

Cite as: P. Bastard *et al.*, *Science*
10.1126/science.abd4585 (2020).

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard^{1,2,3*†}, Lindsey B. Rosen^{4†}, Qian Zhang^{3†}, Eleftherios Michailidis^{5†}, Hans-Heinrich Hoffmann^{5†}, Yu Zhang^{4†}, Karim Dorgham^{6†}, Quentin Philippot^{1,2†}, Jérémie Rosain^{1,2†}, Vivien Béziat^{1,2,3†}, Jérémy Manry^{1,2}, Elana Shaw⁴, Liis Haljasmägi⁷, Pärt Peterson⁷, Lazaro Lorenzo^{1,2}, Lucy Bizien^{1,2}, Sophie Trouillet-Assant^{8,9}, Kerry Dobbs⁴, Adriana Almeida de Jesus⁴, Alexandre Belot^{10,11,12}, Anne Kallaste¹³, Emilie Catherinot¹⁴, Yacine Tandjaoui-Lambiotte¹⁵, Jeremie Le Pen⁵, Gaspard Kerner^{1,2}, Benedetta Bigio³, Yoann Seeleuthner^{1,2}, Rui Yang³, Alexandre Bolze¹⁶, Andrés N. Spaan^{3,17}, Ottavia M. Delmonte⁴, Michael S. Abers⁴, Alessandro Aiuti¹⁸, Giorgio Casari¹⁸, Vito Lampasona¹⁸, Lorenzo Piemonti¹⁸, Fabio Ciceri¹⁸, Kaya Bilguvar¹⁹, Richard P. Lifton^{19,20,21}, Marc Vasse²², David M. Smadja²³, Mélanie Migaud^{1,2}, Jérôme Hadjadj²⁴, Benjamin Terrier²⁵, Darragh Duffy²⁶, Lluís Quintana-Murci^{27,28}, Diederik van de Beek²⁹, Lucie Roussel^{30,31}, Donald C. Vinh^{30,31}, Stuart G. Tangye^{32,33}, Filomeen Haerynck³⁴, David Dalman³⁵, Javier Martinez-Picado^{36,37,38}, Petter Brodin^{39,40}, Michel C. Nussenzweig^{41,42}, Stéphanie Boisson-Dupuis^{1,2,3}, Carlos Rodríguez-Gallego^{43,44}, Guillaume Vogt⁴⁵, Trine H. Mogensen^{46,47}, Andrew J. Oler⁴⁸, Jingwen Gu⁴⁸, Peter D. Burbelo⁴⁹, Jeffrey Cohen⁵⁰, Andrea Biondi⁵¹, Laura Rachele Bettini⁵¹, Mariella D'Angio⁵¹, Paolo Bonfanti⁵², Patrick Rossignol⁵³, Julien Mayaux⁵⁴, Frédéric Rieux-Laucat²⁴, Eystein S. Husebye^{55,56,57}, Francesca Fusco⁵⁸, Matilde Valeria Ursini⁵⁸, Luisa Imberti⁵⁹, Alessandra Sottini⁵⁹, Simone Paghera⁵⁹, Eugenia Quiros-Roldan⁶⁰, Camillo Rossi⁶¹, Riccardo Castagnoli⁶², Daniela Montagna^{63,64}, Amelia Licari⁶², Gian Luigi Marseglia⁶², Xavier Duval^{65,66,67,68,69}, Jade Ghosn^{68,69}, HGID Lab§, NIAID-USUHS Immune Response to COVID Group§, COVID Clinicians§, COVID-STORM Clinicians§, Imagine COVID Group§, French COVID Cohort Study Group§, The Milieu Intérieur Consortium§, CoV-Contact Cohort§, Amsterdam UMC Covid-19 Biobank§, COVID Human Genetic Effort§, John S. Tsang^{70,71}, Raphaela Goldbach-Mansky⁴, Kai Kisand⁷, Michail S. Lionakis⁴, Anne Puel^{1,2,3}, Shen-Ying Zhang^{1,2,3}, Steven M. Holland^{4¶}, Guy Gorochoff^{6,72¶}, Emmanuelle Jouanguy^{1,2,3¶}, Charles M. Rice^{5¶}, Aurélie Cobat^{1,2,3¶}, Luigi D. Notarangelo^{4¶}, Laurent Abel^{1,2,3¶}, Helen C. Su^{4#}, Jean-Laurent Casanova^{1,2,3,42,73*#}

