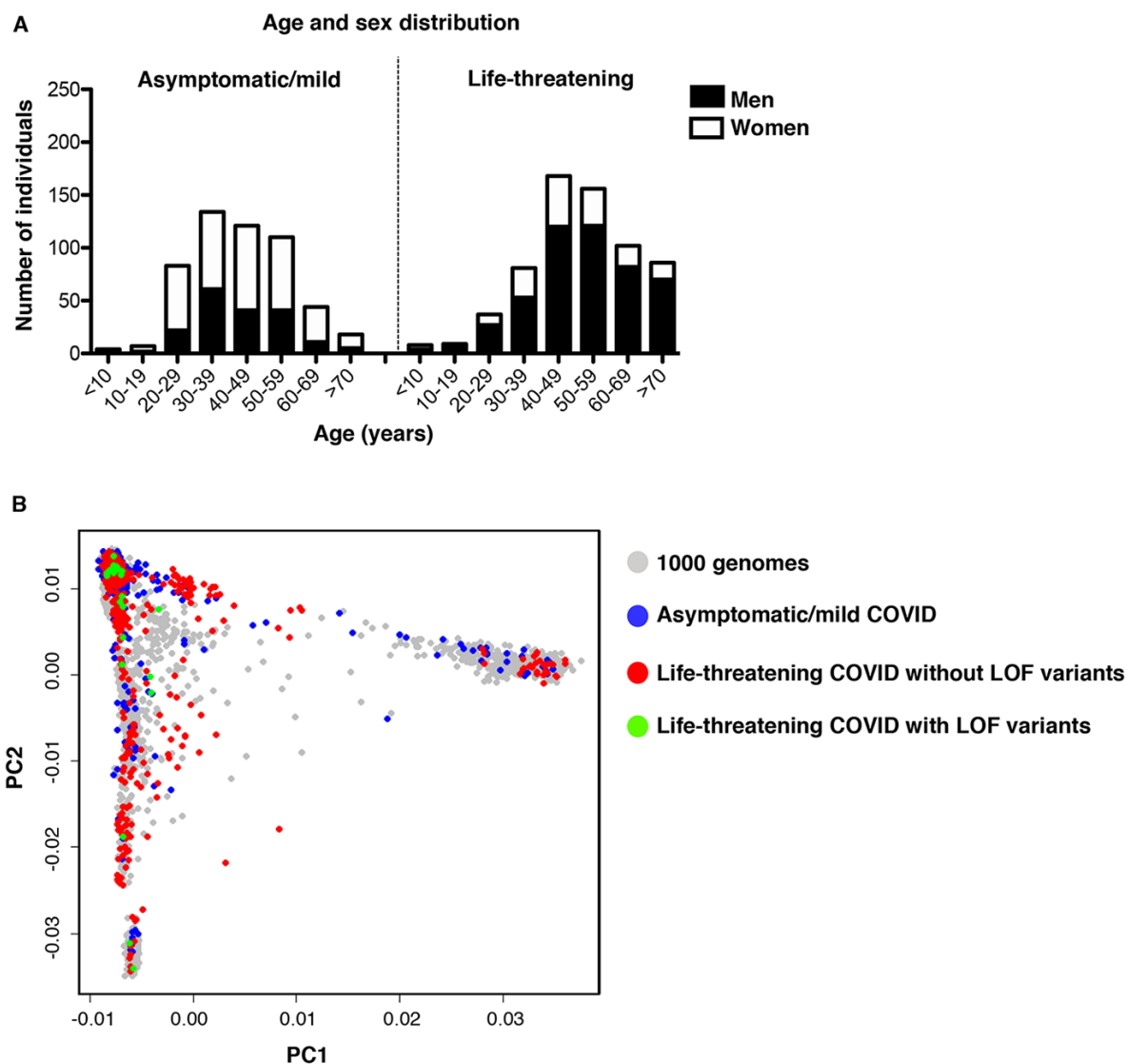


Fig. 1. Demographic and genetic data for the COVID-19 cohort. (A) Age and sex distribution of patients with life-threatening COVID-19. **(B)** PCA of patient and control cohorts (patients with mild/asymptomatic disease and individuals from the 1000 Genomes Project).

