

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

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

Qian Zhang *et al.*

INTRODUCTION: Clinical outcomes of human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection range from silent infection to lethal coronavirus disease 2019 (COVID-19). Epidemiological studies have identified three risk factors for severe disease: being male, being elderly, and having other medical conditions. However, interindividual clinical variability remains huge in each demographic category. Discovering the root cause and detailed molecular, cellular, and tissue- and body-level mechanisms underlying life-threatening COVID-19 is of the utmost biological and medical importance.

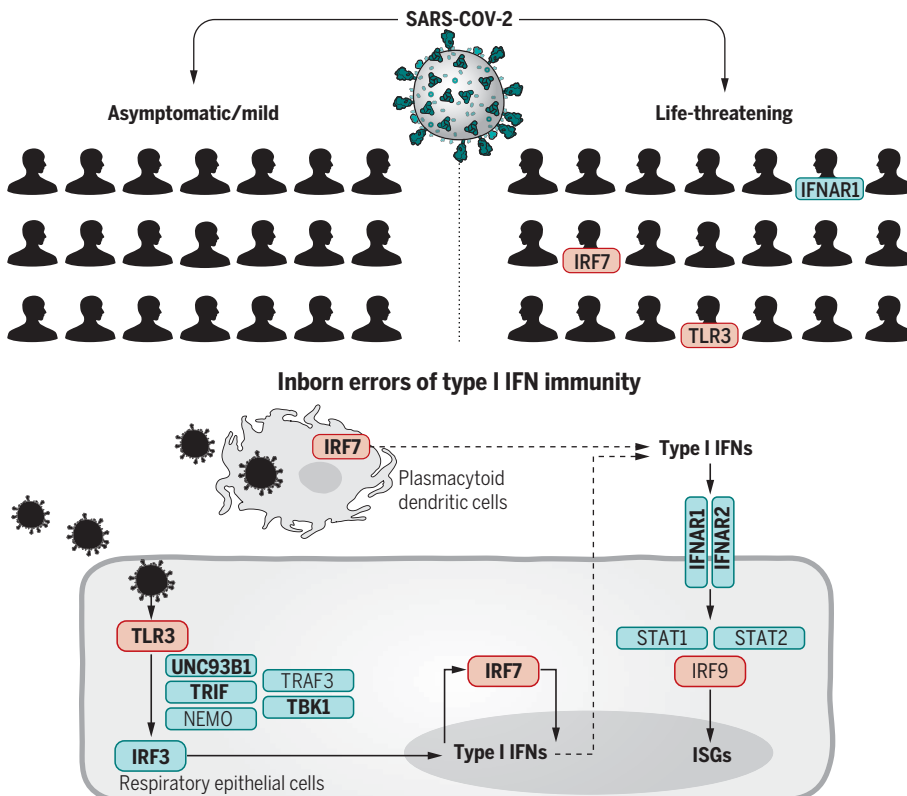
RATIONALE: We established the COVID Human Genetic Effort (www.covidhge.com) to test

the general hypothesis that life-threatening COVID-19 in some or most patients may be caused by monogenic inborn errors of immunity to SARS-CoV-2 with incomplete or complete penetrance. We sequenced the exome or genome of 659 patients of various ancestries with life-threatening COVID-19 pneumonia and 534 subjects with asymptomatic or benign infection. We tested the specific hypothesis that inborn errors of Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (IRF7)-dependent type I interferon (IFN) immunity that underlie life-threatening influenza pneumonia also underlie life-threatening COVID-19 pneumonia. We considered three loci identified as mutated in patients with life-threatening influenza: *TLR3*, *IRF7*, and *IRF9*. We also con-

sidered 10 loci mutated in patients with other viral illnesses but directly connected to the three core genes conferring influenza susceptibility: *TICAM1/TRIF*, *UNC93B1*, *TRAF3*, *TBK1*, *IRF3*, and *NEMO/IKBKG* from the TLR3-dependent type I IFN induction pathway, and *IFNAR1*, *IFNAR2*, *STAT1*, and *STAT2* from the IRF7- and IRF9-dependent type I IFN amplification pathway. Finally, we considered various modes of inheritance at these 13 loci.

RESULTS: We found an enrichment in variants predicted to be loss-of-function (pLOF), with a minor allele frequency <0.001, at the 13 candidate loci in the 659 patients with life-threatening COVID-19 pneumonia relative to the 534 subjects with asymptomatic or benign infection ($P = 0.01$). Experimental tests for all 118 rare nonsynonymous variants (including both pLOF and other variants) of these 13 genes found in patients with critical disease identified 23 patients (3.5%), aged 17 to 77 years, carrying 24 deleterious variants of eight genes. These variants underlie autosomal-recessive (AR) deficiencies (*IRF7* and *IFNAR1*) and autosomal-dominant (AD) deficiencies (*TLR3*, *UNC93B1*, *TICAM1*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, and *IFNAR2*) in four and 19 patients, respectively. These patients had never been hospitalized for other life-threatening viral illness. Plasmacytoid dendritic cells from IRF7-deficient patients produced no type I IFN on infection with SARS-CoV-2, and *TLR3*^{-/-}, *TLR3*^{+/-}, *IRF7*^{-/-}, and *IFNAR1*^{-/-} fibroblasts were susceptible to SARS-CoV-2 infection in vitro.

CONCLUSION: At least 3.5% of patients with life-threatening COVID-19 pneumonia had known (AR *IRF7* and *IFNAR1* deficiencies or AD *TLR3*, *TICAM1*, *TBK1*, and *IRF3* deficiencies) or new (AD *UNC93B1*, *IRF7*, *IFNAR1*, and *IFNAR2* deficiencies) genetic defects at eight of the 13 candidate loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs. This discovery reveals essential roles for both the double-stranded RNA sensor TLR3 and type I IFN cell-intrinsic immunity in the control of SARS-CoV-2 infection. Type I IFN administration may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection. ■



Inborn errors of TLR3- and IRF7-dependent type I IFN production and amplification underlie life-threatening COVID-19 pneumonia. Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia with incomplete penetrance, and deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. Molecules represented in bold are encoded by genes with variants that also underlie critical COVID-19 pneumonia.

The full author list and the list of affiliations is available in the full article online.
Corresponding author: Jean-Laurent Casanova (casanova@rockefeller.edu)
This is an open-access article distributed under the terms of the Creative Commons Attribution license (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Cite this article as Q. Zhang *et al.*, *Science* 370, eabd4570 (2020). DOI: 10.1126/science.abd4570

READ THE FULL ARTICLE AT
<https://doi.org/10.1126/science.abd4570>

RESEARCH ARTICLE

CORONAVIRUS

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

Qian Zhang¹, Paul Bastard^{2,3*}, Zhiyong Liu^{1*}, Jérémie Le Pen^{4*}, Marcela Moncada-Velez^{1*}, Jie Chen^{1*}, Masato Ogishi^{1*}, Ira K. D. Sabli^{5*}, Stephanie Hodeib^{5*}, Cecilia Korol^{2*}, Jérémie Rosain^{2,3*}, Kaya Bilguvar^{6*}, Junqiang Ye^{7*}, Alexandre Bolze^{8*}, Benedetta Bigio^{1*}, Rui Yang^{1*}, Andrés Augusto Arias^{1,9,10*}, Qinhuo Zhou^{1*}, Yu Zhang^{11,12*}, Fanny Onodji¹³, Sarantis Korniotis¹³, Léa Karpf¹³, Quentin Philippot^{2,3}, Marwa Chbihi^{2,3}, Lucie Bonnet-Madin¹⁴, Karim Dorgham¹⁵, Nikaia Smith¹⁶, William M. Schneider⁴, Brandon S. Razoooky⁴, Hans-Heinrich Hoffmann⁴, Eleftherios Michailidis⁴, Leen Moens¹⁷, Ji Eun Han¹, Lazaro Lorenzo^{2,3}, Lucy Bizien^{2,3}, Philip Meade¹⁸, Anna-Lena Neehus^{2,3}, Aileen Camille Ugurbil¹, Aurélien Corneau¹⁹, Gaspard Kerner^{2,3}, Peng Zhang¹, Franck Rapaport¹, Yoann Seeleuthner^{2,3}, Jeremy Manry^{2,3}, Cecile Masson²⁰, Yohann Schmitt²⁰, Agatha Schlüter²¹, Tom Le Voyer^{2,3}, Taushif Khan²², Juan Li¹, Jacques Fellay^{23,24,25}, Lucie Roussel²⁶, Mohammad Shahrooei^{27,28}, Mohammed F. Alosaimi²⁹, Davood Mansouri^{30,31,32}, Haya Al-Saud³³, Fahd Al-Mulla³⁴, Feras Almourfi³³, Saleh Zaid Al-Muhsen³⁵, Fahad Alshohime²⁹, Saeed Al Turki^{36,37}, Rana Hasanato²⁹, Diederik van de Beek³⁸, Andrea Biondi³⁹, Laura Rachele Bettini³⁹, Mariella D'Angio³⁹, Paolo Bonfanti⁴⁰, Luisa Imberti⁴¹, Alessandra Sottini⁴¹, Simone Paghera⁴¹, Eugenia Quiros-Roldan⁴², Camillo Rossi⁴³, Andrew J. Oler⁴⁴, Miranda F. Tompkins⁴⁵, Camille Alba⁴⁵, Isabelle Vandernoot⁴⁶, Jean-Christophe Goffard⁴⁷, Guillaume Smits⁴⁶, Isabelle Migeotte⁴⁸, Filomeen Haerynck⁴⁹, Pere Soler-Palacin⁵⁰, Andrea Martin-Nalda⁵⁰, Roger Colobran⁵¹, Pierre-Emmanuel Morange⁵², Sevgi Keles⁵³, Fatma Çölkesen⁵⁴, Tayfun Ozcelik⁵⁵, Kadriye Kart Yasar⁵⁶, Sevtaç Senoglu⁵⁶, Şemsi Nur Karabela⁵⁶, Carlos Rodríguez-Gallego^{57,58}, Giuseppe Novelli⁵⁹, Sami Hraiech⁶⁰, Yacine Tandjaoui-Lambiotte^{61,62}, Xavier Duval^{63,64}, Cédric Laouénan^{63,64,65}, COVID-STORM Clinicians†, COVID Clinicians†, Imagine COVID Group†, French COVID Cohort Study Group†, CoV-Contact Cohort†, Amsterdam UMC Covid-19 Biobank†, COVID Human Genetic Effort†, NIAID-USUHS/TAGC COVID Immunity Group†, Andrew L. Snow⁶⁶, Clifton L. Dalgard^{45,67}, Joshua D. Milner⁶⁸, Donald C. Vinh²⁶, Trine H. Mogensen^{69,70}, Nico Marr^{22,71}, Andrés N. Spaan^{1,72}, Bertrand Boisson^{1,2,3}, Stéphanie Boisson-Dupuis^{1,2,3}, Jacinta Bustamante^{1,2,3,73}, Anne Puel^{1,2,3}, Michael J. Ciancanelli^{1,74}, Isabelle Meyts^{17,75}, Tom Maniatis^{7,76}, Vassili Soumelis^{12,3,77}, Ali Amara¹⁴, Michel Nussenzweig^{78,79}, Adolfo García-Sastre^{18,80,81,82}, Florian Kramer¹⁸, Aurora Pujol²¹, Darragh Duffy¹⁶, Richard P. Lifton^{83,84,85}†, Shen-Ying Zhang^{1,2,3}†, Guy Gorochov¹⁵†, Vivien Béziat^{1,2,3}†, Emmanuelle Jouanguy^{1,2,3}†, Vanessa Sancho-Shimizu⁵†, Charles M. Rice⁴†, Laurent Abel^{1,2,3}†, Luigi D. Notarangelo^{11,12}§, Aurélie Cobat^{1,2,3}§, Helen C. Su^{11,12}§, Jean-Laurent Casanova^{1,2,3,79,86}§¶

Clinical outcome upon infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ranges from silent infection to lethal coronavirus disease 2019 (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 Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (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 defined LOF variants underlying autosomal-recessive or autosomal-dominant deficiencies in 23 patients (3.5%) 17 to 77 years of age. We show that human fibroblasts with mutations affecting this circuit 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.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already claimed at least 1 million 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: (i) increasing age, decade by decade, after the age of 50, (ii) being male,

and (iii) having various underlying medical conditions (1). However, even taking these factors into account, there is immense inter-individual 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 in some patients, life-threatening coronavirus disease 2019 (COVID-19) may be

caused 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 between 1 month and 99 years of age (Fig. 1A). These patients were hospitalized for life-threatening pneumonia caused by 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 13 human loci that govern immunity to influenza virus

We first tested the specific hypothesis that inborn errors of Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (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: *TICAMI/TRIF* (9), *UNC93B1* (10), *TRAF3* (11), *TBK1* (12), *IRF3* (13), and *NEMO/IKBKG* (14) in the TLR3-dependent type I IFN induction pathway, and *IFNARI* (15), *IFNAR2* (16), *STAT1* (17), and *STAT2* (18) in the IRF7- and IRF9-dependent type I IFN amplification pathway. We collected both monoallelic and biallelic nonsynonymous variants with a minor allele frequency (MAF) <0.001 at all 13 loci. Twelve of the 13 candidate loci are autosomal, whereas *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*, *IFNARI*, *IFNAR2*, *STAT2*, and *IRF9*). Nevertheless, we 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 that 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 LOF at the influenza susceptibility loci

We found four unrelated patients with biallelic variants of *IRF7* or *IFNARI* (Table 1 and table S1). We also found 113 patients carrying 113 monoallelic variants at 12 loci: *TLR3* ($N = 7$ patients/7 variants), *UNC93B1* ($N = 10/9$), *TICAMI* ($N = 17/15$), *TRAF3* ($N = 6/6$), *TBK1* ($N = 12/11$), *IRF3* ($N = 5/5$), *IRF7* ($N = 20/13$), *IFNARI* ($N = 14/13$), *IFNAR2* ($N = 17/15$), *STAT1* ($N = 4/4$), *STAT2* ($N = 11/11$), and *IRF9* ($N = 4/4$). We detected no copy number variation

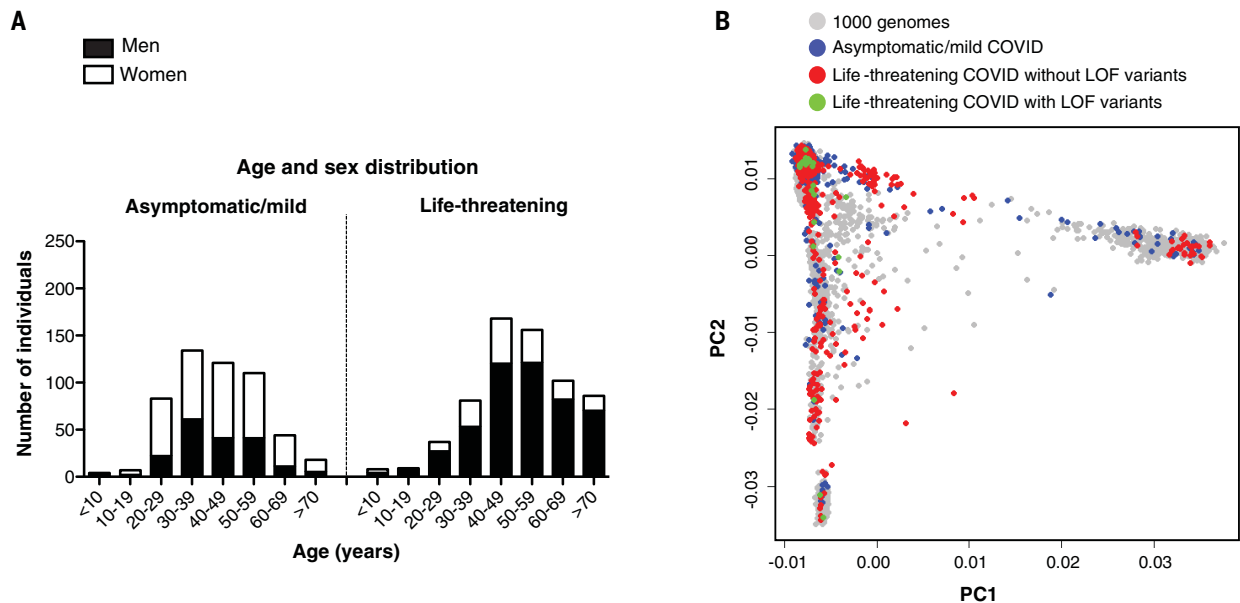


Fig. 1. Demographic and genetic data for the COVID-19 cohort. (A) Age and sex distribution of patients with life-threatening COVID-19. (B) PCA of patient (with or without LOF variants in the 13 candidate genes) and control cohorts (patients with mild or asymptomatic disease and individuals from the 1000 Genomes Project).