¹Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France. ²University of Paris, Imagine Institute, Paris, France. ³St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. ⁴Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, USA. ⁵Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, USA. ⁶Sorbonne Université, INSERM, Centre d'Immunologie et des Maladies Infectieuses, (CIMI- Paris), Paris, France. ⁷Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia. ⁸Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France. ⁹International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. ¹⁰International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. ¹¹National Referee Centre for Rheumatic and Autoimmune and Systemic Diseases in Children (RAISE), Lyon, France. ¹²Lyon Immunopathology Federation (LIFE), Hospices Civils de Lyon, Lyon, France. ¹³Internal Medicine Clinic, Tartu University Hospital, Tartu, Estonia. ¹⁴Pneumology Department, Foch Hospital, Suresne, France. ¹⁵Avicenne Hospital, Assistance Publique Hôpitaux de Paris (AP-HP), Bobigny, INSERM U1272 Hypoxia and Lung, Bobigny, France. ¹⁶Helix, San Mateo, CA, USA. ¹⁷Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands. ¹⁸IRCCS San Raffaele Hospital and Vita-Salute San Raffaele University, Milan, Italy. ¹⁹Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. ²⁰Yale Center for Genome Analysis, Yale University School of Medicine, New Haven, CT, USA. ²¹Laboratory of Human Genetics and Genomics, The Rockefeller University, New York, NY, USA. ²²Service de Biologie Clinique and UMR-S 1176, Hôpital Foch, Suresnes, France. ²³INSERM UMR-S 1140, Biosurgical Research Lab (Carpentier Foundation), Paris University and European Georges Pompidou Hospital, Paris, France. ²⁴Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, INSERM UMR 1163, University of Paris, Imagine Institute, Paris, France. ²⁵Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP), University of Paris, Paris, France. ²⁶Translational Immunology Lab, Institut Pasteur, Paris, France. ²⁷Human Evolutionary Genetics Unit, Institut Pasteur, CNRS UMR 2000, 75015, Paris, France. ²⁸Human Genomics and Evolution, Collège de France, Paris, France. ²⁹Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands. ³⁰Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, Québec, Canada. ³¹Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, Québec, Canada. ³²Garvan Institute of Medical Research, Darlinghurst 2010, NSW, Sydney, Australia. ³³St Vincent's Clinical School, Faculty of Medicine, University of New South Wales Sydney, Darlinghurst 2010, NSW, Australia. ³⁴Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPiG), PID Research Lab, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent, Belgium. ³⁵Infectious Diseases and HIV Service, Hospital Universitari Mutua Terrassa, Universitat de Barcelona, Fundació Docència i Recerca Mutua Terrassa, Terrassa, Barcelona, Catalonia, Spain. ³⁶IrsiCaixa AIDS Research Institute and Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona, Spain. ³⁷University of Vic-Central University of Catalonia (UVic-UCC), Vic, Spain. ³⁸Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain. ³⁹Science for Life Laboratory, Department of Women's and Children's Health, Karolinska Institutet, Karolinska, Sweden. ⁴⁰Department of Pediatric Rheumatology, Karolinska University Hospital, Karolinska, Sweden. ⁴¹Laboratory of Molecular Immunology, The Rockefeller University, New York, NY, USA. ⁴²Howard Hughes Medical Institute, New York, NY, USA. ⁴³Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁴⁴University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁴⁵Neglected Human Genetics Laboratory, INSERM, University of Paris, Paris, France. ⁴⁶Department of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark.