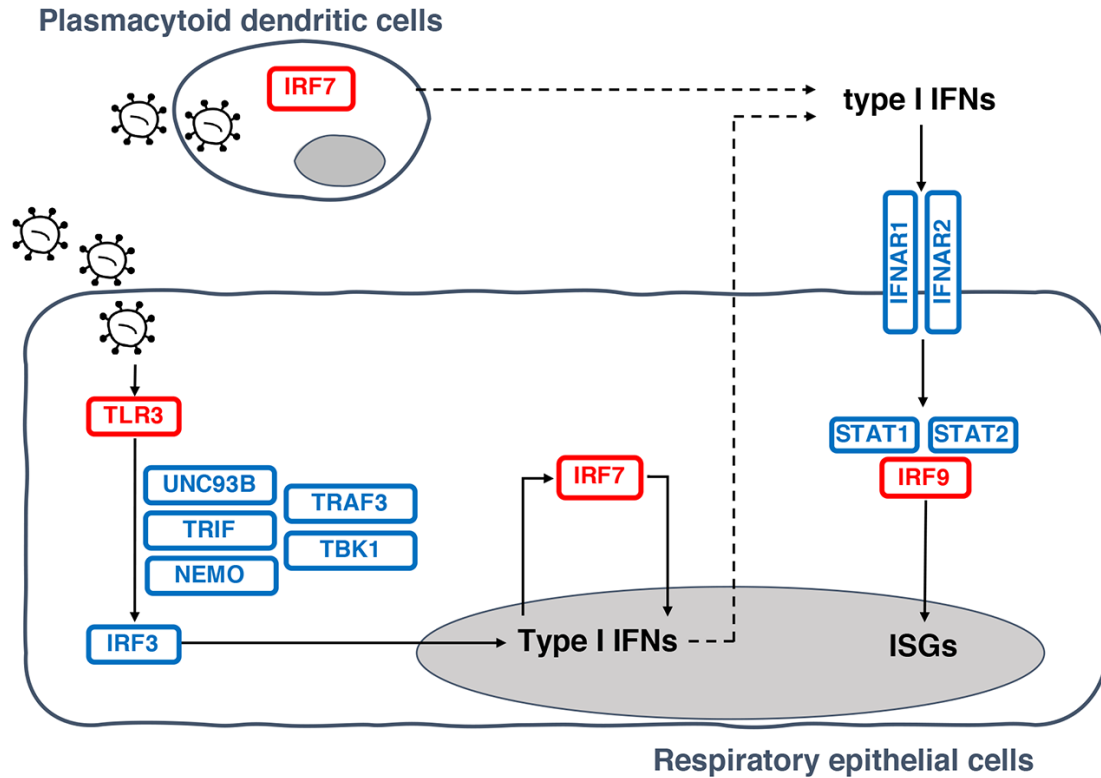


Fig. 2. Illustration of TLR3- and IRF7-dependent type I IFN production and amplification pathway. Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia, with incomplete penetrance, while deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. ISGs: interferon-stimulated genes.