¹St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. ²Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France. ³University of Paris, Imagine Institute, Paris, France. ⁴Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, USA. ⁵Department of Paediatric Infectious Diseases & Virology, Imperial College London, London, UK. ⁶Yale Center for Genome Analysis and Department of Genetics, Yale School of Medicine, New Haven, CT, USA. ⁷Zukerman Mind Brain Behavior Institute, Columbia University, New York, NY, USA. ⁸Helix, San Mateo, CA, USA. ⁹Primary Immunodeficiencies Group, University of Antioquia UdeA, Medellin, Colombia. ¹⁰School of Microbiology, University of Antioquia UdeA, Medellin, Colombia. ¹¹Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ¹²NIAID Clinical Genomics Program, NIH, Bethesda, MD, USA. ¹³Université de Paris, Institut de Recherche Saint-Louis, INSERM U976, Hôpital Saint-Louis, Paris, France. ¹⁴Laboratory of Genomes & Cell Biology of Disease, INSERM U944, CNRS UMR 7212, Université de Paris, Institut de Recherche Saint-Louis, Hôpital Saint-Louis, Paris, France. ¹⁵Sorbonne Université, Inserm, Centre d'Immunologie et des Maladies Infectieuses-Paris (CIMI PARIS), Assistance Publique-Hôpitaux de Paris (AP-HP) Hôpital Pitié-Salpêtrière, Paris, France. ¹⁶Translational Immunology Lab, Institut Pasteur, Paris, France. ¹⁷Laboratory for Inborn Errors of Immunity, Department of Microbiology, Immunology and Transplantation, Department of Pediatrics, University Hospitals Leuven, KU Leuven, Leuven, Belgium. ¹⁸Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁹Sorbonne Université, UMS037, PASS, Plateforme de Cytométrie de la Pitié-Salpêtrière CyPS, Paris, France. ²⁰Bioinformatics Platform, Structure Fédérative de Recherche Necker, INSERM UMR1163, Université de Paris, Imagine Institute, Paris, France. ²¹Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, CIBERER U759, and Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain. ²²Department of Immunology, Research Branch, Sidra Medicine, Doha, Qatar. ²³School of Life sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland. ²⁴Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ²⁵Swiss Institute of Bioinformatics, Lausanne, Switzerland. ²⁶Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, Québec, Canada. ²⁷Specialized Immunology Laboratory of Dr. Shahrooei, Sina Medical Complex, Ahvaz, Iran. ²⁸Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. ²⁹Department of Pathology and Laboratory Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia. ³⁰Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ³¹The Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti, University of Medical Sciences, Tehran, Iran. ³²Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti, Iran. ³³National Center of Genomics Technology, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia. ³⁴Dasman Diabetes Institute, Department of Genetics and Bioinformatics, Kuwait. ³⁵Immunology Research Laboratory, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. ³⁶Translational Pathology, Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, Misery of National Guard Health Affairs, Riyadh, Saudi Arabia. ³⁷Cancer & Blood Research, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia. ³⁸Amsterdam UMC, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands. ³⁹Pediatric Department and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM-Ospedale, San Gerardo, Monza, Italy. ⁴⁰Department of Infectious Diseases, San Gerardo Hospital-University of Milano-Bicocca, Monza, Italy. ⁴¹CREA Laboratory, Diagnostic Laboratory, ASST Spedali Civili di Brescia, Brescia, Italy. ⁴²Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali di Brescia, Brescia, Italy. ⁴³Chief Medical Officer, ASST Spedali Civili di Brescia, Brescia, Italy. ⁴⁴Bioinformatics and Computational Biosciences Branch, Office of Cyber Infrastructure and Computational Biology, NIAID, NIH, Bethesda, MD, USA. ⁴⁵PRIMER, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁴⁶Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ⁴⁷Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ⁴⁸Fonds de la Recherche Scientifique (FNRS) and Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ⁴⁹Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPiG), PID Research Lab, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent, Belgium. ⁵⁰Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain. ⁵¹Immunology Division, Genetics Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, UAB, Barcelona, Catalonia, Spain. ⁵²Aix Marseille Univ, INSERM, INRAE, C2VN, CHU Timone, Marseille, France. ⁵³Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. ⁵⁴Department of Infectious Diseases and Clinical Microbiology, Konya Training and Research Hospital, Konya, Turkey. ⁵⁵Department of Molecular Biology and Genetics, Bilkent University, Bilkent-Ankara, Turkey. ⁵⁶Departments of Infectious Diseases and Clinical Microbiology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ⁵⁷Department of Immunology, Hospital Universitario de G.C. Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁵⁸University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁵⁹Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy. ⁶⁰Intensive Care Unit, AP-HM, Marseille, France. ⁶¹Avicenne Hospital Intensive Care Unit, APHP, Bobigny, INSERM U1272 Hypoxia & Lung, Paris, France. ⁶²PH Réanimation CHU Avicenne, Bobigny, INSERM U1272 Hypoxie & Poumon, Paris, France. ⁶³Université de Paris, IAME UMR-S 1137, INSERM, Paris, France. ⁶⁴Inserm CIC 1425, Paris, France. ⁶⁵AP-HP, Département Épidémiologie Biostatistiques et Recherche Clinique, Hôpital Bichat, Paris, France. ⁶⁶Department of Pharmacology & Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁶⁷Department of Anatomy, Physiology & Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁶⁸Division of Pediatric Allergy, Immunology and Rheumatology, Columbia University, New York, USA. ⁶⁹Department of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark. ⁷⁰Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁷¹College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar. ⁷²Department of Medical Microbiology, Utrecht UMC, Utrecht, Netherlands. ⁷³Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, Paris, France. ⁷⁴Turnstone Biologics, New York, NY, USA. ⁷⁵Department of Pediatrics, University Hospitals Leuven, KU Leuven, Leuven, Belgium. ⁷⁶New York Genome Center, New York, NY, USA. ⁷⁷AP-HP, Hôpital Saint-Louis, Laboratoire d'Immunologie, Paris, France. ⁷⁸Laboratory of Molecular Immunology, Rockefeller University, New York, NY, USA. ⁷⁹Howard Hughes Medical Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁸⁰Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁸¹Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁸²The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁸³Laboratory of Genetics and Genomics, The Rockefeller University, New York, NY, USA. ⁸⁴Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. ⁸⁵Yale Center for Genome Analysis, Yale School of Medicine, New Haven, CT, USA. ⁸⁶Pediatric Hematology and Immunology Unit, Necker Hospital for Sick Children, AP-HP, Paris, France.

*These authors contributed equally to this work.

†All collaborators and their affiliations appear at the end of this paper.

‡These authors contributed equally to this work.

§These authors contributed equally to this work.

¶Corresponding author. Email: casanova@rockefeller.edu

for these 13 genes. Unexpectedly, 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 LOF (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 [$P = 0.01$; odds ratio (OR) = 8.28; 95% confidence interval (CI) = 1.04 to 65.64] 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 patients

We tested these 118 variants experimentally in ad hoc overexpression systems. We found that 24 variants of eight genes were deleterious (including all the pLOF variants) because they were loss-of-expression, LOF, or severely hypomorphic: *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 94 variants were biochemically neutral. Twenty-three patients carried these 24 deleterious variants, resulting in four autosomal-recessive (AR) deficiencies (homozygosity or compound heterozygosity

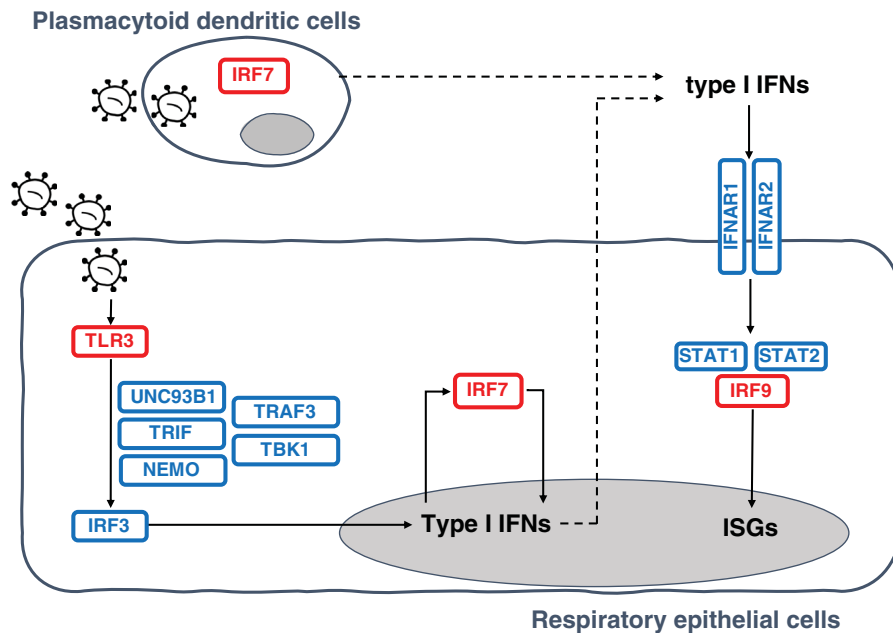


Fig. 2. Illustration of TLR3- and IRF7-dependent type I IFN production and amplification circuit.

Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia with incomplete penetrance; deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. Type I IFNs also induce themselves. ISGs, interferon-stimulated genes.

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

Gene	Inheritance	Genetic form	Genotype	Gender	Age [years]	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	Colombia/Spain	Survived
<i>UNC93B1</i>	AD	New	p.Glu96*/WT	M	48	Venezuela/Spain	Survived
<i>TICAM1</i>	AD	Known	p.Thr41le/WT	M	49	Italy	Survived
<i>TICAM1</i>	AD	Known	p.Ser60Cys/WT	F	61	Vietnam/France	Survived
<i>TICAM1</i>	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
<i>TBK1</i>	AD	Known	p.Phe24Ser/WT	F	46	Venezuela/Spain	Survived
<i>TBK1</i>	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
<i>IRF3</i>	AD	Known	p.Glu49del/WT	F	23	Bolivia/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	Italy/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	China/Italy	Survived
<i>IFNAR2</i>	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

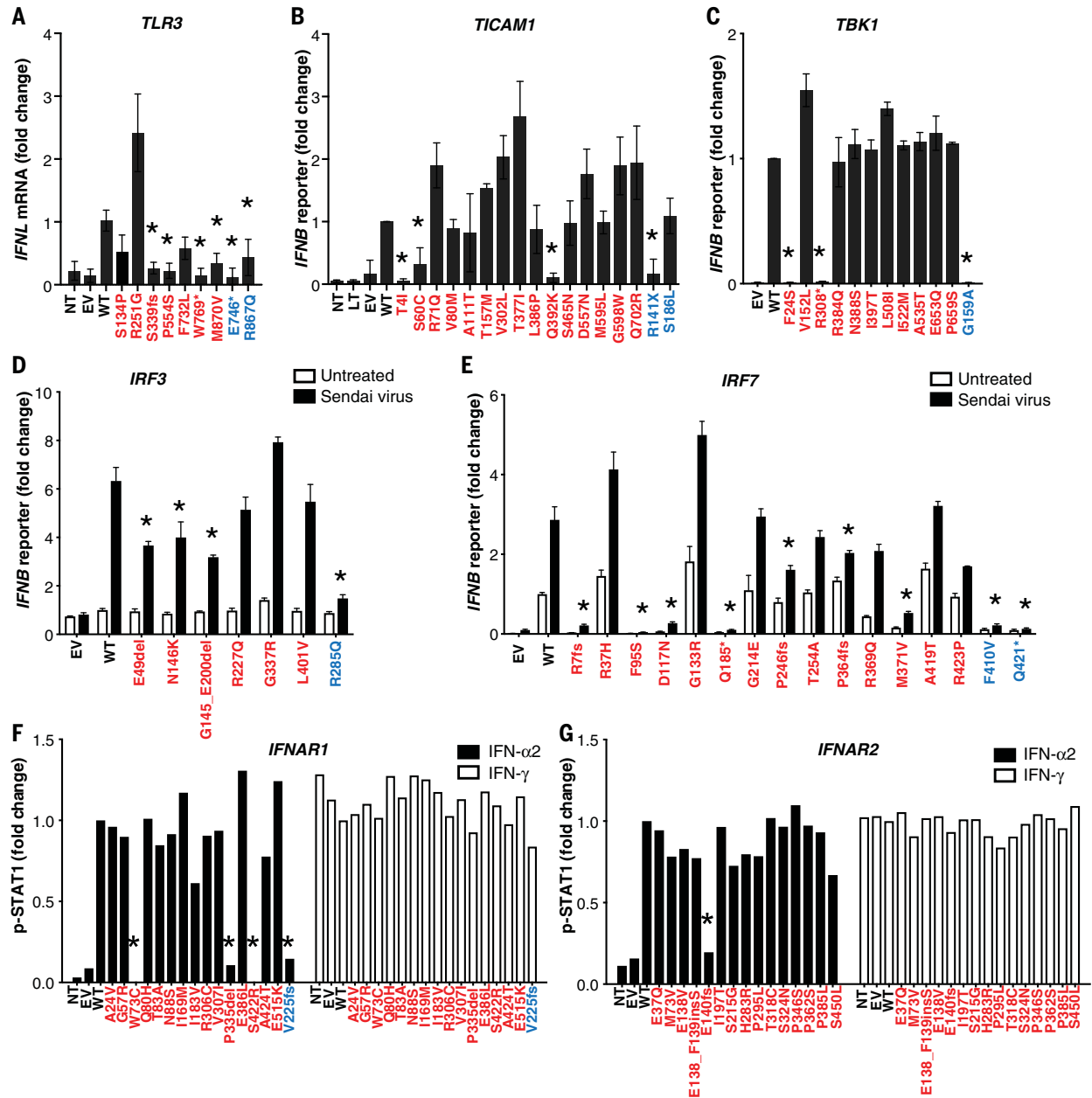


Fig. 3. Impact of *TLR3*, *TICAM1*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, and *IFNAR2* variants on type I IFN signaling.

(A) *TLR3*-deficient P2.1 fibrosarcoma cells were stably transfected with plasmids expressing WT or mutant forms of *TLR3*, and *IFNL1* mRNA levels were determined by reverse transcription quantitative PCR. *IFNL1* mRNA levels were expressed relative to the housekeeping gene *GUS* and then normalized. *IFNL1* was undetectable in unstimulated cells. The differences between variants and WT were tested using one-way ANOVA ($*P < 0.05$). (B) *TICAM1*-deficient SV40-Fib cells were transiently transfected with WT 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 WT were tested using one-way ANOVA ($*P < 0.05$). (C) HEK293T cells were transiently transfected with WT 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 WT were tested using one-way ANOVA ($*P < 0.05$). (D) *IRF3*-deficient HEK293T cells were transiently transfected with WT 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 WT were tested using two-way ANOVA ($*P < 0.05$). (E) HEK293T cells were transiently transfected with WT 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 WT were tested using two-way ANOVA ($*P < 0.05$). (F and G) *IFNAR1*- or *IFNAR2*-deficient SV40-Fib cells were transiently transfected with WT or mutant forms of *IFNAR1* for 36 hours, and either left untreated or stimulated with IFN- $\alpha 2$ or IFN- γ . Fluorescence-activated cell sorting (FACS) staining with anti-p-STAT1 antibody and the z-score of the MFI were assessed. Asterisks indicate variants with MFI $< 50\%$ of WT. 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. Three technical repeats were performed for (A) to (E). Means and SD are shown in the columns and horizontal bars when appropriate.

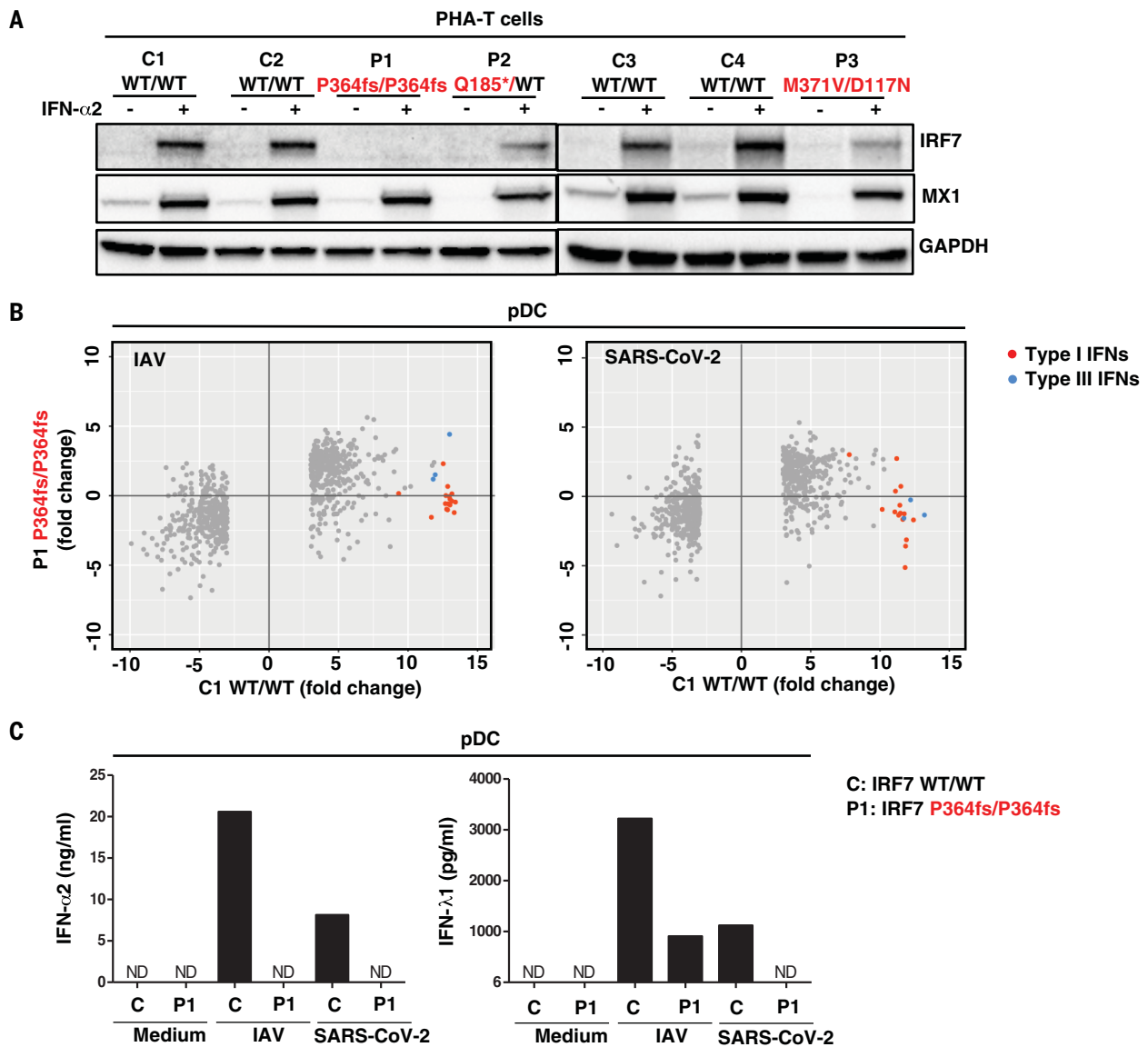


Fig. 4. Type I IFN responses in patient cells defective for IRF7. (A) Levels of the IRF7 protein in PHA-T cells from two patients with AR IRF7 deficiency (P1 and P3), one patient with AD IRF7 deficiency (P2), and four healthy donors (C1 to C4). Cells were either left untreated or stimulated with IFN- 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

infected with influenza A virus (IAV) or SARS-CoV-2, and RNA-seq was performed. Genes with expression >2.5-fold higher or lower in C1 after infection are plotted as the fold change in expression. Red dots are type I IFN genes; blue dots are type III IFN genes. (C) pDCs isolated from 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.