⁴⁷Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁴⁸Bioinformatics and Computational Biosciences Branch, Office of Cyber Infrastructure and Computational Biology, NIAID, NIH, Bethesda, MD, USA. ⁴⁹Division of Intramural Research, National Institute of Dental Craniofacial Research (NIDCR), NIH, Bethesda, MD, USA. ⁵⁰Laboratory of Infectious Diseases, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ⁵¹Pediatric Department and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM-Ospedale, San Gerardo, Monza, Italy. ⁵²Department of Infectious Diseases, San Gerardo Hospital - University of Milano-Bicocca, Monza, Italy. ⁵³University of Lorraine, Plurithematic Clinical Investigation Centre INSERM CIC-P 1433, INSERM U1116, CHRU Nancy Hopitaux de Brabois, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France. ⁵⁴Intensive Care Unit, Pitié-Salpêtrière Hospital, Paris University, AP-HP, Paris, France. ⁵⁵Department of Clinical Science and K.G. Jebsen Center for Autoimmune Disorders, University of Bergen, Bergen, Norway. ⁵⁶Department of Medicine, Haukeland University Hospital, Bergen, Norway. ⁵⁷Department of Medicine (Solna), Karolinska Institutet, Stockholm, Sweden. ⁵⁸Human Molecular Genetics Laboratory, Institute of Genetics and Biophysics, "A. Buzzati-Traverso" Consiglio Nazionale delle Ricerche, Naples, Italy. ⁵⁹Centro di Ricerca Emato-oncologica AIL (CREA) Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia, Brescia, Italy. ⁶⁰Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali di Brescia, Brescia, Italy. ⁶¹Direzione Sanitaria, ASST Spedali Civili di Brescia, Brescia, Italy. ⁶²Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. ⁶³Laboratory of Immunology and Transplantation, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ⁶⁴Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy. ⁶⁵INSERM CIC 1425, Paris, France. ⁶⁶AP-HP, University Hospital of Bichat, Paris, France. ⁶⁷University Paris Diderot, Paris 7, UFR de Médecine-Bichat, Paris, France. ⁶⁸Infection, Antimicrobials, Modelling, Evolution (IAME), INSERM, UMR1137, University of Paris, Paris, France. ⁶⁹AP-HP, Bichat Claude Bernard Hospital, Infectious and Tropical Diseases Department, Paris, France. ⁷⁰Center for Human Immunology, NIH, Bethesda, MD, USA. ⁷¹Multiscale Systems Biology Section, Laboratory of Immune System Biology, NIAID, NIH, Bethesda, MD, USA. ⁷²Département d'Immunologie, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France. ⁷³Pediatric Hematology and Immunology Unit, Necker Hospital for Sick Children, AP-HP, Paris, France.

*Corresponding author. Email: jean-laurent.casanova@rockefeller.edu (J.-L.C.); paul.bastard@institutimagine.org (P.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.

Interindividual clinical variability in the course of SARS-CoV-2 infection is immense. We report that at least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against IFN- ω (13 patients), the 13 types of IFN- α (36), or both (52), at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1,227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 were men. A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

Mycobacteriosis, staphylococcosis, and candidiasis can be driven by monogenic inborn errors of IFN- γ , IL-6, and IL-17A/F, respectively, or by their genetically driven auto-immune phenocopies, with the production of neutralizing auto-Abs against these cytokines (1–8). Type I IFNs, first described in 1957, are ubiquitously expressed cytokines that contribute to both innate immunity (via their secretion by plasmacytoid dendritic cells and other leukocytes) and cell-intrinsic immunity (in most if not all cell types) against viral infections (9–13). Their receptors are ubiquitously expressed and trigger the induction of IFN stimulated genes (ISGs) via phosphorylated STAT1-STAT2-IRF9 trimers (14). Neutralizing IgG auto-Abs against type I IFNs can occur in patients treated with IFN- α 2 or IFN- β (15) and exist in almost all patients with autoimmune polyendocrinopathy syndrome type I (APS-1) (16). They are also seen in women with systemic lupus erythematosus (17).

These patients do not seem to suffer from unusually severe viral infections, although human inborn errors of type I IFNs can underlie severe viral diseases, respiratory and otherwise (18). In 1984, Ion Gresser described a patient with unexplained auto-Abs against type I IFNs suffering from severe chickenpox and shingles (19, 20). More recently, auto-Abs against type I IFNs have been found in a few patients with bi-allelic, hypomorphic *RAG1* or *RAG2* mutations and viral diseases, including severe chickenpox and viral pneumonias (21). Our attention was drawn to three patients with APS-1, with known pre-existing anti-type I IFN auto-Abs, and life-threatening COVID-19 pneumonia (22) (detailed case

reports in Methods). While searching for inborn errors of type I IFNs (18, 23), we hypothesized that neutralizing auto-Abs against type I IFNs might also underlie life-threatening COVID-19 pneumonia.

Auto-Abs against IFN- α 2 and/or IFN- ω in patients with critical COVID-19

We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-19 pneumonia. We also examined 663 individuals infected with SARS-CoV-2 presenting asymptomatic or mild disease, and 1,227 healthy controls whose samples were collected before the COVID-19 pandemic. Plasma or serum samples were collected from patients with critical COVID-19 during the acute phase of disease. Multiplex particle-based flow cytometry revealed a high fluorescence intensity (FI; >1,500) for IgG auto-Abs against IFN- α 2 and/or IFN- ω in 135 patients (13.7%) with life-threatening COVID-19 (Fig. 1A). We found that 49 of these 135 patients were positive for Abs against both IFN- α 2 and IFN- ω , whereas 45 were positive only for Abs against IFN- α 2, and 41 were positive only for Abs against IFN- ω .