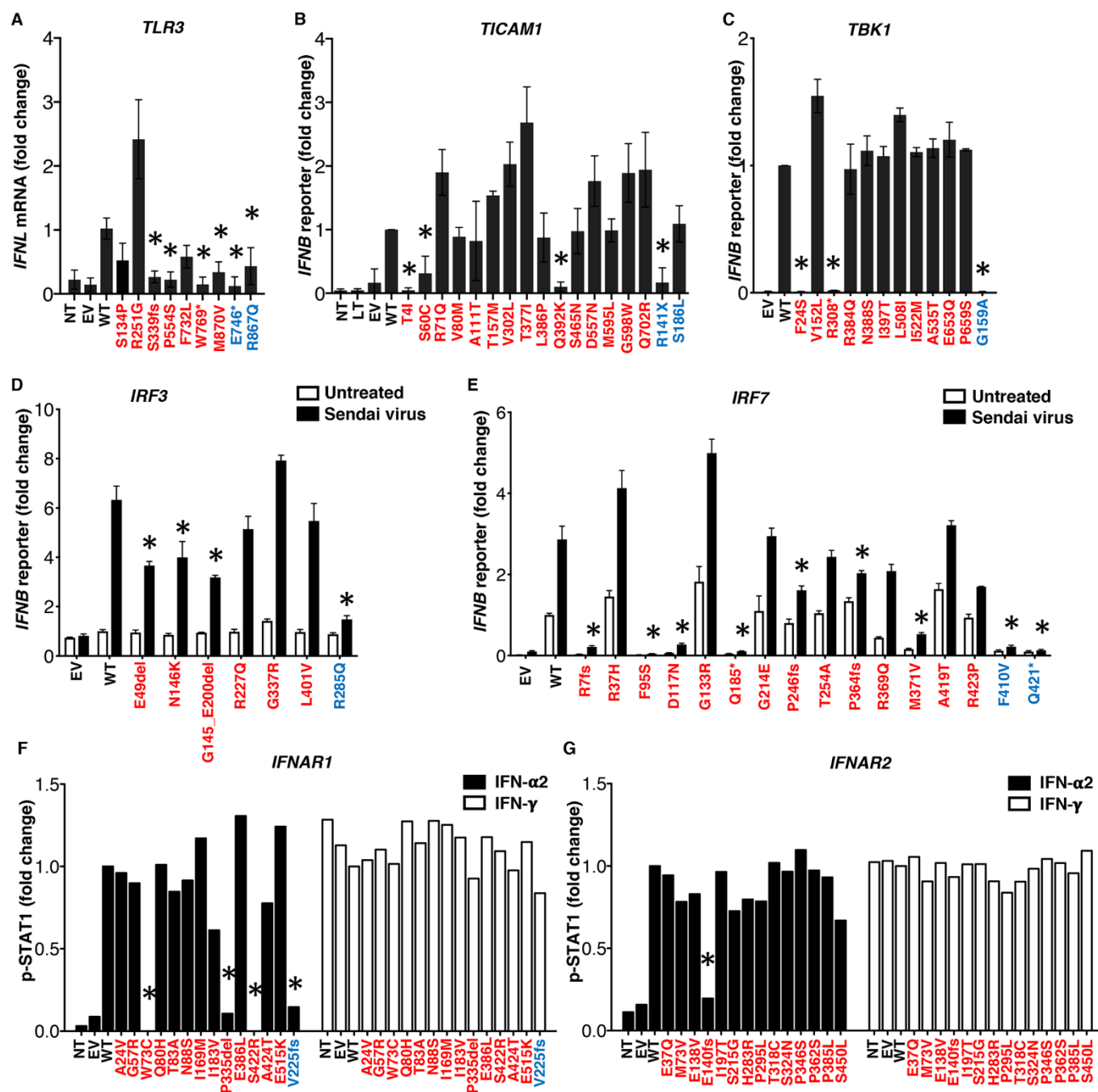


Fig. 3. Impact of TLR3, TICAM1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2 variants on type I IFN signaling. (A) TLR3-deficient P2.1 fibrosarcoma cells were stably transfected with plasmids expressing wild-type or mutant forms of *TLR3* and *IFNL1* mRNA levels were determined by RT-qPCR. *IFNL1* mRNA levels are expressed relative to housekeeping gene *GUS*, and then normalized. *IFNL1* was undetectable in unstimulated cells. The differences between variants and wild-type were tested in one-way ANOVA (* $p < 0.05$). (B) TICAM1-deficient SV40-Fib was transiently transfected with wild-type or mutant forms of *TICAM1*, together with an IFN- β -luciferase reporter and a constitutively expressed reporter. Normalized luciferase induction was measured 24 hours after transfection. The differences between variants and wild-type were tested in one-way ANOVA (* $p < 0.05$). (C) HEK293T cells were transiently transfected with wildtype and mutant forms of *TBK1*, together with an IFN- β -luciferase reporter and a constitutively expressed reporter. Normalized luciferase activity was measured 24 hours after transfection. The differences between variants and wild-type were tested in one-way ANOVA (* $p < 0.05$). (D) IRF3-deficient HEK293T cells were transiently transfected with wild-type and mutant forms of *IRF3*, together with an IFN- β -luciferase reporter and a constitutively expressed reporter. Cells were either left untreated or infected with Sendai virus for 24 hours, before the normalized measurement of luciferase activity. The differences between variants and wild-type were evaluated in two-way ANOVA (* $p < 0.05$). (E) HEK293T cells were transiently transfected with wild-type and mutant forms of *IRF7*, together with an IFN- β -luciferase reporter and a constitutively expressed reporter. Cells were either left untreated or infected with Sendai virus for 24 hours before the normalized measurement of luciferase activity. The differences between variants and wild-type were tested in two-way ANOVA (* $p < 0.05$). (F) and (G) IFNAR1- or IFNAR2-deficient SV40-Fib cells were transiently transfected with wild-type or mutant forms of *IFNAR1* for 36 hours and were either left untreated or stimulated with IFN- $\alpha 2$ or - γ . FACS staining with anti-p-STAT1 antibody and the z-score of median fluorescence intensity (MFI) were assessed (*variants with MFI less than 50% of wild-type). Variants in red were identified in COVID-19 patients. Variants in blue are known deleterious variants and served as negative controls. EV: empty vector; LT: Lipofectamine; WT: wild-type. Three technical repeats were performed for A-E. Mean and standard deviation (SD) were shown in column and horizontal bars when appropriate.