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* or *IFNAR1*) (7, 15), 11 with a known AD disorder (*TLR3*, *TICAM1*, *TBKI*, or *IRF3*) (6, 9, 12, 13, 20), and eight with a previously unknown AD genetic disorder (*UNC93B1*, *IRF7*, *IFNAR1*, or *IFNAR2*).

Impaired TLR3- and IRF7-dependent type I immunity in patient cells in vitro

We tested cells from patients with selected genotypes and 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), enzyme-linked immunosorbent assay (ELISA), and RNA sequencing (RNA-seq) (Fig. 4, B and C). We also showed that PHA-T cells from a patient with AR IFN- α / β receptor 1 (*IFNAR1*) deficiency had impaired *IFNAR1* expression and responses to IFN- α 2 or IFN- β , and that the patient's SV40-transformed fibroblast (SV40-Fib) cells did not respond to IFN- α 2 or IFN- β (Fig. 5). We then infected *TLR3*^{-/-}, *TLR3*^{+/-}, *IRF7*^{-/-} SV40-Fib cells, and *IRF7*^{-/-} SV40-Fib cells rescued with wild-type (WT) *IRF7*; *IFNAR1*^{-/-} SV40-Fib cells, and *IFNAR1*^{-/-} SV40-Fib cells rescued with WT

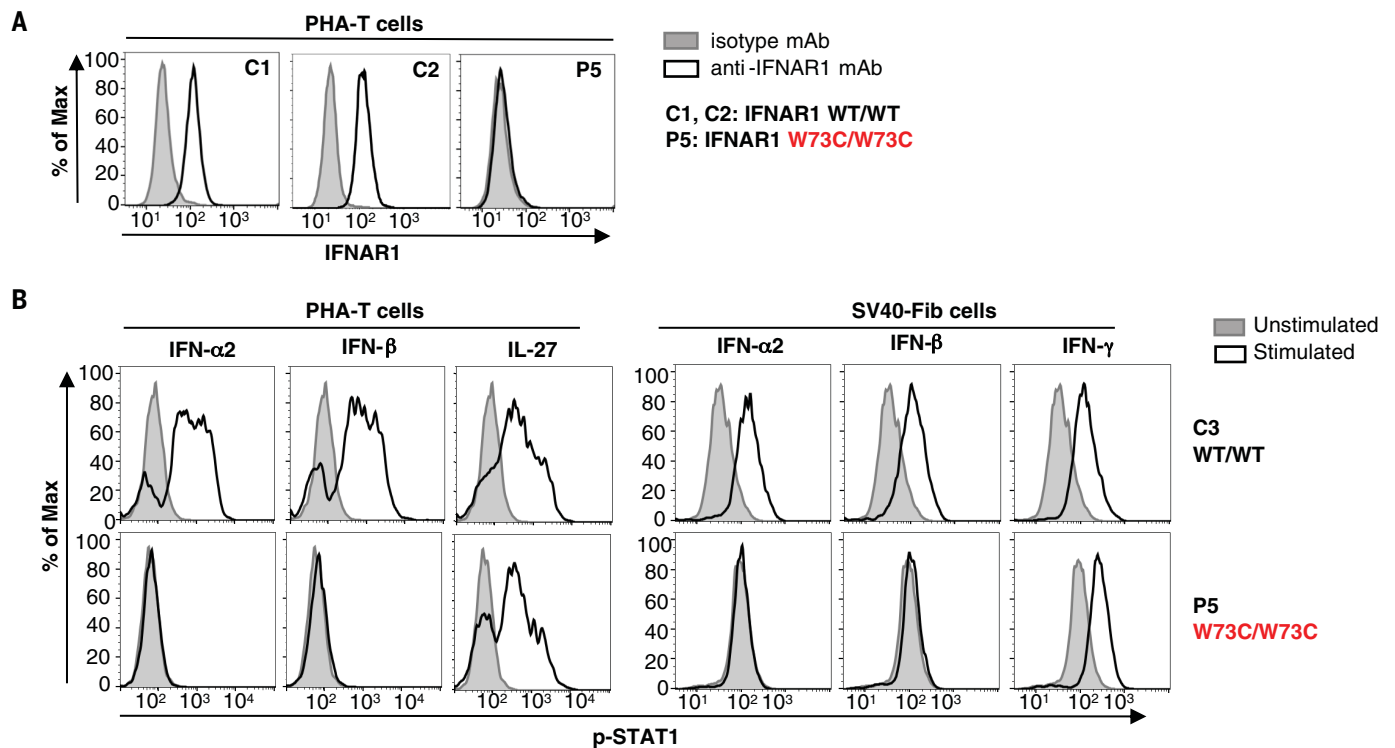


Fig. 5. Type I IFN responses in patient cells defective for IFNAR1. (A) FACS staining of IFNAR1 on the surface of PHA-T cells from a patient with AR IFNAR1 deficiency (P5) and healthy donors (C1 and C2). (B) PHA-T cells and SV40-Fib from a patient with AR IFNAR1 deficiency (P5) and a healthy donor (C3)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

IFNAR1, all of which were previously transduced with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2). SARS-CoV-2 infection levels were higher in mutant cells than in cells from healthy donors, and transduction of WT *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 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 <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 analysis of variance (ANOVA), $P = 1.4 \times 10^{-7}$; Fig. 7] (27, 28). Another 29 patients from our cohort displaying auto-antibodies (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. 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; 95% CI = 1.13 to 71.09).

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 had 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 double-stranded RNA 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). 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, and none of the four patients had a prior history of life-threatening infections (Table 1). One patient with *IRF7* deficiency was tested and 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 production, which is also impaired by defects of TLR3, *IRF7*, and *IRF9* (5). This conclusion is also supported by our accompanying report of neutralizing auto-Abs against type I IFNs, but not type III IFNs, in other patients with life-threatening COVID-19 pneumonia (29). Inborn errors of TLR3- and

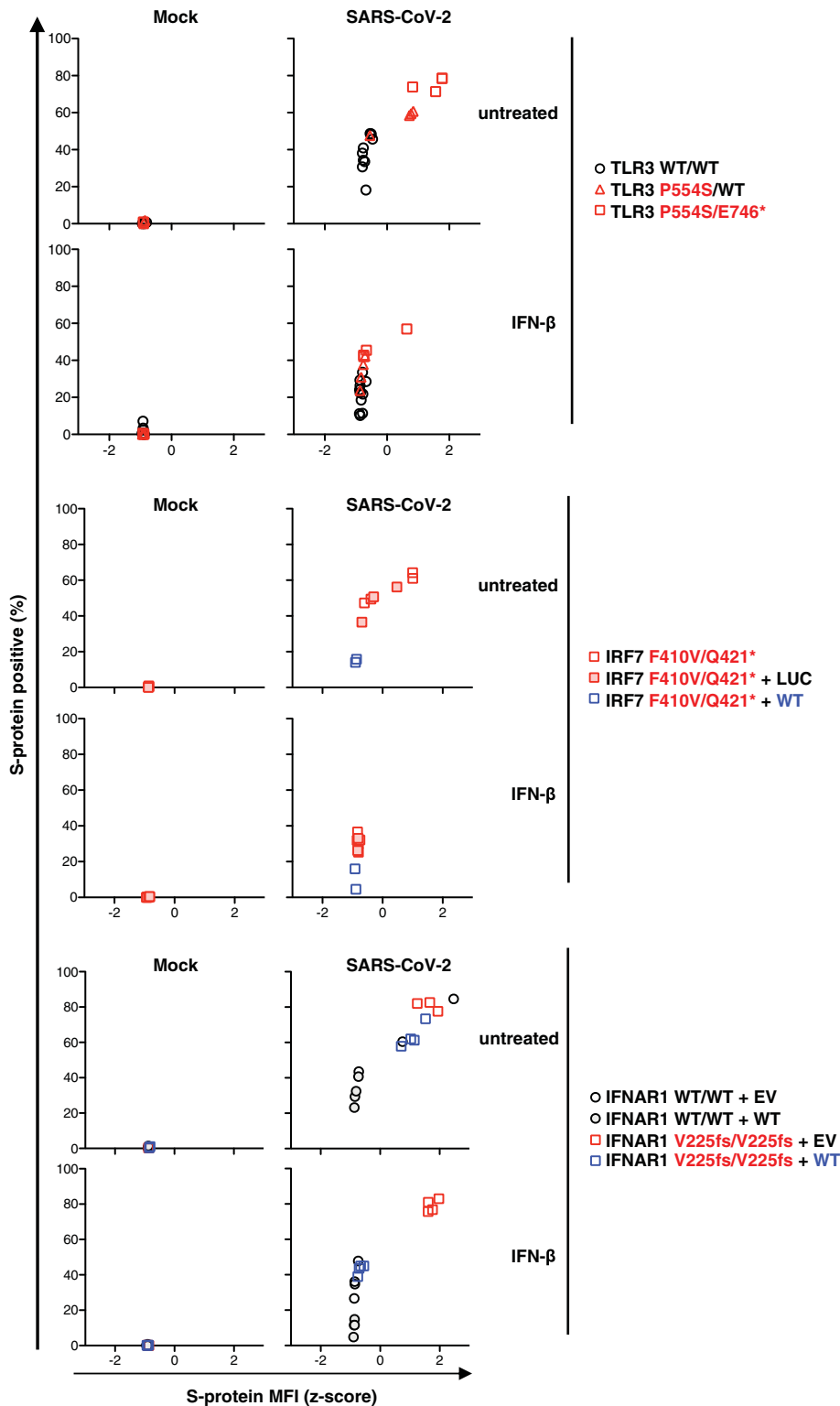


Fig. 6. Cell-intrinsic type I IFN response to SARS-CoV-2. SV40-Fib cells of TLR3^{-/-}, TLR3^{+/-}, IRF7^{-/-}, and IRF7^{-/-} SV40-Fib cells rescued with WT IRF7; IFNAR1^{-/-} SV40-Fib cells, and IFNAR1^{-/-} SV40-Fib cells rescued with WT IFNAR1 were transduced with ACE2 and TMPRSS2 and then either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

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 intensive care unit. Patients who developed Kawasaki-like syndrome were excluded. The age of the patients ranged from 0.1 to 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 polymerase chain reaction (PCR) and/or serological test and/or the presence of typical symptoms such as anosmia or ageusia after exposure to a confirmed COVID-19 case, who remained asymptomatic or developed mild, self-healing, ambulatory disease.

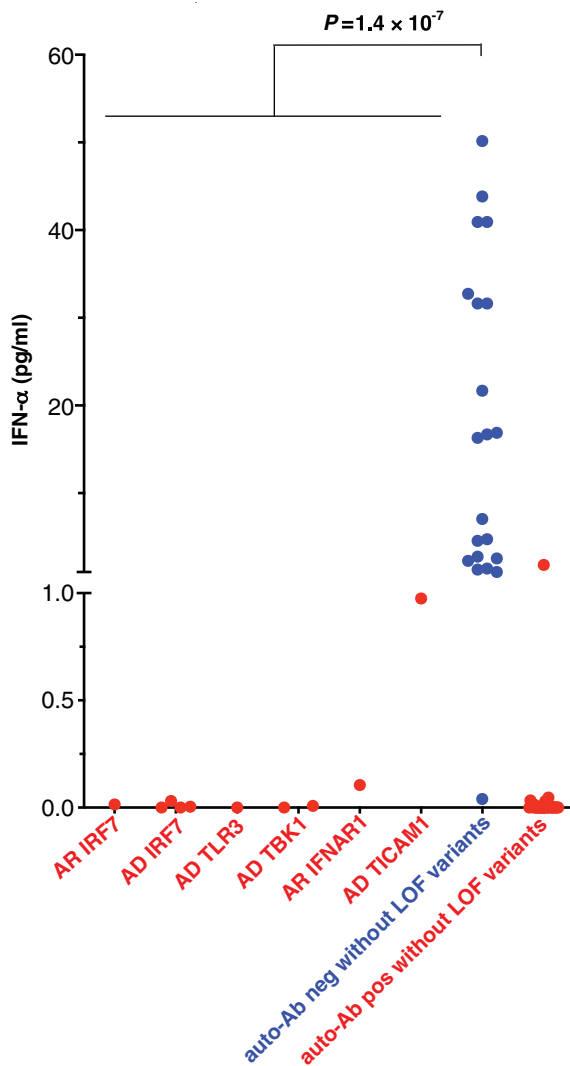
Next-generation sequencing

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 whole-exome-sequencing data (30). We aligned the reads obtained with the human reference genome (hg19) using the maximum exact matches algorithm in Burrows-Wheeler Aligner software (31). PCR duplicates were removed with Picard tools (<http://broadinstitute.github.io/picard/>). The GATK base quality score recalibrator was applied to correct sequencing artifacts.

All of the variants were manually curated using Integrative Genomics Viewer (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 were 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

Fig. 7. In vivo type I IFN responses to SARS-CoV-2 infections.

Plasma levels of 13 IFN- α were measured by Simoa. Auto-Ab(+) without LOF variants indicates COVID-19 patients with neutralizing anti-IFN- α auto-Abs in our accompanying report (29). *P* values indicated were evaluated using one-way ANOVA.



(NM_005419.4), and 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 next-generation-sequencing 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 <0.001 (gnomAD version 2.1.1) after experimentally demonstrating that all of 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 ac-

counted 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 version 1.9 software on whole-exome- and whole-genome-sequencing data and the 1000 Genomes (1kG) Project phase 3 public database as a reference, using 27,480 exonic variants with a MAF >0.01 and a call rate >0.99. The OR 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 WT, 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) according to the manufacturer's instructions. *Firefly* luciferase activity was normalized against *Renilla* luciferase activity and expressed as a fold change. TRAF3-deficient human embryonic kidney (HEK) 293T cells were kindly provided by M. 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 (A/PR/8/34, 2 μ g/ml; Charles River Laboratories), 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 using CBA analysis (BD Biosciences) in accordance with the manufacturer's protocol using a 20 pg/ml detection limit. IFN- λ 1 secretion was measured in an ELISA (R&D Systems, DuoSet DY7246), in accordance with the manufacturer's instructions.

SARS-CoV-2 infection in patient SV40-Fib

To make patient-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 ID: 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 (11415-1, PBL Assay Science) 4 hours before infection. Cells were infected with SARS-CoV-2 (MOI = 0.5) for 1 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 and 1 μ g/ml, respectively). Primary antibodies were as follows: for SARS-CoV-2, human monoclonal anti-spike-SARS-CoV-2 C121 antibody (40), and for ACE2, mouse monoclonal Alexa Fluor 488-conjugated antibody (FAB9332G-100UG, R&D Systems). Images were acquired with an ImageXpress Micro XLS microscope (Molecular Devices) using the 4 \times objective. MetaXpress software (Molecular Devices) was used to obtain single-cell mean fluorescence intensity (MFI) values.

Data analysis on single-cell MFI values was done in the R environment (version 4.0.2). ACE2/TMPRSS2-transduced cells were classified as ACE2 positive when the ACE2 log MFI was superior to the log mean MFI of mock-transduced cells plus 2.5 SDs. We excluded all wells with <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 MFI of mock-infected cells plus 4 SDs. 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 using Simoa technology, with reagents and procedures obtained from Quanterix Corporation (Quanterix Simoa™ 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.

