

CORONAVIRUS

X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19

Takaki Asano^{1†}, Bertrand Boisson^{1,2,3,*†}, Fanny Onodi^{4‡}, Daniela Matuozzo^{2,3‡}, Marcela Moncada-Velez^{1‡}, Majistor Raj Luxman Maglorius Renkilaraj^{2,3‡}, Peng Zhang^{1‡}, Laurent Meertens^{4‡}, Alexandre Bolze^{5‡}, Marie Materna^{2,3‡}, Sarantis Korniotis⁶, Adrian Gervais^{2,3}, Estelle Talouarn^{2,3}, Benedetta Bigio¹, Yoann Seeleuthner^{2,3}, Kaya Bilguvar⁷, Yu Zhang^{8,9}, Anna-Lena Neehus^{2,3}, Masato Ogishi¹, Simon J. Pelham¹, Tom Le Voyer^{2,3}, Jérémie Rosain^{2,3}, Quentin Philippot^{2,3}, Pere Soler-Palacín^{10,11,12}, Roger Colobran^{12,13,14}, Andrea Martin-Nalda^{10,11,12}, Jacques G. Rivière^{10,11,12}, Yacine Tandjaoui-Lambiotte^{15,16}, Khalil Chaïbi^{17,18}, Mohammad Shahrooei^{19,20}, Ilad Alavi Darazam^{21,22}, Nasrin Alipour Olyaei^{19,20}, Davood Mansouri^{23,24,25}, Nevin Hatipoğlu²⁶, Figen Palabiyik²⁶, Tayfun Ozcelik²⁷, Giuseppe Novelli²⁸, Antonio Novelli²⁹, Giorgio Casari^{30,31}, Alessandro Aiuti^{30,32}, Paola Carrera³¹, Simone Bondesan³¹, Federica Barzaghi³², Patrizia Rovere-Querini^{30,33}, Cristina Tresoldi³⁴, Jose Luis Franco³⁵, Julian Rojas³⁵, Luis Felipe Reyes³⁶, Ingrid G. Bustos³⁶, Andres Augusto Arias^{1,35,37}, Guillaume Morelle³⁸, Christèle Kyheng³⁸, Jesús Troya³⁹, Laura Planas-Serra^{40,41}, Agatha Schlüter^{40,41}, Marta Gut⁴², Aurora Pujol^{40,41,43}, Luis M. Allende^{44,45}, Carlos Rodriguez-Gallego^{46,47}, Carlos Flores^{48,49,50,51}, Oscar Cabrera-Marante⁴⁴, Daniel E. Pleguezuelo⁴⁴, Rebeca Pérez de Diego⁵², Sevgi Keles⁵³, Gokhan Aytekin⁵⁴, Ozge Metin Akcan⁵³, Yenan T. Bryceson⁵⁵, Peter Bergman^{56,57}, Petter Brodin⁵⁸, Daniel Smole⁵⁹, C. I. Edvard Smith^{57,60}, Anna-Carin Norlin⁵⁷, Tessa M. Campbell⁵⁵, Laura E. Covill⁵⁵, Lennart Hammarström⁶¹, Qiang Pan-Hammarström⁶¹, Hassan Abolhassani^{61,62}, Shrikant Mane⁶³, Nico Marr⁶⁴, Manar Ata⁶⁴, Fatima Al Ali⁶⁴, Taushif Khan⁶⁴, András N. Spaan^{1,65}, Clifton L. Dalgard^{66,67}, Paolo Bonfanti⁶⁸, Andrea Biondi⁶⁹, Sarah Tubiana^{70,71}, Charles Burdet^{70,72}, Robert Nussbaum⁷³, Amanda Kahn-Kirby⁷³, Andrew L. Snow⁷⁴, COVID Human Genetic Effort[§], COVID-STORM Clinicians[§], COVID Clinicians[§], Imagine COVID Group[§], French COVID Cohort Study Group[§], CoV-Contact Cohort[§], Amsterdam UMC Covid-19 Biobank[§], NIAID-USUHS COVID Study Group[§], Jacinta Bustamante^{1,2,3,75}, Anne Puel^{1,2,3}, Stéphanie Boisson-Dupuis^{1,2,3}, Shen-Ying Zhang^{1,2,3}, Vivien Béziat^{1,2,3}, Richard P. Lifton^{7,76||}, Paul Bastard^{1,2,3||}, Luigi D. Notarangelo^{8,9||}, Laurent Abel^{1,2,3||}, Helen C. Su^{8,9,77||}, Emmanuelle Jouanguy^{1,2,3||}, Ali Amara^{4||}, Vassili Soumelis^{6,78||}, Aurélie Cobat^{1,2,3||}, Qian Zhang^{1,2,3||}, Jean-Laurent Casanova^{1,2,3,79,*||}

Autosomal inborn errors of type I IFN immunity and autoantibodies against these cytokines underlie at least 10% of critical COVID-19 pneumonia cases. We report very rare, biochemically deleterious X-linked *TLR7* variants in 16 unrelated male individuals aged 7 to 71 years (mean, 36.7 years) from a cohort of 1202 male patients aged 0.5 to 99 years (mean, 52.9 years) with unexplained critical COVID-19 pneumonia. None of the 331 asymptotically or mildly infected male individuals aged 1.3 to 102 years (mean, 38.7 years) tested carry such *TLR7* variants ($P = 3.5 \times 10^{-5}$). The phenotypes of five hemizygous relatives of index cases infected with SARS-CoV-2 include asymptomatic or mild infection ($n = 2$) or moderate ($n = 1$), severe ($n = 1$), or critical ($n = 1$) pneumonia. Two patients from a cohort of 262 male patients with severe COVID-19 pneumonia (mean, 51.0 years) are hemizygous for a deleterious *TLR7* variant. The cumulative allele frequency for deleterious *TLR7* variants in the male general population is $<6.5 \times 10^{-4}$. We show that blood B cell lines and myeloid cell subsets from the patients do not respond to *TLR7* stimulation, a phenotype rescued by wild-type *TLR7*. The patients' blood plasmacytoid dendritic cells (pDCs) produce low levels of type I IFNs in response to SARS-CoV-2. Overall, X-linked recessive *TLR7* deficiency is a highly penetrant genetic etiology of critical COVID-19 pneumonia, in about 1.8% of male patients below the age of 60 years. Human *TLR7* and pDCs are essential for protective type I IFN immunity against SARS-CoV-2 in the respiratory tract.

INTRODUCTION

Interindividual clinical variability in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is vast, ranging from silent infection to lethal disease (1). The greatest risk factor for life-threatening coronavirus disease 2019 (COVID-19) pneumonia is age, with a doubling in risk every 5 years from the age

of 5 years onward and a sharp rise after the age of 65 years (2, 3). Other epidemiological risk factors, including common genetic variants, have only modest effects, with odds ratios of <2 and typically <1.5 (2). One intriguing observation is the about 1.5 times higher risk in men, which seems to be age independent (2–4). The COVID Human Genetic Effort consortium (www.covidhge.com) has enrolled

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an international cohort of patients, with the aim of investigating genetic and immunological causes of life-threatening COVID-19 pneumonia. We previously tested the hypothesis that critical influenza and critical COVID-19 can be allelic (5–7) and showed that life-threatening COVID-19 pneumonia can be caused by rare in-born errors of autosomal genes controlling Toll-like receptor 3 (TLR3)– and interferon (IFN) regulatory factor 7 (IRF7)–dependent type I IFN immunity (8). These disorders were found in 23 men and women aged 17 to 77 years (mean, 48 years). Four unrelated patients aged 25 to 50 years had autosomal recessive IFNAR1 ($n = 2$) or IRF7 ($n = 2$) deficiency. These patients had no previous history of severe viral illness, including influenza pneumonia, implying

that these genetic disorders unexpectedly show incomplete penetrance for critical influenza. These findings revealed that TLR3- and IRF7-dependent type I IFN immunity is essential for host defense against SARS-CoV-2 infection in the respiratory tract.

We also found preexisting neutralizing auto-antibodies (auto-Abs) against type I IFN in at least 10% of the patients from this cohort (9). These auto-Abs were found in 101 patients, mostly men (95%), and older members of the cohort, which included patients with in-born errors, as they were aged 25 to 87 years (mean, 65 years). These findings have been replicated in five other cohorts (10–15). These auto-Abs predated SARS-CoV-2 infection and were highly likely to be causal for critical COVID-19 pneumonia, because (i) they were

¹St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA. ²Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France. ³Imagine Institute, University of Paris, Paris, France. ⁴Laboratory of Genomes and Cell Biology of Disease, INSERM U944, CNRS UMR7212, University of Paris, Research Institute of Saint-Louis, Saint-Louis Hospital, Paris, France. ⁵Helix, San Mateo, CA, USA. ⁶University of Paris, INSERM U976, F-75006 Paris, France. ⁷Yale Center for Genome Analysis and Department of Genetics, Yale School of Medicine, New Haven, CT, USA. ⁸Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ⁹NIAID Clinical Genomics Program, NIH, Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ¹⁰Infection in Immunocompromised Pediatric Patients Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ¹¹Pediatric Infectious Diseases and Immunodeficiencies Unit, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Autonomous University of Barcelona (UAB), Barcelona, Catalonia, Spain. ¹²Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain. ¹³Diagnostic Immunology Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ¹⁴Immunology Division, Genetics Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Autonomous University of Barcelona (UAB), Barcelona, Catalonia, Spain. ¹⁵AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France. ¹⁶INSERM U1272, Hypoxia and Lung, Bobigny, France. ¹⁷Anesthesiology and Critical Care Medicine Department, AP-HP, Avicenne Hospital, Bobigny, France. ¹⁸Common and Rare Kidney Diseases, Sorbonne University, INSERM UMR-S 1155, Paris, France. ¹⁹Specialized Immunology Laboratory of Dr. Shahrooei, Sina Medical Complex, Ahvaz, Iran. ²⁰Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. ²¹Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²²Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²³Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²⁴Clinical 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. ²⁵Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²⁶Pediatric Infectious Diseases Unit, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ²⁷Department of Molecular Biology and Genetics, University of Bilkent, Bilkent-Ankara, Turkey. ²⁸Department of Biomedicine and Prevention, University of Rome "Tor Vergata," Rome, and Neuromed Institute, IRCCS, Pozzilli (IS), Italy. ²⁹Laboratory of Medical Genetics, Translational Cytogenomics Research Unit, Bambino Gesù Children Hospital, IRCCS, Rome, Italy. ³⁰Vita-Salute San Raffaele University, Milan, Italy. ³¹Clinical Genomics, IRCCS San Raffaele Scientific Institute, Milan, Italy. ³²San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) and Pediatric Immunohematology Unit and BMT Program, IRCCS San Raffaele Scientific Institute, Milan, Italy. ³³Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy. ³⁴Molecular Hematology Unit, IRCCS Ospedale San Raffaele, Milan, Italy. ³⁵Primary Immunodeficiencies Group, Department of Microbiology and Parasitology, School of Medicine, University of Antioquia UdeA, Medellín, Colombia. ³⁶Universidad de La Sabana, Chia, Colombia. ³⁷School of Microbiology, University of Antioquia UdeA, Medellín, Colombia. ³⁸Department of General Pediatrics, Hôpital Bichat, AP-HP, University of Paris Saclay, Le Kremlin-Bicêtre, France. ³⁹Department of Internal Medicine, Infanta Leonor University Hospital, Madrid, Spain. ⁴⁰Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain. ⁴¹Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Madrid, Spain. ⁴²CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST), Baldiri Reixac 4, 08028 Barcelona, Spain. ⁴³Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain. ⁴⁴Immunology Department, University Hospital 12 de Octubre, Research Institute Hospital 12 de Octubre (I+12), Madrid, Spain. ⁴⁵Complutense University, Madrid, Spain. ⁴⁶Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁴⁷Department of Clinical Sciences, University of Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁴⁸Genomics Division, Institute of Technology and Renewable Energies (ITER), Santa Cruz de Tenerife, Spain. ⁴⁹CIBER de Enfermedades Respiratorias, Health Institute of Carlos III, Madrid, Spain. ⁵⁰Research Unit, University Hospital of N.S. de Candelaria, Santa Cruz de Tenerife, Spain. ⁵¹Institute of Biomedical technologies (ITB), University of La Laguna, San Cristóbal de La Laguna, Spain. ⁵²Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, University Hospital "La Paz", Madrid, Spain. ⁵³Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. ⁵⁴Konya City Hospital, Division of Allergy and Immunology, Konya, Turkey. ⁵⁵Centre for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institute, Stockholm, Sweden. ⁵⁶Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institute, Stockholm, Sweden. ⁵⁷Immunodeficiency Unit, Infectious Disease Clinic, Karolinska University Hospital, Stockholm, Sweden. ⁵⁸Science for Life Laboratory, Department of Women's and Children's Health, Karolinska Institute, Solna, Sweden. ⁵⁹Central Hospital-Anesthesia and Intensive Care Unit, Karlstad, Sweden. ⁶⁰Department of Laboratory Medicine, Division of Biomolecular and Cellular Medicine, Karolinska Institute, Stockholm, Sweden. ⁶¹Department of Biosciences and Nutrition, Karolinska Institute, Stockholm, Sweden. ⁶²Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran. ⁶³Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. ⁶⁴Department of Immunology, Research Branch, Sidra Medicine, Doha, Qatar. ⁶⁵Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands. ⁶⁶Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁶⁷American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁶⁸Department of Infectious Diseases, San Gerardo Hospital—University of Milano-Bicocca, Monza, Italy. ⁶⁹Pediatric Department and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN, University of Milano, Bicocca-Fondazione MBM, Ospedale San Gerardo, Monza, Italy. ⁷⁰Centre d'Investigation Clinique, INSERM CIC 1425, Paris, France. ⁷¹Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁷²Université de Paris, IAME, INSERM UMR 1137, Paris, France. ⁷³Invitae, San Francisco, CA, USA. ⁷⁴Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁷⁵Center for the Study of Primary Immunodeficiencies, Necker Hospital for Sick Children, AP-HP, Paris, France. ⁷⁶Laboratory of Genetics and Genomics, Rockefeller University, New York, NY, USA. ⁷⁷Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁷⁸AP-HP, Hôpital Saint-Louis, Department of Immunology-Histocompatibility, 75010 Paris, France. ⁷⁹Howard Hughes Medical Institute, New York, NY, USA.

*Corresponding author. Email: casanova@rockefeller.edu (J.-L.C.); bebo283@rockefeller.edu (B.B.)

†These authors contributed equally to this work.

‡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.

found in samples drawn before infection in some patients (9), (ii) they were found in about 0.3% of the general population before the age of 65 years (9), (iii) they were absent from patients with asymptomatic or paucisymptomatic (mild) SARS-CoV-2 infection (9), (iv) they were of childhood onset in patients with various disorders—including autoimmune polyendocrinopathy type I—known to be at very high risk of life-threatening COVID-19 (16), and (v) they have been shown to underlie a third of adverse reactions to the live attenuated viral vaccine for yellow fever (17). Collectively, these studies showed that type I IFNs are essential for protective immunity to SARS-CoV-2 in the respiratory tract but are otherwise unexpectedly redundant. Auto-Abs against type I IFNs also provide a first explanation for both the biased sex ratio and the higher risk of critical COVID-19 in patients over the age of 65 years. Here, we tested the hypothesis that critical and unexplained COVID-19 pneumonia in men may be due to rare variants on the X chromosome.

RESULTS

Enrichment for very rare *TLR7* nonsynonymous variants in male patients

We tested the hypothesis of genetic homogeneity for X-linked recessive (XR) disorders in male individuals with critical COVID-19 pneumonia (hereafter referred to as “patients”; see Materials and Methods). We analyzed an international cohort of 1202 unrelated male patients aged 6 months to 99 years (mean, 52.9 years) that had no known inborn errors of TLR3- and IRF7-dependent type I IFN immunity (8) and without neutralizing auto-Abs against type I IFNs (9) [reported in an accompanying paper (18)] (table S1). We also analyzed 331 asymptomatic or paucisymptomatic infected male participants aged 1.3 to 102 years (mean, 38.7 years), with positive results for polymerase chain reaction (PCR) and/or serological screening for SARS-CoV-2 infection (hereafter referred to as “controls”) (table S1). We sequenced the exomes ($n = 1035$) or genomes ($n = 498$) of these patients and controls. We selected in-frame and out-of-frame nonsynonymous variants of protein-coding exons that are very rare, that is, with a minor allele frequency (MAF) below 10^{-4} in the full gnomAD database (v2.1.1) containing sequences from both male and female individuals. We compared the proportions of patients and controls carrying at least one qualifying variant, by Firth bias-corrected logistic regression adjusted for age and ethnicity (fig. S1A) (19). We found nonsynonymous variants in at least five patients for 226 of 731 genes on the X chromosome, resulting in a Bonferroni-corrected significance threshold of 2.2×10^{-4} (data file S1). *TLR7* was the highest ranked of these genes (uncorrected $P = 3.5 \times 10^{-5}$) and the only gene that remained significant after correction for multiple testing (corrected $P = 7.8 \times 10^{-3}$), with 21 unrelated patients carrying one very rare ($n = 4$ patients), two very rare ($n = 1$ patient), or one private ($n = 16$ patients) nonsynonymous variant (Fig. 1A and table S2). One variant (L988S) was recurrent, found in three patients, including a patient carrying two very rare variants (M854I and L988S). No such variants were found in the controls. The same analysis performed on very rare (MAF $< 10^{-4}$) synonymous *TLR7* variants showed no enrichment in patients (one carrier) relative to controls (three carriers).

Human TLR7 is an endosomal receptor of ribonucleic acids expressed by B cells and myeloid subsets (20–24), the stimulation of which in plasmacytoid dendritic cells (pDCs) results in the production of large amounts of type I IFN (25–27). We observed no

significant enrichment for coding nonsynonymous variants of the X-linked gene *TLR8* ($P = 0.68$; table S2), the product of which, TLR8, is endosomal and can be stimulated by some synthetic TLR7 agonists, with an expression pattern and signaling pathway overlapping those of TLR7 (28, 29). Unlike TLR7, TLR8 is expressed on granulocytes but not on pDCs, possibly accounting for its gain-of-function mutations underlying a phenotype different from type I interferonopathies (30–32). Overall, we found an enrichment in very rare or private nonsynonymous *TLR7* variants among the male patients with critical COVID-19 pneumonia ($n = 21$, 1.7%) of our cohort ($n = 1202$), including one man over the age of 60 years.

The *TLR7* mutant alleles of 16 of the 21 unrelated patients with critical COVID-19 pneumonia are biochemically deleterious

The 21 unrelated patients carried 20 different *TLR7* alleles. We expressed the 20 TLR7 mutant proteins in human embryonic kidney (HEK) 293T cells, which have no endogenous TLR7 and TLR8 expression (33), by transient transfection with the corresponding complementary DNAs (cDNAs). Immunoblotting of protein extracts with a TLR7-specific monoclonal Ab (mAb) showed an absence of TLR7 protein for p.N158Tfs*11 and p.L227fs* and the presence of truncated proteins for K684* and F670Lfs*8 (Fig. 1B). The other mutant TLR7 proteins were produced in normal amounts (Fig. 1B). We tested their function by cotransfection with a nuclear factor κ B (NF- κ B)-specific luciferase reporter. We measured luciferase activity upon stimulation with R848, an agonist of both TLR7 and TLR8 (Fig. 1C). Twelve of the 20 alleles were loss of function (LOF) (including L988S in two patients and M854I;L988S in another), three (p.L372M, p.I657T, and p.P715S) were hypomorphic ($< 25\%$ activity), and the remaining five were neutral (Fig. 1C and data file S2). Similar results were obtained with imiquimod and CL264, two TLR7-specific agonists (fig. S1, B and C). We also tested eight other private (p.S301P, p.Q710Rfs*18, and p.V795F), very rare (MAF $< 10^{-4}$; p.A288V), or rare (MAF between 10^{-4} and 10^{-2} ; p.V219I, p.A448V, p.R920K, and p.A1032T) *TLR7* variants previously reported in patients with critical COVID-19 (34, 35). These variants were expressed as truncated or full-length proteins (fig. S1D). The proteins encoded by the three private variants were found to be LOF, that encoded by the very rare variant (p.A288V) was hypomorphic, and those encoded by the four rare variants were neutral (Fig. 1C and fig. S1B). Collectively, these findings suggest that 16 of the 21 patients in our cohort (Table 1) and only 6 of the previously reported 12 patients carry deleterious *TLR7* variants.