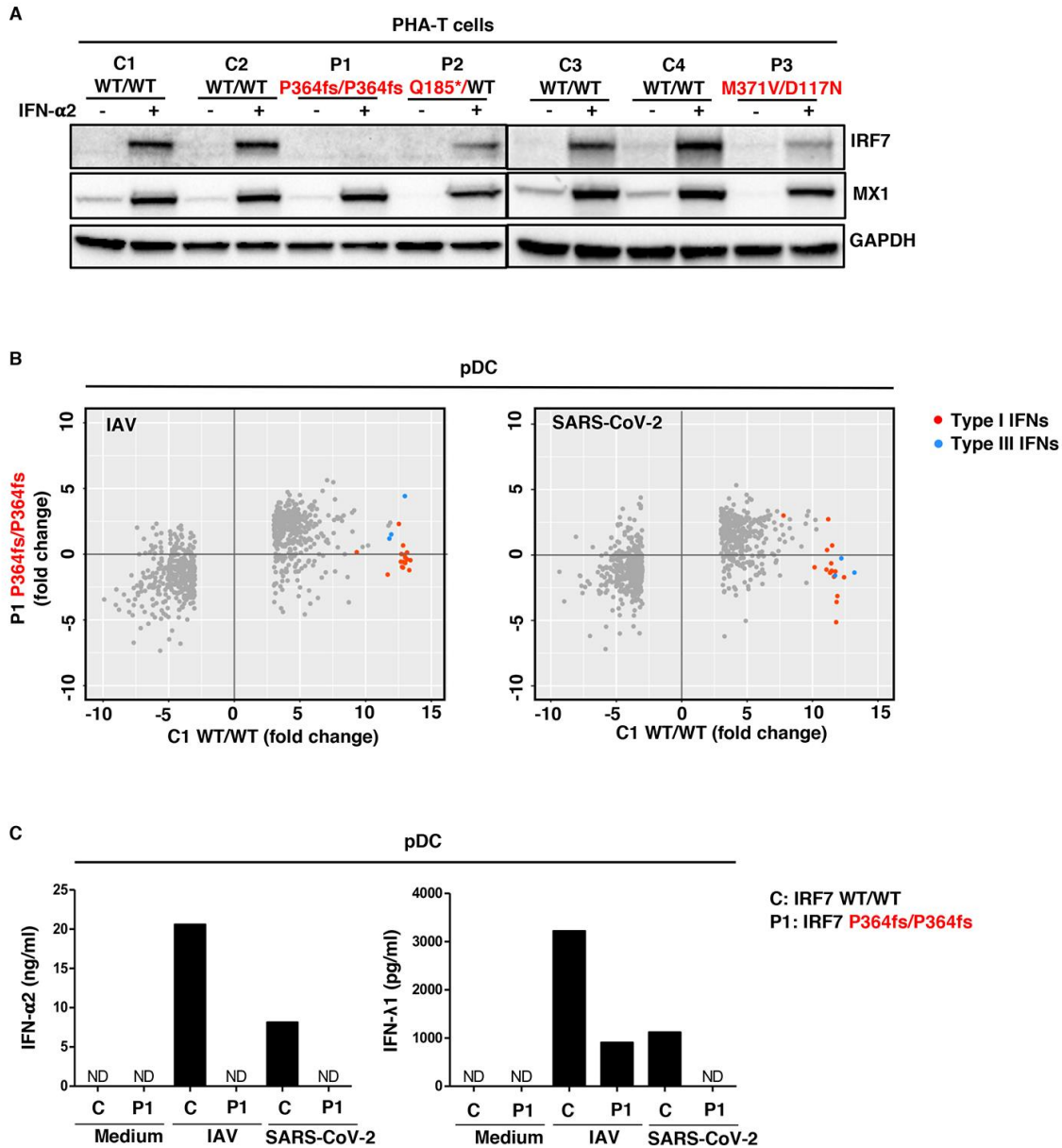


Fig. 4. Type I IFN responses in patient cells defective for IRF7. (A) Levels of IRF7 protein in PHA-T cells from two patients with AR IRF7 deficiency (P1, P3) and one patient with AD IRF7 deficiency (P2), and four healthy donors (C1-4). Cells were either left untreated or were stimulated with IFN- α 2 for 24 hours and protein levels were measured by Western blotting. MX1 was used as a positive control for IFN- α 2 treatment. (B) pDCs isolated from an AR IRF7-deficient patient (P1) and a healthy donor (C1) were either left untreated, or were infected with influenza A virus (IAV) or SARS-CoV-2, and RNAseq was performed. Genes with expression >2.5 fold higher or lower in C1 after infection are plotted, by fold change in expression. Red dots: type I IFN genes; blue dots: type III IFN genes. (C) pDCs isolated from a healthy donor (C) and IRF7-deficient patient (P1) were either left untreated (Medium) or infected with IAV or SARS-CoV-2, and the production of IFN- α 2 and IFN- λ 1 was measured by CBA and ELISA, respectively, on the supernatant. ND: not detected.