REFERENCES AND NOTES

- D. M. Morens, A. S. Fauci, Emerging pandemic diseases: How we got to COVID-19. *Cell* **182**, 1077–1092 (2020). doi: [10.1016/j.cell.2020.08.021](https://doi.org/10.1016/j.cell.2020.08.021); pmid: [32846157](https://pubmed.ncbi.nlm.nih.gov/32846157/)
- J. L. Casanova, L. Abel, Lethal Infectious Diseases as Inborn Errors of Immunity: Toward a Synthesis of the Germ and Genetic Theories. *Annu. Rev. Pathol.* (2020). pmid: [32289233](https://pubmed.ncbi.nlm.nih.gov/32289233/)
- J. L. Casanova, L. Abel, The human genetic determinism of life-threatening infectious diseases: Genetic heterogeneity and physiological homogeneity? *Hum. Genet.* **139**, 681–694 (2020). doi: [10.1007/s00439-020-02184-w](https://doi.org/10.1007/s00439-020-02184-w); pmid: [32462426](https://pubmed.ncbi.nlm.nih.gov/32462426/)
- J. L. Casanova, H. C. Su; COVID Human Genetic Effort. A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection. *Cell* **181**, 1194–1199 (2020). doi: [10.1016/j.cell.2020.05.016](https://doi.org/10.1016/j.cell.2020.05.016); pmid: [32405102](https://pubmed.ncbi.nlm.nih.gov/32405102/)
- Q. Zhang, Human genetics of life-threatening influenza pneumonitis. *Hum. Genet.* **139**, 941–948 (2020). doi: [10.1007/s00439-019-02108-3](https://doi.org/10.1007/s00439-019-02108-3); pmid: [32025908](https://pubmed.ncbi.nlm.nih.gov/32025908/)
- H. K. Lim *et al.*, Severe influenza pneumonitis in children with inherited TLR3 deficiency. *J. Exp. Med.* **216**, 2038–2056 (2019). doi: [10.1084/jem.20181621](https://doi.org/10.1084/jem.20181621); pmid: [31217193](https://pubmed.ncbi.nlm.nih.gov/31217193/)
- M. J. Ciancanelli *et al.*, Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science* **348**, 448–453 (2015). doi: [10.1126/science.1258157](https://doi.org/10.1126/science.1258157); pmid: [25814066](https://pubmed.ncbi.nlm.nih.gov/25814066/)
- N. Hernandez *et al.*, Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. *J. Exp. Med.* **215**, 2567–2585 (2018). doi: [10.1084/jem.20180628](https://doi.org/10.1084/jem.20180628); pmid: [30143481](https://pubmed.ncbi.nlm.nih.gov/30143481/)
- V. Sancho-Shimizu *et al.*, Herpes simplex virus encephalitis in children with autosomal recessive and dominant TRIF deficiency. *J. Clin. Invest.* **121**, 4889–4902 (2011). doi: [10.1172/JCI59259](https://doi.org/10.1172/JCI59259); pmid: [22105173](https://pubmed.ncbi.nlm.nih.gov/22105173/)
- A. Casrouge *et al.*, Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science* **314**, 308–312 (2006). doi: [10.1126/science.1128346](https://doi.org/10.1126/science.1128346); pmid: [16973841](https://pubmed.ncbi.nlm.nih.gov/16973841/)
- R. Pérez de Diego *et al.*, Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. *Immunity* **33**, 400–411 (2010). doi: [10.1016/j.immuni.2010.08.014](https://doi.org/10.1016/j.immuni.2010.08.014); pmid: [20832341](https://pubmed.ncbi.nlm.nih.gov/20832341/)
- M. Herman *et al.*, Heterozygous TBK1 mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood. *J. Exp. Med.* **209**, 1567–1582 (2012). doi: [10.1084/jem.20111316](https://doi.org/10.1084/jem.20111316); pmid: [22851595](https://pubmed.ncbi.nlm.nih.gov/22851595/)
- L. L. Andersen *et al.*, Functional IRF3 deficiency in a patient with herpes simplex encephalitis. *J. Exp. Med.* **212**, 1371–1379 (2015). doi: [10.1084/jem.20142274](https://doi.org/10.1084/jem.20142274); pmid: [26216125](https://pubmed.ncbi.nlm.nih.gov/26216125/)
- M. Audry *et al.*, NEMO is a key component of NF- κ B- and IRF-3-dependent TLR3-mediated immunity to herpes simplex virus. *J. Allergy Clin. Immunol.* **128**, 610–617.e4 (2011). doi: [10.1016/j.jaci.2011.04.059](https://doi.org/10.1016/j.jaci.2011.04.059); pmid: [21729247](https://pubmed.ncbi.nlm.nih.gov/21729247/)
- N. Hernandez *et al.*, Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. *J. Exp. Med.* **216**, 2057–2070 (2019). doi: [10.1084/jem.20182295](https://doi.org/10.1084/jem.20182295); pmid: [31270247](https://pubmed.ncbi.nlm.nih.gov/31270247/)
- C. J. Duncan *et al.*, Human IFNAR2 deficiency: Lessons for antiviral immunity. *Sci. Transl. Med.* **7**, 307ra154 (2015). doi: [10.1126/scitranslmed.aac4227](https://doi.org/10.1126/scitranslmed.aac4227); pmid: [26424569](https://pubmed.ncbi.nlm.nih.gov/26424569/)
- S. Dupuis *et al.*, Impaired response to interferon- α /beta and lethal viral disease in human STAT1 deficiency. *Nat. Genet.* **33**, 388–391 (2003). doi: [10.1038/ng1097](https://doi.org/10.1038/ng1097); pmid: [12590259](https://pubmed.ncbi.nlm.nih.gov/12590259/)
- S. Hambleton *et al.*, STAT2 deficiency and susceptibility to viral illness in humans. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 3053–3058 (2013). doi: [10.1073/pnas.1220098110](https://doi.org/10.1073/pnas.1220098110); pmid: [23391734](https://pubmed.ncbi.nlm.nih.gov/23391734/)
- R. Döffinger *et al.*, X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF- κ B signaling. *Nat. Genet.* **27**, 277–285 (2001). doi: [10.1038/85837](https://doi.org/10.1038/85837); pmid: [11242109](https://pubmed.ncbi.nlm.nih.gov/11242109/)
- S. Y. Zhang *et al.*, TLR3 deficiency in patients with herpes simplex encephalitis. *Science* **317**, 1522–1527 (2007). doi: [10.1126/science.1139522](https://doi.org/10.1126/science.1139522); pmid: [17872438](https://pubmed.ncbi.nlm.nih.gov/17872438/)
- G. Zhang *et al.*, A proline deletion in IFNAR1 impairs IFN-signaling and underlies increased resistance to tuberculosis in humans. *Nat. Commun.* **9**, 85 (2018). doi: [10.1038/s41467-017-02611-z](https://doi.org/10.1038/s41467-017-02611-z); pmid: [29311663](https://pubmed.ncbi.nlm.nih.gov/29311663/)
- M. M. Thomsen *et al.*, Identification of an IRF3 variant and defective antiviral interferon responses in a patient with severe influenza. *Eur. J. Immunol.* **49**, 2111–2114 (2019). doi: [10.1002/eji.201848083](https://doi.org/10.1002/eji.201848083); pmid: [31250433](https://pubmed.ncbi.nlm.nih.gov/31250433/)
- M. M. Thomsen *et al.*, Defective interferon priming and impaired antiviral responses in a patient with an IRF7 variant and severe influenza. *Med. Microbiol. Immunol. (Berl.)* **208**, 869–876 (2019). doi: [10.1007/s00430-019-00623-8](https://doi.org/10.1007/s00430-019-00623-8); pmid: [31172279](https://pubmed.ncbi.nlm.nih.gov/31172279/)
- S. G. Tangye *et al.*, Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. *J. Clin. Immunol.* **40**, 24–64 (2020). doi: [10.1007/s10875-019-00737-x](https://doi.org/10.1007/s10875-019-00737-x); pmid: [31953710](https://pubmed.ncbi.nlm.nih.gov/31953710/)
- A. Bousfiha *et al.*, Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. *J. Clin. Immunol.* **40**, 66–81 (2020). doi: [10.1007/s10875-020-00758-x](https://doi.org/10.1007/s10875-020-00758-x); pmid: [32048120](https://pubmed.ncbi.nlm.nih.gov/32048120/)
- L. D. Notarangelo, R. Bacchetta, J.-L. Casanova, H. C. Su, Human inborn errors of immunity: An expanding universe. *Sci. Immunol.* **5**, eabb1662 (2020). doi: [10.1126/sciimmunol.abb1662](https://doi.org/10.1126/sciimmunol.abb1662); pmid: [32651211](https://pubmed.ncbi.nlm.nih.gov/32651211/)
- J. Hadjadj *et al.*, Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* **369**, 718–724 (2020). doi: [10.1126/science.abc6027](https://doi.org/10.1126/science.abc6027); pmid: [32661059](https://pubmed.ncbi.nlm.nih.gov/32661059/)
- S. Trouillet-Assant *et al.*, Type I IFN immunoprofiling in COVID-19 patients. *J. Allergy Clin. Immunol.* **146**, 206–208.e2 (2020). doi: [10.1016/j.jaci.2020.04.029](https://doi.org/10.1016/j.jaci.2020.04.029); pmid: [32360285](https://pubmed.ncbi.nlm.nih.gov/32360285/)
- P. Bastard *et al.*, Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **10.1126/science.abd4585** (2020).
- M. A. DePristo *et al.*, A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nat. Genet.* **43**, 491–498 (2011). doi: [10.1038/ng.806](https://doi.org/10.1038/ng.806); pmid: [21478889](https://pubmed.ncbi.nlm.nih.gov/21478889/)
- H. Li, R. Durbin, Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754–1760 (2009). doi: [10.1093/bioinformatics/btp324](https://doi.org/10.1093/bioinformatics/btp324); pmid: [19451168](https://pubmed.ncbi.nlm.nih.gov/19451168/)
- B. Boisson *et al.*, Rescue of recurrent deep intronic mutation underlying cell type-dependent quantitative NEMO deficiency. *J. Clin. Invest.* **129**, 583–597 (2019). doi: [10.1172/JCI124011](https://doi.org/10.1172/JCI124011); pmid: [30422821](https://pubmed.ncbi.nlm.nih.gov/30422821/)
- T. Gambin *et al.*, Homozygous and hemizygous CNV detection from exome sequencing data in a Mendelian disease cohort. *Nucleic Acids Res.* **45**, 1633–1648 (2017). pmid: [27980096](https://pubmed.ncbi.nlm.nih.gov/27980096/)
- D. Backenroth *et al.*, CANOES: Detecting rare copy number variants from whole exome sequencing data. *Nucleic Acids Res.* **42**, e97 (2014). doi: [10.1093/nar/gku345](https://doi.org/10.1093/nar/gku345); pmid: [24771342](https://pubmed.ncbi.nlm.nih.gov/24771342/)
- M. Bouaziz, J. Mullaert, B. Bigio, Y. Seelthner, J.-L. Casanova, A. Alcais, L. Abel, A. Cobat, Controlling for human population stratification in rare variant association studies. bioRxiv 969477 [Preprint]. 28 February 2020. doi: [10.1101/2020.02.28.969477](https://doi.org/10.1101/2020.02.28.969477)
- E. Perysn, R. Redon, L. Bellanger, C. Dina, The impact of a fine-scale population stratification on rare variant association test results. *PLOS ONE* **13**, e0207677 (2018). doi: [10.1371/journal.pone.0207677](https://doi.org/10.1371/journal.pone.0207677); pmid: [30521541](https://pubmed.ncbi.nlm.nih.gov/30521541/)
- Y. Zhang, X. Shen, W. Pan, Adjusting for population stratification in a fine scale with principal components and sequencing data. *Genet. Epidemiol.* **37**, 787–801 (2013). doi: [10.1002/gepi.21764](https://doi.org/10.1002/gepi.21764); pmid: [24123217](https://pubmed.ncbi.nlm.nih.gov/24123217/)
- S. Boisson-Dupuis *et al.*, Tuberculosis and impaired IL-23-dependent IFN- γ immunity in humans homozygous for a common TYK2 missense variant. *Sci. Immunol.* **3**, eaau8714 (2018). doi: [10.1126/sciimmunol.aau8714](https://doi.org/10.1126/sciimmunol.aau8714); pmid: [30578352](https://pubmed.ncbi.nlm.nih.gov/30578352/)
- S. Fochi *et al.*, TRAF3 Is Required for NF- κ B Pathway Activation Mediated by HTLV Tax Proteins. *Front. Microbiol.* **10**, 1302 (2019). doi: [10.3389/fmicb.2019.01302](https://doi.org/10.3389/fmicb.2019.01302); pmid: [31244811](https://pubmed.ncbi.nlm.nih.gov/31244811/)
- D. F. Robbiani *et al.*, Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature* **584**, 437–442 (2020). doi: [10.1038/s41586-020-2456-9](https://doi.org/10.1038/s41586-020-2456-9); pmid: [32555388](https://pubmed.ncbi.nlm.nih.gov/32555388/)
- Q. Zhang, P. Bastard, Z. Liu, J. Le Pen, M. Moncada-Velez, J. Chen, M. Ogishi, I. K. D. Sabli, S. Hodeib, C. Korol, J. Rosain, K. Bilguvar, J. Ye, A. Bolze, B. Bigio, R. Yang, A. Augusto Arias Sierra, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbibi, L. Bonnet-Madin, K. Dorgham, N. Smith, W. M. Schneider, B. S. Razooky, H.-H. Hoffmann, E. Michailidis, L. Moens, J. E. Han, L. Lorenzo, L. Bizien, P. Meade, A.-L. Neehus, A. C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seelthner, J. Many, C. Masson, Y. Schmitt, A. Schlüter, T. Le Voyer, T. Khan, J. Li, J. Fellay, L. Roussel, M. Shahrooei, M. F. Alosaimi, D. Mansouri, H. Al-Saud, F. Al-Mulla, F. Almourfi, S. Z. Al-Muhsen, F. Alshime, S. Al Turki, R. Hasanato, D. van de Beek, A. Biondi, L. R. Bettini, M. D'Angio, P. Bonfanti, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, A. J. Oler, M. F. Tompkins, C. Alba, I. Vandernoot, J.-C. Goffard, G. Smits, I. Migeotte, F. Haerynk, P. Soler-Palacin, A. Martin-Nalda, R. Colobran, P.-E. Morange, S. Keles, F. Çöklesen, A. Orzelik, K. K. Yazar, S. Senoglu, Ş. N. Karabela, C. Rodríguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Lauenan, COVID-STORM Clinicians, COVID Clinicians, Imagine COVID Group, French COVID Cohort Study Group, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, NIAID-USUHS/TAGC COVID Immunity Group, A. L. Snow, C. L. Dalgard, J. Milner, D. C. Vinh, T. H. Mogensen, M. Marr, A. N. Spaan, B. Boisson, S. Boisson-Dupuis, J. Bustamante, A. Puel, M. Ciancanelli, I. Meyts, T. Maniatis, V. Soumelis, A. Amara, M. Nussenzweig, A. García-Sastre, F. Krammer, A. Pujol, D. Duffy, R. Lifton, S.-Y. Zhang, G. Gorochov, V. Béziat, E. Jouanguy, V. Sancho-Shimizu, C. M. Rice, L. Abel, L. D. Notarangelo, A. Cobat, H. C. Su, J.-L. Casanova, Detailed genotype counts for all coding variants for: Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Dryad (2020). doi: [10.5061/dryad.8pk0p2nkk](https://doi.org/10.5061/dryad.8pk0p2nkk)

ACKNOWLEDGMENTS

We thank the patients, their families, and healthy donors for placing their trust in us; Y. Nemirovskaya, D. Papandrea, M. Woollet, D. Liu, C. Rivalain, and C. Patissier for administrative assistance; A. Adeleye, D. Bacikova, E. McGrath Martinez, A. R. Soltis, K. Dobbs, J. Danielson, H. Matthews, and S. Weber for technical and other assistance; M. M. A. Ata and F. Al Ali for their contribution to VirScan experiments; S. Elledge (Brigham and Women's Hospital and Harvard Medical School, Boston, MA) for kindly providing the VirScan phage library used in this study; A. W. Ashbrook, the BSL3 manager of the Rice laboratory assistance; M. Lazzaro, Director of Immigration and Academic Appointments, for assistance; W. Chung, K. Kiryuk, S. O'Byrne, D. Pendrick, J. Williamson, C. Andrews, and M. Disco in the I.M. lab for assistance; M. Andreoni (Tor Vergata, Italy) for his clinical contribution; and A. Novelli (Bambino Gesù Hospital, Italy) for his collaboration. We thank the GEN-COVID Multicenter study (<https://sites.google.com/dbm.unisi.it/gen-covid>). This study used the high-performance computational resources of the National Institutes of Health (NIH) HPC Biowulf cluster (<http://hpc.nih.gov>) and the Office of Cyber Infrastructure and Computational Biology (OCIB) 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 the Uniformed Services University of the Health Sciences (USUHS) or the U.S. Department of Defense (DOD). **Funding:** This work was supported by a generous donation from the Fisher Center for Alzheimer's Research Foundation. The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the NIH (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), the NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercurius 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 GENCOVID 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 immunitaria in pazienti con COVID-19 e comorbidità"), 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 cofunded by the "Fondation pour la Recherche Médicale"), University of Paris ("Plan de Soutien Covid-19": RACP20FIRO1-COVID-SOUL). I.M. is a senior clinical investigator with the FWO Vlaanderen; I.M. and L.M. 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". L.K. was supported by a fellowship from the French Ministry of Research. V.S.-S. is supported by a UKRI Future Leaders Fellowship (MR/S032304/1). S.Z.A.-M. is supported by the Elite Journals Program at King Saud University through grant no. PEJP-16-107. The J.M. laboratory is supported by Columbia University COVID biobank and grant no. UL1TR001873. Work in the Laboratory of Virology and Infectious Disease was supported by NIH grants P01AI138398-S1, 2U19AI118125, and R01AI091707-10S1; a George Mason University Fast Grant; and the G. Harold and Leila Y. Mathers Charitable Foundation. J.L.P. 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 no. 824110 (EasiGenomics grant no. 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. H.S. 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 A.G.-S. laboratory 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 HRO011-19-2-0020, by CRIP (Center for Research on Influenza Pathogenesis), a NIAID funded Center of Excellence for Influenza Research and Surveillance (CEIRS, contract HHSN272201400008C), by a 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(53844)) and anonymous donors. The Virscan analysis presented in fig. S11 was performed with financial support from Sidra Medicine. J.R.H. is supported by Biomedical Advanced Research and Development Authority under Contract (HHS010201600031C).

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.S., 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.H.M., V.S.-S., V.S., V.B., W.S., X.D., Y.S., and Z.D. 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., and 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., and S.N.K. evaluated and recruited patients to COVID and/or control cohorts. Q.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 interests. J.-L.C. is listed as an inventor on patent application US63/055,155 filed by The Rockefeller University that encompasses aspects of this publication. R.L. is a non-executive director of Roche and its subsidiary Genentech. **Data and materials availability:** Plasma, cells, and genomic DNA are available from J.-L.C. or D.V. under a material transfer agreement with Rockefeller University/Research Institute-McGill University Health Centre. pSCRPSY_TMRSS2-2A-Neor_ACE2 and Huh-7.5 cells are available upon request from C.R. under a material transfer 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 (D.v.d.B.) under a material transfer agreement with Amsterdam UMC. Material and reagents used are almost exclusively commercially available and nonproprietary. Requests for materials derived from human samples may be made available, subject to any underlying restrictions on such samples. J.-L.C. 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 Dryad (41). The whole-genome sequencing 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 the manuscript or the 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.

COVID-STORM Clinicians Giuseppe Foti¹, Giacomo Bellani¹, Giuseppe Citerio¹, Ernesto Contro¹, Alberto Pesci², Maria Grazia Valsecchi³, Marina Cazzaniga⁴

¹Department of Emergency, Anesthesia and Intensive Care, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ²Department of Pneumology, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ³Center of Bioinformatics and Biostatistics, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ⁴Phase I Research Center, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy.