The cumulative MAF of deleterious *TLR7* alleles is $< 6.5 \times 10^{-4}$

We also investigated the production and function of all 100 remaining nonsynonymous *TLR7* variants identified in the general population (141,456 individuals in gnomAD v2.1) that had been reported in men or had a general MAF of $> 10^{-5}$ (Fig. 1D, fig. S1E, and data file S2). In total, 96 of these variants were missense, and three were in-frame small deletions; 10 were weakly expressed, whereas the others had normal levels of expression (fig. S1F and data file S2). One variant was a small deletion creating a frameshift found in one man and resulting in an absence of protein production (fig. S1F and data file S2). Seven of the 100 variants were LOF, and 15 were hypomorphic ($< 25\%$ activity) (data file S2). There were, thus, 24 deleterious *TLR7* variants, including the L988S and A288V variants found

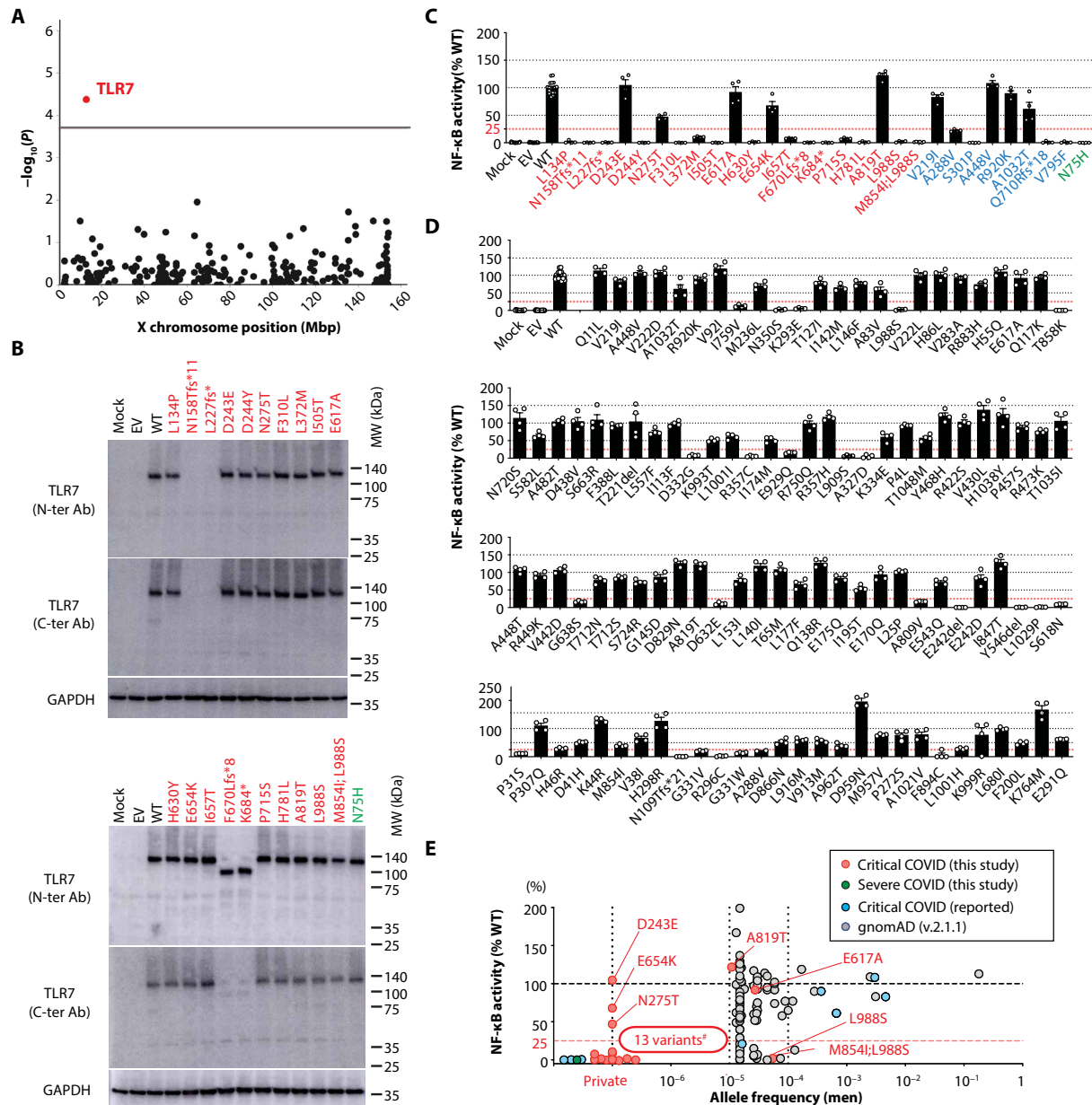


Fig. 1. Enrichment in rare *TLR7* deleterious alleles among men with critical COVID-19 pneumonia. (A) Manhattan plot showing the results of the variant enrichment test for the 190 genes of the X chromosome with at least five patients carrying nonsynonymous variants. The gray line indicates the corresponding Bonferroni-corrected significance threshold. (B) Western blot of extracts from nontransfected HEK293T cells (mock), HEK293T cells transfected with pCMV6 empty vector (EV), the WT *TLR7* allele, or one of the *TLR7* variant alleles of interest. All extracts were probed with mAbs specific for the leucine-rich repeats to the N terminus (N-ter) or amino acid 1000 to the C terminus (C-ter) within the human *TLR7* protein. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MW, molecular weight. (C and D) Luciferase assay on HEK293T cells transfected with the pGL4.32 luciferase reporter construct and an expression vector for *Renilla* luciferase together with no vector (mock), EV, WT, or *TLR7* variants: (C) 21 variants found in our cohort and eight previously reported variants and (D) 109 variants found in male individuals from the gnomAD database. After 24 hours, transfected cells were left untreated or were treated by incubation with R848 (1 μ g/ml) for 24 hours. These data were established from two independent experiments. The y axis represents NF- κ B transcriptional activity as a percentage of the WT. The x axis indicates the alleles used for transfection. (E) Diagram showing the correlation between allele frequency and NF- κ B activity (percentage of WT). The 20 variants from 21 patients with critical SARS-CoV-2 from our cohort are shown in red, one variant from two patients with severe SARS-CoV-2 from our cohort are shown in green, the eight previously reported variants are shown in blue and the 109 variants found in the general population (allele frequency above 10^{-5} in men) are shown in gray. Activity of all LOF/hypomorphic alleles compared with WT allele was statistically significant [one-way analysis of variance (ANOVA) with Dunnett's post hoc test, $P < 0.01$].

in four patients with critical COVID-19 pneumonia. Each of these 24 deleterious variants had an individual MAF of $<1.3 \times 10^{-4}$ in men, and their cumulative MAF in men was 6.5×10^{-4} (data file S2 and table S3). The cumulative MAF of strictly LOF *TLR7* alleles (excluding

hypomorphic alleles) in men is about 2.2×10^{-4} (data file S2). Overall, we found 12 LOF and 3 hypomorphic *TLR7* alleles in 16 unrelated men with critical COVID-19 pneumonia, whereas deleterious alleles were not found in men with asymptomatic or paucisymptomatic

Table 1. X-linked *TLR7* deleterious variants in 16 unrelated male patients with life-threatening COVID-19 pneumonia. GME Variome, Greater Middle Eastern Variome Project.

Patient	Genotype	Age (years)	Ethnicity	Ancestry/residence	Outcome
P1	L134P/Y	45	Admixed American	Paraguay/Spain	Survived
P2	N158Tfs11*/Y	60	European	France	Deceased
P3	L227fs*/Y	34	Middle East	Iran	Survived
P4	D244Y/Y	13	Middle East	Turkey	Survived
P5	F310L/Y	39	Middle East	Iran	Survived
P6	L372M	7	Caucasian (Central Asia based on GME Variome)	Iran	Survived
P7	I505T/Y	55	European	Italy	Survived
P8	H630Y/Y	50	European	Spain	Survived
P9	I657T/Y	18	European	Italy	Survived
P10	F670Lfs*8	31	European	Sweden	Survived
P11*	F670Lfs*8	29	European	Sweden	Survived
P12	K684*/Y	30	European	Spain	Survived
P13	P715S/Y	40	Latino	Colombia	Survived
P14	H781L/Y	13	Middle East	Russia/France	Survived
P15	L988S/Y	26	Middle East	Iran	Deceased
P16	L988S/Y	20	Middle East	Turkey	Survived
P17	M854I;L988S/Y	71	European	Italy	Survived

*P10's brother (not included in the cohort of 1202 critical patients with critical COVID-19 pneumonia).

infection. Moreover, deleterious *TLR7* alleles in the general population had individual and cumulative MAF values in men of $<1.3 \times 10^{-4}$ and $<6.5 \times 10^{-4}$, respectively (Fig. 1E and data file S2). The rarity of *TLR7* deficiency in the general population is consistent with *TLR7* deficiency underlying critical COVID-19. Collectively, these findings suggest that XR *TLR7* deficiency is a genetic etiology of life-threatening COVID-19 pneumonia in men.

High clinical penetrance of inherited *TLR7* deficiency in the patients’ families

The 16 patients were of three major ethnic origins, as confirmed by principal components analysis (PCA) of their exomes or genomes (36), and they were resident in seven countries (France, $n = 2$; Spain, $n = 3$; Italy, $n = 3$; Turkey, $n = 2$; Sweden, $n = 1$; Iran, $n = 4$; Colombia, $n = 1$) (Fig. 2, A and C; Table 1; fig. S1; and data file S3). The patients were hospitalized for critical COVID-19 between March 2020 and June 2021. Blood samples (diluted 1:10) from these 16 patients contained no auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml) (9, 18). The patients were aged 7 to 71 years, and their mean age was lower than that of the total cohort (mean age of 34.4 years versus 52.9 years for the total cohort, in which age ranged from 0.5 to 99 years). *TLR7*-deficient patients accounted for about 1.8% of the patients below the age of 60 years (15 patients) and 1.3% of the entire cohort (16 patients). Two patients died and 14 survived (Fig. 2A and Table 1). Sanger sequencing of the *TLR7* locus in the relatives of these patients identified the deleterious alleles in 16 heterozygous women from 11 families and 7 hemizygous men from seven families (Fig. 2A). On the basis of the 10 DNA samples available from the patients’ mothers, only one of the *TLR7* variants (L372M) was de novo in the index case. Five of the seven hemizygous relatives of the index cases had Abs

against SARS-CoV-2 (Fig. 2A and data file S3). One 29-year-old adult (kindred J, P11) was hospitalized for critical pneumonia, and another 27-year-old adult (L.II.3) was hospitalized for severe pneumonia [with low-flow oxygen (<6 liter/min)]. The remaining three were two 5-year-old boys, one of whom had been hospitalized for moderate COVID-19 pneumonia (without oxygen therapy) (D.II.2) and the other having no relevant clinical history (M.II.2), and one 38-year-old adult with no relevant clinical history (E.II.4) (data file S3). The other two male carriers did not report SARS-CoV-2 infection and had negative serological results for Abs against the SARS-CoV-2 S and N proteins.

Inherited *TLR7* deficiency in patients with severe COVID-19 pneumonia

Given these results, we also analyzed 262 other, unrelated male patients with severe (but not critical) COVID-19 pneumonia (mean age, 51.0 years). We identified a new private LOF variant (p.N75H) in two male patients from two Turkish families (P18 and P19), aged 12 and 7 years, respectively, who were subsequently found to be fourth-degree relatives (Figs. 1, B to D, and 2B; fig. S1B; and data files S2 and S3). Their mothers are heterozygous for this variant. The clinical penetrance of critical COVID-19 in men is therefore high, but not complete, and *TLR7* deficiency can also underlie severe COVID-19. The absence of biochemically deleterious *TLR8* variants in our cohort of patients with critical COVID-19 (fig. S2) and its lack of expression on pDCs suggest that *TLR8* is not a modifier of the SARS-CoV-2–related clinical phenotype of *TLR7* deficiency, although it is adjacent to *TLR7* on the X chromosome and can be stimulated by overlapping molecules. Perhaps more relevant to the understanding of the incomplete penetrance is the age of the patients. Of the 23 male

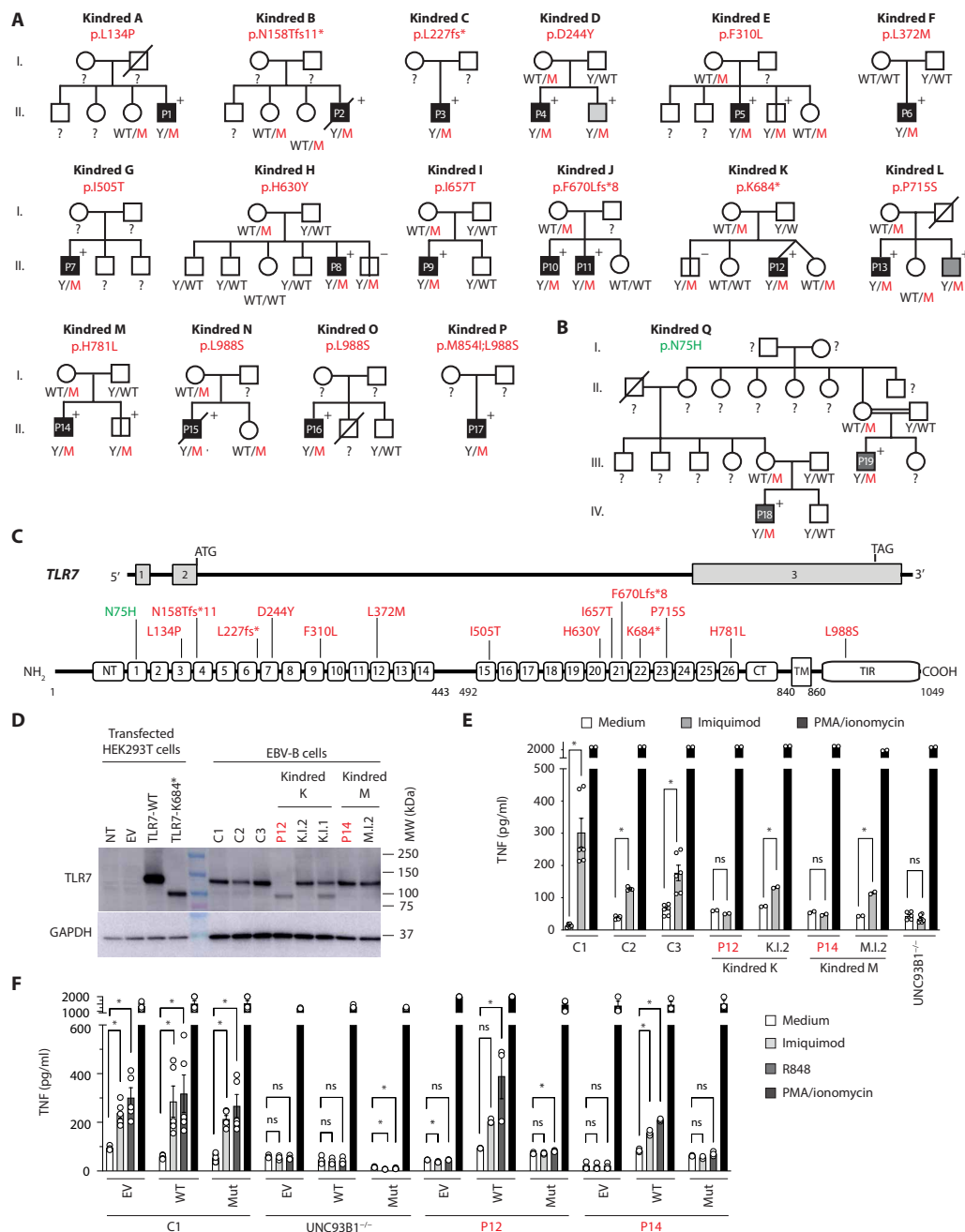


Fig. 2. XR TLR7 deficiency in 16 kindreds. (A) Pedigrees of the 16 kindreds containing 17 patients with life-threatening COVID-19 pneumonia (P1 to P17) bearing deleterious *TLR7* alleles. The mutations are indicated above each pedigree. Solid black symbols indicate patients with critical COVID-19, solid dark gray symbols indicate severe cases, and solid light gray symbols indicate mild/moderate cases. The genotype is indicated under each symbol, with M corresponding to the mutation found in each kindred. "+" and "-" indicate the presence and absence, respectively, of Abs against SARS-CoV-2 in the serum of the individual. Asymptomatic or paucisymptomatic family members hemizygous for the mutation are indicated by bold vertical lines. (B) Pedigree of one kindred containing two patients with severe COVID-19. (C) Schematic representation of *TLR7*. The upper part represents the genomic organization of the *TLR7* locus, with rectangles for the various exons of the gene, and exon numbers indicated within the rectangle. The bottom part shows the primary structure of *TLR7*. The N-terminal portion and the leucine-rich repeat containing 26 leucine residues are located in the lumen of the endosome, and TM indicates the transmembrane domain. The Toll/IL-1 receptor (TIR) domain is cytoplasmic. The deleterious mutations reported in this study are indicated. (D) TLR7 expression in unstimulated EBV-B cells from two patients with XR TLR7 deficiency (P12 and P14), the fathers of P12 and P14, and the mother of P12, and three healthy donors (controls 1 to 3), determined by Western blotting with detection with a specific TLR7 Ab. (E) TNF production by XR TLR7-deficient EBV-B cells from two independent experiments. Cells were either left untreated or were stimulated with imiquimod (5 µg/ml; gray) or PMA (25 ng/ml) and 0.25 µM ionomycin (black) for 24 hours, and TNF production were measured by ELISA. (F) TNF production in XR TLR7-deficient EBV-B cells reexpressing WT TLR7 from three independent experiments. EBV-B cells from a control, P12, P14, or an UNC-93B-deficient patient, cultured in the presence of IRAK4 inhibitor (PF06650833; 5 µM) were transduced with lentiviral particles that were empty or contained the WT TLR7 or mutant TLR7 cDNA. The cells were incubated for 24 hours without IRAK4 inhibitor and were then left untreated or were stimulated with imiquimod (5 µg/ml; light gray), R848 (1 µg/ml; dark gray), or PMA (25 ng/ml) and 0.25 µM ionomycin (black) for 24 hours, and TNF production were measured by ELISA. Statistical tests were performed using one-way ANOVA with Dunnett's post hoc test (*P < 0.05; ns, not significant).

patients carrying deleterious alleles of *TLR7* infected with SARS-CoV-2, the 20 patients who developed severe ($n = 3$) or critical ($n = 17$) COVID-19 were aged 7 to 71 years (mean, 32.4 years), whereas the three patients who developed asymptomatic, mild, or moderate infection were younger: 5, 5, and 38 years (mean, 16 years). Blood pDC counts decrease with age (37–39), and this may contribute to the apparent increase in penetrance with age. In addition, a VirScan study of the serum samples of five index cases and three *TLR7* hemizygous relatives revealed prior infection with diverse viruses (fig. S3). None had previously been hospitalized for a severe viral illness, including influenza pneumonia. This cohort of patients thus suggests that *TLR7* deficiency does not underlie severe disease caused by common viral infections other than SARS-CoV-2, or if so, with lower penetrance.

Deleterious *TLR7* alleles abolish B cell responses to *TLR7* agonists

As a first approach to testing the impact of deleterious *TLR7* alleles in the patients' cells, we tested Epstein-Barr virus-transformed B cell lines (EBV-B cells) from healthy controls and patients carrying the hemizygous p.K684* (P12) or p.H781L (P14) variants. The endogenous expression of the p.H781L *TLR7* protein was normal, whereas p.K684* generated a truncated protein (Fig. 2D). In response to agonists of *TLR7* (imiquimod) or *TLR7* and *TLR8* (R848), the EBV-B cell lines carrying these two mutations failed to produce tumor necrosis factor (TNF; Fig. 2E and fig. S4, A and B). The lentiviral transduction of these *TLR7*-deficient EBV-B cells (from P12 and P14) with a wild-type (WT) *TLR7* cDNA was unsuccessful, despite numerous attempts, and this was also the case for control EBV-B cells, perhaps because the overproduction of *TLR7* is toxic in B cells (40). Consistent with this view, we were able to express this cDNA in interleukin-1 (IL-1) receptor-associated kinase 4 (IRAK4)- or myeloid differentiation factor 88 (MyD88)-deficient EBV-B cells. We therefore investigated whether the addition of an IRAK4 inhibitor (PF06650833) would permit the expression of WT *TLR7* in control and *TLR7*-mutated EBV-B cells. This approach was successful, and WT *TLR7* expression restored responses to *TLR7* agonists (after removal of the inhibitor) (Fig. 2F and fig. S4C). Hemizygosity for LOF *TLR7* alleles thus abolished responses to *TLR7* stimulation in EBV-B cells, a phenotype that was rescued by WT *TLR7* expression. Collectively, these findings further suggest that XR *TLR7* deficiency is a genetic etiology of severe/critical COVID-19 pneumonia.