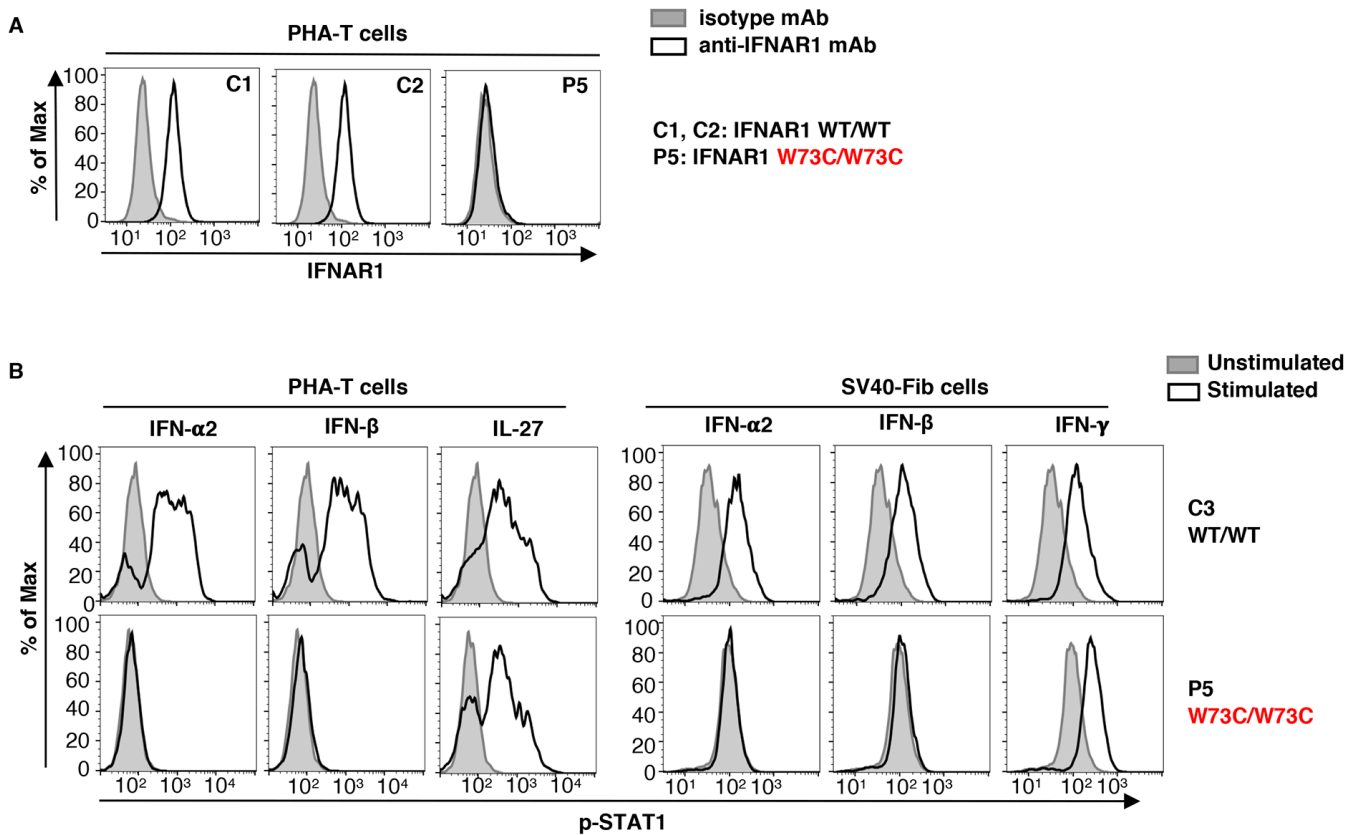


Fig. 5. Type I IFN responses in patient cells defective for IFNAR1. (A) FACS staining of IFNAR1 on the surface of PHA-T cells from a patient with AR IFNAR1 deficiency (P5) and healthy donors (C1, C2). (B) PHA-T cells and SV40-Fib from a patient with AR IFNAR1 deficiency (P5) and a healthy donor (C3) were stimulated with IFN- α 2 or - β , and p-STAT1 levels were determined by FACS. IL-27 stimulation served as a positive control on PHA-T cells, whereas IFN- γ stimulation served as a positive control on SV40-Fib cells.