COVID Clinicians Jorge Abad¹, Sergio Aguilera-Albesa², Ozge Metin Akcan³, Ilad Alavi Darazam⁴, Juan C. Aldave⁵, Miquel Alfonso Ramos⁵, Seyed Alireza Nadjfi⁶, Gulsum Alkan⁶, Jerome Allardet-Servent⁷, Luis M. Allende⁸, Laia Aisina¹, Marie-Alexandra Alyanakian¹², Blanca Amador-Borrero¹³, Zahir Amoura¹⁴, Arnau Antolí¹⁵, Svekter Arslan¹⁶, Sophie Assant¹⁷, Teresa Auguste¹⁸, Axelle Azot¹⁹, Fanny Bajolle²⁰, Aurélie Baldolli²¹, Maite Ballester²², Hagit Baris Feldman²³, Benoit Barrou²⁴, Alexandra Beurton²⁵, Agurtzane Bilbao²⁶, Geraldine Blanchard-Rohner²⁷, Ignacio Blanco²⁸, Adeline Blandinières²⁹, Daniel Blazquez-Gamero²⁹, Marketa Bloomfield³⁰, Mireia Bolívar-Prados³¹, Raphael Borrie³², Cédric Bostels³³, Ahmed A. Boufina³⁴, Claire Bouvattier³⁵, Oksana Boyarchuk³⁶, Maria Rita P. Bueno³⁷, Jacinta Bustamante³⁸, Juan José Cáceres Agra³⁸, Semra Calimli³⁹, Ruggero Capra⁴⁰, Maria Carrabba⁴¹, Carlos Casasnovas⁴², Marion Caseris⁴³, Martin Castelle⁴⁴, Francesco Castell⁴⁵, Martín Castillo de Vera⁴⁶, Mateus V. Castro³⁷, Emilie Catherinot⁴⁷, Martin Chalumeau⁴⁸, Bruno Charbit⁴⁹, Matthew P. Cheng⁵⁰, Père Clavé⁵¹, Bonaventura Clotet⁵¹, Anna Codina⁵², Fatih Colkesen⁵³, Fatma Çöklesen⁵⁴, Roger Colobran⁵⁵, Cloé Comarmond⁵⁶, David Dalmau⁵⁷, David Ross Darby⁵⁸, Nicolas Dauby⁵⁹, Stéphane Dauge⁶⁰, Loïc de Pontual⁶¹, Amin Dehban⁶², Geoffroy Delplanq⁶³, Alexandre Demoule⁶⁴, Jean-Luc Diehl⁶⁵, Stephanie Dobbelaere⁶⁶, Sophie Durand⁶⁷, Waleed Eldars⁶⁸, Mohamed Elgamal⁶⁹, Marwa H. Elmagdy⁷⁰, Melike Emiroglu⁷¹, Emine Hafize Erdeniz⁷², Selma Erol Aytekin⁷³, Romain Evrard⁷⁴, Recep Evcan⁷⁵, Giovanna Fabio⁴¹, Laurence Faivre⁷⁶, Antonin Falck⁴³, Muriel Fartoukh⁷⁹, Morgane Faure⁷⁹, Mergel Fernandez Arquer⁷⁹, Carlos Flores⁸⁰, Bruno Francois⁸¹, Victoria Fumadó⁸², Francesca Fusco⁸³, Blanca Garcia Solis⁸⁴, Pascale Gaussem⁸⁵, Juana Gil-Herrera⁸⁶, Laurent Gilardin⁸⁷, Monica Girona Alarcón⁸⁸, Mónica Girona-Alarcón⁸⁸, Jean-Christophe Goffard⁸⁹, Funda Gök⁹⁰, Rafaela González-Montelongo⁹¹, Antoine Guerder⁹², Yahya Gul⁹³, Sukru Nail Guner⁹³, Marta Gut⁹⁴, Jérôme Hadjiadi⁹⁵, Filomeen Haerynck⁹⁶, Rabih Halwan⁹⁷, Lennart Hammarström⁹⁸, Nevin Hatipoglu⁹⁹, Elisa Hernandez-Brito¹⁰⁰,

Catherine Heijmans¹⁰¹, María Soledad Holanda-Peña¹⁰², Juan Pablo Horcajada¹⁰³, Levi Hoste¹⁰⁴, Eric Hoste¹⁰⁵, Sami Hraiech¹⁰⁶, Linda Humbert¹⁰⁷, Alejandro D. Iglesias¹⁰⁸, Antonio Íñigo-Campos⁹¹, Matthieu Jamme¹⁰⁹, María Jesús Arranz¹¹⁰, Iolanda Jordan¹¹¹, Philippe Jorens¹¹², Fikret Kanat¹¹³, Hasan Kapakli¹¹⁴, Iskender Kara¹¹⁵, Adem Karbuz¹¹⁶, Kadiyve Kart Yasa¹¹⁷, Sevgi Keles¹¹⁸, Yasemin Kendir Demirkol¹¹⁹, Adam Klopper¹²⁰, Zbigniew J. Król¹²¹, Paul Kuentz¹²², Yat Wah M. Kwan¹²³, Jean-Christophe Lagier¹²⁴, Bart N. Lambrecht¹²⁵, Yu-Lung Lau¹²⁵, Fleur Le Bourgeois¹²⁶, Yee-Sin Leo¹²⁶, Rafael Leon Lopez¹²⁷, Daniel Leung¹²⁵, Michael Levin¹²⁸, Michael Levy⁶⁰, Romain Lévy²⁰, Zhi Li⁴⁹, Agnes Linglart²⁹, Bart Loeys¹³⁰, José M. Lorenzo-Salazar¹³¹, Céline Louape¹³¹, Catherine Lubetzki¹³¹, Charles-Edouard Luyt¹³², David C. Lye¹³³, Davoud Mansouri¹³⁴, Majid Marjani¹³⁵, Jesus Marquez Pereira¹³⁶, Andrea Martin¹³⁷, David Martínez Puyo¹³⁸, Javier Martínez-Picado¹³⁹, Iciar Marzana¹⁴⁰, Alexis Mathian¹⁴, Larissa R. B. Matos³⁷, Gail W. Matthews¹⁴¹, Julien Mayaux¹⁴², Jean-Louis Mège¹⁴³, Isabelle Melki¹⁴⁴, Jean-François Merit¹⁴⁵, Ozge Metin¹⁴⁶, Isabelle Meyts¹⁴⁷, Mehdi Mezidi¹⁴⁸, Isabelle Migeotte¹⁴⁹, Maude Millereux¹⁵⁰, Tristan Mirault¹⁵¹, Clotilde Mircher⁶⁷, Mehdi Mirsalehi¹⁵², Abián Montedeoca Melián¹⁵³, Antonio Morales Martínez¹⁵⁴, Pierre Morange¹⁵⁵, Clémence Mordacq¹⁰⁷, Guillaume Morelle¹⁵⁶, Stéphane Mouly¹⁶³, Adrián Muñoz-Barrera⁹¹, Leslie Naesens¹⁵⁷, Cyril Nafati¹⁵⁸, João Farelá Neves¹⁵⁹, Lisa F.P. Ng¹⁶⁰, Yeray Novoa Medina¹⁶¹, Esmeralda Nuñez Cuadros¹⁶², J. Gonzalo Oceo-Vinyals¹⁶³, Zerrin Orbak¹⁶⁴, Mehdi Oualha²⁰, Tayfun Özçelik¹⁶⁵, Qiang Pan-Hammarström¹⁶⁶, Christophe Parizot¹⁴², Tiffany Pascreau¹⁶⁷, Estela Paz-Artal¹⁶⁸, Sandra Pellegrini¹⁶⁹, Rebeca Pérez de Diego⁸⁴, Aurélien Philippe¹⁶⁹, Quentin Philippot⁷⁷, Laura Planas-Serra¹⁷⁰, Dominique Ploin¹⁷¹, Julien Pottin¹⁷², Géraldine Poncelet¹⁷³, Marie Pouletty¹⁷³, Paul Quentric¹⁷⁴, Didier Raouil⁴³, Anne-Sophie Rebillat¹⁷⁵, Ismail Reisi¹⁷⁶, Pilar Ricart¹⁷⁵, Jean-Christophe Richard¹⁷⁶, Nadia Rivet²⁹, Jacques G. Rivière¹⁷⁷, Gemma Rocamora Blanch¹⁵, Carlos Rodrigo¹, Carlos Rodríguez-Gallego¹⁷⁸, Agustí Rodríguez-Palmero¹⁷⁹, Carolina Soledad Romero¹⁸⁰, Anya Rothenbühler¹⁸¹, Flore Rozenberg¹⁸², Maria Yolanda Ruiz del Prado¹⁸³, Joan Sabater Riera¹⁵, Oliver Sanchez²⁸⁴, Silvia Sánchez-Ramón¹⁸⁵, Agatha Schluter¹⁷⁰, Matthieu Schmidt¹⁸⁶, Cyril E. Schweitzer¹⁸⁷, Francesco Scolari¹⁸⁸, Anna Sediva¹⁹⁰, Luis M. Seijo¹⁹⁰, Damien Sene¹³, Sevtap Senoglu¹¹⁷, Mikko R. J. Seppänen¹⁹¹, Alex Serra Illovich¹⁹², Mohammad Shahrroo¹⁹³, Hans Stabnynek¹⁹³, David M. Smadja¹⁹⁴, Ali Sobh¹⁹⁵, Xavier Solanich Moreno¹⁹⁵, Jordi Solé-Violant¹⁹⁶, Catherine Soler¹⁹⁷, Pere Soler-Palacin¹⁹⁷, Yuri Stepanovskiy¹⁹⁸, Annabelle Stoclin¹⁹⁹, Fabio Taccone¹⁴⁹, Yacine Tandjaoui-Lambiotte²⁰⁰, Jean-Luc Taupin²⁰¹, Simon J. Tavernier²⁰², Benjamin Terrier²⁰³, Caroline Thumerelle¹⁰⁷, Gabriele Tomasoni²⁰⁴, Julie Toubiana⁴⁸, Josep Trenado Alvarez²⁰⁵, Sophie Trouillet-Assant²⁰⁶, Jesús Troya²⁰⁷, Alessandra Tucci²⁰⁸, Matilde Valeria Ursini⁸³, Yurdagul Uzunhan²⁰⁹, Pierre Vabres²¹⁰, Juan Valencia-Ramos²¹¹, Eva Van Braeckel³³, Stijn Van de Velde²¹², Ana Maria Van Den Rym⁸⁴, Jens Van Praet²¹³, Isabelle Vandernoot²¹⁴, Hulya Vatanses²¹⁵, Valentina Vélez-Santamaría¹⁸⁶, Sébastien Viel¹⁷¹, Cédric Vilain²¹⁶, Marie E. Vilarej⁵⁷, Audrey Vincent³⁵, Guillaume Voiriot²¹⁷, Fanny Vuotto¹⁰⁷, Alper Yosunkaya⁹⁰, Barnaby E. Young¹²⁶, Fatih Yucel²¹⁸, Faiez Zannad²¹⁹, Mayana Zatz²²⁰, Alexandre Belot^{220*},

¹University Hospital and Research Institute "Germans Trias i Pujol", Badalona, Spain. ²Navarra Health Service Hospital, Pamplona, Spain. ³Division of Pediatric Infectious Diseases, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁴Department of Infectious Diseases, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁵Hospital Nacional Edgardo Rebagliatti Martins, Lima, Peru. ⁶Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain. ⁷Virology Research Center, National Institutes of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁸Division of Pediatric Infectious Diseases, Faculty of Medicine, Selcuk University, Konya, Turkey. ⁹Intensive Care Unit, Hôpital Européen, Marseille, France. ¹⁰Immunology Department, University Hospital 12 de Octubre, Research Institute imas12, and Complutense University, Madrid, Spain. ¹¹Clinical Immunology and Primary Immunodeficiencies Unit, Hospital Sant Joan de Déu, Barcelona, Spain. ¹²Department of Biological Immunology, Necker Hospital for Sick Children, APHP and INEM, Paris, France. ¹³Internal Medicine Department, Hôpital Lariboisière, APHP; Université de Paris, Paris, France. ¹⁴Internal Medicine Department, Pitié-Salpêtrière Hospital, Paris, France. ¹⁵Hospital Universitari de Bellvitge, Barcelona, Spain. ¹⁶Division of Clinical Immunology and Allergy, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ¹⁷Joint Research Unit, Hospices Civils de Lyon-bio Mérieux, Hospices Civils de Lyon, Lyon Sud Hospital, Lyon, France. ¹⁸Hospital U. de Tarragona Joan XXIII, Universitat Rovira i Virgili (URV), IISPV, Tarragona, Spain. ¹⁹Private practice, Paris, France. ²⁰Necker Hospital for Sick Children, AP-HP, Paris, France. ²¹Department of Infectious