The *TLR7*-mutated patients' myeloid cells, including pDCs, do not respond to *TLR7* agonists

Human *TLR7* is known to be expressed and functional only in leukocyte subsets: plasmacytoid and myeloid DCs [pDCs and myeloid (mDCs)], monocytes (classical, intermediate, and nonclassical), and B cells (28, 33, 41). *TLR8* is expressed in mDCs but not pDCs, monocytes but not B cells, and neutrophils (unlike *TLR7*) (28, 33, 41). Neither *TLR7* nor *TLR8* mRNAs have been detected in the lung or pulmonary epithelial cells (42). Deep immunophenotyping by cytometry by time-of-flight in seven patients with *TLR7* deficiency revealed no major abnormalities in 18 peripheral blood leukocyte subsets, including pDCs, mDCs, monocytes, and B cells (Fig. 3A and fig. S5A). We previously reported inherited IRF7 deficiency in a child with critical influenza pneumonia (5) and two unrelated adults with critical COVID-19 pneumonia (8). This defect disrupts the amplification of type I IFNs in all cell types, including pDCs, which are normally the main

producers of type I IFN upon blood cell stimulation with *TLR7* agonists or viruses, due to their constitutive expression of IRF7 (28, 43–45). We hypothesized that *TLR7* deficiency in pDCs impairs the production of type I IFN by these cells in response to single-stranded RNA. We confirmed that *TLR7* was expressed on pDCs and that *TLR8* was not (Fig. 3B and fig. S5, B and C). We measured the production of type I IFNs by purified leukocyte subsets (pDCs, mDCs, monocytes, B cells, and T cells), in response to *TLR7*, *TLR8*, and *TLR9* agonists (Fig. 3C and fig. S5D). We confirmed that pDCs produced 100 to 1000 times more type I IFN per cell than other leukocyte subsets upon *TLR7* stimulation (Fig. 3C and fig. S5D). We purified pDCs from P8 and P14 and analyzed their production of type I IFNs in response to CL264 and class C CpG oligonucleotide (CpG-c), relative to that of pDCs from healthy relatives, using a cytometric bead array (CBA) (Fig. 3D). pDCs from P8 and P14 did not produce type I IFNs (or IL-6) upon stimulation with a *TLR7* agonist, whereas they responded to a *TLR9* agonist (Fig. 3D). Moreover, agonist-induced up-regulation of programmed death ligand 1 (PD-L1) and CD80 defines the maturation of pDCs into the S1 (PD-L1^{high}/CD80^{low}), S2 (PD-L1^{high}/CD80^{high}), and S3 (PD-L1^{low}/CD80^{high}) subsets (46). This maturation was not observed in the pDCs of P8 and P14 but was detected in the pDCs of healthy relatives and controls (Fig. 3E and fig. S5E). Thus, pDCs from patients with *TLR7* mutations do not respond to *TLR7* agonists in terms of maturation into specialized subsets and type I IFN production.

The *TLR7*-deficient patients' pDCs respond poorly to SARS-CoV-2

A plausible mechanism accounting for the severity of COVID-19 in *TLR7*-deficient patients is the impairment of type I IFN production by pDCs upon stimulation with SARS-CoV-2, which can enter these cells but cannot replicate productively within them (46, 47). We previously showed that the activation of human pDCs by SARS-CoV-2 depends on IRAK4 and UNC-93B but not *TLR3* (46). We tested the hypothesis that *TLR7* is an essential pDC sensor of SARS-CoV-2, upstream from IRAK4 and UNC-93B, by infecting pDCs and pDC-depleted leukocytes from healthy controls and *TLR7*-deficient patients with SARS-CoV-2 for 24 hours. Control pDC-depleted leukocytes infected with SARS-CoV-2 displayed no significant up- or down-regulation of gene expression (fig. S6A). By contrast, transcriptomic analysis showed a strong up-regulation of the type I IFN transcriptional module in pDCs from healthy controls, which was greatly reduced in pDCs from *TLR7*-deficient patients (Fig. 4A). Induction of the 17 type I IFN genes in pDCs from *TLR7*-deficient patients was 10 to 100 times weaker than that in pDCs from healthy individuals (Fig. 4B and fig. S6B). We also analyzed the functional specialization of pDC subsets (S1, S2, and S3 pDC subsets) in response to SARS-CoV-2 activation (46, 48). pDCs from P14 cultured with SARS-CoV-2 for 24 hours displayed abnormally low levels of maturation into the S1 subset, the pDC subset principally responsible for IFN- α production upon SARS-CoV-2 infection (fig. S6C). Last, we evaluated the amount of type I IFNs secreted by SARS-CoV-2-infected pDCs. All 13 individual IFN- α forms were produced in significantly smaller amounts by *TLR7*-deficient pDCs than by control pDCs (Fig. 4C and fig. S6D). However, IFN- α production by *TLR7*-deficient pDCs upon SARS-CoV-2 infection was impaired but not entirely abolished, as in UNC-93B- or IRF7-deficient pDCs (8, 46), implying that there are also *TLR7*-independent sensors of SARS-CoV-2 in pDCs and suggesting that *TLR9* is involved. The

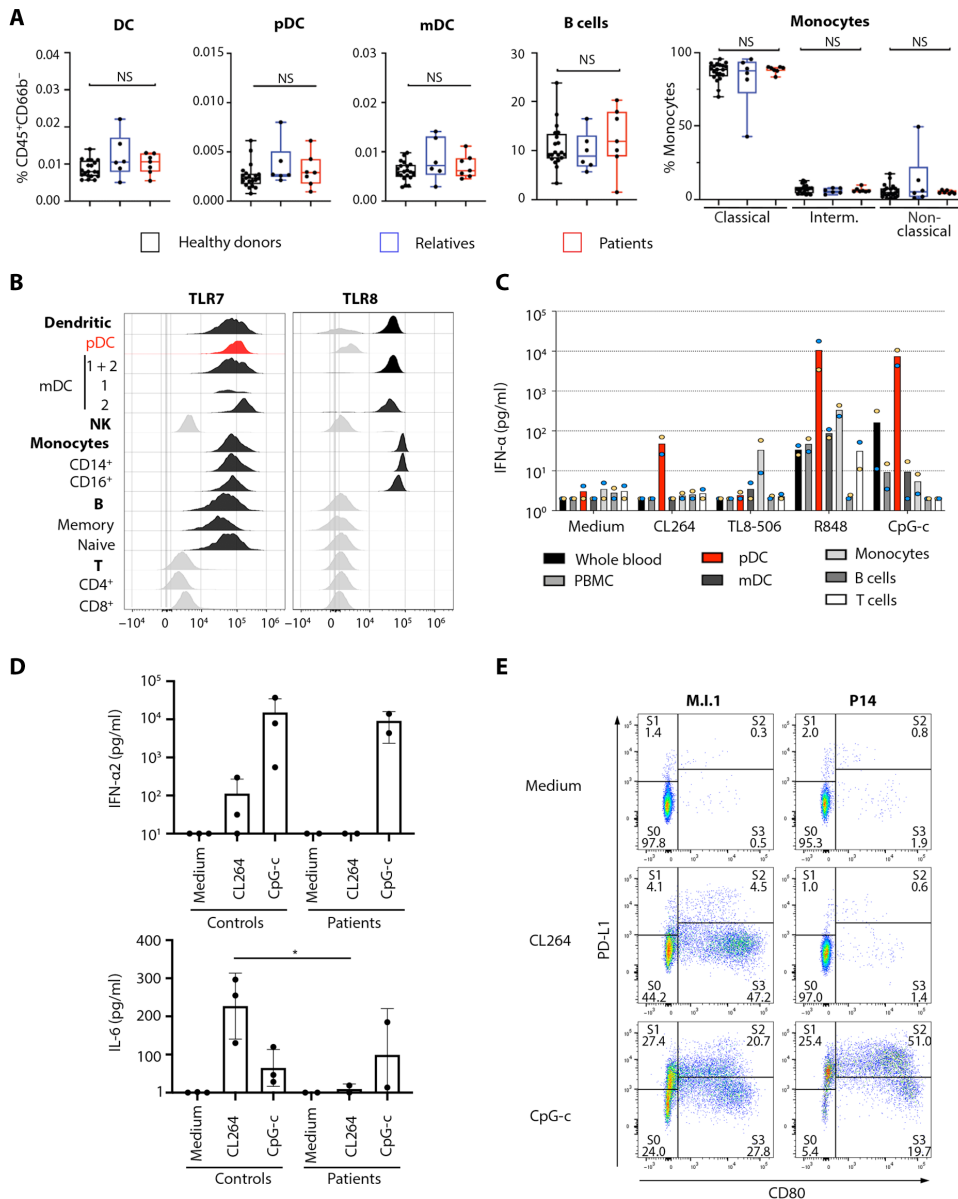


Fig. 3. Type I IFN responses to TLR7 agonist in TLR7-deficient pDCs and leukocytes. (A) Frequencies of five leukocyte subsets in whole blood, determined by CyTOF. Healthy donors (black rectangles), relatives not carrying deleterious *TLR7* alleles (blue rectangles) and hemizygous *TLR7* variant carriers (red rectangles) are depicted. (B) TLR7 and TLR8 expression in different leukocyte subsets, determined by flow cytometry for the healthy control (C1). The result for another healthy control (C2) is shown in fig. S5C. Gating strategy for the classification in each cell subset is shown in data file S6. NK, natural killer. (C) IFN-α production in purified leukocyte subsets from two healthy donors (blue or yellow dot) with and without stimulation with various TLR7, TLR8, or TLR9 agonists [CL264 (1 μg/ml), TL8-506 (100 ng/ml), R848 (1 μg/ml), or 2 μM CpG-c] for 24 hours. The y axis shows IFN-α production on a logarithmic scale. The red bar corresponds to pDCs. (D) pDCs isolated from healthy donors and TLR7-deficient patients (P8 and P14) were either left untreated (medium) or were stimulated with CL264 or CpG-c, and the production of IFN-α2 and IL-6 was assessed with CBAs on the supernatant. (E) Dot plot showing pDC diversification into subsets S1, S2, and S3 from magnetically sorted blood. pDCs from a TLR7-deficient patient (P14) and a healthy relative (M.I.1) were cultured for 24 hours with medium alone or with CL264 (1 μg/ml) or 2 μM CpG-c. Statistical tests were performed using unpaired two-sample t test (**P* < 0.05).

TLR7-deficient pDCs' normal response to TLR9 agonists (Figs. 3D and 4, A and B, and fig. S6D) is consistent with this hypothesis, while also suggesting that genetic or epigenetic variations of TLR9 responses may contribute to the apparently age-dependent penetrance of TLR7

deficiency. Thus, SARS-CoV-2 triggers type I IFN induction in pDCs in a manner that is dependent on TLR7, but not exclusively so. Because pDCs are normally the main leukocytes producing type I IFN under such conditions and type I IFN is essential for protective immunity to SARS-CoV-2 (8, 9), these findings suggest that XR TLR7 deficiency underlies critical or severe COVID-19 pneumonia by disrupting TLR7- and pDC-dependent type I IFN production.

DISCUSSION

We report XR TLR7 deficiency as a genetic etiology of severe/critical COVID-19 pneumonia in 20 unrelated male patients, aged 7 to 71 years, from seven countries. Only one of these 20 patients (5%) was older than 60 years, consistent with our previous observation that only 5 of 23 patients (21.7%) with inborn errors of TLR3-dependent type I IFN immunity were older than 60 years (8). This suggests that these genetic defects are mostly found in the youngest patients. This contrasts with the situation for auto-Abs against type I IFNs, which are found mostly in patients over the age of 60 years (8, 9, 18). Patients with these auto-Abs do not overlap with those bearing inborn errors of TLR3- or TLR7-dependent type I IFNs. TLR7-deficient patients accounted for about 1.8% of the unrelated male patients with critical COVID-19 pneumonia below the age of 60 years in our cohort and accounted for 1.3% of the total cohort. This proportion remained around the same when severe COVID-19 pneumonia was also taken into account (1.7% males below 60 years; 1.2% of all the male patients in the total cohort). We also found that six of the 12 previously reported patients with a *TLR7* variant had TLR7 deficiency (34, 35). It would be interesting to test experimentally the undisclosed *TLR7* variants reported to be enriched in another study (49). Our discovery provides an explanation for the higher risk of severe and critical disease in men than in women under the age of 60 years, complementing our previous observation of a much higher frequency of neutralizing auto-Abs against type I IFNs in men than in women with critical COVID-19 pneumonia for patients over the age of 60 years (9).

Previous reports of patients with critical COVID-19 pneumonia due to inborn errors of TLR3-dependent type I IFN immunity (8),

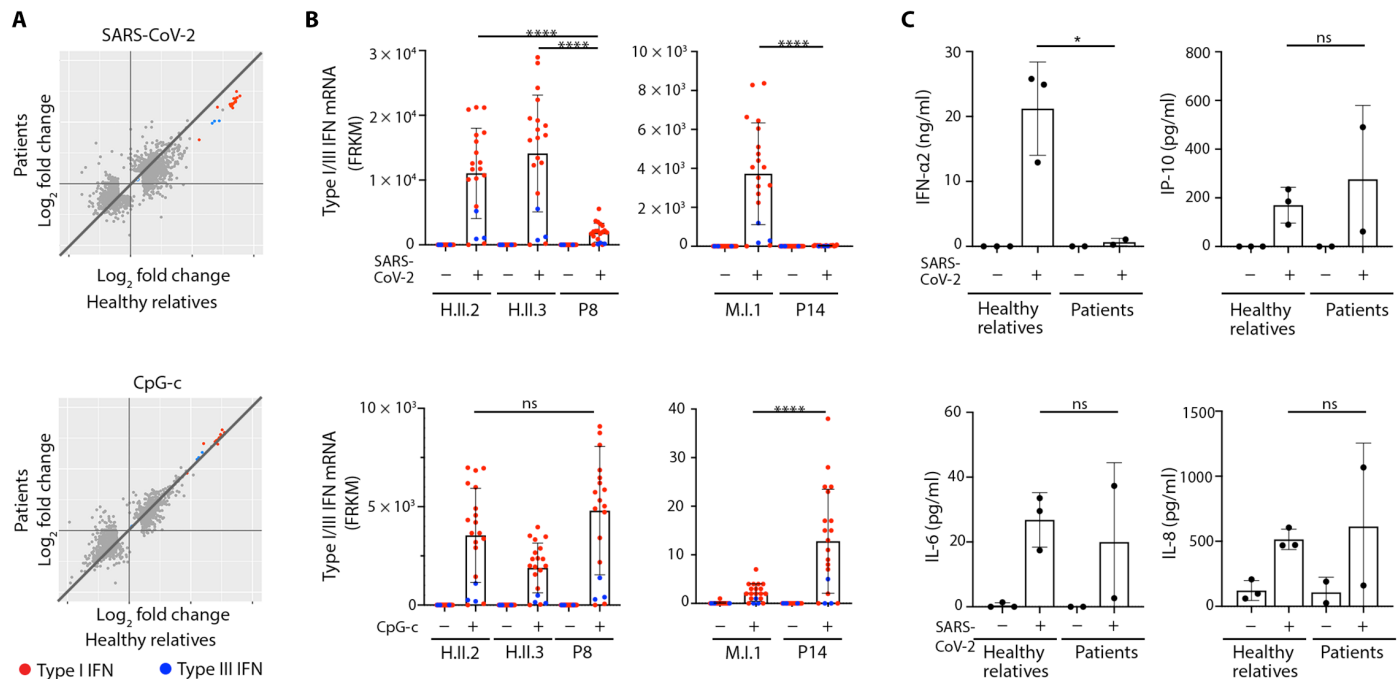


Fig. 4. Type I IFN responses to SARS-CoV-2 infection in TLR7-deficient pDCs. (A) pDCs isolated from healthy relatives and TLR7-deficient patients (P8 and P14) were either left untreated or were infected with SARS-CoV-2 for 24 hours. RNA profiles were then determined by RNA-seq. Genes with an expression of >2.0-fold higher or lower in controls after stimulation or infection are plotted as the fold change in expression. (B) Induction of the type I and III IFN genes from (A) infected with SARS-CoV-2 for 24 hours (top) or stimulated with CpG-c (bottom). (C) pDCs isolated from healthy relatives and TLR7-deficient patients (P8 and P14) were either left untreated or were infected with SARS-CoV-2 for 24 hours, and the production of IFN-α2, IP-10, IL-6, and IL-8 was measured with CBAs on the supernatant. Statistical tests were performed using unpaired two-sample *t* test (**P* < 0.05 and *****P* < 0.0001).

including autosomal recessive IRF7 or IFNAR1 deficiency (5, 6), or due to auto-Abs neutralizing type I IFNs (9, 11–14, 16, 17), strongly suggest that critical disease in TLR7-deficient patients is a consequence of impaired type I IFN production upon SARS-CoV-2 infection. The absence of biochemically deleterious X-linked *TLR8* variants in our cohort of patients suggests that TLR8 is not essential for host defense against SARS-CoV-2. This is consistent with the modest capacity of TLR8 to induce type I IFN and its lack of expression on pDCs (28) and with the inflammatory phenotype of TLR8 gain-of-function mutations, which do not underlie a type I interferonopathy (30–32). Patients with inherited IRAK4 or MyD88 deficiency, whose cells do not respond to the stimulation of IL-1Rs and TLRs other than TLR3, including TLR7, have not been reported to display any severe viral illness over the almost 20 years since the discovery of IRAK-4 deficiency (50–53). Moreover, UNC-93B-deficient pDCs produced normal amounts of type I IFN in response to seasonal influenza virus (5). This was intriguing, as strong negative selection operates at the human *TLR7*, *TLR8*, and *TLR9* loci (50, 54). Our study provides an answer to this riddle, by establishing that TLR7 is essential for protective immunity to SARS-CoV-2. Patients with IRAK4, MyD88, or UNC-93B deficiency are now predicted to be vulnerable to SARS-CoV-2 (55–57). Critical COVID-19 and seasonal influenza can be caused by inborn errors of TLR3-dependent type I IFN immunity (5–8), but susceptibility to these infections is not allelic at the *TLR7* locus. It is, nevertheless, tempting to speculate that TLR7 might also be essential for host defense against more virulent, pandemic viruses, including both coronavirus and influenza viruses.

Through the discovery of the essential nature of TLR7 for the induction of type I IFN in response to SARS-CoV-2, our study also reveals the essential function of human pDCs in host defense. The constitutively high levels of IRF7 in these cells make them the most potent producers of type I IFN in the blood, and perhaps in the entire human body, and this has long suggested a possible key role in antiviral immunity (26). However, the essential and redundant roles of this leukocyte subset have yet to be determined, in the absence of human pDC-specific deficiencies causally underlying a clinical phenotype. It has long been suspected, but never proved, that pDCs are essential for host defense under natural conditions (27, 58–60). Inherited IRF7 deficiency, which underlies critical influenza or COVID-19 pneumonia, disrupts the production of type I IFNs not only by pDCs (5, 8) but also by all other cell types, including pulmonary epithelial cells (5). Likewise, patients with GATA2 deficiency, who are prone to critical influenza (61), lack pDCs, but these patients also lack many other blood cell subsets (62–65). Inherited IFNAR1 deficiency underlies critical COVID-19 probably due to its broad cellular impact (5, 6, 8). By contrast, inborn errors of the TLR3 pathway underlie critical influenza or COVID-19 pneumonia by impairing the production of type I IFNs by cells other than pDCs, such as pulmonary epithelial cells (5–8, 66). Our study indicates that pulmonary epithelial cells are not sufficient for host defense against SARS-CoV-2, as these cells do not express TLR7. Inborn errors of TLR7 are pathogenic by impairing the production of type I IFNs by blood pDCs, which are unique in their production of large amounts of both TLR7 and IRF7 (67, 68). pDCs express other viral sensors, including TLR9 (for DNA), melanoma differentiation-associated protein 5 (MDA5), and retinoic

acid-inducible gene I (RIG-I) (for double-stranded RNA) (69), but TLR7 deficiency impairs their capacity to produce large enough amounts of type I IFN in response to SARS-CoV-2 in the respiratory tract. Overall, by disrupting pDC-dependent type I IFN production, XR TLR7 deficiency accounts for at least 1% of cases of life-threatening COVID-19 pneumonia in men under 60 years.