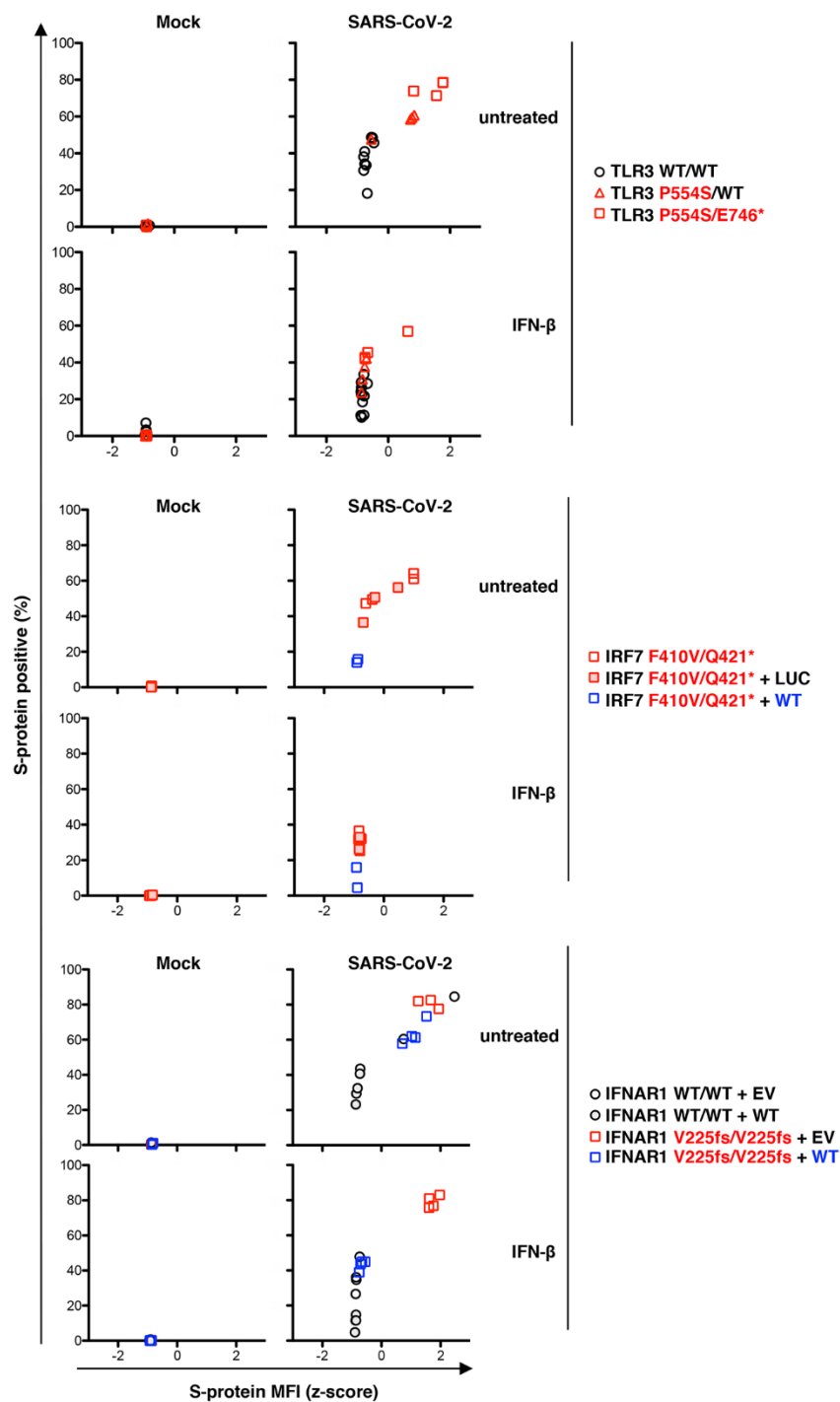


Fig. 6. Cell-intrinsic type I IFN response to SARS-CoV-2. SV40-Fib of TLR3^{-/-}, TLR3^{+/-}, IRF7^{-/-}, IRF7^{+/-} rescued with wild-type IRF7, IFNAR1^{-/-}, and IFNAR1^{+/-} rescued with wild-type IFNAR1 were transduced with ACE2 and TMPRSS2 and then either left untreated or treated with IFN-β for 4 hours. Cells were then infected with SARS-CoV-2 (MOI = 0.5). ACE2 and viral S-protein levels were measured by high-content microscopy, after staining, with gating on ACE2⁺ cells. IRF7 deficient SV40-Fib cells were previously transduced with either wild-type IRF7 (WT IRF7) or negative control (Luc). IFNAR1 deficient cells were previously transduced with either wild-type IFNAR1 (WT IFNAR1) or empty vector (EV).