- Diseases, CHU de Caen, Caen, France. ²²Consorcio Hospital General Universitario, Valencia, Spain. ²³The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ²⁴Department of Urology, Nephrology, and Transplantation, APHP-SU, Sorbonne Université, INSERM U 1082, Paris, France. ²⁵Service de Médecine Intensive-Réanimation et Pneumologie, APHP Hôpital Pitié-Salpêtrière, Paris, France. ²⁶Cruces University Hospital, Bizkaia, Spain. ²⁷Paediatric Immunology and Vaccinology Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland. ²⁸Hematology, Georges Pompidou Hospital, APHP, Paris, France. ²⁹Pediatric Infectious Diseases Unit, Instituto de Investigación 12 de Octubre imas12, and Hospital Universitario 12 de Octubre, Madrid, Spain. ³⁰Department of Immunology, Motol University Hospital, 2nd Faculty of Medicine, Charles University, Department of Pediatrics, Thomayer's Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic. ³¹Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain. ³²Service de Pneumologie, Hôpital Bichat, APHP, Paris, France. ³³Department of Pulmonology, Ghent University Hospital, Ghent, Belgium. ³⁴Clinical Immunology Unit, Pediatric Infectious Disease Department, Faculty of Medicine and Pharmacy, Averroes University Hospital, LICIA Laboratoire d'Immunologie Clinique, d'Inflammation et d'Allergie, Hassani li University, Casablanca, Morocco. ³⁵Endocrinology Unit, APHP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ³⁶Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. ³⁷Human Genome and Stem-Cell Research Center, University of São Paulo, São Paulo, Brazil. ³⁸Hospital Insular, Las Palmas de Gran Canaria, Spain. ³⁹Division of Critical Care Medicine, Department of Anesthesiology and Reanimation, Konya State Hospital, Konya, Turkey. ⁴⁰MS Center, Spedali Civili, Brescia, Italy. ⁴¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. ⁴²Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain. ⁴³Hôpital Robert Debré, Paris, France. ⁴⁴Pediatric Immuno-hematology Unit, Necker Enfants Malades Hospital, AP-HP, Paris, France. ⁴⁵Department of Infectious and Tropical Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ⁴⁶Doctoral Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁴⁷Hôpital Foch, Suresnes, France. ⁴⁸Necker Hospital for Sick Children, Paris University, AP-HP, Paris, France. ⁴⁹Pasteur Institute, Paris, France. ⁵⁰McGill University Health Centre, Montreal, Canada. ⁵¹University Hospital and Research Institute "Germans Trias i Pujol," IrsiCaixa AIDS Research Institute, Uvic-UCC, Badalona, Spain. ⁵²Clinical Biochemistry, Pathology, Paediatric Neurology and Molecular Medicine Departments and Biobank, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Espulgues, Spain. ⁵³Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁵⁴Department of Infectious Diseases and Clinical Microbiology, Konya Training and Research Hospital, Konya, Turkey. ⁵⁵Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁵⁶Pitié-Salpêtrière Hospital, Paris, France. ⁵⁷Fundació Docència i Recerca Mútua Terrassa, Barcelona, Spain; Hospital Universitari Mutua Terrassa, Universitat de Barcelona, Terrassa, Catalonia, Spain. ⁵⁸UNSW Medicine, St. Vincent's Clinical School, and Department of Thoracic Medicine, St. Vincent's Hospital Darlinghurst, Sydney, Australia. ⁵⁹CHU Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium. ⁶⁰Pediatric Intensive Care Unit, Robert-Debré University Hospital, APHP, Paris, France. ⁶¹Sorbonne Paris Nord, Hôpital Jean Verdier, APHP, Bondy, France. ⁶²Specialized Immunology Laboratory of Dr. Shahroei, Sina Medical Complex, Ahvaz, Iran. ⁶³Centre de Génétique Humaine, CHU Besançon, Besançon, France. ⁶⁴Sorbonne Université Médecine and APHP Sorbonne Université Site Pitié-Salpêtrière, Paris, France. ⁶⁵Intensive Care Unit, Georges Pompidou Hospital, APHP, Paris, France. ⁶⁶Department of Pneumology, AZ Delta, Roeselare, Belgium. ⁶⁷Institut Jérôme Lejeune, Paris, France. ⁶⁸Department of Microbiology and Immunology, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ⁶⁹Department of Chest, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ⁷⁰Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ⁷¹Faculty of Medicine, Division of Pediatric Infectious Diseases, Selcuk University, Konya, Turkey. ⁷²Division of Pediatric Infectious Diseases, Ondokuz Mayıs University, Samsun, Turkey. ⁷³Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. ⁷⁴Centre Hospitalier Fleyriat, Bourg-en-Bresse, France. ⁷⁵Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁷⁶Centre de Génétique, CHU Dijon, Dijon, France. ⁷⁷APHF Tenon Hospital, Paris, France. ⁷⁸Sorbonne Universités, UPMC Medical University of Paris, Paris, France. ⁷⁹Department of Clinical Immunology, Hospital Clínico San Carlos, Madrid, Spain. ⁸⁰Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristóbal de La Laguna, Spain. ⁸¹CHU Limoges and Inserm CIC 1435 and UMR 1092, Limoges, France. ⁸²Infectious Diseases Unit, Department of Pediatrics, Hospital Sant Joan de Déu, Barcelona, Spain; Institut de Recerca Sant Joan de Déu, Spain; Universitat de Barcelona (UB), Barcelona, Spain. ⁸³Institute of Genetics and Biophysics "Adriano Buzzati-Traverso," IGB-CNR, Naples, Italy. ⁸⁴Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ⁸⁵Hematology, APHP, Hôpital Européen Georges Pompidou and Inserm UMR-S1140, Paris, France. ⁸⁶Hospital General Universitario and Instituto de Investigación Sanitaria "Gregorio Marañón," Madrid, Spain. ⁸⁷Bégin military Hospital, Bégin, France. ⁸⁸Pediatric Intensive Care Unit, Hospital Sant Joan de Déu, Barcelona, Spain. ⁸⁹Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ⁹⁰Division of Critical Care Medicine, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁹¹Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain. ⁹²Assistance Publique Hôpitaux de Paris, Paris, France. ⁹³Division of Allergy and Immunology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁹⁴CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST); Universitat Pompeu Fabra (UPF), Barcelona, Spain. ⁹⁵Department of Internal Medicine, National Reference Center for Rare Systemic Autoimmune Diseases, AP-HP, APHP-CUP, Hôpital Cochin, Paris, France. ⁹⁶Ghent University Hospital, Ghent, Belgium. ⁹⁷Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, UAE. ⁹⁸Department of Laboratory Medicine, SE14186, Huddinge, Karolinska Institutet, Stockholm, Sweden. ⁹⁹Pediatric Infectious Diseases Unit, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹⁰⁰Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁰¹Department of Pediatric Hemato-Oncology, Jolimont Hospital; Department of Pediatric Hemato-Oncology, HUIDEF, Brussels, Belgium. ¹⁰²Intensive Care Unit, Marqués de Valdecilla Hospital, Santander, Spain. ¹⁰³Hospital del Mar, Parc de Salut Mar, Barcelona, Spain. ¹⁰⁴Department of Pediatric Pulmonology and Immunology, Ghent University Hospital, Ghent, Belgium. ¹⁰⁵Department of Intensive Care Unit, Ghent University Hospital, Ghent, Belgium. ¹⁰⁶Intensive Care Unit, APHM, Marseille, France. ¹⁰⁷CHU Lille, Lille, France. ¹⁰⁸Department of Pediatrics, Columbia University, New York, NY, USA. ¹⁰⁹Centre Hospitalier Intercommunal Poissy Saint Germain en Laye, Poissy, France. ¹¹⁰Fundació Docència i Recerca Mútua Terrassa, Terrassa, Spain. ¹¹¹Hospital Sant Joan de Déu, Kids Corona Platform, Barcelona, Spain. ¹¹²Department of Intensive Care Unit, University Hospital Antwerp, Antwerp, Belgium. ¹¹³Selcuk University, Faculty of Medicine, Chest Diseases Department, Konya, Turkey. ¹¹⁴Division of Allergy and Immunology, Balikesir Ataturk City Hospital, Balikesir, Turkey. ¹¹⁵Division of Critical Care Medicine, Selcuk University, Faculty of Medicine, Konya, Turkey. ¹¹⁶Division of Pediatric Infectious Diseases, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey. ¹¹⁷Departments of Infectious Diseases and Clinical Microbiology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹¹⁸Meram Medical Faculty, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ¹¹⁹Health Sciences University, Umraniye Education and Research Hospital, Istanbul, Turkey. ¹²⁰Department of Immunology, 2nd Faculty of Medicine, Charles University and University Hospital in Motol, Prague, Czech Republic. ¹²¹Central Clinical Hospital of Ministry of the Interior and Administration in Warsaw, Warsaw, Poland. ¹²²Oncobiologie Génétique Bioinformatique, PC Bio, CHU Besançon, Besançon, France. ¹²³Paediatric Infectious Disease Unit, Hospital Authority Infectious Disease Center, Princess Margaret Hospital, Hong Kong (Special Administrative Region), China. ¹²⁴Aix Marseille University, IRD, MEPHI, IHU Méditerranée Infection, Marseille, France. ¹²⁵Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China. ¹²⁶National Centre for Infectious Diseases, Singapore. ¹²⁷Hospital Universitario Reina Sofía, Córdoba, Spain. ¹²⁸Imperial College, London, UK. ¹²⁹Endocrinology and Diabetes for Children, AP-HP, Bicêtre Paris-Saclay Hospital, Le Kremlin-Bicêtre, France. ¹³⁰Department of Medical Genetics, University Hospital Antwerp, Antwerp, Belgium. ¹³¹Neurology Unit, APHP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹³²Intensive Care Unit, APHP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹³³National Centre for Infectious Diseases; Tan Tock Seng Hospital; Yong Loo Lin School of Medicine; Lee Kong Chian School of Medicine, Singapore. ¹³⁴Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹³⁵Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRIITD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹³⁶Hospital Sant Joan de Déu and University of Barcelona, Barcelona, Spain. ¹³⁷Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain. ¹³⁸Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain. ¹³⁹IrsiCaixa AIDS Research Institute, ICREA, Uvic-UCC, Research Institute "Germans Trias i Pujol," Badalona, Spain. ¹⁴⁰Department of Laboratory, Cruces University Hospital, Barakaldo, Bizkaia, Spain. ¹⁴¹University of New South Wales, New South Wales, Australia. ¹⁴²APHF Pitié-Salpêtrière Hospital, Paris, France. ¹⁴³Aix-Marseille University, APHM, Marseille, France. ¹⁴⁴Robert Debré University Hospital, Paris, France. ¹⁴⁵APHF Cohin Hospital, Paris, France. ¹⁴⁶Necmettin Erbakan University Meram Faculty of Medicine Department of Pediatric Infectious Diseases, Konya, Turkey. ¹⁴⁷University Hospitals Leuven, Leuven, Belgium. ¹⁴⁸Hospices Civils de Lyon, Hôpital de la Croix-Roussé, Lyon, France. ¹⁴⁹Hôpital Erasme, Brussels, Belgium. ¹⁵⁰CH Gonesse, Gonesse, France. ¹⁵¹Vascular Medicine, Georges Pompidou Hospital, APHP, Paris, France. ¹⁵²Division of Pulmonary and Critical Care, University of Miami, Miami, FL, USA. ¹⁵³Guanarterm Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁵⁴Regional University Hospital of Málaga, Málaga, Spain. ¹⁵⁵Aix-Marseille Université, Marseille, France. ¹⁵⁶Department of General Paediatrics, Hôpital Bicêtre, AP-HP, University of Paris Saclay, Le Kremlin-Bicêtre, France. ¹⁵⁷Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium. ¹⁵⁸CHU de La Timone, Marseille, France. ¹⁵⁹Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal. ¹⁶⁰Infectious Diseases Horizontal Technology Centre, A*STAR, Singapore Immunology Network, A*STAR, Singapore. ¹⁶¹Department of Pediatrics, Complejo Hospitalario Universitario Insular-Materno Infantil, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁶²Regional University Hospital of Málaga, Málaga, Spain. ¹⁶³Hospital Universitario Marqués de Valdecilla, Santander, Spain. ¹⁶⁴Faculty of Medicine, Ataturk University, Erzurum, Turkey. ¹⁶⁵Department of Molecular Biology and Genetics, Bilkent University, Ankara, Turkey. ¹⁶⁶Department of Biosciences and Nutrition, Karolinska Institutet, SE14183, Stockholm, Sweden. ¹⁶⁷L'Hôpital Foch, Suresnes, France. ¹⁶⁸Department of Immunology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre imas12, Madrid, Spain. ¹⁶⁹APHF Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ¹⁷⁰Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona; CIBERER U759, ISCIII, Madrid, Spain. ¹⁷¹Hospices Civils de Lyon, Lyon, France. ¹⁷²Université de Lille, Inserm U1285, CHU Lille, Paris, France. ¹⁷³Department of General Pediatrics, University Hospital Robert Debré, APHP, Paris, France. ¹⁷⁴Necmettin Erbakan University, Konya, Turkey. ¹⁷⁵Germans Trias i Pujol Hospital, Badalona, Spain. ¹⁷⁶Medical Intensive Care Unit, Hôpital de la Croix-Roussé, Hospices Civils de Lyon, Lyon, France. ¹⁷⁷Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. ¹⁷⁸Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁷⁹University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ¹⁸⁰Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona, Spain. ¹⁸¹APHF Hôpitaux Universitaires Paris-Sud, Paris, France. ¹⁸²Virology Unit, Université de Paris, Cohin Hospital, APHP, Paris, France. ¹⁸³Hospital San Pedro, Logroño, Spain. ¹⁸⁴Respiratory Medicine, Georges Pompidou Hospital, APHP, Paris, France. ¹⁸⁵Department of Immunology, Hospital Clínico San Carlos, Madrid, Spain. ¹⁸⁶Service de Médecine Intensive Réanimation, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France. ¹⁸⁷CHRU de Nancy, Hôpital d'Enfants, Vandoeuvre, France. ¹⁸⁸Chair of Nephrology, University of Brescia, Brescia, Italy. ¹⁸⁹Department of Immunology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague,

Czech Republic. ¹⁹⁰Clinica Universidad de Navarra, Madrid, Spain. ¹⁹¹HUS Helsinki University Hospital, Children and Adolescents, Rare Disease Center, and Inflammation Center, Adult Immunodeficiency Unit, Majakka, Helsinki, Finland. ¹⁹²Fundació Docència i Recerca Mútua Terrassa, Terrassa, Spain. ¹⁹³Department of Pulmonology, ZNA Middelheim, Antwerp, Belgium. ¹⁹⁴INSERM UMR-S 1140, Biosurgical Research Lab (Carpentier Foundation), Paris University and Hospital Européen Georges Pompidou, Paris, France. ¹⁹⁵Department of Pediatrics, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ¹⁹⁶Critical Care Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁹⁷CHU de Saint Etienne, Saint-Priest-en-Jarez, France. ¹⁹⁸Shupky National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹⁹⁹Gustave Roussy Cancer Campus, Villejuif, France. ²⁰⁰Intensive Care Unit, Avicenne Hospital, APHP, Bobigny, France. ²⁰¹Laboratory of Immunology and Histocompatibility, Saint-Louis Hospital, Paris University, Paris, France. ²⁰²Department of Internal Diseases and Pediatrics, Primary Immune Deficiency Research Lab, Centre for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent, Belgium. ²⁰³Department of Internal Medicine, Université de Paris, INSERM, U970, PARCC, F-75015, Paris, France. ²⁰⁴First Division of Anesthesiology and Critical Care Medicine, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ²⁰⁵Intensive Care Department, Hospital Universitari Mutua Terrassa, Universitat Barcelona, Terrassa, Spain. ²⁰⁶Hospices Civils de Lyon, Lyon Sud Hospital, Lyon, France. ²⁰⁷Infanta Leonor University Hospital, Madrid, Spain. ²⁰⁸Hematology Department, ASST Spedali Civili di Brescia, Brescia, Italy. ²⁰⁹Pneumologie, Hôpital Avicenne, APHP, INSERM U1272, Université Sorbonne Paris Nord, Bobigny, France. ²¹⁰Dermatology Unit, Laboratoire GAD, INSERM UMR1231 LNC, Université de Bourgogne, Dijon, France. ²¹¹University Hospital of Burgos, Burgos, Spain. ²¹²Intensive Care Unit, M. Middelares Ghent, Ghent, Belgium. ²¹³Department of Nephrology and Infectiology, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium. ²¹⁴Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ²¹⁵Department of Chest Diseases, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ²¹⁶CHU de Caen, Caen, France. ²¹⁷Sorbonne Université, Service de Médecine Intensive Réanimation, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France. ²¹⁸General Intensive Care Unit, Konya Training and Research Hospital, Konya, Turkey. ²¹⁹CHU de Nancy, Nancy, France. ²²⁰University of Lyon, CIRI, INSERM U1111, National Reference Centre RAISE, Pediatric Rheumatology, HFME, Hospices Civils de Lyon, Lyon, France. *Leader of COVID Clinicians.

Imagine COVID Group Christine Bole-Feyssot, Stanislas Lyonnet*, Cécile Masson, Patrick Nitschke, Aureole Pouliet, Yoann Schmitt, Frederic Tores, Mohammed Zahrate

Imagine Institute, Université de Paris, INSERM UMR 1163, Paris, France. *Leader of the Imagine COVID Group.

French COVID Cohort Study Group Laurent Abel¹, Claire Andrejak², François Angoulvant³, Delphine Bachelet⁴, Romain Basmaci⁵, Sylvie Behillil⁶, Marine Beluze⁷, Dehbia Benkerrou⁸, Krishna Bhavsar⁹, François Bompard⁹, Lila Bouadma⁴, Maude Bouscambert¹⁰, Mireille Caralp¹¹, Minerva Cervantes-Gonzalez¹², Anissa Chair⁴, Alexandra Coelho¹³, Camille Couffignal⁴, Sandrine Couffin-Cadiergues¹⁴, Eric D'Ortenzio¹², Charlene Da Silveira⁴, Marie-Pierre Debray⁴, Dominique Deplanque¹⁵, Diane Descamps¹⁶, Mathilde Desvallées¹⁷, Alpha Diallo¹⁸, Alphonsine Diouh¹², Céline Dorival⁸, François Dubos¹⁹, Xavier Duval⁴, Philippine Eloy⁴, Vincent VE Enouf²⁰, Hélène Espéro²¹, Marina Esposito-Faresse⁴, Manuel Etienne²², Nadia Elthalhaoui⁴, Nathalie Gault⁴, Alexandre Gaymard⁴, Jade Ghosn⁴, Tristan Gigante²³, Isabelle Gorenne⁴, Jérémie Guedj²⁴, Alexandre Hochtini¹³, Isabelle Hoffmann⁴, Salma Jaoufara⁴, Ouifia Kaffi¹, Florentine Kaguelidou²⁵, Sabina Kali⁴, Antoine Khalil⁴, Coralie Khan¹⁷, Cédric Laouénan⁴, Samira Laribi⁴, Minh Le⁴, Quentin Le Hingrat⁴, Soizic Le Mestre¹⁹, Hervé Le Nagard⁴, François-Xavier Lescuré⁴, Yves Lévy²⁶, Claire Levy-Marchal²⁷, Bruno Lina¹⁰, Guillaume Lingas²⁴, Jean Christophe Lucet⁴, Denis Malvy²⁸, Marina Mamberti²⁹, France Mentre⁴, Noémie Mercier¹⁸, Amira Meziane³⁰, Hugo Mouquet³⁰, Jimmy Mullera⁴, Nadège Neant²⁴, Marion Noret²⁹, Justine Pages³⁰, Aurélie Papadopoulos²¹, Christelle Paul¹⁸, Nathan Peiffer-Smadja⁴, Ventsislava Petrov-Sanchez²⁸, Gilles Peytavin⁴, Olivier Picone³¹, Oriane Puéchal¹², Manuel Rosa-Calatrava¹⁰, Bénédicte Rossignol²³, Patrick Rossignol³², Carine Roy⁴, Marion Schneider⁴, Caroline Semaille³², Nassima Si Mohammed⁴, Lysa Taghersat⁴, Coralie Tardion⁴, Marie-Capucine Tellier⁴,

François Téoulé⁸, Olivier Terrier¹⁰, Jean-François Timsit⁴, Théo Trioux⁴, Christelle Tuai³³, Sarah Tubiana⁴, Sylvie van der Werf³⁴, Noémie Vanel³⁵, Aurélie Veilinger³³, Benoît Visseaux¹⁶, Aurélie Wiedemann²⁶, Yazdan Yazdanpanah³⁶

¹INSERM UMR 1163, Paris, France. ²CHU Amiens, France. ³Hôpital Necker, Paris, France. ⁴Hôpital Bichat, Paris, France. ⁵Hôpital Louis Mourier, Colombes, France. ⁶Institut Pasteur, Paris, France. ⁷F-CRIN Partners Platform, AP-HP, Université de Paris, Paris, France. ⁸INSERM UMR 1136, Paris, France. ⁹Drugs for Neglected Diseases Initiative, Geneva, Switzerland. ¹⁰INSERM UMR 1111, Lyon, France. ¹¹INSERM Transfert, Paris, France. ¹²REACTing, Paris, France. ¹³INSERM UMR 1018, Paris, France. ¹⁴INSERM, Pôle Recherche Clinique, Paris, France. ¹⁵CIC 1403 Inserm-CHU Lille, Paris, France. ¹⁶Université de Paris, IAME, INSERM UMR 1137, AP-HP, University Hospital Bichat Claude Bernard, Virology, Paris, France. ¹⁷INSERM UMR 1219, Bordeaux, France. ¹⁸ANRS, Paris, France. ¹⁹CHU Lille, Lille, France. ²⁰Pasteur Institute, Paris, France. ²¹INSERM sponsor, Paris, France. ²²CHU Rouen-SMIT, Rouen, France. ²³FCRIN INI-CRCT, Nancy, France. ²⁴INSERM UMR 1137, Paris, France. ²⁵Centre d'Investigation Clinique, Inserm CIC1426, Hôpital Robert Debré, Paris, France. ²⁶INSERM UMR 955, Créteil, France; Vaccine Research Institute (VRI), Paris, France. ²⁷F-CRIN INI-CRCT, Paris, France. ²⁸CHU de Bordeaux-SMIT, Bordeaux, France. ²⁹RENARCI, Annecy, France. ³⁰Hôpital Robert Debré, Paris, France. ³¹Hôpital Louis Mourier-Gynécologie, Colombes, France. ³²University of Lorraine, Plurithematic Clinical Investigation Centre Inserm CIC-P; 1433, Inserm U1116, CHRU Nancy Hôpitaux de Braibois, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trials), Paris, France. ³³INSERM CIC-1414, Rennes, France. ³⁴Institut Pasteur, UMR 3569 CNRS, Université de Paris, Paris, France. ³⁵Hôpital la Timone, Marseille, France. ³⁶Bichat-SMIT, Paris, France.

CoV-Contact Cohort Loubna Alavoine¹, Karine K. A. Amat², Sylvie Behillil³, Julia Bielicki⁴, Patricia Brujning⁵, Charles Burdet⁶, Eric Caumes⁷, Charlotte Charpentier⁸, Bruno Coignard⁹, Yolande Costa¹, Sandrine Couffin-Cadiergues¹⁰, Florence Diamond⁸, Aline Dechanet¹¹, Christelle Delmas¹⁰, Diane Descamps⁸, Xavier Duval¹, Jean-Luc Ecobichon¹¹, Vincent Enouf³, Hélène Espéro¹⁰, Wahiba Frezouls¹, Nadhira Houhou¹¹, Emila Illic-Habensusch¹, Ouifia Kaffi¹, John Kikoine¹¹, Quentin Le Hingrat⁸, David Lebeaux¹², Jean Leclercq¹, Jonathan Lehacuy¹¹, Sophie Letrou¹, Bruno Lina³, Anne Christophe Lucet¹⁴, Denis Malvy¹⁵, Pauline Manchon¹¹, Milica Mandic¹, Mohamed Meghadecha¹⁶, Justina Motiejunaite¹⁷, Mariama Nourouline¹, Valentine Piquard¹¹, Andreea Postolache¹¹, Caroline Quintin¹, Jade Rexach¹, Layidé Roufal¹⁰, Zaven Terzian¹¹, Michael Thy¹⁸, Sarah Tubiana¹, Sylvie van der Werf³, Valérie Vignali¹, Benoît Visseaux⁸, Yazdan Yazdanpanah¹⁴

¹Centre d'Investigation Clinique, Inserm CIC 1425, Hôpital Bichat Claude Bernard, APHP, Paris, France. ²IMEA Fondation Léon M'Ba, Paris, France. ³Institut Pasteur, UMR 3569 CNRS, Université de Paris, Paris, France. ⁴University of Basel Children's Hospital. ⁵Julius Center for Health Sciences and Primary Care, Utrecht, Netherlands. ⁶Université de Paris, IAME, Inserm UMR 1137, F-75018, Paris, France, Hôpital Bichat Claude Bernard, APHP, Paris, France. ⁷Hôpital Pitie Salpêtrière, APHP, Paris. ⁸Université de Paris, IAME, INSERM UMR 1137, AP-HP, University Hospital Bichat Claude Bernard, Virology, Paris, France. ⁹Santé Publique France, Saint Maurice, France. ¹⁰Pole Recherche Clinique, Inserm, Paris, France. ¹¹Hôpital Bichat Claude Bernard, APHP, Paris, France. ¹²APHP, Paris, France. ¹³Virpath Laboratory, International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. ¹⁴IAME Inserm UMR 1138, Hôpital Bichat Claude Bernard, APHP, Paris, France. ¹⁵Service des Maladies Infectieuses et Tropicales; Groupe Pellegrin-Place Amélie-Raba-Léon, Bordeaux, France. ¹⁶Hôpital Hotel Dieu, APHP, Paris, France. ¹⁷Service des Explorations Fonctionnelles, Hôpital Bichat-Claude Bernard, APHP, Paris, France. ¹⁸Center for Clinical Investigation, Assistance Publique-Hôpitaux de Paris, Bichat-Claude Bernard University Hospital, Paris, France.