We also performed ELISA and the results obtained were consistent with those obtained with Luminex technology (fig. S1A). We also found that 11 and 14 of 23 patients tested had low levels of IgM and IgA auto-Abs against IFN- ω and IFN- α 2, respectively (Fig. 1B and fig. S1B). Auto-Abs against type I IFNs were detected in two unrelated patients for whom we had plasma samples obtained before SARS-CoV-2 infection, indicating that these antibodies were present before SARS-

CoV-2 infection and were not triggered by this infection. As a control, we confirmed that all 25 APS-1 patients tested had high levels of auto-Abs against IFN- α 2 and IFN- ω (fig. S1C). Overall, we found that 135 of 987 patients (13.7%) with life-threatening COVID-19 pneumonia had IgG auto-Abs against at least one type I IFN.

The auto-Abs neutralize IFN- α 2 and IFN- ω in vitro

We then tested whether auto-Abs against IFN- α 2 and IFN- ω were neutralizing in vitro. We incubated PBMCs from healthy controls with 10 ng/mL IFN- α 2 or IFN- ω in the presence of plasma from healthy individuals or from patients with auto-Abs. A complete abolition of STAT1 phosphorylation was observed in 101 patients with auto-Abs against IFN- α 2 and/or IFN- ω (table S1). The antibodies detected were neutralizing against both IFN- α 2 and IFN- ω in 52 of these 101 patients (51%), against IFN- α 2 only in 36 patients (36%), and against IFN- ω only in 13 patients (13%), at the IFN- α 2 and IFN- ω concentrations tested (Fig. 1, C and D). IgG depletion from patients with auto-Abs restored normal pSTAT1 induction after IFN- α 2 and IFN- ω stimulation, whereas the purified IgG fully neutralized this induction (Fig. 1C and fig. S1D). Furthermore, these auto-Abs neutralized high amounts of IFN- α 2 (fig. S1E) and were neutralizing at high dilutions (Fig. 1E and fig. S1F). Interestingly, 15 patients with life-threatening COVID-19 and auto-Abs against IFN- α 2 and/or IFN- ω also had auto-Abs against other cytokines (IFN- γ , GM-CSF, IL-6, IL-10, IL-12p70, IL-22, IL-17A, IL-17F, and/or TNF- β), only three of which (IL-12p70, IL-22, IL-6) were neutralizing (in four patients) (fig. S2, A to C). Similar proportions were observed in the other cohorts (fig. S2, D to L).

We also analyzed ISG induction after 2 hours of stimulation with IFN- α 2, IFN- β or IFN- γ , in the presence of plasma from healthy individuals or from patients with auto-Abs. With plasma from 8 patients with auto-Abs against IFN- α 2, the induction of ISG *CXCL10* was abolished after IFN- α 2 stimulation but maintained after stimulation with IFN- γ (Fig. 1F). We then found that plasma from the five patients with neutralizing auto-Abs tested neutralized the protective activity of IFN- α 2 in MDBK cells infected with vesicular stomatitis virus (table S2). Overall, we found that 101 of 987 patients (10.2%), including 95 males (94%), with life-threatening COVID-19 pneumonia, had neutralizing IgG auto-Abs against at least one type I IFN. By contrast, auto-Abs were detected in only four of 1,227 healthy controls (0.33%) (Fisher exact test, p -value < 10^{-16}) and in none of the 663 patients with asymptomatic or mild SARS-CoV-2 infection tested (Fisher exact test, p -value < 10^{-16}).