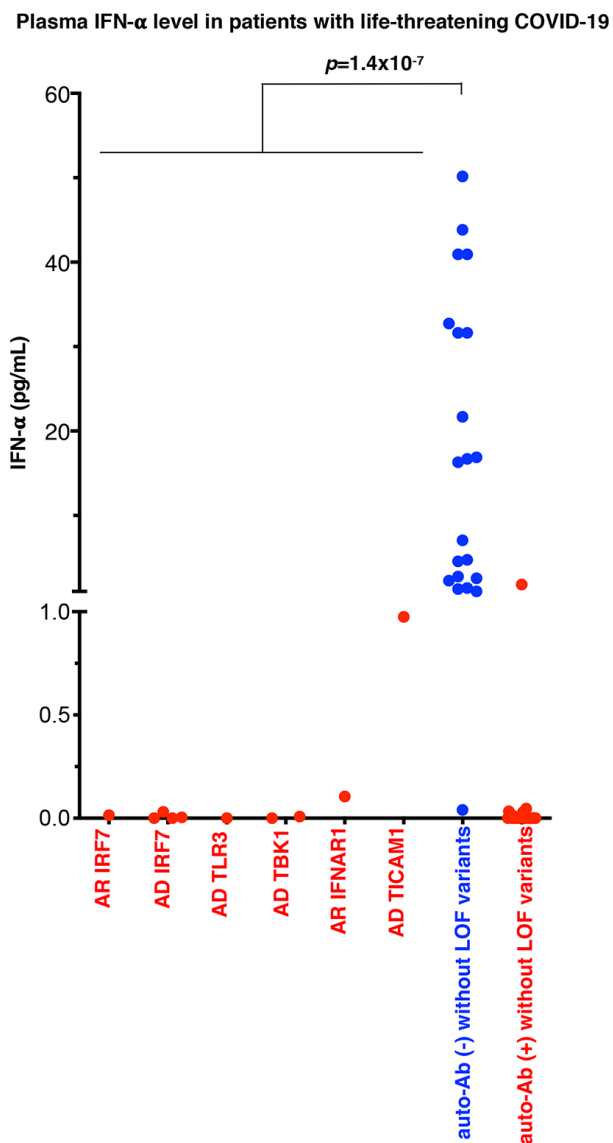


Fig. 7. In vivo type I IFN responses to SARS-CoV-2 infections. Plasma levels of 13 IFN- α were measured by Simoa. AD: autosomal dominant; AR: autosomal recessive; Auto-Ab(+) without LOF variants: COVID-19 patients with neutralizing anti-IFN- α auto-Abs in our accompanying report (29). *P* value indicated were evaluated in one-way ANOVA.

Table 1. Disease-causing variants identified in patients with life-threatening COVID-19.

Gene	Inheritance	Genetic form	Genotype	Gender	Age (year)	Ancestry/Residence	Outcome
<i>TLR3</i>	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
<i>TLR3</i>	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
<i>TLR3</i>	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
<i>TLR3</i>	AD	Known	p.Met870Val/WT	M	56	Colombian/Spain	Survived
<i>UNC93B1</i>	AD	New	p.Glu96*/WT	M	48	Venezuelan/Spain	Survived
<i>TICAM1</i>	AD	Known	p.Thr4Ile/WT	M	49	Italy	Survived
<i>TICAM1</i>	AD	Known	p.Ser60Cys/WT	F	61	Vietnamese/France	Survived
<i>TICAM1</i>	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
<i>TBK1</i>	AD	Known	p.Phe24Ser/WT	F	46	Venezuelan/Spain	Survived
<i>TBK1</i>	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
<i>IRF3</i>	AD	Known	p.Glu49del/WT	F	23	Bolivian/Spain	Survived
<i>IRF3</i>	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
<i>IRF7</i>	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italian/Belgium	Survived
<i>IRF7</i>	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
<i>IRF7</i>	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
<i>IRF7</i>	AD	New	p.Gln185*/WT	M	44	France	Survived
<i>IRF7</i>	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
<i>IRF7</i>	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
<i>IRF7</i>	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
<i>IFNAR1</i>	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
<i>IFNAR1</i>	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
<i>IFNAR1</i>	AD	New	p.Pro335del/WT	F	23	Chinese/Italy	Survived
<i>IFNAR2</i>	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

AD: autosomal dominant; AR: autosomal recessive; WT: wild-type.

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

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published online September 24, 2020 originally published online September 24, 2020

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