MATERIALS AND METHODS

Study design

We searched for X-linked inborn errors of immunity in male patients with critical SARS-CoV-2 pneumonia. We screened our whole-exome sequencing (WES) database of 1202 male patients with critical SARS-CoV-2 pneumonia (patients) and 331 male participants with asymptomatic or paucisymptomatic infection (controls). We tested the association of X-linked genes with critical SARS-CoV-2 pneumonia using a Firth bias-corrected logistic regression model including the first five principal components of the PCA to account for the ethnic heterogeneity of the cohorts and age in years. We then tested the activity of *TLR7* variants in transduced cell lines and of *TLR7* genotypes in hemizygous patients' cell lines. Last, we tested the patients' pDCs for their response to both TLR7 agonists and SARS-CoV-2.

Cohort recruitment and consent

This study included 1202 male patients with life-threatening COVID-19 pneumonia, defined as patients with pneumonia who developed critical disease, whether pulmonary with high-flow oxygen (>6 liter/min) or mechanical ventilation [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), and intubation], septic shock, or any other type of organ damage requiring intensive care unit admission. This study also included patients with severe COVID-19 pneumonia, defined as hospitalized patients with pneumonia that required low-flow oxygen (<6 liter/min); moderate COVID-19 pneumonia, defined as patients with pneumonia but did not require oxygen therapy; and mild COVID-19, defined as patients with mild upper respiratory symptoms but without pneumonia. Patients who developed Kawasaki-like syndrome were excluded. The age of the patients ranged from 0.5 to 99 years, with a mean age of 52.9 years (SD, 16.4 years). Asymptomatic or paucisymptomatic individuals ($n = 331$) were recruited on the basis of positive PCR or serological tests for SARS-CoV-2 in the absence of symptoms. These individuals were close contacts of patients or were recruited after clinical screening. The age of the asymptomatic or paucisymptomatic individuals ranged from 1.3 to 102 years, with a mean age of 38.7 years (SD, 17.2 years).

All the enrolled participants provided written informed consent and were collected through protocols conforming to local ethics requirements. For patients enrolled in the French COVID cohort (ClinicalTrials.gov NCT04262921), ethics approval was obtained from the Comité de Protection des Personnes Ile De France VI (ID RCB, 2020-A00256-33) or the Ethics Committee of Erasme Hospital (P2020/203). For participants enrolled in the COV-Contact study (ClinicalTrials.gov NCT04259892), ethics approval was obtained from the CPP IDF VI (ID RCB, 2020-A00280-39). For patients enrolled in the Italian cohort, ethics approval was obtained from the University of Milano-Bicocca School of Medicine, San Gerardo Hospital, Monza—Ethics Committee of the National Institute of Infectious Diseases Lazzaro Spallanzani (84/2020) (Italy), and the Comitato Etico Provinciale (NP 4000—Studio CORONALab). STORM-Health care workers were enrolled in the STudio OsseRvazionale sullo screening

dei laboratori ospedalieri per COVID-19 (STORM-HCW) study, with approval from the local institutional review board (IRB) obtained on 18 June 2020. Patients and relatives from San Raffaele Hospital (Milan) were enrolled in protocols COVID-BioB/Gene-COVID and, for additional studies, TIGET-06, which were approved by local ethical committee. For patients enrolled in Spain, the study was approved by the Committee for Ethical Research of the Infanta Leonor University Hospital, code 008-20; Committee for Ethical Research of the University Hospital 12 de Octubre, code 16/368; the Bellvitge University Hospital, code PR127/20; the University Hospital of Gran Canaria Dr. Negrín, code 2020-200-1 COVID-19; and the Vall d'Hebron University Hospital, code PR(AMI)388/2016. Anonymized samples were sequenced at the National Institute of Allergy and Infectious Diseases (NIAID) through Uniformed Services University of the Health Sciences (USUHS)/the American Genome Center (TAGC) under nonhuman subject research conditions; no additional IRB consent was required at the National Institutes of Health (NIH). For patients enrolled in the Swedish COVID cohort, ethics approval was obtained from the Swedish Ethical Review Agency (2020-01911 05).

Next-generation sequencing

Genomic DNA was extracted from whole blood. For the 1533 patients included, the whole exome ($n = 1035$) or whole genome ($n = 498$) was sequenced at several sequencing centers, including the Genomics Core Facility of the Imagine Institute (Paris, France), the Yale Center for Genome Analysis (USA), the New-York Genome Center (NY, USA), and TAGC (USUHS, Bethesda, USA), and the Genomics Division—Institute of Technology and Renewable Energies (ITER) of the Canarian Health System sequencing hub (Canary Islands, Spain).

For WES, libraries were generated with the Twist Bioscience kit (Twist Human Core Exome Kit), the xGen Exome Research Panel from Integrated DNA Technologies (IDT; xGen), the Agilent SureSelect V7 Kit or the SeqCap EZ MedExome Kit from Roche, and the Nextera Flex for Enrichment-Exome kit (Illumina). Massively parallel sequencing was performed on a HiSeq 4000 or NovaSeq 6000 system (Illumina). For WES analysis performed at Centro Nacional de Análisis Genómico (CNAG) Barcelona, Spain, capture was performed with the SeqCap EZ Human Exome Kit v3.0 (Roche Nimblegen, USA), and 100–base pair (bp) paired-end read sequences were obtained on a HiSeq 2000–4000 platform (Illumina Inc. USA). For the Ospedale San Raffaele (OSR) Italian cohort, WES was performed with the Agilent SureSelect V7 Kit on a NovaSeq6000 system (Illumina).

For whole-genome sequencing of patients from the Italian cohort (TAGC), genomic DNA samples were dispensed into the wells of a Covaris 96 microTUBE plate (1000 ng per well) and sheared with the Covaris LE220 Focused-ultrasonicator, at settings targeting a peak size of 410 bp [t , 78; duty, 18; Peak Incident Power (PIP), 450; 200 cycles]. Sequencing libraries were generated from fragmented DNA with the Illumina TruSeq DNA PCR-Free HT Library Preparation Kit, with minor modifications for automation (Hamilton STAR Liquid Handling System), with IDT for Illumina TruSeq DNA UD Index (96 indices, 96 samples) adapters. Library size distribution was assessed and the absence of free adapters or adapter dimers was checked by automated capillary gel electrophoresis (Advanced Analytical Fragment Analyzer). Library concentration was determined by quantitative PCR (qPCR) with the KAPA qPCR Quantification Kit (Roche Light Cycler 480 Instrument II). Sequencing libraries were normalized and combined as 24-plex pools and

quantified as above, before dilution to 2.9 nM and sequencing on an Illumina NovaSeq 6000 with the S4 Reagent Kit (300 cycles) and 151 + 8 + 8 + 151 cycle run parameters. Primary sequencing data were demultiplexed with the Illumina HAS2.2 pipeline, and sample-level quality control was performed for base quality, coverage, duplicates, and contamination (FREEMIX < 0.05 by VerifyBamID). For patients enrolled in the Swedish COVID cohort, sequencing was performed at the Clinical Genomics Stockholm unit of the SciLifeLab (Stockholm, Sweden).

We used the Genome Analysis Software Kit (GATK) (version 3.4-46 or 4) best-practice pipeline to analyze our WES data (70). We aligned the reads obtained with the human reference genome (hg19), using the maximum exact matches algorithm in the Burrows-Wheeler Aligner (71). PCR duplicates were removed with Picard tools (picard.sourceforge.net). The GATK base quality score recalibrator was applied to correct sequencing artifacts. Genotyping was performed with GATK GenotypeGVCFs in the interval intersecting all the capture kits of ± 50 bp. Sample genotypes with a coverage of $< 8\times$, a genotype quality of < 20 , or a ratio of reads for the less covered allele (reference or variant allele) over the total number of reads covering the position (minor read ratio) of $< 20\%$ were filtered out. We filtered out variant sites (i) with a call rate of $< 50\%$ in gnomAD genomes and exomes, (ii) with a non-PASS filter in the gnomAD database, (iii) falling in low-complexity or decoy regions, (iv) that were multiallelic with more than four alleles, (v) with more than 20% missing genotypes in our cohort, and (vi) spanning more than 20 nucleotides. Variant effects were predicted with the Ensembl Variant Effect Predictor (72) and the Ensembl GRCh37.75 reference database, retaining the most deleterious annotation obtained from Ensembl canonical transcripts overlapping with RefSeq transcripts.

Statistical analysis

We performed an enrichment analysis focusing on X chromosome genes on our cohort of 1202 male patients with life-threatening COVID-19 pneumonia without known inborn errors of TLR3- and IRF7-dependent type I IFN immunity (8) and without neutralizing auto-Abs against type I IFNs (9) and 331 male individuals with asymptomatic or paucisymptomatic infection (table S1). We considered variants that were predicted to be LOF or missense, with a MAF below 0.0001 (gnomAD v2.1.1). We compared the proportion of patients and controls carrying at least one nonsynonymous using the Firth bias-corrected logistic likelihood ratio test implemented in EPACTS (Efficient and Parallelizable Association Container Toolbox) (<http://genome.sph.umich.edu/wiki/EPACTS>) extended to gene-based enrichment analysis. In Firth's regression, a penalty term is placed on the standard maximum likelihood function used to estimate parameters of a logistic regression model (19). Firth's can handle genes with no carriers among cases or controls. With no covariates, this corresponds to adding 0.5 in every cell of a 2 by 2 table of allele counts versus case-control status. We accounted for the ethnic heterogeneity of the cohorts by including the first five principal components of the PCA in the Firth's logistic regression model. Analyses were also adjusted for age in years. We checked that our adjusted burden test was well calibrated by also performing an analysis of enrichment in rare (MAF < 0.0001) synonymous variants. PCA was performed with Plink v1.9 software on whole-exome and whole-genome sequencing data, with the 1000 Genomes Project phase 3 public database as a reference, using 18,917 exonic variants with an MAF of > 0.01 and a call rate of > 0.99 .

Cell culture

EBV-B cell lines derived from the patients were grown in complete RPMI 1640 (Life Technologies) supplemented with 10% heat-inactivated fetal bovine serum (FBS). HEK293T cells, derived from the HEK293 cell line, which expresses a mutant version of the SV40 large T antigen, were grown in complete Dulbecco's modified Eagle's medium (Life Technologies) supplemented with 10% FBS. Cells were incubated at 37°C in the presence of 5% CO₂.

Expression vectors and transfection experiments

All the *TLR7* variants in our analysis were generated by site-directed mutagenesis (data file S4). The WT or variant alleles were reintroduced into a Myc-DDK-pCMV6 vector (OriGene). HEK293T cells, which have no endogenous TLR7 or TLR8 expression, were transfected with the Myc-DDK-pCMV6 vector, empty or containing the WT, or a variant allele, in the presence of the X-tremeGENE 9 DNA Transfection Reagent (Sigma-Aldrich), according to the manufacturer's instructions.

Western blotting

For whole-cell extracts, the cells were lysed by incubation in the following buffer [50 mM Tris-HCl (pH 8.0), 150 mM NaCl, and 1% NP-40], supplemented with a mixture of protease inhibitors (Sigma-Aldrich), for 30 min at 4°C. The lysates were then centrifuged at 21,000g for 20 min at 4°C. The supernatants were processed directly for Western blotting. Western blotting was performed on 10 µg of total extract from transfected HEK293T cells, with mAbs specific for the leucine-rich repeats to the N terminus within the human TLR7 protein (Cell Signaling Technology, clone, D7) or for amino acid 1000 to the C terminus with the human TLR7 protein [Abcam, clone, EPR2088(2)].

Luciferase reporter assay

HEK293T cells, which have no endogenous *TLR7* expression, were transfected with the pCMV6 vector bearing WT or variant *TLR7* (50 ng), the reporter construct pGL4.32 (100 ng), and an expression vector for *Renilla* luciferase (10 ng), with the X-tremeGENE 9 DNA Transfection Reagent kit (Sigma-Aldrich). The pGL4.32 (luc2P/NF-κB-RE/Hygro) (Promega) reporter vector contains five copies of the NF-κB-responsive element (NF-κB-RE) linked to the luciferase reporter gene *luc2P*. After 24 hours, the transfected cells were left unstimulated or were stimulated with R848 (1 µg/ml; resiquimod), for activation via TLR7/8 (Invivogen), or R837 (5 µg/ml; imiquimod) (Invivogen), or CL264 (5 µg/ml; Invivogen), human TLR7-specific agonists, for 24 hours. Relative luciferase activity was then determined by normalizing the values against the firefly-*Renilla* luciferase signal ratio.

RNA extraction and reverse transcription qPCR

Total RNA was extracted with the RNeasy Mini Kit (QIAGEN), according to the manufacturer's instructions. Reverse transcription was performed on 1 µg of RNA with random primers and the SuperScript III reverse transcriptase (Invitrogen), according to the manufacturer's protocol. qPCR was then performed with the TaqMan Fast Universal PCR Master Mix (2X) and the FAM-MGB *TaqMan* *TNF* exons 1 and 2 (Hs99999-43_m1) probes. The VIC-TAMRA probe for *GUSB* (Applied Biosystems, catalog no. 4310888E) was used as an endogenous control. Real-time PCR amplification was monitored with the 7500 Fast Real-Time PCR System (Applied Biosystems). Relative expression levels were determined according to the $\Delta\Delta C_t$ method.

Enzyme-linked immunosorbent assay analysis of TNF production in EBV-B cells

Enzyme-linked immunosorbent assay (ELISA) was performed as previously described (51). We suspended 1×10^6 EBV-B cells per well in RPMI 1640 supplemented with 10% FBS. The cells were activated by incubation with R848 (1 μ g/ml) and imiquimod (5 μ g/ml) for 24 hours. The supernatants were harvested after 24 hours of activation. ELISA determinations of TNF in cell culture supernatants were performed with a kit (Thermo Fisher Scientific), according to the manufacturer's instructions.

Stable transduction

The WT coding sequence of *TLR7* was inserted into pTRIP-CMV-puro-2A. For lentivirus production, HEK293T cells were transfected with 1.6 μ g of pTRIP-CMV-puro-2A-TLR7-WT (or mutant, K684*), 0.2 μ g of pCMV-VSV-G (Addgene), 0.2 μ g of pHXB2 (NIH-AIDS Reagent 22 Program), and 1 μ g of psPAX2 (Addgene), with X-treme gene 9 (Roche), according to the manufacturer's instructions. Supernatants were harvested after 24 hours, and protamine sulfate (8 μ g/ml) was added. The lentiviral suspension obtained was used to transduce 2×10^5 EBV-B cells by spinoculation at 1200g for 2 hours. The transduced cells were selected by incubation on medium containing puromycin (1 μ g/ml) for 2 days. The cells were then selected by incubation for a further 2 days on medium containing puromycin (2 μ g/ml). During viral transduction, the cells were cultured with 5 μ M IRAK4 inhibitor (PF06650833) (Bio-Techne) to prevent cell death due to the overproduction of TLR7. Selected transduced cells were then stimulated with R848 (1 μ g/ml) or imiquimod (5 μ g/ml) for 24 hours without IRAK4 inhibitor. The supernatants were harvested after 24 hours of activation. ELISA determinations of TNF in cell culture supernatants were performed with a kit (Thermo Fisher Scientific), according to the manufacturer's instructions.

VirScan analysis

Patient serum was analyzed by VirScan in two independent experiments as previously described (73). Briefly, an oligonucleotide library encoding 56-amino acid peptides tiling across the genomes of 206 viral species was synthesized on a releasable DNA microarray and cloned into T7 phage. Patient serum containing 2 μ g of immunoglobulin G was added to the phage library, and immunoprecipitation was performed with Protein A and G beads. Enriched peptides were identified by PCR and Illumina sequencing of the peptide cassette from the immunoprecipitated phage.

Deep immunophenotyping by mass cytometry (CyTOF)

CyTOF was performed on whole blood with the Maxpar Direct Immune Profiling Assay (Fluidigm), according to the manufacturer's instructions. Cells were frozen at -80°C after overnight staining to eliminate dead cells, and acquisition was performed on a Helios machine (Fluidigm). All the samples were processed within 24 hours of sampling. Data analysis was performed with OMIQ software. Ab information is listed in the Supplementary Materials (data file S5).

Peripheral blood mononuclear cells enrichment using magnetic-activated cell sorting (MACS) system

Blood were collected from two healthy individuals and separated by the concentration gradient method with Ficoll Paque Plus (Cytiva). After isolations of peripheral blood mononuclear cells (PBMCs),

leucocyte subset (T cell, B cell, monocyte, pDC, and mDC) was purified by negative selection using MACS beads system (Miltenyi Biotec). Cells were plated into a U-bottomed 96-well plate at a density of 2×10^4 cells per well for T cells, B cells, monocytes, pDCs, or mDCs in RPMI 1640 (200 μ l per well) with GlutaMAX supplemented with 10% FBS or 10×10^4 cells per well for whole blood and PBMCs. Cells were left unstimulated or stimulated with CL264 (1 μ g/ml), TL8-506 (100 ng/ml; Invivogen), R848 (1 μ g/ml), 2 μ M CpG-c (Invivogen), or phorbol 12-myristate 13-acetate (PMA; 12.5 ng/ml) and 0.125 μ M ionomycin for 24 hours. The supernatants were harvested after 24 hours of activation. Cytokines production were determined by ELISA [IFN- α , PBL Assay Science; IFN- β , PBL Assay Science; IFN- γ (IL-29), Invivogen; IFN- ω , Invitrogen; or IL-8, R&D Systems], according to the manufacturer's instructions.