Amsterdam UMC Covid-19 Biobank Michiel van Agtmael¹, Anna Geke Algera², Frank van Baarle², Diane Bax³, Martijn Beudel⁴, Harm Jan Bogaard⁵, Marije Bomers¹, Liewue Bos², Michela Botta², Justin de Brabander⁶, Godelieve de Bree⁶, Matthijs C. Brouwer⁴, Sanne de Bruin⁷, Marianna Bugiani⁷, Esther Bulle², Osoul Chouchane¹, Alex Coherly⁷, Paul Elbers⁵, Lucas Fleuren², Suzanne Geerlings¹, Bart Geerts⁸, Theo Geijtenbeek⁹, Armand Girbes², Bram Goohuis¹, Martin P. Grobusch¹, Floriane Hafkamp⁹, Laura Hagens², Jorg Hamann¹⁰, Vanessa Harris¹, Robert Hemke¹, Sabine M. Hermans¹, Leo Heunks⁷, Markus W. Hollmann⁸, Janneke Horn², Joppe W. Hovius¹,

Menno D. de Jong¹², Rutger Koning⁴, Niels van Mourik², Jeanine Nellen¹, Frederique Paulus², Edgar Peters¹, Tom van der Pol¹, Benedikt Preckel¹, Jan M. Prins¹, Jorinde Raasveld², Tom Reijnders¹, Michiel Schinkel¹, Marcus J. Schultz², Alex Schuurman¹³, Kim Sigaloff¹, Marry Smit², Cornelis S. Stijns¹, Willemke Stijlma², Charlotte Teunissen¹⁴, Patrick Thorat¹, Anissa Tsonas², Marc van der Valk¹, Denise Veelo⁸, Alexander P.J. Vlaar¹⁵, Heder de Vries², Michèle van Vugt¹, W. Joost Wiersinga¹, Dorien Wouters¹⁶, A. H. (Koo) Zwinderman¹⁷, Diederik van de Beek^{4*}

¹Department of Infectious Diseases, Amsterdam UMC, Amsterdam, Netherlands. ²Department of Intensive Care, Amsterdam UMC, Amsterdam, Netherlands. ³Experimental Immunology, Amsterdam UMC, Amsterdam, Netherlands. ⁴Department of Neurology, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, Netherlands. ⁵Department of Pulmonology, Amsterdam UMC, Amsterdam, Netherlands. ⁶Department of Infectious Diseases, Amsterdam UMC, Amsterdam, Netherlands. ⁷Department of Pathology, Amsterdam UMC, Amsterdam, Netherlands. ⁸Department of Anesthesiology, Amsterdam UMC, Amsterdam, Netherlands. ⁹Department of Experimental Immunology, Amsterdam UMC, Amsterdam, Netherlands. ¹⁰Amsterdam UMC Biobank Core Facility, Amsterdam UMC, Amsterdam, Netherlands. ¹¹Department of Radiology, Amsterdam UMC, Amsterdam, Netherlands. ¹²Department of Medical Microbiology, Amsterdam UMC, Amsterdam, Netherlands. ¹³Department of Internal Medicine, Amsterdam UMC, Amsterdam, Netherlands. ¹⁴Neurochemical Laboratory, Amsterdam UMC, Amsterdam, Netherlands. ¹⁵Department of Intensive Care, Amsterdam UMC, Amsterdam, Netherlands. ¹⁶Department of Clinical Chemistry, Amsterdam UMC, Amsterdam, Netherlands. ¹⁷Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, Amsterdam, Netherlands. ¹⁸Department of Neurology, Amsterdam UMC, Amsterdam, Netherlands. *Leader of the AMC Consortium.

COVID Human Genetic Effort Laurent Abel¹, Alessandro Aiuti², Saleh Al Muhsen³, Fahd Al-Mulla⁴, Mark S. Anderson⁵, Andrés Augusto Arias⁶, Hagit Baris Feldman⁷, Susan Bogunovic⁸, Alexandre Bolze⁹, Anastasia Bondarenko¹⁰, Ahmed A. Bousfiha¹¹, Petter Brodin¹², Yanan Bryceon¹², Carlos D. Bustamante¹³, Manish Butte¹⁴, Giorgio Casari¹⁵, Samya Chakravorty¹⁶, John Christodoulou¹⁷, Elizabeth Cirulli³, Antonio Condino-Neto¹⁸, Megan A. Cooper¹⁹, Clifton L. Dalgaard²⁰, Alessia David²¹, Joseph L. DeRisi²², Mukesh Desai²³, Beth A. Droleat²⁴, Sara Espinosa²⁵, Jacques Fellay²⁶, Carlos Flores²⁷, Jose Luis Franco²⁸, Peter K. Gregersen²⁹, Filomen Heerink³⁰, David Hagin³¹, Rabih Halwani³², Jim Heath³³, Sarah E. Henrickson³⁴, Elena Hsieh³⁵, Kohsuke Imai³⁶, Yuval Itan⁸, Timokratis Karamitros³⁷, Kai Kisand³⁸, Cheng-Lung Ku³⁹, Yu-Lung Lau⁴⁰, Yun Ling⁴¹, Carrie L. Lucas⁴², Tom Maniatis⁴³, Davoud Mansouri⁴⁴, Laszlo Marodi⁴⁵, Isabelle Meys⁴⁶, Joshua Milner⁴⁷, Kristina Mironska⁴⁸, Trine Mogensen⁴⁹, Tomohiro Morio⁵⁰, Lisa FP. Ng⁵¹, Luigi D. Notarangelo⁵², Antonio Novelli⁵³, Giuseppe Ozelik⁵⁷, Rebeca Perez de Diego⁵⁸, Anna M. Planas⁵⁹, Carolina Prando⁶⁰, Aurora Pujol⁶¹, Luis Quintana-Murci⁶², Laurent Renia⁶³, Alessandra Renieri⁶⁴, Carlos Rodríguez-Gallego⁶⁵, Vanessa Sancho-Shimizu⁶⁶, Vijay Sankaran⁶⁷, Kelly Schiabor Barrett⁶⁸, Mohammed Shahrooei⁶⁸, Andrew Snow⁶⁹, Pere Soler-Palacin⁷⁰, Andrés N. Spaan⁷¹, Stuart Tangye⁷², Stuart Turvey⁷³, Furkan Uddin⁷⁴, Mohammed J. Uddin⁷⁵, Diederik van de Beek⁷⁶, Sara E. Vazquez⁷⁷, Donald C. Vinh⁷⁸, Horst von Bernuth⁷⁹, Nicole Washington⁸⁰, Pawel Zawadzki⁸⁰, Helen C. Su⁸², Jean-Laurent Casanova⁸¹

¹INSERM U1163, University of Paris, Imagine Institute, Paris, France. ²San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, Milan, Italy. ³King Saud University, Riyadh, Saudi Arabia. ⁴Kuwait University, Kuwait City, Kuwait. ⁵University of California, San Francisco, San Francisco, CA, USA. ⁶Universidad de Antioquia, Group of Primary Immunodeficiencies, Antioquia, Colombia. ⁷The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁸cahn School of Medicine at Mount Sinai, New York, NY, USA. ⁹Helix, San Mateo, CA, USA. ¹⁰Shupky National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹¹Clinical Immunology Unit, Pediatric Infectious Disease Department, Faculty of Medicine and Pharmacy, Averroes University Hospital; LICIA Laboratoire d'Immunologie Clinique, d'Inflammation et d'Allergie, Hassani II University, Casablanca, Morocco. ¹²Karolinska Institute, Stockholm, Sweden. ¹³Stanford University, Stanford, CA, USA. ¹⁴University of California, Los Angeles, CA, USA. ¹⁵Medical Genetics, IRCCS Ospedale San Raffaele, Milan, Italy. ¹⁶Emory University Department of Pediatrics and Children's Healthcare of Atlanta, Atlanta, GA, USA. ¹⁷Murdoch

Children's Research Institute, Victoria, Australia. ¹⁸University of São Paulo, São Paulo, Brazil. ¹⁹Washington University School of Medicine, St. Louis, MO, USA. ²⁰The American Genome Center; Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ²¹Centre for Bioinformatics and System Biology, Department of Life Sciences, Imperial College London, South Kensington Campus, London, UK. ²²University of California, San Francisco, CA, USA; Chan Zuckerberg Biohub, San Francisco, CA, USA. ²³Bai Jerbai Wadia Hospital for Children, Mumbai, India. ²⁴School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. ²⁵Instituto Nacional de Pediatría (National Institute of Pediatrics), Mexico City, Mexico. ²⁶Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland. ²⁷Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Canarian Health System, Santa Cruz de Tenerife, Spain. ²⁸University of Antioquia, Medellín, Colombia. ²⁹Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA. ³⁰Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPiG), PID Research Lab, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Edegem, Belgium. ³¹The Genetics Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. ³²Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, UAE. ³³Institute for Systems Biology, Seattle, WA, USA. ³⁴Children's Hospital of Philadelphia, Philadelphia, PA, USA. ³⁵Anschutz Medical Campus, Aurora, CO, USA. ³⁶Riken, Tokyo, Japan. ³⁷Hellenic Pasteur Institute, Athens, Greece. ³⁸University of Tartu, Tartu, Estonia. ³⁹Chang Gung University, Taoyuan County, Taiwan. ⁴⁰The University of Hong Kong, Hong Kong, China. ⁴¹Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. ⁴²Yale School of Medicine, New Haven, CT, USA. ⁴³New York Genome Center, New York, NY, USA. ⁴⁴Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁴⁵Semmelweis University Budapest, Budapest, Hungary. ⁴⁶KU Leuven, Department of Immunology, Microbiology and Transplantation, Leuven, Belgium. ⁴⁷Columbia University Medical Center, New York, NY, USA. ⁴⁸University Clinic for Children's Diseases, Skopje, North Macedonia. ⁴⁹Aarhus University, Aarhus, Denmark. ⁵⁰Tokyo Medical & Dental University Hospital, Tokyo, Japan. ⁵¹Singapore Immunology Network, Singapore. ⁵²National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. ⁵³Bambino Gesù Children's

Hospital, Rome, Italy. ⁵⁴Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy. ⁵⁵Trinity College, Dublin, Ireland. ⁵⁶Hiroshima University, Hiroshima, Japan. ⁵⁷Bilkent University, Ankara, Turkey. ⁵⁸Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ⁵⁹IBB-CSIC, IDIBAPS, Barcelona, Spain. ⁶⁰Faculdades Pequeno Príncipe e Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ⁶¹Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran I Reynals; Catalan Institution for Research and Advanced Studies (ICREA); CIBERER U759, ISCIII Madrid Spain, Barcelona, Spain. ⁶²Institut Pasteur (CNRS UMR2000) and Collège de France, Paris, France. ⁶³Infectious Diseases Horizontal Technology Center and Singapore Immunology Network, Agency for Science Technology (A*STAR), Singapore. ⁶⁴Medical Genetics, University of Siena, Siena, Italy; Genetica Medica, Azienda Ospedaliero-Universitaria Senese, Italy; GEN-COVID Multicenter Study. ⁶⁵Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Canary Islands, Spain. ⁶⁶Imperial College London, London, UK. ⁶⁷Boston Children's Hospital, Harvard Medical School, Boston, MA, USA. ⁶⁸Saeed Pathobiology and Genetic Lab, Tehran, Iran. ⁶⁹Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁷⁰Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁷¹University Medical Center Utrecht, Amsterdam, The Netherlands. ⁷²Garvan Institute of Medical Research, Sydney, Australia. ⁷³The University of British Columbia, Vancouver, Canada. ⁷⁴Holy Family Red Crescent Medical College; Centre for Precision Therapeutics, NeuroGen Children's Healthcare; Genetics and Genomic Medicine Centre, NeuroGen Children's Healthcare, Dhaka, Bangladesh. ⁷⁵Mohammed Bin Rashid University of Medicine and Health Sciences, College of Medicine, Dubai, UAE; The Centre for Applied Genomics, Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada. ⁷⁶Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, The Netherlands. ⁷⁷University of California, San Francisco, CA, USA. ⁷⁸McGill University Health Centre, Montreal, Canada. ⁷⁹Charité-Berlin University Hospital Center, Berlin, Germany. ⁸⁰Molecular Biophysics Division, Faculty of Physics, A. Mickiewicz University, Uniwersytetu Poznańskiego 2, Poznań, Poland.

⁸¹Rockefeller University, Howard Hughes Medical Institute, Necker Hospital, New York, NY, USA.

*Leaders of the COVID Human Genetic Effort.

NIAID-USUHS/TAGC COVID Immunity Group Huie Jing^{1,2}, Wesley Tung^{1,2}, Christopher R. Luthers³, Brady M. Bauman³, Samantha Shafer^{2,4}, Lixin Zheng^{2,4}, Zinan Zhang^{2,4}, Satoshi Kubo^{2,4}, Samuel D. Chauvin^{2,4}, Kazuyuki Meguro^{1,2}, Elana Shaw^{1,2}, Michael Lenardo^{2,4}, Justin Lack⁵, Eric Karlins⁶, Daniel M. Hupalow⁷, John Rosenberger⁷, Gauthaman Sukumar⁷, Matthew D. Wilkerson⁷, Xijun Zhang⁷

¹Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ²NIAID Clinical Genomics Program, National Institutes of Health, Bethesda, MD, USA. ³Department of Pharmacology & Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁴Laboratory of Immune System Biology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ⁵NIAID Collaborative Bioinformatics Resource, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD, USA. ⁶Bioinformatics and Computational Biosciences Branch, Office of Cyber Infrastructure and Computational Biology, NIAID, NIH, Bethesda, MD, USA. ⁷The American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.

SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/370/6515/eabd4570/suppl/DC1

Materials and Methods

Figs. S1 to S11

Tables S1 and S2

References (42 and 43)

MDAR Reproducibility Checklist

[View/request a protocol for this paper from Bio-protocol.](#)