Analysis for TLR7 and TLR8 expression pattern in PBMCs by flow cytometry

Freshly thawed PBMCs from healthy donors were dispensed into a V-bottomed 96-well plate at a density of 1×10^6 cells per well, in 200 μ l of phosphate-buffered saline (PBS) per well. Briefly, cells were stained by incubation with the LIVE/DEAD fixable blue dead-cell staining kit (Thermo Fisher Scientific; 1:800) and Fc receptor blocking reagent (Miltenyi Biotec; 1:25) on ice for 15 min. For surface staining, cells were incubated with anti-TCR $\gamma\delta$ -BUV611 (BD Biosciences; 1:50), anti-CD183-BV750 (BD Biosciences; 1:20), and anti-CD194-BUV615 (BD Biosciences; 1:20) Abs on ice for 30 min in 0.1% bovine serum albumin and 0.01% sodium azide in PBS. They were then incubated with anti-CD141-BB515 (BD Biosciences; 1:40), anti-CD57-FITC (BioLegend; 1:83), anti-TCR V δ 2-PerCP (BioLegend; 1:166), anti-TCR V α 7.2-PerCP/Cyanine5.5 (BioLegend; 1:40), anti-TCR V δ 1-PerCP-Vio 700 (Miltenyi Biotec; 1:100), anti-CD14-Spark Blue 550 (BioLegend; 1:40), anti-CD1c-Alexa Fluor 647 (BioLegend; 1:50), anti-CD38-APC/Fire 810 (BioLegend; 1:30), anti-CD27-APC-H7 (BD Biosciences; 1:50), anti-CD127-APC-R700 (BD Biosciences; 1:50), anti-CD19-Spark NIR 685 (BioLegend; 1:83), anti-CD45RA-BUV395 (BD Biosciences; 1:83), anti-CD16-BUV496 (BD Biosciences; 1:166), anti-CD11b-BUV563 (BD Biosciences; 1:100), anti-CD56-BUV737 (BD Biosciences; 1:83), anti-CD8-BUV805 (BD Biosciences; 1:83), anti-hMR1-BV421 (NIH Tetramer Facility; 1:100), anti-CD11c-BV480 (BD Biosciences; 1:40), anti-CD45-BV510 (BioLegend; 1:83), anti-CD33-BV570 (BioLegend; 1:83), anti-iNKT-BV605 (BioLegend; 1:25), anti-CD161-BV650 (BD Biosciences; 1:25), anti-CCR6-BV711 (BioLegend; 1:83), anti-CCR7-BV785 (BioLegend; 1:40), anti-CD3-Pacific Blue (BioLegend; 1:83), anti-CD20-Pacific Orange (Life Technologies; 1:50), anti-CD123-Super Bright 436 (Invitrogen; 1:40), anti-CD24-PE-Alexa Fluor 610 (Life Technologies; 1:25), anti-CD25-PE-Alexa Fluor 700 (Life Technologies; 1:25), anti-CD294-biotin (Invitrogen; 1:50), anti-CD209-PE/Cyanine7 (BioLegend; 1:25), anti-CD117-PE/Dazzle 594 (BioLegend; 1:83), anti-HLA-DR-PE/Fire 810 (BioLegend; 1:50), and anti-CD4-cFluor YG584 (Cytex; 1:83) Abs on ice for at least 30 min. The cells were then washed and stained by incubation with streptavidin-PE/Cy5 (BioLegend; 1:3000) on ice for 30 min. The cells were then fixed and permeabilized for intracellular staining with anti-TLR7-PE (Invitrogen) and anti-TLR8-APC (BioLegend) Abs, with the eBioscience Foxp3/Transcription Factor Staining Buffer Set (Invitrogen), according to the manufacturer's instructions. The cells were then washed and acquired with a five-laser Cytex Aurora (Cytex) flow cytometer. Ab clone information is added in the Supplementary Materials (data file S6).

pDC activation

Freshly purified pDCs were cultured in 96-well plates at a concentration of 5×10^5 cells/ml in the presence of medium alone [RPMI 1640 with GlutaMAX, 10% FBS, 1% minimum essential medium non-essential amino acid (NEAA), 1% sodium pyruvate, and 1% penicillin/streptomycin], CL264 (Invivogen; 1 µg/ml), or the SARS-CoV-2 primary strain 220_95 (46) at a multiplicity of infection of 1. After 24 hours of culture, the pDC supernatant was collected for cytokine quantification, and the pDCs were collected for diversification assessment by flow cytometry. In some experiments, RNA was purified from the pDCs that were analyzed by RNA sequencing (RNA-seq; see below).

Flow cytometry analysis for human pDCs

For assessments of pDC diversification, cells were stained with a Zombie Violet fixable viability dye (BioLegend), BV711 anti-CD123 (BioLegend, clone 6H6), PE anti-CD80 (BD Biosciences, clone L307.4), and PerCP-eFluor 710 anti-PD-L1 (eBioscience, clone MIH1) Abs. Data were acquired with an LSRFortessa (BD Biosciences) flow cytometer and analyzed with FlowJo software (Tree Star). Flow cytometry analyses were performed at the flow cytometry core facility of Institut de recherche Saint Louis (Paris, France).

RNA sequencing

We collected cells from five individuals in two families: one patient (P8) and two healthy controls (H.II.2 and H.II.3) from family H and one patient (P14) and one healthy control (M.I.1) from family M. These cells were stimulated with three conditions: nonstimulation, SARS-CoV-2, and CpG-c. Total RNA was extracted from pDC cells with RNeasy Micro kits (QIAGEN). RNA-seq libraries were prepared with the Illumina SMART-Seq v4 PLUS Kit (TaKaRa) and sequenced on the Illumina NextSeq 4000 platform with single-end 75-bp configuration. The RNA-seq fastq raw data were inspected with multiQC v1.10 (74) to ensure the high quality of data. The sequencing reads were mapped onto the human reference genome GRCh38 with STAR aligner v2.7 (75), and the mapped reads were then quantified to determine the gene-level read counts with featureCounts V2.0.2 (76) and GENCODE human gene annotation GRCh38.p13 (77). The gene-level read counts were normalized and $\log_2$ -transformed by DESeq2 (78), to obtain the gene expression profile of all samples for differential expression analysis. The differential gene expression was analyzed by applying trimmed mean of M values (TMM) normalization and gene-wise generalized linear model regression with edgeR (79). The genes displaying significant differential expression were selected on the basis of $|\log_2\text{-FoldChange}| \geq 2$ and a false discovery rate of ≤ 0.05 . The gene-level read counts of IFN genes were transformed to reads per kilobase of transcript, per Million mapped reads by our own scripts, to compare the IFN gene expression of different samples under different stimulations.

Determination of secreted inflammatory cytokines

We measured the production, by pDCs, of IFN- α 2, IL-8, IL-6, and interferon gamma-induced protein 10 (IP-10), by determining the levels of these cytokines in culture supernatants with the BD CBA, according to the manufacturer's protocol, with a limit of detection of 20 pg/ml. Acquisitions were performed on an LSRFortessa (BD Biosciences) flow cytometer, and cytokine concentrations were determined with FCAP Array software (BD Biosciences).

SUPPLEMENTARY MATERIALS

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Figs. S1 to S6

Tables S1 to S3

Data files S1 to S7

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

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Members of COVID Human Genetic Effort: Laurent Abel¹, Alessandro Aiuti², Saleh Al-Muhsen³, Fahd Al-Mulla⁴, Mark S. Anderson⁵, Evangelos Andreaskos⁶, Andrés A. Arias⁷, Hagit Baris Feldman⁸, Alexandre Belot⁹, Catherine M. Biggs¹⁰, Dusan Bogunovic¹¹, Alexandre Bolze¹², Anastasiia Bondarenko¹³, Ahmed A. Bousfiha¹⁴, Petter Brodin¹⁵, Yenan Bryceson¹⁶, Carlos D. Bustamante¹⁷, Manish J. Butte¹⁸, Giorgio Casari¹⁹, Samya Chakravorty²⁰, John Christodoulou²¹, Antonio Condino-Neto²², Stefan N. Constantinescu²³, Megan A. Cooper²⁴, Clifton L. Dalgaard²⁵, Murkesh Desai²⁶, Beth A. Drolot²⁷, Jamila El Baghdadi²⁸, Sara Espinosa-Padilla²⁹, Jacques Fellay³⁰, Carlos Flores³¹, José Luis Franco³², Antoine Froidure³², Peter K. Gregersen³³, Filomeen Haerynck³⁴, David Hagin³⁵, Rabih Halwani³⁶, Lennart Hammarström³⁷, James R. Heath³⁸, Sarah E. Henrickson³⁹, Elena W. Y. Hsieh⁴⁰, Eystein Husebye⁴¹, Kohsuke Imai⁴², Yuval Itan⁴³, Erich D. Jarvis⁴⁴, Timokratis Karamitros⁴⁵, Kai Kisand⁴⁶, Cheng-Lung Ku⁴⁷, Yu-Lung Lau⁴⁸, Yun Ling⁴⁹, Carrie L. Lucas⁵⁰, Tom Maniatis⁵¹, Davoud Mansouri⁵², László Maródi⁵³, Isabelle Meyts⁵⁴, Joshua D. Milner⁵⁵, Kristina Mironska⁵⁶, Trine H. Mogensen⁵⁷, Tomohiro Morio⁵⁸, Lisa F. P. Ng⁵⁹, Luigi D. Notarangelo⁶⁰, Antonio Novelli⁶¹, Giuseppe Novelli⁶², Cliona O'Farrelly⁶³, Satoshi Okada⁶⁴, Tayfun Ozcelik⁶⁵, Qiang Pan-Hammarström³⁷, Rebeca Perez de Diego⁶⁶, Anna M. Planas⁶⁷, Carolina Prando⁶⁸, Aurora Pujol⁶⁹, Lluís Quintana-Murci⁷⁰, Laurent Renia⁵⁹, Igor Resnick⁷¹, Carlos Rodriguez-Gallego⁷², Vanessa Sanchina-Shimizu⁷³, Anna Sediva⁷⁴, Mikko R. J. Seppänen⁷⁵, Mohammed Shahrrooei⁷⁶, Anna Shcherbina⁷⁷, Ondrej Slaby⁷⁸, Andrew L. Snow⁷⁹, Pere Soler-Palacin⁸⁰, Andrés N. Spaan⁸¹, Ivan Tancevski⁸², Stuart G. Tangye⁸³, Ahmad Abou Tayoun⁸⁴, Sathishkumar Ramaswamy⁸⁴, Stuart E. Turvey⁸⁵, Furkan Uddin⁸⁶, Mohammed J. Uddin⁸⁷, Diederik van de Beek⁸⁸, Donald C. Vinh⁸⁹, Horst von Bernuth⁹⁰, Mayana Zatz⁹¹, Pawel Zawadzki⁹², Helen C. Su⁶⁰, Jean-Laurent Casanova⁹³

¹INSERM U1163, University of Paris, Imagine Institute, Paris, France. ²San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, and Vita Salute San Raffaele University, Milan, Italy. ³Immunology Research Laboratory, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. ⁴Dasman Diabetes Institute, Department of Genetics and Bioinformatics, Dasman, Kuwait. ⁵Diabetes Center, University of California, San Francisco, CA, USA. ⁶Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ⁷Group of Primary Immunodeficiencies, Universidad de Antioquia UdeA, Medellín, Colombia. ⁸Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁹Pediatric Nephrology, Rheumatology, Dermatology, HFME, Hospices Civils de Lyon, National Referee Centre RAISE, and INSERM U1111, Université de Lyon, Lyon, France. ¹⁰Department of Pediatrics, British Columbia Children's Hospital, University of British Columbia, Vancouver, BC, Canada. ¹¹Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹²Helix, San Mateo, CA, USA. ¹³Shupryk National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹⁴Clinical Immunology Unit, Department of Pediatric Infectious Disease, CHU Ibn Rushd and LICIA, Laboratoire d'Immunologie Clinique, Inflammation et Allergie, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco. ¹⁵SciLifeLab, Department Of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden. ¹⁶Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden. ¹⁷Stanford University, Stanford, CA, USA. ¹⁸Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics and the Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, Los Angeles, CA, USA. ¹⁹Clinical Genomics, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy. ²⁰Department of Pediatrics and Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA. ²¹Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia. ²²Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil. ²³de Duve Institute and Ludwig Cancer Research, Brussels, Belgium. ²⁴Washington University School of Medicine, St. Louis, MO, USA. ²⁵Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ²⁶Bai Jerbai Wadia Hospital for Children, Mumbai, India. ²⁷School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. ²⁸Genetics Unit, Military Hospital Mohamed V, Rabat, Morocco. ²⁹Instituto Nacional de Pediatría (National Institute of Pediatrics), Mexico City, Mexico. ³⁰School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ³¹Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, 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; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. ³²Pulmonology Department, Cliniques Universitaires Saint-Luc;

Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium. ³³Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA. ³⁴Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPIG), PID Research Laboratory, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent, Belgium. ³⁵Genetics Institute Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. ³⁶Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates. ³⁷Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. ³⁸Institute for Systems Biology, Seattle, WA, USA. ³⁹Department of Pediatrics, Division of Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁰Departments of Pediatrics, Immunology and Microbiology, University of Colorado, School of Medicine, Aurora, CO, USA. ⁴¹Department of Medicine, Haukeland University Hospital, Bergen, Norway. ⁴²Department of Community Pediatrics, Perinatal and Maternal Medicine, Tokyo Medical and Dental University (TMDU), Tokyo, Japan. ⁴³Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁴⁴Laboratory of Neurogenetics of Language and Howard Hughes Medical Institute, Rockefeller University, New York, NY, USA. ⁴⁵Bioinformatics and Applied Genomics Unit, Hellenic Pasteur Institute, Athens, Greece. ⁴⁶Molecular Pathology, Department of Biomedicine, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia. ⁴⁷Chang Gung University, Taoyuan County, Taiwan. ⁴⁸Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong, China. ⁴⁹Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. ⁵⁰Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA. ⁵¹Columbia University Zuckerman Institute, New York, NY, USA. ⁵²Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, 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. ⁵³Primary Immunodeficiency Clinical Unit and Laboratory, Department of Dermatology, Venerology and Dermatocology, Semmelweis University, Budapest, Hungary. ⁵⁴Department of Pediatrics, University Hospitals Leuven; KU Leuven, Department of Microbiology, Immunology and Transplantation; Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium. ⁵⁵Department of Pediatrics, Columbia University Irving Medical Center, New York, NY, USA. ⁵⁶University Clinic for Children's Diseases, Department of Pediatric Immunology, Medical Faculty, University "St.Cyril and Methodij," Skopje, North Macedonia. ⁵⁷Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁵⁸Tokyo Medical and Dental University Hospital, Tokyo, Japan. ⁵⁹A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore, Singapore; Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore, Singapore. ⁶⁰National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. ⁶¹Laboratory of Medical Genetics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. ⁶²Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy. ⁶³Comparative Immunology Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland. ⁶⁴Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ⁶⁵Department of Molecular Biology and Genetics, Bilkent University, Bilkent-Ankara, Turkey. ⁶⁶Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ⁶⁷IIBB-CSIC, IDIBAPS, Barcelona, Spain. ⁶⁸Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain; Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Barcelona, Spain. ⁷⁰Human Evolutionary Genetics Unit, CNRS U2000, Institut Pasteur, Paris, France; Human Genomics and Evolution, Collège de France, Paris, France. ⁷¹University Hospital St. Marina, Varna, Bulgaria. ⁷²Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁷³Department of Paediatric Infectious Diseases and Virology, Imperial College London, London, UK; Centre for Paediatrics and Child Health, Faculty of Medicine, Imperial College London, London, UK. ⁷⁴Department of Immunology, Second Faculty of Medicine Charles University, V Uvalu, University Hospital in Motol, Prague, Czech Republic. ⁷⁵Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Rare Diseases Center and Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. ⁷⁶Saeed Pathobiology and Genetics Lab, Tehran, Iran; Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. ⁷⁷Department of Immunology, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia. ⁷⁸Central European Institute of Technology and Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czech Republic. ⁷⁹Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁸⁰Pediatric Infectious Diseases and Immunodeficiencies

Unit, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain.⁸¹St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA; Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands.⁸²Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria.⁸³Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, NSW, Australia.⁸⁴Al Jalila Children's Hospital, Dubai, UAE.⁸⁵BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada.⁸⁶Centre for Precision Therapeutics, Genetic and Genomic Medicine Centre, NeuroGen Children Healthcare, Dhaka, Bangladesh; Holy Family Red Crescent Medical College, Dhaka, Bangladesh.⁸⁷College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE; Cellular Intelligence (Ci) Lab, GenomeArc Inc., Toronto, ON, Canada.⁸⁸Department of Neurology, Amsterdam Neuroscience, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands.⁸⁹Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, QC, Canada; Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, QC, Canada.⁹⁰Department of Pediatric Pneumology, Immunology and Intensive Care, Charité Universitätsmedizin, Berlin University Hospital Center, Berlin, Germany; Labor Berlin GmbH, Department of Immunology, Berlin, Germany; Berlin Institutes of Health (BIH), Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany.⁹¹Biosciences Institute, University of São Paulo, São Paulo, Brazil.⁹²Molecular Biophysics Division, Faculty of Physics, A. Mickiewicz University, Poznań, Poland.⁹³Rockefeller University and Howard Hughes Medical Institute, New York, NY, USA; Necker Hospital for Sick Children and INSERM, Paris, France.

Members of 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.

Members of COVID Clinicians: Jorge Abad¹, Giulia Accordino², Cristian Achille³, Sergio Aguilera-Albesa⁴, Aina Aguiló-Cucurull⁵, Alessandro Aiuti⁶, Esra Akıyüz Özkan⁷, İlad Alavi Darazam⁸, Jonathan Antonio Roblero Albisures⁹, Juan C. Aldave¹⁰, Miquel Alfonso Ramos¹¹, Taj Ali Khan¹², Anna Alberti¹³, Seyed Alireza Nadjil¹⁴, Gulsum Alkan¹⁵, Suzan A. AlKhatir¹⁶, Jerome Allardet-Servent¹⁷, Luis M. Allende¹⁸, Rebeca Alonso-Arias¹⁹, Mohammed S. Alshahrani²⁰, Laia Alsina²¹, Marie-Alexandra Alyanakian²², Blanca Amador Borrero²³, Zahir Amoura²⁴, Arnau Antolí²⁵, Romain Arrestier²⁶, Mélodie Aubart²⁷, Teresa August²⁸, Iryna Avramenko²⁹, Gökhan Aytekin³⁰, Axelle Azot³¹, Seiamak Bahram³², Fanny Bajolle³³, Fausto Baldanti³⁴, Aurélie Baldolli³⁵, Maite Ballester³⁶, Hagit Baris Feldman³⁷, Benoit Barrou³⁸, Federica Barzaghi³⁹, Sabrina Basso³⁹, Gulsum İclal Bayhan⁴⁰, Alexandre Belot⁴¹, Liliana Bezrodnik⁴², Agurtzane Bilbao⁴³, Geraldine Blanchard-Rohner⁴⁴, Ignacio Blanco⁴⁵, Adeline Blandinières⁴⁶, Daniel Blázquez-Gamero⁴⁷, Alexandre Bleibtreu⁴⁸, Marketa Bloomfield⁴⁹, Mireia Bolívar-Prados⁵⁰, Ana Anastasiia Bondarenko⁵¹, Alessandro Borghesi⁵², Raphael Borie⁵³, Elisabeth Botdthlo-Nevers⁵⁴, Ahmed A. Bousfiha⁵⁴, Aurore Bousquet⁵⁵, David Boutolleau⁵⁶, Claire Bouvattier⁵⁷, Oksana Boyarchuk⁵⁸, Juliette Bravais⁵⁹, M. Luisa Briones⁶⁰, Marie-Eve Brunner⁶¹, Raffaele Bruno⁶², Maria Rita P. Bueno⁶³, Huda Bukhari⁶⁴, Jacinta Bustamante⁶⁵, Juan José Cáceres Agra⁶⁵, Ruggero Capra⁶⁶, Raphael Carapito⁶⁷, Maria Carrabba⁶⁸, Giorgio Casan⁶⁹, Carlos Casasnovas⁶⁹, Marion Caseris⁷⁰, Irene Cassaniti³⁴, Martin Castelle⁷¹, Francesco Castelli⁷², Martin Castillo de Vera⁷³, Mateus V. Castro⁶³, Emilie Catherine⁷⁴, Jale Bengi Celik⁷⁵, Alessandro Ceschi⁷⁶, Martin Chalumeau⁷⁷, Bruno Charbit⁷⁸, Matthew P. Cheng⁷⁹, Pèrre Clavé⁸⁰, Bonaventura Clotet⁸⁰, Anna Codina⁸¹, Yves Cohen⁸², Roger Colobran⁸³, Cloé Comarmond⁸⁴, Alain Combes⁸⁵, Patrizia Comoli³⁹, Angelo G. Corsico², Taner Coşkun⁸⁶, Aleksandar Cvetkovski⁸⁷, Cyril Cyrus⁸⁸, David Dalmau⁸⁹, François Danion⁹⁰, David Ross Darley⁹¹, Vincent Das⁹², Nicolas Dauby⁹³, Stéphane Dauter⁹⁴, Paul De Munter⁹⁵, Loïc de Pontual⁹⁶, Amin Dehban⁹⁷, Geoffroy Delplanche⁹⁸, Alexandre Demoule⁹⁹, Isabelle Desguerre¹⁰⁰, Antonio Di Sabatino¹⁰¹, Jean-Luc Diehl¹⁰², Stephanie Dobbela¹⁰³, Elena Domínguez-Garrido¹⁰⁴, Clément Dubost¹⁰⁵, Olov Ekwali¹⁰⁶, Şefika Elmas Bozdemir¹⁰⁷, Marwa H. Elnagdy¹⁰⁸, Melike Emiroglu¹⁵, Akifumi Endo¹¹⁰, Emine Hafize Erdeniz¹¹⁰, Selma Erol Aytekin¹¹¹, Maria Pilar Etxart Lasa¹¹², Romain Euvrad¹¹³, Giovanna Fabio⁶⁸, Laurence Faivre¹¹⁴, Antonin Falck¹¹⁵, Muriel Fartoukh¹¹⁶, Morgane Faure¹¹⁷, Miguel Fernandez Arquer¹¹⁸, Ricard Ferrer¹¹⁹, Jose Ferreres¹²⁰, Carlos Flores¹²¹, Bruno Francois¹²², Victoria Fumadó¹²³, Kitty S. C. Fung¹²⁴, Francesca Fusco¹²⁵, Alenka Gagro¹²⁶, Blanca García Solís¹²⁷, Pierre Garçon³⁴⁵, Pascale Gaussem¹²⁸, Zeynep Gayretli¹²⁹, Juana Gil-Herrera¹³⁰, Laurent Gilardin¹³¹, Audrey Giraud Gatinéau¹³², Mónica Girona-Alarcón¹³³, Karen Alejandra Cifuentes Godínez¹³⁴, Jean-Christophe Goffard¹³⁵, Nacho Gonzales¹³⁶, Luis I. Gonzalez-Granado¹³⁷, Rafaela González-Montelongo¹³⁸, Antoine Guerder¹³⁹, Belgün Gülhan¹⁴⁰, Victor Daniel Gumucio¹⁴¹, Leif Gunnar Hanitsch¹⁴², Jan Gunst¹⁴³, Marta Gut¹⁴⁴, Jérôme Hadjadj¹⁴⁵, Filomene Haerynck¹⁴⁶, Rabi Halwani¹⁴⁷, Lennart Hammarström¹⁴⁸, Selda Hancerli¹⁴⁹, Tetyana Hariyan¹⁵⁰, Nevlin Hatipoglu¹⁵¹, Deniz Heppekan¹⁵², Elisa Hernandez-Brito¹⁵³, Po-ki Ho¹⁵⁴, María Soledad Holanda-Peña¹⁵⁵, Juan P. Horcajada¹⁵⁶, Sami Hraiech¹⁵⁷, Linda Humbert¹⁵⁸, Ivan F. N. Hung¹⁵⁹, Alejandro D. Iglesias¹⁶⁰, Antonio Íñigo-Campos¹³⁸, Matthieu Jamme¹⁶¹, María Jesús Arranz⁸⁹, Marie-Thérèse Jimeno¹⁶², Iolanda Jordan¹³³, Saliha Kanik Yükses¹⁶³, Yalcin Burak Kara¹⁶⁴, Aydin Karahan¹⁶⁵, Adem Karbuz¹⁶⁶, Kadiye Kart Yasar¹⁶⁷, Ozgur Kasapcopur¹⁶⁸, Kenichi Kashimada¹⁶⁹, Sevgi Keles¹¹¹, Yasemin Kendir Demirkol¹⁷⁰, Yasutoshi Kido¹⁷¹, Can Kizil¹⁷², Ahmet Osman Kiliç¹⁷³, Adam Klocperk¹⁷⁴, Antonia Koutsoukou¹⁷⁵, Zbigniew J. Król¹⁷⁶, Hatem Ksour¹⁷⁷, Paul Kuentz¹⁷⁸, Arthur M. C. Kwan¹⁷⁹, Yat Wah M. Kwan¹⁸⁰, Janette S. Y. Kwok¹⁸¹, Jean-Christophe Lagier¹⁸², David S. Y. Lam¹⁸³, Vicky Lampropoulou¹⁸⁴, Fanny Lantermier¹⁸⁵, Yu-Lung Lau¹⁸⁶, Fleur Le Bourgeois⁹⁴, Yee-Sin Leo¹⁸⁷, Rafael Leon Lopez¹⁸⁸, Daniel Leung¹⁸⁶, Michael Levin¹⁸⁹, Michael Levy⁹⁴, Romain Lévy³³, Zhi Li⁷⁶, Daniele Lillieri³⁴, Edson Jose Adrian Bolanos Lima¹⁹⁰, Agnes Linglart¹⁹¹, Eduardo López-Collazo¹⁹², José M. Lorenzo-Salazar¹³⁸, Céline Louapre¹⁹³, Catherine Lubetzki¹⁹³, Kwok-Cheung Lung¹⁹⁴, Charles-Edouard Luyt¹⁹⁵, David C. Lye¹⁹⁶, Cynthia Magnone¹⁹⁷, Davood Mansouri¹⁹⁸, Enrico Marchioni¹⁹⁹, Carola Marioli², Majid Marjani²⁰⁰, Laura Marques²⁰¹, Jesus Marquez Pereira²⁰², Andrea Martin-Nalda²⁰³, David Martínez Pueyo²⁰⁴, Javier Martínez-Picado²⁰⁵, İciar Marzana²⁰⁶, Carmen Mata-Martínez²⁰⁷, Alexis Mathian²⁴, Larissa R. B. Matos⁶³, Gail V. Matthews²⁰⁸, Julien Mayaux²⁰⁹, Raquel McLaughlin-García²¹⁰, Philippe Meersseman²¹¹, Jean-Louis Mège²¹², Armand Mekontso-Dessap²¹³, Isabelle Melki¹¹⁵, Federica Meloni², Jean-François Meritet²¹⁴, Paolo Merlani²¹⁵, Özge Metin Akcan²¹⁶, Isabelle Meyts²¹⁷, Mehdi Mezidi²¹⁸, Isabelle Migeotte²¹⁹, Maude Millereux²²⁰, Matthieu Million²²¹, Tristan Mirault²²², Clotilde Mircher²²³, Mehdi Mirsaeidi²²⁴, Yoko Mizoguchi²²⁵, Bhavi P. Modi²²⁶, Francesco Mojoli¹³, Elsa Moncomble²²⁷, Abián Montesdeoca Melián²²⁸, Antonio Morales Martinez²²⁹, Francisco Morandeira²³⁰, Pierre-Emmanuel Morange²³¹, Clémence Mordacq¹⁵⁸, Guillaume Morelle³³², Stéphane J. Mouly²³³, Adrián Muñoz-Barrera¹³⁸, Cyril Nafati²³⁴, Shintaro Nagashima²³⁵, Yu Nakagama¹⁷¹, Bénédicte Neven²³⁶, João Farela Neves²³⁷, Lisa F. P. Ng²³⁸, Yuk-Yung Ng²³⁹, hubert Nielly¹⁰⁵, Yera Novoa Medina²¹⁰, Esmeralda Nuñez Cuadros²⁴⁰, J. Gonzalo Océjo-Vinyals²⁴¹, Keisuke Okamoto¹⁰⁹, Mehdi Oualha³³, Amani Ouedran²², Tayfun Özçelik²⁴², Aslinur Ozkaya-Parlakay¹⁴⁰, Michele Paganì¹³, Qiang Pan-Hammarström¹⁴⁸, Maria Papadaki²⁴³, Christophe Parizot²⁰⁹, Philippe Parola²⁴⁴, Tiffany Pascreau²⁴⁵, Stéphane Paul²⁴⁶, Estela Paz-Alt²⁴⁷, Sigifredo Pedraza²⁴⁸, Nancy Carolina González Pellecer¹³⁴, Silvia Pellegrini²⁴⁹, Rebeca Pérez de Diego¹²⁷, Xosé Luis Pérez-Fernández¹⁴¹, Aurélien Philippe²⁵⁰, Quentin Philippot¹¹⁶, Adrien Picod²⁵¹, Marc Pineton de Chambrun⁸⁵, Antonio Piralla³⁴, Laura Planas-Serra²⁵², Dominique Ploin²⁵³, Julien Poissy²⁵⁴, Géraldine Poncelet⁷⁰, Garyphallia Poulakou¹⁷⁵, Marie S. Pouletty²⁵⁵, Persia Pourshahzadi²⁵⁶, Jia Li Qiu-Chen²⁵⁷, Paul Quentrec²⁰⁹, Thomas Rambaud²⁵⁸, Didier Raoult²¹², Violette Raoult²⁵⁹, Anne-Sophie Rebillat²²³, Claire Redin²⁶⁰, Léa Resmini²⁶¹, Pilar Ricart²⁶², Jean-Christophe Richard²⁶³, Raúl Rigo-Bonnin²⁶⁴, Nadia rivet⁴⁶, Jacques G. Rivière²⁶⁵, Gemma Rocamora-Blanch²⁷, Mathieu P. Rodero²⁶⁶, Carlos Rodrigo²⁶⁷, Luis Antonio Rodriguez¹⁹⁰, Carlos Rodriguez-Gallego²⁶⁸, Agustí Rodríguez-Palmero²⁶⁹, Carolina Soledad Romero²⁷⁰, Anya Rothenbuhler²⁷¹, Damien Roux²⁷², Nikolett Rovina¹⁷⁵, Flore Rozenberg²⁷³, Yvon Ruch⁹⁰, Montse Ruiz²⁷⁴, María Yolanda Ruiz del Prado²⁷⁵, Juan Carlos Ruiz-Rodríguez¹¹⁹, Joan Sabater-Riera¹⁴¹, Kai Saks²⁷⁶, Maria Salagianni¹⁸⁴, Oliver Sanchez²⁷⁷, Adrián Sánchez-Montalvá²⁷⁸, Silvia Sánchez-Ramón²⁷⁹, Laire Schidlowski²⁸⁰, Agatha Schluter²⁵², Julien Schmidt²⁸¹, Matthieu Schmidt²⁸², Catharina Schuetz²⁸³, Cyril E. Schweitzer²⁸⁴, Francesco Scolari²⁸⁵, Anna Sediva²⁸⁶, Luis Seijo²⁸⁷, Analia Gisela Seminario⁴², Damien Sene²³, Piseth Seng²²¹, Sevtap Senoglu¹⁶⁷, Mikko Seppänen²⁸⁸, Alex Serra Llovich²⁸⁹, Mohammad Shahrooei⁹⁷, Anna Shcherbina²⁹⁰, Virginie Siguret²⁹¹, Eleni Siouti²⁹², David M. Smađja²⁹³, Niklas Smith⁷⁸, Ali Sobh²⁹⁴, Xavier Solanich²⁵, Jordi Solé-Violán²⁹⁵, Catherine Soler²⁹⁶, Pere Soler-Palacin²⁹⁷, Betül Sözer⁸⁶, Giulia Maria Stella², Yuriy Stepanovskiy²⁹⁸, Annabelle Stodien²⁹⁹, Fabio Taccone²¹⁹, Yacine Tandjaoui-Lambiotte³⁰⁰, Jean-Luc Taupin³⁰¹, Simon J. Tavernier³⁰², Loreto Vidaur Tello¹¹², Benjamin Terrier³⁰³, Guillaume Thier³⁰⁴, Christian Thorbal²⁶⁰, Karolina Thorne³⁰⁵, Caroline Thumerelle¹⁵⁸, Imran Tipu³⁰⁶, Martin Tolstrup³⁰⁷, Gabriele Tomasoni³⁰⁸, Julie Toubiana⁷⁷, Josep Trenado Alvarez³⁰⁹, Vasiliki Triantafyllia³¹⁰, Sophie Trouillet-Assant³¹¹, Jesús Troya³¹², Owen T. Y. Tsang³¹³, Liina Tserel³¹⁴, Eugene Y. K. Tso³¹⁵, Alessandra Tucci³¹⁶, Şadiye Kübra Tüter Öz¹⁵, Matilde Valeria Ursini¹²⁵, Takanori Utsumi²²⁵, Yurdagul Uzunhan³¹⁷, Pierre Vabres³¹⁸, Juan Valencia-Ramos³¹⁹, Ana Maria Van Den Rym¹²⁷, Isabelle Vandernoot³²⁰, Valentina Velez-Santamaria³²¹, Silvia Patricia Zuniga Veliz³²⁴, Mateus C. Vidigal³²², Sébastien Viel²⁵³, Cédric Vilain³²³, Marie E. Vilaire-Meunier²²³, Judit Villar-García³²⁴, Audrey Vincent²⁷, Guillaume Vogt³²⁵, Guillaume Voirit³²⁶, Alla Volokha³²⁷, Fanny Vouty¹⁵⁸, Els Wauters³²⁸, Joost Wauters³²⁹, Alan K. L. Wu³³⁰, Tak-Chiu Wu³³¹, Aysun Yahşi³³², Osman Yesilbas³³³, Mehmet Yildiz¹⁶⁸, Barnaby E. Young¹⁸⁷, Ufuk Yükselmis³³⁴, Mayana Zatz⁶³, Marco Zecca³⁹, Valentina Zuccaro⁶², Jens Van Praet³³⁵, Bart N. Lambrecht³³⁶, Eva Van Braeckel³³⁶, Cédric Boesteels³³⁶, Levi Hoste³³⁷, Eric Hoste³³⁸, Fré Bouteux³³⁶, Jozefien De Clercq³³⁶, Catherine Heijmans³³⁹, Hans Slabbynck³⁴⁰, Leslie Naessens³⁴¹, Benoît Florkin³⁴², Cécile Boulanger³⁴³, Dimitri Vanderlinden³⁴⁴

Milan, Italy. ⁷Ondokuz Mayıs University Medical Faculty Pediatrics, Samsun, Turkey.

⁸Department of Infectious Diseases, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁹Hospital Regional de Huehuetenango, "Dr. Jorge Vides de Molina," Huehuetenango, Guatemala. ¹⁰Hospital Nacional Edgardo Rebagliatti Martins, Lima, Peru. ¹¹Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat Spain. ¹²Khyber Medical University, Khyber Pakhtunkhwa, Pakistan. ¹³Anesthesia and Intensive Care, Rianimazione I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ¹⁴Virology Research Center, National Institutes of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹⁵Department of Pediatrics, Division of Pediatric Infectious Diseases, Selcuk University Faculty of Medicine, Konya, Turkey. ¹⁶College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; Department of Pediatrics, King Fahad Hospital of the University, Al-Khobar, Saudi Arabia. ¹⁷Intensive Care Unit, Hôpital Européen, Marseille, France. ¹⁸Immunology Department, Hospital 12 de Octubre, Research Institute imas12, Complutense University, Madrid, Spain. ¹⁹Immunology Department, Asturias Central University Hospital, Biosanitary Research Institute of the Principality of Asturias (ISPA), Oviedo, Spain. ²⁰Emergency and Critical Care Medicine Departments, College of Medicine, Imam Abdulrahman Ben Faisal University, Dammam, Saudi Arabia. ²¹Clinical Immunology and Primary Immunodeficiencies Unit, Hospital Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, Barcelona, Spain; Universitat de Barcelona, Barcelona, Spain. ²²Department of Biological Immunology, Necker Hospital for Sick Children, AP-HP and INEM, Paris, France. ²³Internal Medicine Department, Hôpital Lariboisière, AP-HP, Paris, France; Université de Paris, Paris, France. ²⁴Internal Medicine Department, Pitié-Salpêtrière Hospital, Paris, France. ²⁵Department of Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²⁶Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, AP-HP, Créteil, France; Groupe de Recherche Clinique CARMAS, Faculté de Santé de Créteil, Université Paris Est Créteil, Créteil, France. ²⁷INSERM U1163, University of Paris, Imagine Institute, Paris, France and Pediatric Neurology Department, Necker-Enfants malades Hospital, AP-HP, Paris, France. ²⁸Hospital U. de Tarragona Joan XXIII. Universitat Rovira i Virgili (URV). IISPV, Tarragona, Spain. ²⁹Department of Propedeutics of Pediatrics and Medical Genetics, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine. ³⁰Department of Immunology and Allergy, Konya City Hospital, Konya, Turkey. ³¹Private Practice, Paris, France. ³²INSERM U1109, University of Strasbourg, Strasbourg, France. ³³Necker Hospital for Sick Children, AP-HP, Paris, France. ³⁴Molecular Virology Unit, Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ³⁵Department of Infectious Diseases, CHU de Caen, Caen, France. ³⁶Consorcio Hospital General Universitario, Valencia, Spain. ³⁷Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ³⁸Department of Urology, Nephrology, Transplantation, AP-HP-SU, Sorbonne Université, INSERM U 1082, Paris, France. ³⁹Cell Factory and Pediatric Hematology-Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ⁴⁰Yildirim Beyazit University, Faculty of Medicine, Ankara City Hospital, Children's Hospital, Ankara, Turkey. ⁴¹University of Lyon, CIRI, INSERM U1111, National Referee Centre RAISE, Pediatric Rheumatology, HFME, Hospices Civils de Lyon, Lyon, France. ⁴²Center for Clinical Immunology, CABA, Buenos Aires, Argentina. ⁴³Cruces University Hospital, Bizkaia, Spain. ⁴⁴Paediatric Immunology and Vaccinology Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland. ⁴⁵University Hospital and Research Institute "Germans Trias i Pujol," Badalona, Spain. ⁴⁶Hematology, Georges Pompidou Hospital, AP-HP, Paris, France. ⁴⁷Pediatric Infectious Diseases Unit, Instituto de Investigación Hospital 12 de Octubre (imas12), Hospital Universitario 12 de Octubre, Universidad Complutense, Madrid, Spain. ⁴⁸Infectious disease Unit, Pitié-Salpêtrière Hospital, AP-AP, Paris, France. ⁴⁹Department of Pediatrics, Thomayer's Hospital, first Faculty of Medicine, Charles University, Prague, Czech Republic; Department of Immunology, Motol University Hospital, Second Faculty of Medicine, Charles University, Prague, Czech Republic. ⁵⁰Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain. ⁵¹Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. ⁵²Service de Pneumologie, Hôpital Bichat, AP-HP, Paris, France. ⁵³Department of Infectious Diseases, CIC1408, GIMAP CIRI INSERM U1111, University Hospital of Saint-Etienne, Saint-Etienne, France. ⁵⁴Clinical 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. ⁵⁵Bégin Military Hospital, St Mandé, France. ⁵⁶Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), AP-HP, Hôpital Pitié Salpêtrière, Service de Virologie, Paris, France. ⁵⁷Endocrinology Unit, AP-HP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ⁵⁸Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. ⁵⁹Pneumology Unit, Tenon Hospital, AP-HP, Paris, France. ⁶⁰Department of Respiratory Diseases, Hospital Clínico y Universitario de Valencia, Valencia, Spain. ⁶¹Intensive Care Unit, Réseau Hospitalier Neuchâtelois, Neuchâtel, Switzerland. ⁶²Infectious Diseases Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ⁶³Human Genome and Stem Cell Research Center, University of São Paulo, São Paulo, Brazil. ⁶⁴Department of Internal Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. ⁶⁵Hospital Insular, Las Palmas de Gran Canaria, Spain. ⁶⁶MS Center, Spedali Civili, Brescia, Italy. ⁶⁷Laboratoire d'Immunorhumatologie Moléculaire, plateforme GENOMAX, INSERM UMR_S

1109, Faculté de Médecine, ITI TRANSPLANTE NG, Université de Strasbourg, Strasbourg, France. ⁶⁸Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