22 June 2020; accepted 16 September 2020

Published online 24 September 2020

10.1126/science.abd4570

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

Qian Zhang Paul Bastard Zhiyong Liu Jérémie Le Pen Marcela Moncada-Velez Jie Chen Masato Ogishima K. D. Sabli Stephanie Hodeib Cecilia Korol Jérémie Rosain Kaya Bilguvar Junqiang Ye Alexandre Bolze Benedetta Bigio Rui Yang Andrés Augusto Arias Qinhua Zhou Yu Zhang Fanny Onodi Sarantis Korniotis Léa Karpf Quentin Philippot Marwa Chbihi Lucie Bonnet-Madin Karim Dorgham Nikaia Smith William M. Schneider Brandon S. Razoogy Hans-Heinrich Hoffmann Eleftherios Michailidis Leen Moens Ji Eun Han Lazaro Lorenzo Lucy Bizien Philip Meade Anna-Lena Neehus Aileen Camille Ugurbil Aurélien Corneau Gaspard Kerner Peng Zhang Franck Rapaport Yoann Seeleuthner Jeremy Manry Cecile Masson Johann Schmitt Agatha Schlüter Tom Le Voyer Taushif Khan Juan Li Jacques Fellay Lucie Rousset Mohammad Shahrooei Mohammed F. Alosaimi Davood Mansouri Haya Al-Saud Fahd Al-Mulla Feras Almourfi Saleh Zaid Al-Muhsen Fahad Alsohime Saeed Al Turki Rana Hasanato Diederik van de Beek Andrea Biondi Laura Rachele Bettini Mariella D'Angio Paolo Bonfanti Luisa Imberti Alessandra Sottini Simone Paghera Eugenia Quiros-Roldan Camillo Rossi Andrew J. Oler Miranda F. Tompkins Camille Albalsabelle Vandernoot Jean-Christophe Goffard Guillaume Smits Isabelle Migeotte Filomeen Haerynck Pere Soler-Palacin Andrea Martin-Nalda Roger Colobran Pierre-Emmanuel Morange Sevgi Keles Fatma Çölkesen Tayfun Ozcelik Kadriye Kart Yasar Sevta Senoglu #emsi Nur Karabela Carlos Rodriguez-Gallego Giuseppe Novelli Sami Hraiech Yacine Tandjaoui-Lambiotte Xavier Duval Cédric Laouénan Andrew L. Snow Clifton L. Dalgard Joshua D. Milner Donald C. Vinh Trine H. Mogensen Nico Marr Andrés N. Spaan Bertrand Boisson Stéphanie Boisson-Dupuis Jacinta Bustamante Anne Puell Michael J. Ciancanelli Isabelle Meyts Tom Maniatis Vassili Soumelis Ali Amara Michel Nussenzweig Adolfo Garcia-Sastre Florian Krammer Aurora Pujol Darragh Duffy Richard P. Lifton Shen-Ying Zhang Guy Gorochov Vivien Béziat Emmanuelle Jouanguy Vanessa Sancho-Shimizu Charles M. Rice Laurent Abel Luigi D. Notarangelo Aurélie Cobat Helen C. Su Jean-Laurent Casanova, and Giuseppe Foti, and Giacomo Bellani, and Giuseppe Citerio, and Ernesto Contro, and Alberto Pesci, and Maria Grazia Valsecchi, and Marina Cazzaniga, and Jorge Abad, and Sergio Aguilera-Albesa, and Ozge Metin Akcan, and Ilad Alavi Darazam, and Juan C. Aldave, and Miquel Alfonso Ramos, and Seyed Alireza Nadji, and Gulsum Alkan, and Jerome Allardet-Servent, and Luis M. Allende, and Laia Alsina, and Marie-Alexandra Alyanakian, and Blanca Amador-Borrero, and Zahir Amoura, and Arnau Antolí, and Sevket Arslan, and Sophie Assant, and Terese Auguet, and Axelle Azot, and Fanny Bajolle, and Aurélie Baldolli, and Maite Ballester, and Hagit Baris Feldman, and Benoit Barrou, and Alexandra Beurton, and Agurtzane Bilbao, and Geraldine Blanchard-Rohner, and Ignacio Blanco, and Adeline Blandinières, and Daniel Blazquez-Gamero, and Marketa Bloomfield, and Mireia Bolivar-Prados, and Raphael Borie, and Cédric Bosteels, and Ahmed A. Bousfiha, and Claire Bouvattier, and Oksana Boyarchuk, and Maria Rita P. Bueno, and Jacinta Bustamante, and Juan José Cáceres Agra, and Semra Calimli, and Ruggero Capra, and Maria Carrabba, and Carlos Casasnovas, and Marion Caseris, and Martin Castelle, and Francesco Castelli, and Martín Castillo de Vera, and Mateus V. Castro, and Emilie Catherinot, and Martin Chalumeau, and Bruno Charbit, and Matthew P. Cheng, and Père Clavé, and Bonaventura Clotet, and Anna Codina, and Fatih Colkesen, and Fatma Çölkesen, and Roger Colobran, and Cloé Comarmond, and David Dalmau, and David Ross Darley, and Nicolas Dauby, and Stéphane Dauter, and Loïc de Pontual, and Amin Dehban, and Geoffroy Delplancq, and Alexandre Demoule, and Jean-Luc Diehl, and Stephanie Dobbelaere, and Sophie Durand, and Waleed Eldars, and Mohamed Elgamel, and Marwa H. Elnagdy, and Melike Emiroglu, and Emine Hafize Erdeniz, and Selma Erol Aytekin, and Romain Euvrard, and Recep Evcen, and Giovanna Fabio, and Laurence Faivre, and Antonin Falck, and Muriel Fartoukh, and Morgane Faure, and Miguel Fernandez Arquero, and Carlos Flores, and Bruno Francois, and Victoria Fumadó, and Francesca Fusco, and Blanca Garcia Solis, and Pascale Gaussem, and Juana Gil-Herrera, and Laurent Gilardin, and Monica Girona Alarcon, and Mónica Girona-Alarcón, and Jean-Christophe Goffard, and Funda Gok, and Rafaela González-Montelongo, and Antoine Guerder, and Yahya Gul, and Sukru Nail Guner, and Marta Gut, and Jérôme Hadjadj, and Filomeen Haerynck, and Rabi Halwani, and Lennart Hammarström, and Nevin Hatipoglu, and Elisa Hernandez-Brito, and Cathérine Heijmans, and María Soledad Holanda-Peña, and Juan Pablo Horcajada, and Levi Hoste, and Eric Hoste, and Sami Hraiech, and Linda Humbert, and Alejandro D. Iglesias, and Antonio Íñigo-Campos, and Matthieu Jamme, and María Jesús Arranz, and Iolanda Jordan, and Philippe Jorens, and Fikret Kanat, and Hasan Kapakli, and Iskender Kara, and Adem Karbuz, and Kadriye Kart Yasar, and Sevgi Keles, and Yasemin Kendir Demirkol, and Adam Klocperk, and Zbigniew J. Król, and Paul Kuentz, and Yat Wah M. Kwan, and Jean-Christophe Lagier, and Bart N. Lambrecht, and Yu-Lung Lau, and Fleur Le Bourgeois, and Yee-Sin Leo, and Rafael Leon Lopez, and Daniel Leung, and Michael Levin, and Michael Levy, and Romain Lévy, and Zhi Li, and Agnes Linglart, and Bart Loeys, and José M. Lorenzo-Salazar, and Céline Louapre, and Catherine Lubetzki, and Charles-Edouard Luyt, and David C. Lye, and Davood Mansouri, and Majid Marjani, and Jesus Marquez Pereira, and Andrea Martin, and David Martínez Pueyo, and Javier Martínez-Picado, and Iciar Marzana, and Alexis Mathian, and Larissa R. B. Matos, and Gail V. Matthews, and Julien Mayaux, and Jean-Louis Mège, and Isabelle Melki, and Jean-François Meritet, and Ozge Metin, and Isabelle Meyts, and Mehdi Mezidi, and Isabelle Migeotte, and Maude Millereux, and Tristan Mirault, and Clotilde Mircher, and Mehdi Mirsaedi, and Abián Montesdeoca Melián, and

Use of think article is subject to the [Terms of service](#)

Antonio Morales Martinez, and Pierre Morange, and Clémence Mordacq, and Guillaume Morelle, and Stéphane Mouly, and Adrián Muñoz-Barrera, and Leslie Naesens, and Cyril Nafati, and João Fabela Neves, and Lisa F. P. Ng, and Yeray Novoa Medina, and Esmeralda Nuñez Cuadros, and J. Gonzalo Ocejo-Vinyals, and Zerrin Orbak, and Mehdi Oualha, and Tayfun Özçelik, and Qiang Pan-Hammarström, and Christophe Parizot, and Tiffany Pascreau, and Estela Paz-Artal, and Sandra Pellegrini, and Rebeca Pérez de Diego, and Aurélien Philippe, and Quentin Philippot, and Laura Planas-Serra, and Dominique Ploin, and Julien Poissy, and Géraldine Poncelet, and Marie Pouletty, and Paul Quentric, and Didier Raoult, and Anne-Sophie Rebillat, and Ismail Reisli, and Pilar Ricart, and Jean-Christophe Richard, and Nadia Rivet, and Jacques G. Rivière, and Gemma Rocamora Blanch, and Carlos Rodrigo, and Carlos Rodríguez-Gallego, and Agustí Rodríguez-Palmero, and Carolina Soledad Romero, and Anya Rothenbuhler, and Flore Rozenberg, and María Yolanda Ruiz del Prado, and Joan Sabater Riera, and Oliver Sanchez, and Silvia Sánchez-Ramón, and Agatha Schluter, and Matthieu Schmidt, and Cyril E. Schweitzer, and Francesco Scolari, and Anna Sediva, and Luis M. Seijo, and Damien Sene, and Sevtap Senoglu, and Mikko R. J. Seppänen, and Alex Serra Ilovich, and Mohammad Shahrooei, and Hans Slabbynck, and David M. Smadja, and Ali Sobh, and Xavier Solanich Moreno, and Jordi Solé-Violán, and Catherine Soler, and Pere Soler-Palacín, and Yuri Stepanovskiy, and Annabelle Stoclin, and Fabio Taccone, and Yacine Tandjaoui-Lambiotte, and Jean-Luc Taupin, and Simon J. Tavernier, and Benjamin Terrier, and Caroline Thumerelle, and Gabriele Tomasoni, and Julie Toubiana, and Josep Trenado Alvarez, and Sophie Trouillet-Assant, and Jesús Troya, and Alessandra Tucci, and Matilde Valeria Ursini, and Yurdagul Uzunhan, and Pierre Vabres, and Juan Valencia-Ramos, and Eva Van Braeckel, and Stijn Van de Velde, and Ana Maria Van Den Rym, and Jens Van Praet, and Isabelle Vandernoot, and Hulya Vatansév, and Valentina Vélez-Santamaria, and Sébastien Viel, and Cédric Vilain, and Marie E. Vilaire, and Audrey Vincent, and Guillaume Voirit, and Fanny Vuotto, and Alper Yosunkaya, and Barnaby E. Young, and Fatih Yucel, and Faiez Zannad, and Mayana Zatz, and Alexandre Belot, and Christine Bole-Feysot, and Stanislas Lyonnet, and Cécile Masson, and Patrick Nitschke, and Aurore Pouliet, and Yoann Schmitt, and Frederic Tores, and Mohammed Zarhrate, and Laurent Abel, and Claire Andrejak, and François Angoulvant, and Delphine Bachelet, and Romain Basmaci, and Sylvie Behillil, and Marine Beluze, and Dehbia Benkerrou, and Krishna Bhavsar, and François Bompard, and Lila Bouadma, and Maude Bouscambert, and Mireille Caralp, and Minerva Cervantes-Gonzalez, and Anissa Chair, and Alexandra Coelho, and Camille Couffignal, and Sandrine Couffin-Cadiergues, and Eric D'Ortenzio, and Charlene Da Silveira, and Marie-Pierre Debray, and Dominique Deplanque, and Diane Descamps, and Mathilde Desvallées, and Alpha Diallo, and Alphonsine Diouf, and Céline Dorival, and François Dubos, and Xavier Duval, and Philippine Eloy, and Vincent VE Enouf, and Héléne Esperou, and Marina Esposito-Farese, and Manuel Etienne, and Nadia Ettalhaoui, and Nathalie Gault, and Alexandre Gaymard, and Jade Ghosn, and Tristan Gigante, and Isabelle Gorenne, and Jérémie Guedj, and Alexandre Hocin, and Isabelle Hoffmann, and Salma Jaafoura, and Ouifiya Kafif, and Florentia Kaguelidou, and Sabina Kali, and Antoine Khalil, and Coralie Khan, and Cédric Laouénan, and Samira Laribi, and Minh Le, and Quentin Le Hingrat, and Soizic Le Mestre, and Hervé Le Nagard, and François-Xavier Lescure, and Yves Lévy, and Claire Levy-Marchal, and Bruno Lina, and Guillaume Lingas, and Jean Christophe Lucet, and Denis Malvy, and Marina Mambert, and France Mentré, and Noémie Mercier, and Amina Meziane, and Hugo Mouquet, and Jimmy Mullaert, and Nadège Neant, and Marion Noret, and Justine Pages, and Aurélie Papadopoulos, and Christelle Paul, and Nathan Peiffer-Smadja, and Ventzislava Petrov-Sanchez, and Gilles Peytavin, and Olivier Picone, and Oriane Puéchal, and Manuel Rosa-Calatrava, and Bénédicte Rossignol, and Patrick Rossignol, and Carine Roy, and Marion Schneider, and Caroline Semaille, and Nassima Si Mohammed, and Lysa Tagherst, and Coralie Tardivon, and Marie-Capucine Tellier, and François Téoulé, and Olivier Terrier, and Jean-François Timsit, and Théo Trioux, and Christelle Tual, and Sarah Tubiana, and Sylvie van der Werf, and Noémie Vanel, and Aurélie Veislinger, and Benoit Visseaux, and Aurélie Wiedemann, and Yazdan Yazdanpanah, and Loubna Alavoine, and Karine K. A. Amat, and Sylvie Behillil, and Julia Bielicki, and Patricia Bruijning, and Charles Burdet, and Eric Caumes, and Charlotte Charpentier, and Bruno Coignard, and Yolande Costa, and Sandrine Couffin-Cadiergues, and Florence Damond, and Aline Dechanet, and Christelle Delmas, and Diane Descamps, and Xavier Duval, and Jean-Luc Ecobichon, and Vincent Enouf, and Héléne Espérou, and Wahiba Frezouls, and Nadhira Houhou, and Emilia Ilic-Habensus, and Ouifiya Kafif, and John Kikoine, and Quentin Le Hingrat, and David Lebeaux, and Anne Leclercq, and Jonathan Lehacaut, and Sophie Letrou, and Bruno Lina, and Jean-Christophe Lucet, and Denis Malvy, and Pauline Manchon, and Milica Mandic, and Mohamed Meghadecha, and Justina Motiejunaite, and Mariama Nouroudine, and Valentine Piquard, and Andreea Postolache, and Caroline Quintin, and Jade Rexach, and Layidé Roufai, and Zaven Terzian, and Michael Thy, and Sarah Tubiana, and Sylvie van der Werf, and Valérie Vignali, and Benoit Visseaux, and Yazdan Yazdanpanah, and Michiel van Agtmael, and Anna Geke Algera, and Frank van Baarle, and Diane Bax, and Martijn Beudel, and Harm Jan Bogaard, and Marije Bomers, and Lieuwe Bos, and Michela Botta, and Justin de Brabander, and Godelieve de Bree, and Matthijs C. Brouwer, and Sanne de Bruin, and Marianna Bugiani, and Esther Bulle, and O. Chouchane, and Alex Cloherty, and Paul Elbers, and Lucas Fleuren, and Suzanne Geerlings, and Bart Geerts, and Theo Geijtenbeek, and Armand Girbes, and Bram Goorhuis,

Use of think article is subject to the [Terms of service](#)

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.

Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works

and Martin P. Grobusch, and Florianne Hafkamp, and Laura Hagens, and Jorg Hamann, and Vanessa Harris, and Robert Hemke, and Sabine M. Hermans, and Leo Heunks, and Markus W. Hollmann, and Janneke Horn, and Joppe W. Hovius, and Menno D. de Jong, and Rutger Koning, and Niels van Mourik, and Jeaninne Nellen, and Frederique Paulus, and Edgar Peters, and Tom van der Poll, and Benedikt Preckel, and Jan M. Prins, and Jorinde Raasveld, and Tom Reijnders, and Michiel Schinkel, and Marcus J. Schultz, and Alex Schuurman, and Kim Sigaloff, and Marry Smit, and Cornelis S. Stijnis, and Willemke Stilma, and Charlotte Teunissen, and Patrick Thoral, and Anissa Tsonas, and Marc van der Valk, and Denise Veelo, and Alexander P.J. Vlaar, and Heder de Vries, and Michèle van Vugt, and W. Joost Wiersinga, and Dorien Wouters, and A. H. (Koo) Zwinderman, and Diederik van de Beek, and Laurent Abel, and Alessandro Aiuti, and Saleh Al Muhsen, and Fahd Al-Mulla, and Mark S. Anderson, and Andrés Augusto Arias, and Hagit Baris Feldman, and Dusan Bogunovic, and Alexandre Bolze, and Anastasiia Bondarenko, and Ahmed A. Bousfiha, and Petter Brodin, and Yen-an Bryceson, and Carlos D. Bustamante, and Manish Butte, and Giorgio Casari, and Samya Chakravorty, and John Christodoulou, and Elizabeth Cirulli, and Antonio Condino-Neto, and Megan A. Cooper, and Clifton L. Dalgard, and Alessia David, and Joseph L. DeRisi, and Murkesh Desai, and Beth A. Drolet, and Sara Espinosa, and Jacques Fellay, and Carlos Flores, and Jose Luis Franco, and Peter K. Gregersen, and Filomeen Haerynck, and David Hagin, and Rabih Halwani, and Jim Heath, and Sarah E. Henrickson, and Elena Hsieh, and Kohsuke Imai, and Yuval Itan, and Timokratis Karamitros, and Kai Kisand, and Cheng-Lung Ku, and Yu-Lung Lau, and Yun Ling, and Carrie L. Lucas, and Tom Maniatis, and Davoud Mansouri, and Laszlo Marodi, and Isabelle Meyts, and Joshua Milner, and Kristina Mironska, and Trine Mogensen, and Tomohiro Morio, and Lisa F. P. Ng, and Luigi D. Notarangelo, and Antonio Novelli, and Giuseppe Novelli, and Cliona O'Farrelly, and Satoshi Okada, and Tayfun Ozcelik, and Rebeca Perez de Diego, and Anna M. Planas, and Carolina Prando, and Aurora Pujol, and Lluís Quintana-Murci, and Laurent Renia, and Alessandra Renieri, and Carlos Rodríguez-Gallego, and Vanessa Sancho-Shimizu, and Vijay Sankaran, and Kelly Schiabor Barrett, and Mohammed Shahrooei, and Andrew Snow, and Pere Soler-Palacín, and Andrés N. Spaan, and Stuart Tangye, and Stuart Turvey, and Furkan Uddin, and Mohammed J. Uddin, and Diederik van de Beek, and Sara E. Vazquez, and Donald C. Vinh, and Horst von Bernuth, and Nicole Washington, and Pawel Zawadzki, and Helen C. Su, and Jean-Laurent Casanova, and Huie Jing, and Wesley Tung, and Christopher R. Luthers, and Bradley M. Bauman, and Samantha Shafer, and Lixin Zheng, and Zinan Zhang, and Satoshi Kubo, and Samuel D. Chauvin, and Kazuyuki Meguro, and Elana Shaw, and Michael Lenardo, and Justin Lack, and Eric Karlins, and Daniel M. Hupal, and John Rosenberger, and Gauthaman Sukumar, and Matthew D. Wilkerson, and Xijun Zhang

Science, 370 (6515), eabd4570. • DOI: 10.1126/science.abd4570

The genetics underlying severe COVID-19

The immune system is complex and involves many genes, including those that encode cytokines known as interferons (IFNs). Individuals that lack specific IFNs can be more susceptible to infectious diseases. Furthermore, the autoantibody system dampens IFN response to prevent damage from pathogen-induced inflammation. Two studies now examine the likelihood that genetics affects the risk of severe coronavirus disease 2019 (COVID-19) through components of this system (see the Perspective by Beck and Aksentijevich). Q. Zhang *et al.* used a candidate gene approach and identified patients with severe COVID-19 who have mutations in genes involved in the regulation of type I and III IFN immunity. They found enrichment of these genes in patients and conclude that genetics may determine the clinical course of the infection. Bastard *et al.* identified individuals with high titers of neutralizing autoantibodies against type I IFN-#2 and IFN-# in about 10% of patients with severe COVID-19 pneumonia. These autoantibodies were not found either in infected people who were asymptomatic or had milder phenotype or in healthy individuals. Together, these studies identify a means by which individuals at highest risk of life-threatening COVID-19 can be identified.

Science, this issue p. eabd4570, p. eabd4585; see also p. 404

Use of think article is subject to the [Terms of service](#)

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.

Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works

Science

View the article online

<https://www.science.org/doi/10.1126/science.abd4570>

Permissions

<https://www.science.org/help/reprints-and-permissions>

Use of think article is subject to the [Terms of service](#)

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.
Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works