⁶⁹Neuromuscular Unit, Neurology Department, Hospital Universitari de Bellvitge-IDIBELL and CIBERER, Barcelona, Spain. ⁷⁰Hôpital Robert Debré, Paris, France. ⁷¹Pediatric Immunohematology Unit, Necker Enfants Malades Hospital, AP-HP, Paris, France. ⁷²Department of Infectious and Tropical Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ⁷³Doctoral Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁷⁴Hôpital Foch, Suresnes, France. ⁷⁵Selcuk University Faculty of Medicine, Department of Anesthesiology and Reanimation, Intensive Care Medicine Unit, Konya, Turkey. ⁷⁶Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale and Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland. ⁷⁷Necker Hospital for Sick Children, Paris University, AP-HP, Paris, France. ⁷⁸Pasteur Institute, Paris, France. ⁷⁹McGill University Health Centre, Montreal, Canada. ⁸⁰University Hospital and Research Institute "Germans Trias i Pujol," IrsiCaixa AIDS Research Institute, Uvic-UCC, Badalona, Spain. ⁸¹Clinical Biochemistry, Pathology, Pediatric Neurology and Molecular Medicine Departments and Biobank, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Esplugues, Spain. ⁸²AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; University Sorbonne Paris Nord, Bobigny, France; INSERM, U942, F-75010, Paris, France. ⁸³Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁸⁴Pitié-Salpêtrière Hospital, Paris, France. ⁸⁵Service de médecine Intensive Réanimation, Groupe Hospitalier Pitié-Salpêtrière, Sorbonne Université, Paris, France. ⁸⁶Umranıye Training and Research Hospital, Istanbul, Turkey. ⁸⁷Faculty of Medical Sciences at University "Goce Delcev," Shkup, North Macedonia. ⁸⁸Department of Biochemistry, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. ⁸⁹Fundació Docència i Recerca Mutua Terrassa, Barcelona, Spain. ⁹⁰Maladies Infectieuses et Tropicales, Nouvel Hôpital Civil, CHU Strasbourg, Strasbourg, France. ⁹¹UNSW Medicine, St Vincent's Clinical School, Sydney, NSW, Australia; Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst, Sydney, NSW, Australia. ⁹²Intensive Care Unit, Montreuil Hospital, Montreuil, France. ⁹³CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium. ⁹⁴Pediatric Intensive Care Unit, Robert-Debré University Hospital, AP-HP, Paris, France. ⁹⁵General Internal Medicine, University Hospitals Leuven, Leuven, Belgium. ⁹⁶Hôpital Jean Verdier, AP-HP, Bondy, France. ⁹⁷Specialized Immunology Laboratory of Dr. Shahrooei, Sina Medical Complex, Ahvaz, Iran. ⁹⁸Centre de génétique humaine, CHU Besançon, Besançon, France. ⁹⁹Sorbonne Université médecine and AP-HP Sorbonne université site Pitié-Salpêtrière, Paris, France. ¹⁰⁰Pediatric Neurology Department, Necker-Enfants Malades Hospital, AP-HP, Paris, France. ¹⁰¹Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. ¹⁰²Intensive Care Unit, Georges Pompidou Hospital, AP-HP, Paris, France. ¹⁰³Department of Pneumology, AZ Delta, Roeselare, Belgium. ¹⁰⁴Molecular Diagnostic Unit, Fundación Rioja Salud, Logroño, La Rioja, Spain. ¹⁰⁵Bégin Military Hospital, Saint Mandé, France. ¹⁰⁶Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ¹⁰⁷Bursa City Hospital, Bursa, Turkey. ¹⁰⁸Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ¹⁰⁹Tokyo Medical and Dental University, Tokyo, Japan. ¹¹⁰Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey. ¹¹¹Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. ¹¹²Intensive Care Medicine, Donostia University Hospital, Biodonostia Institute of Donostia, CIBER Enfermedades Respiratorias ISCIII, Donostia, Spain. ¹¹³Internal Medicine, University Hospital Edouard Herriot, Hospices Civils de Lyon, Lyon, France. ¹¹⁴Centre de Génétique, CHU Dijon, Dijon, France. ¹¹⁵Robert Debré Hospital, Paris, France. ¹¹⁶AP-HP Tenon Hospital, Paris, France. ¹¹⁷Sorbonne Universités, UPMC University of Paris, Paris, France. ¹¹⁸Department of Clinical Immunology, Hospital Clínico San Carlos, Madrid, Spain. ¹¹⁹Intensive Care Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain; Shock, Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ¹²⁰Intensive Care Unit, Hospital Clínico y Universitario de Valencia, Valencia, Spain. ¹²¹Genomics 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, Santa Cruz de Tenerife, Spain. ¹²²CHU Limoges and INSERM CIC 1435 and UMR 1092, Limoges, France. ¹²³Infectious 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. ¹²⁴Department of Pathology, United Christian Hospital, Hong Kong, China. ¹²⁵Institute of Genetics and Biophysics "Adriano Buzzati-Traverso," IGB-CNR, Naples, Italy. ¹²⁶Department of Pediatrics, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Josip Juraj Strossmayer University of Osijek, Medical Faculty Osijek, Osijek, Croatia. ¹²⁷Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ¹²⁸Hematology, AP-HP, Hôpital Européen Georges Pompidou and INSERM UMR-S1140, Paris, France. ¹²⁹Faculty of Medicine, Department of Pediatrics, Division of

Pediatric Infectious Diseases, Karadeniz Technical University, Trabzon, Turkey. ¹³⁰Division of Immunology, Hospital General Universitario and Instituto de Investigación Sanitaria "Gregorio Marañón," Madrid, Spain. ¹³¹Bégin Military Hospital, Bégin, France. ¹³²Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, IHU Méditerranée Infection, Marseille, France, French Armed Forces Center for Epidemiology and Public Health (CESPA), Marseille, France. ¹³³Pediatric Intensive Care Unit, Hospital Sant Joan de Déu, Barcelona, Spain. ¹³⁴Gestión Integral en Salud, Guatemala. ¹³⁵Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ¹³⁶Immunodeficiencies Unit, Research Institute Hospital, Madrid, Spain. ¹³⁷Primary Immunodeficiencies Unit, Pediatrics, University Hospital 12 de Octubre, Madrid, Spain; School of Medicine Complutense University of Madrid, Madrid, Spain. ¹³⁸Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain. ¹³⁹Assistance Publique Hôpitaux de Paris, Paris, France. ¹⁴⁰Ankara City Hospital, Ankara, Turkey. ¹⁴¹Department of Intensive Care, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ¹⁴²Immunodeficiency Outpatient Clinic, Institute for Medical Immunology, FOCIS Center of Excellence, Charité Universitätsmedizin Berlin, Germany. ¹⁴³Surgical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. ¹⁴⁴CNAG-CRG, Barcelona Institute of Science and Technology, Barcelona, Spain. ¹⁴⁵Department of Internal Medicine, National Reference Center for Rare Systemic Autoimmune Diseases, AP-HP, APHP-CUP, Hôpital Cochin, Paris, France. ¹⁴⁶Department of Paediatric Immunology and Pulmonology, Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Center, PID Research Lab, Ghent University Hospital, Ghent, Belgium. ¹⁴⁷Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, UAE, Sharjah, UAE. ¹⁴⁸Department of Biosciences and Nutrition, SE14183, Huddinge, Karolinska Institutet, Stockholm, Sweden. ¹⁴⁹Department of Pediatrics (Infectious Diseases), Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey. ¹⁵⁰I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. ¹⁵¹Pediatric Infectious Diseases Unit, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹⁵²Health Sciences University, Darica Farabi Education and Research Hospital, Koçaeli, Turkey. ¹⁵³Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁵⁴Department of Paediatrics, Queen Elizabeth Hospital, Hong Kong, China. ¹⁵⁵Intensive Care Unit, Marqués de Valdecilla Hospital, Santander, Spain. ¹⁵⁶Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), UAB, UPF, Barcelona, Spain. ¹⁵⁷Intensive Care Unit, APHM, Marseille, France. ¹⁵⁸CHU Lille, Lille, France. ¹⁵⁹Department of Medicine, University of Hong Kong, Hong Kong, China. ¹⁶⁰Department of Pediatrics, Columbia University, New York, NY, USA. ¹⁶¹Centre hospitalier intercommunal Poissy Saint Germain en Laye, Poissy, France. ¹⁶²IHU Méditerranée Infection, Service de l'Information Médicale, Hôpital de la Timone, Marseille, France. ¹⁶³Health Science University Ankara City Hospital, Ankara, Turkey. ¹⁶⁴School of Medicine, General Surgery Department Fevzi Çakmak Mah, Marmara University, Istanbul, Turkey. ¹⁶⁵Mersin City Education and Research Hospital, Mersin, Turkey. ¹⁶⁶Division of Pediatric Infectious Diseases, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey. ¹⁶⁷Departments of Infectious Diseases and Clinical Microbiology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹⁶⁸Department of Pediatric Rheumatology, Istanbul University-Cerrahpasa, Istanbul, Turkey. ¹⁶⁹Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan. ¹⁷⁰Health Sciences University, Umraniye Education and Research Hospital, Istanbul, Turkey. ¹⁷¹Department of Parasitology and Research Center for Infectious Disease Sciences, Graduate School of Medicine, Osaka City University, Osaka, Japan. ¹⁷²Pediatric Infectious Diseases Unit of Osman Gazi University Medical School in Eskişehir, Turkey. ¹⁷³Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey. ¹⁷⁴Department of Immunology, Second Faculty of Medicine, Charles University and University Hospital in Motol, Prague, Czech Republic. ¹⁷⁵ICU, First Department of Respiratory Medicine, National and Kapodistrian University of Athens, Medical School, "Sotiria" General Hospital of Chest Diseases, Athens, Greece. ¹⁷⁶Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland. ¹⁷⁷Clinique des soins intensifs, HFR Fribourg, Fribourg, Switzerland. ¹⁷⁸Oncobiologie Génétique Bioinformatique, PC Bio, CHU Besançon, Besançon, France. ¹⁷⁹Department of Intensive Care, Tuen Mun Hospital, Hong Kong, China. ¹⁸⁰Paediatric Infectious Disease Unit, Hospital Authority Infectious Disease Center, Princess Margaret Hospital, Hong Kong (Special Administrative Region), China. ¹⁸¹Department of Pathology, Queen Mary Hospital, Hong Kong, China. ¹⁸²Aix Marseille Univ, IRD, MEPIH, IHU Méditerranée Infection, Marseille, France. ¹⁸³Department of Paediatrics, Tuen Mun Hospital, Hong Kong, China. ¹⁸⁴Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ¹⁸⁵Necker Hospital, Paris, France. ¹⁸⁶Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong, China. ¹⁸⁷National Centre for Infectious Diseases, Singapore, Singapore. ¹⁸⁸Hospital Universitario Reina Sofía, Cordoba, Spain. ¹⁸⁹Imperial College, London, England. ¹⁹⁰Hospital General San Juan de Dios, Ciudad de Guatemala, Guatemala. ¹⁹¹Endocrinology and Diabetes for Children, AP-HP, Bicêtre Paris-saclay hospital, Le Kremlin-Bicêtre, France. ¹⁹²Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ¹⁹³Neurology Unit, AP-HP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹⁹⁴Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China. ¹⁹⁵Intensive Care Unit, AP-HP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹⁹⁶National Centre for Infectious Diseases, Singapore, Singapore; Tan Tock Seng Hospital, Singapore, Singapore; Yong Loo Lin School of Medicine, Singapore, Singapore; Lee Kong Chian School of Medicine, Singapore, Singapore. ¹⁹⁷Hospital de Niños Dr. Ricardo Gutierrez, Buenos Aires, Argentina. ¹⁹⁸Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹⁹⁹Neurooncology and Neuroinflammation Unit, IRCCS Mondino Foundation, Pavia, Italy. ²⁰⁰Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²⁰¹Coordenadora da Unidade de Infecçologia e Imunodeficiências do Serviço de Pediatria, Centro Materno-Infantil do Norte, Porto, Portugal. ²⁰²Hospital Sant Joan de Déu and University of Barcelona, Barcelona, Spain. ²⁰³Pediatric 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. ²⁰⁴Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain. ²⁰⁵IrsiCaixa AIDS Research Institute, ICREA, UVic-UCC, Research Institute "Germans Trias i Pujol," Badalona, Spain. ²⁰⁶Department of Laboratory, Cruces University Hospital, Barakaldo, Bizkaia, Spain, Bizkaia, Spain. ²⁰⁷Intensive Care Unit, Hospital General Universitario "Gregorio Marañón," Madrid, Spain. ²⁰⁸University of New South Wales, Sydney, NSW, Australia. ²⁰⁹AP-HP Pitié-Salpêtrière Hospital, Paris, France. ²¹⁰Department of Pediatrics, Complejo Hospitalario Universitario Insular-Materno Infantil, Canarian Health System, Las Palmas de Gran Canaria, Spain. ²¹¹Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. ²¹²Aix-Marseille University, APHM, Marseille, France. ²¹³Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris (AP-HP), Groupe de Recherche Clinique CARMAS, Faculté de Santé de Créteil, Université Paris Est Créteil, France. ²¹⁴AP-HP Cohin Hospital, Paris, France. ²¹⁵Department of Critical Care Medicine, Ente Ospedaliero Cantonale, Bellinzona, Switzerland. ²¹⁶Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Infectious Diseases, Konya, Turkey. ²¹⁷Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium; KU Leuven, Department of Microbiology, Immunology and Transplantation; Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium. ²¹⁸Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Lyon, France. ²¹⁹Hôpital Erasme, Brussels, Belgium. ²²⁰Centre hospitalier de gonesse, Gonesse, France. ²²¹Aix Marseille Univ, IRD, AP-HM, MEPIH, IHU Méditerranée Infection, Marseille, France. ²²²Vascular Medicine, Georges Pompidou Hospital, AP-HP, Paris, France. ²²³Institut Jérôme Lejeune, Paris, France. ²²⁴Division of Pulmonary and Critical Care, College of Medicine-Jacksonville, University of Florida, Jacksonville, FL, USA. ²²⁵Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan. ²²⁶BC Children's Hospital Research Institute, University of British Columbia, Vancouver, BC, Canada. ²²⁷Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris (AP-HP), Créteil, France. ²²⁸Guanarteme Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ²²⁹Regional University Hospital of Malaga, Malaga, Spain. ²³⁰Department of Immunology, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²³¹Aix Marseille Univ, INSERM, INRAE, C2VN, Marseille, France. ²³²Department of General Paediatrics, Hôpital Bicêtre, AP-HP, University of Paris Saclay, Le Kremlin-Bicêtre, France. ²³³INSERM U1144, Université de Paris, DMU INVICTUS, AP-HP Nord, Département de Médecine Interne, Lariboisière Hospital, Paris, France. ²³⁴CHU de La Timone, Marseille, France. ²³⁵Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ²³⁶Pediatric Immunology and Rheumatology Department, Necker Hospital, AP-HP, Paris, France. ²³⁷Centro Hospitalar Universitario de Lisboa Central, Lisbon, Portugal. ²³⁸Infectious Disease Horizontal Technology Centre, A*STAR, Singapore, Singapore; Singapore Immunology Network, A*STAR, Singapore. ²³⁹Department of Medicine and Geriatrics, Tuen Mun Hospital, Hong Kong, China. ²⁴⁰Regional University Hospital of Malaga, Málaga, Spain. ²⁴¹Department of Immunology, Hospital Universitario Marqués de Valdecilla, Santander, Spain. ²⁴²Bilkent University, Department of Molecular Biology and Genetics, Ankara, Turkey. ²⁴³BRFAA, Athens, Greece. ²⁴⁴IHU Méditerranée Infection, Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, IHU Méditerranée Infection, Marseille, France. ²⁴⁵L'Hôpital Foch, Suresnes, France. ²⁴⁶Department of Immunology, CIC1408, GIMAP CIRI INSERM U1111, University Hospital of Saint-Etienne, Saint-Etienne, France. ²⁴⁷Department of Immunology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain. ²⁴⁸Unit of Biochemistry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. ²⁴⁹Diabetes Research Institute, IRCCS San Raffaele Hospital, Milan, Italy. ²⁵⁰AP-HP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ²⁵¹AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; INSERM UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), University of Paris, Paris, France. ²⁵²Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona; CIBERER U759, ISCIII Madrid, Spain. ²⁵³Hospices Civils de Lyon, Lyon, France. ²⁵⁴Univ. Lille, INSERM U1285, CHU Lille, Pôle de médecine intensive-réanimation, CNRS, UMR 8576-Unité de Glycobiologie Structurale et Fonctionnelle, Lille, France. ²⁵⁵Department of General pediatrics, Robert Debre Hospital, Paris, France. ²⁵⁶University of British Columbia, Vancouver, BC, Canada. ²⁵⁷Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain; Diagnostic Immunology Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ²⁵⁸AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France;

University Sorbonne Paris Nord, Bobigny, France.²⁵⁹Centre Hospitalier de Saint-Denis, St Denis, France.²⁶⁰Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.²⁶¹Paris Cardiovascular Center, PARCC, INSERM, Université de Paris, Paris, France.²⁶²Germans Trias i Pujol Hospital, Badalona, Spain.²⁶³Medical Intensive Care Unit, Hospital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France.²⁶⁴Department of Clinical Laboratory, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain.²⁶⁵Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus., Barcelona, Spain.²⁶⁶Université de Paris, CNRS UMR-8601, Paris, France; Team Chemistry and Biology, Modeling and Immunology for Therapy, CBMIT, Paris, France.²⁶⁷Germans Trias i Pujol University Hospital and Research Institute, Badalona, Spain.²⁶⁸Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain.²⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), 08908 L'Hospitalet de Llobregat, Barcelona, Spain; University Hospital Germans Trias i Pujol, Badalona, Barcelona, Catalonia, Spain.²⁷⁰Consorcio Hospital General Universitario, Valencia, Spain.²⁷¹AP-HP Hôpitaux Universitaires Paris-Sud, Paris, France.²⁷²Intensive Care Unit, Louis-Mourier Hospital, Colombes, France.²⁷³Virology Unit, Université de Paris, Cochin Hospital, AP-HP, Paris, France.²⁷⁴Neurometabolic Diseases Laboratory and CIBERER U759, Barcelona, Spain.²⁷⁵Hospital San Pedro, Logroño, Spain.²⁷⁶University of Tartu, Institute of Biomedicine and Translational Medicine, Tartu, Estonia.²⁷⁷Respiratory Medicine, Georges Pompidou Hospital, AP-HP, Paris, France.²⁷⁸Infectious Diseases Department, International Health Program of the Catalan Institute of Health (PROSICS), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain.²⁷⁹Hospital Clínico San Carlos and IdSSC, Madrid, Spain.²⁸⁰Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil.²⁸¹AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France.²⁸²Service de Médecine Intensive Réanimation, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France.²⁸³Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.²⁸⁴CHRU de Nancy, Hôpital d'Enfants, Vandoeuvre, France.²⁸⁵Chair of Nephrology, University of Brescia, Brescia, Italy.²⁸⁶Department of Immunology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic.²⁸⁷Clinica Universidad de Navarra and Ciberes, Madrid, Spain.²⁸⁸HUS Helsinki University Hospital, Children and Adolescents, Rare Disease Center, and Inflammation Center, Adult Immunodeficiency Unit, Majakka, Helsinki, Finland.²⁸⁹Fundació Docencia i Recerca Mutua Terrassa, Terrassa, Spain.²⁹⁰D. Rogachev National Medical and Research Center of Pediatric Hematology, Oncology, Immunology, Moscow, Russia.²⁹¹Haematology Laboratory, Lariboisière Hospital, University of Paris, Paris, France.²⁹²Biomedical Research Foundation of the Academy of Athens, Athens, Greece.²⁹³INSERM U1140, University of Paris, European Georges Pompidou Hospital, Paris, France.²⁹⁴Department of Pediatrics, Faculty of Medicine, Mansoura University, Mansoura, Egypt.²⁹⁵Intensive Care Medicine, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain.²⁹⁶CHU de Saint Etienne, Saint-Priest-en-Jarez, France.²⁹⁷Pediatric 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; EU, Barcelona, Spain.²⁹⁸Department of Pediatric Infectious Diseases and Pediatric Immunology, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine.²⁹⁹Gustave Roussy Cancer Campus, Villejuif, France.³⁰⁰Intensive Care Unit, Avicenne Hospital, AP-HP, Bobigny, France.³⁰¹Laboratory of Immunology and Histocompatibility, Saint-Louis Hospital, Paris University, Paris, France.³⁰²Center for Inflammation Research, Laboratory of Molecular Signal Transduction in Inflammation, VIB, Ghent, Belgium.³⁰³Department of Internal Medicine, Université de Paris, INSERM, U970, PARCC, F-75015, Paris, France.³⁰⁴Service de médecine intensive réanimation, CHU de Saint-Etienne, France.³⁰⁵Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.³⁰⁶University of Management and Technology, Lahore, Pakistan.³⁰⁷Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark.³⁰⁸First Division of Anesthesiology and Critical Care Medicine, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy.³⁰⁹Intensive Care Department, Hospital Universitari MutuaTerrassa, Universitat Barcelona, Terrassa, Spain.³¹⁰Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece.³¹¹International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France; Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France.³¹²Infanta Leonor University Hospital, Madrid, Spain.³¹³Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong, China.³¹⁴University of Tartu, Institute of Clinical Medicine, Tartu, Estonia.³¹⁵Department of Medicine, United Christian Hospital, Hong Kong, China.³¹⁶Hematology Department, ASST Spedali Civili di Brescia, Brescia, Italy.³¹⁷Pneumologie, Hôpital Avicenne, AP-HP, INSERM U1272, Université Sorbonne Paris Nord, Bobigny, France.³¹⁸Dermatology Unit, Laboratoire GAD, INSERM UMR1231 LNC, Université de Bourgogne, Dijon, France.³¹⁹University Hospital of Burgos, Burgos, Spain.³²⁰Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.³²¹Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain.³²²University of São Paulo, São Paulo,

Brazil.³²³CHU de Caen, Caen, France.³²⁴Hospital del Mar–IMIM Biomedical Research Institute, Barcelona, Catalonia, Spain.³²⁵Neglected Human Genetics Laboratory, INSERM, University of Paris, Paris, France.³²⁶Sorbonne Université, Service de Médecine Intensive Réanimation, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France.³²⁷Pediatric Infectious Disease and Pediatric Immunology Department, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine.³²⁸Department of Pneumology, University Hospitals Leuven, Leuven, Belgium.³²⁹Laboratory for Clinical Infectious and Inflammatory Disorders, Department of Microbiology, Immunology, and Transplantation, Leuven, Belgium.³³⁰Department of Clinical Pathology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China.³³¹Department of Medicine, Queen Elizabeth Hospital, Hong Kong, China.³³²Ankara City Hospital, Children's Hospital, Ankara, Turkey.³³³Division of Pediatric Infectious Disease, Department of Pediatrics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.³³⁴Health Sciences University, Lütfi Kırdar Kartal Education and Research Hospital, Istanbul, Turkey.³³⁵Department of Nephrology and Infectiology, AZ Sint-Jan, Bruges, Belgium.³³⁶Department of Pulmonology, Ghent University Hospital, Belgium.³³⁷Department of Pediatric Pulmonology and Immunology, Ghent University Hospital, Ghent, Belgium.³³⁸Department of Intensive Care Unit, Ghent University Hospital, Ghent, Belgium.³³⁹Department of Pediatric Hemato-oncology, Jolimont Hospital, La Louvière, Belgium.³⁴⁰Department of Pulmonology, ZNA Middelheim, Antwerp, Belgium.³⁴¹Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium.³⁴²Department of Pediatric Immuno-hématology-rheumatology, CHR Citadelle, Liège, Belgium.³⁴³Department of Pediatric Hemato-oncology, UCL Louvain, Brussels, Belgium.³⁴⁴Department of Pediatrics, Saint Luc, UCL Louvain, Brussels Belgium.³⁴⁵Intensive Care Unit, Grand Hôpital de l'Est Francilien Site de Marne-La-Vallée, Jossigny, France.

Members of Imagine COVID Group: Jean-Philippe Annereau¹, Luis Briseño-Roa¹, Olivier Gribouval², Anna Pelet²

¹Medetia Pharmaceuticals, Paris, France. ²Imagine Institute, Université de Paris, INSERM UMR 1163, Paris, France.

Members of French COVID Cohort Study Group: Laurent Abel¹, Claire Andrejak², François Angoulvant³, Delphine Bachelet⁴, Marie Bartoli⁵, Romain Basmaci⁶, Sylvie Behillil⁷, Marine Beluze⁸, Dehbia Benkerrou⁹, Krishna Bhavsar⁴, Lila Bouadma⁴, Sabelline Bouchez¹⁰, Maude Bouscambert¹¹, Minerva Cervantes-Gonzalez⁴, Anissa Chair⁴, Catherine Chirouze¹², Alexandra Coelho¹³, Camille Couffignal⁴, Sandrine Couffin-Cadiergues¹⁴, Eric d'Ortenzio⁵, Marie-Pierre Debray⁴, Lauren Deconinck⁴, Dominique Deplanque¹⁵, Diane Descamps⁴, Mathilde Desvallée¹⁶, Alpha Diallo⁵, Alphonsine Diour¹³, Céline Dorival⁹, François Dubos¹⁷, Xavier Duval⁸, Brigitte Elharrar¹⁸, Philippine Eloy⁴, Vincent Enouf⁷, Hélène Esperou¹⁴, Marina Esposito-Farese⁴, Manuel Etienne¹⁹, Eglantine Ferrand Devouge¹⁹, Nathalie Gault⁴, Alexandre Gaymard¹¹, Jade Ghosn⁴, Tristan Gigante²⁰, Morgane Gilg²⁰, Jérémie Guedj²¹, Alexandre Hocht¹³, Isabelle Hoffmann⁴, Ikram Houas¹⁴, Jean-Sébastien Hulot²², Salma Jaafoura¹⁴, Ouifia Kafif⁷, Florentia Kaguelidou²³, Sabrina Kali⁴, Antoine Khalil⁴, Coralie Khan¹⁶, Cédric Lauouénan⁴, Samira Laribi⁴, Minh Le⁴, Quentin Le Hingrat⁴, Soizic Le Mestre⁵, Hervé Le Nagard²⁴, François-Xavier Lescure⁴, Sophie Letrou⁴, Yves Levy²⁵, Bruno Lina¹¹, Guillaume Lingas²⁴, Jean Christophe Lucet⁴, Denis Malvy²⁶, Marina Mambert¹³, France Mentré⁴, Amina Meziane⁹, Hugo Mouquet⁷, Jimmy Mullaert⁴, Nadège Neant²⁴, Duc Nguyen²⁶, Marion Noret²⁷, Saad Nseir¹⁷, Aurélie Papadopoulos¹⁴, Christelle Paul⁵, Nathan Peiffer-Smadja⁴, Thomas Perpoint²⁸, Ventzislava Petrov-Sanchez⁵, Gilles Peytavin⁴, Huong Pham⁴, Olivier Picone⁹, Valentine Piquard⁴, Oriane Puéchal²⁹, Christian Rabaud³⁰, Manuel Rosa-Calatrava¹¹, Bénédicte Rossignol²⁰, Patrick Rouégnol³⁰, Carine Roy⁷, Marion Schneider⁴, Richa Su⁴, Coralie Tardivon⁴, Marie-Capucine Tellier⁴, François Téoulé⁹, Olivier Terrier¹¹, Jean-François Timsit⁴, Christelle Tual³¹, Sarah Tubiana⁴, Sylvie Van Der Werf⁷, Noémie Vanel³², Aurélie Veislinger³¹, Benoit Visseaux⁴, Aurélie Wiedemann²⁵, Yazdan Yazdanpanah⁴

¹INSERM UMR 1163, Paris, France. ²CHU Amiens, Amiens, France. ³Hôpital Necker, Paris, France. ⁴Hôpital Bichat, Paris, France. ⁵ANRS, Paris, France. ⁶Hôpital Louis Mourier, Colombes, France. ⁷Pasteur Institute, Paris, France. ⁸F-CRIN Partners Platform, Paris, France. ⁹INSERM UMR 1136, Paris, France. ¹⁰CHU Nantes, France. ¹¹INSERM UMR 111, Lyon, France. ¹²CHRU Jean Minjoz, Besançon, France. ¹³INSERM UMR 1018, Paris, France. ¹⁴INSERM Sponsor, Paris, France. ¹⁵Centre d'Investigation Clinique, INSERM CIC 1403, Centre Hospitalo universitaire de Lille, Lille, France. ¹⁶INSERM UMR 1219, Bordeaux, France. ¹⁷CHU Lille, Lille, France. ¹⁸CHI de Créteil, Créteil, France. ¹⁹CHU Rouen, Rouen, France. ²⁰F-CRIN INI-CRCT, Nancy, France. ²¹Université de Paris, INSERM, IAME, F-75018 Paris, France. ²²Hôpital Européen Georges Pompidou, Paris, France. ²³Hôpital Robert Debré, Paris, France. ²⁴INSERM UMR 1137, Paris, France. ²⁵Vaccine Research Institute (VRI), INSERM UMR 955, Créteil, France. ²⁶CHU Bordeaux, Bordeaux, France. ²⁷RENARCI, Annecy, France. ²⁸CHU Lyon, Lyon, France. ²⁹REACTing, Paris, France. ³⁰CHU Nancy, Nancy, France. ³¹INSERM CIC-1414, Rennes, France. ³²Hôpital la Timone, Marseille, France.

Members of CoV-Contact Cohort: Loubna Alavoine¹, Sylvie Behillil², Charles Burdet³, Charlotte Charpentier⁴, Aline Dechanet⁵, Diane Descamps⁶, Xavier Duval⁷, Jean-Luc Ecobichon¹, Vincent Enouf⁸, Wahiba Frezouls¹, Nadhira Houhou⁵, Ouifia Kafif⁹, Jonathan Lehacaut¹, Sophie Letrou¹, Bruno Lina⁹, Jean-Christophe Lucet¹⁰, Pauline Manchon⁵, Mariama Nourouline¹,

Valentine Piquard⁵, Caroline Quintin¹, Michael Thy¹¹, Sarah Tubiana¹, Sylvie van der Werf⁶, Valérie Vignali¹, Benoit Visseaux¹⁰, Yazdan Yazdanpanah¹⁰, Abir Chahine¹², Nawal Waucquier¹², Maria-Claire Migaud¹², Dominique Deplanque¹², Félix Djossou¹³, Mayka Mergeay-Fabre¹⁴, Aude Locarelli¹⁵, Magalie Demar¹³, Léa Bruneau¹⁶, Patrick Gérardin¹⁷, Adrien Maillot¹⁶, Christine Payet¹⁸, Bruno Laviolle¹⁹, Fabrice Laine¹⁹, Christophe Paris¹⁹, Mireille Desille-Dugast¹⁹, Julie Fouchard¹⁹, Denis Malvy²⁰, Duc Nguyen²⁰, Thierry Pistone²⁰, Pauline Perreau²⁰, Valérie Gissot²¹, Carole L. E. Goas²¹, Samatha Montagne²², Lucie Richard²³, Catherine Chirouze²⁴, Kévin Bouiller²⁴, Maxime Desmaret²⁵, Alexandre Meunier²⁶, Benjamin Lefèvre²⁷, Hélène Jeulin²⁸, Karine Legrand²⁹, Sandra Lomazzi³⁰, Bernard Tardy³¹, Amandine Gagneux-Brunon³², Frédérique Bertholon³³, Elisabeth Botelho-Nevers³², Kouakam Christelle Kouakam Christelle³⁴, Leturque Nicolas Leturque Nicolas³⁴, Layid Roufai³⁴, Karine Amat³⁵, Sandrine Couffin-Cadiergues³⁴, Hélène Espérou³⁶, Samia Hendou³⁴

¹Centre d'Investigation Clinique, INSERM CIC 1425, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ²Institut Pasteur, Paris, France. ³Université de Paris, IAME, INSERM U1137, Paris, France; Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁴Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁵Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁶IAME INSERM U1140, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁷Centre d'Investigation Clinique, INSERM CIC 1425, AP-HP, IAME, Paris University, Paris, France. ⁸Institut Pasteur, U3569 CNRS, Université de Paris, Paris, France. ⁹Virpath Laboratory, International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS U5308, ENS, UCBL, Lyon, France. ¹⁰IAME INSERM U1138, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ¹¹Center for Clinical Investigation, Assistance Publique-Hôpitaux de Paris, Bichat-Claude Bernard University Hospital, Paris, France. ¹²Centre d'Investigation Clinique, INSERM CIC 1403, Centre Hospitalo universitaire de Lille, Lille, France. ¹³Service des maladies infectieuses, Centre Hospitalo universitaire de Cayenne, Guyane, France. ¹⁴Centre d'Investigation Clinique, INSERM CIC 1424, Centre Hospitalier de Cayenne, Cayenne, Guyane Française. ¹⁵Service Hôpital de jour Adulte, Centre Hospitalier de Cayenne, Guyane, France. ¹⁶Centre d'Investigation Clinique, INSERM CIC 1410, Centre Hospitalo universitaire de la Réunion, La Réunion, France. ¹⁷Centre d'Investigation Clinique, INSERM CIC 1410, CHU Reunion, Saint-Pierre, Reunion Island. ¹⁸Centre d'Investigation Clinique, INSERM CIC 1410, Centre de Ressources Biologiques, Centre Hospitalo universitaire de la Réunion, La Réunion, France. ¹⁹Centre d'Investigation Clinique, INSERM CIC 1414, Centre Hospitalo universitaire de Rennes, Rennes, France. ²⁰Service des maladies infectieuses, Centre Hospitalo universitaire de Bordeaux, Bordeaux, France. ²¹Centre d'Investigation Clinique, INSERM CIC 1415, CHRU Tours, Tours, France. ²²CRBT, Centre Hospitalo universitaire de Tours, Tours, France. ²³Pole de Biologie Médicale, Centre Hospitalo universitaire de Tours, Tours, France. ²⁴Service des maladies infectieuses, Centre Hospitalo universitaire de Besançon, Besançon, France. ²⁵Service des maladies infectieuses, Centre d'investigation clinique, INSERM CIC1431, Centre Hospitalier Universitaire de Besançon, Besançon, France. ²⁶Centre de Ressources Biologiques-Filière Microbiologique de Besançon, Centre Hospitalier Universitaire, Besançon, France. ²⁷Université de Lorraine, CHRU-Nancy and APEMAC, Infectious and Tropical Diseases, Nancy, France. ²⁸Laboratoire de Virologie, CHRU de Nancy Brabois, Vandoeuvre-lès-Nancy, France. ²⁹INSERM CIC-EC 1433, Centre Hospitalo universitaire de Nancy, Nancy, France. ³⁰Centre de ressources Biologiques, Centre Hospitalo universitaire de Nancy, Nancy, France. ³¹Centre d'Investigation Clinique, INSERM CIC 1408, Centre Hospitalo universitaire de Saint Etienne, Saint Etienne, France. ³²Service des maladies infectieuses, Centre Hospitalo universitaire de Saint Etienne, Saint Etienne, France. ³³Service des maladies infectieuses, CRB⁴²-BTK, Centre Hospitalo Universitaire de Saint Etienne, Saint Etienne, France. ³⁴Pole Recherche Clinique, INSERM, Paris, France. ³⁵IMEA Fondation Léon M'Ba, Paris, France. ³⁶INSERM Clinical Research Department, Paris, France.

Members of Amsterdam UMC Covid-19 Biobank: Michiel van Agtmael², Anne Geke Algera¹, Brent Appelman², Frank van Baarle¹, Diane Bax², Martijn Beudel¹, Harm Jan Bogaard³, Marije Bomers², Peter Bonta⁵, Lieuwe Bos¹, Michela Botta¹, Justin de Brabander², Godelieve de Bree², Sanne de Bruin¹, David T. P. Buis¹, Marianna Bugiani⁵, Esther Bulle¹, Osoul Chouchane², Alex Cloherty³, Mirjam Dijkstra¹², Dave A. Dongelmans¹, Romein W. G. Dujardin¹, Paul Elbers¹, Lucas Fleuren¹, Suzanne Geerlings⁵, Theo Geijtenbeek³, Armand Girbes¹, Bram Goorhuis², Martin P. Grobusch², Florianne Hafkamp³, Laura Hagens¹, Jorg Hamann⁷, Vanessa Harris², Robert Hemke⁸, Sabine M. Hermans⁵, Leo Heunks¹, Markus Hollmann⁶, Janneke Horn¹, Joppe W. Hovius², Menno D. de Jong⁹, Rutger Koning⁴, Endry H. T. Lim¹, Niels van Mourik¹, Jeaninne Nellen², Esther J. Nossent⁵, Frederique Paulus¹, Edgar Peters², Dan A. I. Pina-Fuentes⁴, Tom van der Poll², Bennedikt Preckel⁶, Jan M. Prins², Jorinde Raasveld¹, Tom Reijnders², Maurits C. F. J. de Rotte¹², Michiel Schinkel², Marcus J. Schultz¹, Femke A. P. Schrauwen¹², Alex Schuurmans¹⁰, Jaap Schuurmans¹, Kim Sigaloff¹, Marleen A. Slim¹², Patrick Smeel⁵, Marry Smit¹, Cornelis S. Stijns², Willemke Stijlma¹, Charlotte Teunissen¹¹, Patrick Thorat¹, Anissa M. Tsonas¹, Pieter R. Tuinman², Marc van der Valk², Denise Veelo⁶, Carolien Volleman¹, Heder de Vries¹, Lonneke A. Vught¹²,

Michèle van Vugt², Dorien Wouters¹², A. H. (Koos) Zwinderman¹³, Matthijs C. Brouwer⁴, W. Joost Wiersinga², Alexander P. J. Vlaar¹, Diederik van de Beek (d.vandebeek@amsterdamumc.nl)⁴

¹Department of Intensive Care, Amsterdam UMC, Amsterdam, Netherlands. ²Department of Infectious Diseases, 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 Anesthesiology, Amsterdam UMC, Amsterdam, Netherlands. ⁷Amsterdam UMC Biobank Core Facility, Amsterdam UMC, Amsterdam, Netherlands. ⁸Department of Radiology, Amsterdam UMC, Amsterdam, Netherlands. ⁹Department of Medical Microbiology, Amsterdam UMC, Amsterdam, Netherlands. ¹⁰Department of Internal Medicine, Amsterdam UMC, Amsterdam, Netherlands. ¹¹Neurochemical Laboratory, Amsterdam UMC, Amsterdam, Netherlands. ¹²Department of Clinical Chemistry, Amsterdam UMC, Amsterdam, Netherlands. ¹³Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, Amsterdam, Netherlands.

Members of NIAID-USUHS COVID Study Group: Miranda F. Tompkins¹, Camille Alba¹, Andrew L. Snow², Daniel N. Hupalo¹, John Rosenberger¹, Gauthaman Sukumar¹, Matthew D. Wilkerson¹, Xijun Zhang¹, Justin Lack³, Andrew J. Oler⁴, Kerry Dobbs⁵, Ottavia M. Delmonte⁵, Jeffrey J. Danielson⁵, Andrea Biondi⁶, Laura Rachele Bettini⁶, Mariella D'Angio⁶, Ilaria Beretta⁷, Luisa Imberti⁸, Alessandra Sottini⁸, Virginia Quaresima⁸, Eugenia Quiros-Roldan⁹, Camillo Rossi¹⁰

¹American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA. ²Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ³NIAID Collaborative Bioinformatics Resource, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research Inc., Frederick, MD, USA. ⁴Bioinformatics and Computational Biosciences Branch, Office of Cyber Infrastructure and Computational Biology, NIAID, NIH, Bethesda, MD, USA. ⁵Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ⁶Pediatric Department and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM-Ospedale, San Gerardo, Monza, Italy. ⁷Department of Infectious Diseases, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ⁸CREA Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia, Brescia, Italy. ⁹Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy. ¹⁰Chief Medical Officer, ASST Spedali Civili di Brescia, Brescia, Italy.

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X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19

Takaki AsanoBertrand BoissonFanny OnodiDaniela MatuozzoMarcela Moncada-VelezMajstor Raj Luxman Maglorius RenkilarajPeng ZhangLaurent MeertensAlexandre BolzeMarie MaternaSarantis KorniotisAdrian GervaisEstelle TalouarnBenedetta BigioYoann SeeleuthnerKaya BilguvarYu ZhangAnna-Lena NeehusMasato OgishiSimon J. PelhamTom Le VoyerJérémie RosainQuentin PhilippotPere Soler-PalacínRoger ColobranAndrea Martin-NaldaJacques G. RivièreYacine Tandjaoui-LambiotteKhalil ChaïbiMohammad Shahrooeillad Alavi DarazamNasrin Alipour OlyaeiDavood MansouriNevin Hatipo#uFigen PalabiyikTayfun OzelciGiuseppe NovelliAntonio NovelliGiorgio CasariAlessandro AiutiPaola CarreraSimone BondesanFederica BarzaghiPatrizia Rovere-QueriniCristina TresoldiJose Luis FrancoJulian RojasLuis Felipe ReyesIngrid G. BustosAndres Augusto AriasGuillaume MorelleChristèle KyhengJesús TroyaLaura Planas-SerraAgatha SchlüterMarta GutAurora PujolLuis M. AllendeCarlos Rodríguez-GallegoCarlos FloresOscar Cabrera-MaranteDaniel E. 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X-linked COVID-19 risk factor

Age and male sex are two prominent risk factors for developing life-threatening COVID-19 after SARS-CoV-2 infection. Asano *et al.* analyzed 1202 critical male COVID-19 patients to examine whether non-synonymous variants in genes on the X chromosome are a risk factor for developing COVID-19 pneumonia. Toll-like receptor 7 (TLR7) variants resulting in TLR7 deficiency occurred in 16 unrelated males, most of which were under age 60. Plasmacytoid dendritic cells (pDCs), primary producers of type I interferon (IFN-I), from TLR7-deficient patients were unresponsive to TLR7 stimulation and displayed impaired production of IFN-I in response to SARS-CoV-2. These results identify X-linked

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recessive TLR7 deficiency as a genetic risk factor for COVID-19 pneumonia in males and demonstrate a key role for intact pDC IFN-I in protective immunity against SARS-CoV-2.

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