Auto-Abs against all 13 IFN- α subtypes in patients with auto-Abs to IFN- α 2

We investigated whether patients with neutralizing auto-Abs against IFN- α 2 only or IFN- α 2 and IFN- ω also had auto-Abs against the other 15 type I IFNs. ELISA showed that all patients tested ($N=22$) with auto-Abs against IFN- α 2 also had auto-Abs against all 13 IFN- α subtypes (IFN- α 1, - α 2, - α 4, - α 5, - α 6, - α 7, - α 8, - α 10, - α 13, - α 14, - α 16, - α 17, and - α 21), whereas only two of the 22 patients tested had auto-Abs against IFN- β , one had auto-Abs against IFN- κ , and two had auto-Abs against IFN- ε (Fig. 2A). The auto-Abs against IFN- β had neutralizing activity against IFN- β (Fig. 1D). We confirmed that all the patients had auto-Abs against all 13 subtypes of IFN- α , by testing the same samples by LIPS (Fig. 2B). For IFN- β , we also screened the whole cohort in a multiplex assay. We found that 19/987 (1.9%) patients had auto-Abs against IFN- β , and that all of them were in our cohort of severe COVID-19 individuals with neutralizing auto-Abs against IFN- α and/or IFN- ω . Of these patients with auto-Abs against IFN- β , only two were neutralizing against IFN- β (Fig. 1, D and F).

Ten of the 17 genes encoding type I IFNs (IFN- α 2, - α 5, - α 6, - α 8, - α 13, - α 14, - α 21, - β , - ω and - κ), have undergone strong negative selection, suggesting that they play an essential role in the general population, whereas the other seven IFN loci in the human genome often carry loss-of-function alleles (24). Moreover, the 13 IFN- α subtypes and IFN- ω are more closely related to each other than to the other three IFNs (IFN- β , IFN- ε and IFN- κ), which are structurally and phylogenetically more distant (Fig. 2C). Thus, all patients with neutralizing auto-Abs against IFN- α 2 tested ($N=22$) had auto-Abs against all 13 IFN- α subtypes, and three of the 22 patients tested (14%) had auto-Abs against 14 or more type I IFNs.

The auto-Abs neutralize IFN- α 2 against SARS-CoV-2 in vitro and IFN- α in vivo

Plasma from eight patients with neutralizing auto-Abs against type I IFN also neutralized the ability of IFN- α 2 to block the infection of Huh7.5 cells with SARS-CoV-2 (Fig. 3A). Plasma from two healthy controls or from seven SARS-CoV-2-infected patients without auto-Abs did not block the protective action of IFN- α 2 (Fig. 3A and fig. S3A). These data provide compelling evidence that the patients' blood carried sufficiently large amounts of auto-Abs to neutralize the corresponding type I IFNs and block their antiviral activity in vitro, including that against SARS-CoV-2.

We also found that all 41 patients with neutralizing auto-Abs against the 13 types of IFN- α tested had low (one patient) or undetectable (40 patients) levels of the 13 types of IFN- α in their plasma during the course of the disease (Fig. 3B) (25, 26). Type I IFNs may be degraded and/or bound to the corresponding circulating auto-Abs. The presence of circulating neutralizing auto-Abs against IFN- α is, therefore,

strongly associated with low serum IFN- α levels (Fisher exact test, p -value $<10^{-6}$). Consistently, in patients with neutralizing auto-Abs against IFN- α 2, the baseline levels of type I IFN-dependent transcripts were low while they were normal for NF- κ B-dependent transcripts (Fig. 3C and fig. S3B). Overall, our findings indicate that the auto-Abs against type I IFNs present in patients with life-threatening COVID-19 were neutralizing in vitro and in vivo.

Strong excess of men in patients with auto-Abs against type I IFNs

There was a strong excess of male patients (95 of 101, 94%) with critical COVID-19 pneumonia and neutralizing auto-Abs against type I IFNs. This proportion of males was higher than that observed in patients with critical COVID-19 without auto-Abs (75%; Fisher exact test p -value $=2.5 \times 10^{-6}$), and much higher than that in male patients within the asymptomatic or pauci-symptomatic cohort (28%, Fisher exact test p -value $<10^{-6}$) (Table 1, Fig. 4A, and fig. S4A). Further evidence for X-linkage was provided by the observation that one of the seven women with auto-Abs and life-threatening COVID-19 had X-linked incontinentia pigmenti (IP), in which cells activate only one single X chromosome (cells having activated the X chromosome bearing the null mutation in *NEMO* dying in the course of development) (27). The prevalence of auto-Abs against type I IFNs in the general population was estimated at 0.33% (0.015-0.67%) in a sample of 1,227 healthy individuals, a value much lower than that in patients with life-threatening COVID-19 pneumonia, by a factor of at least 15.

The patients with auto-Abs were also slightly older than the rest of our cohort (49.5% of patients positive for auto-Abs were over 65 years of age versus 38% for the rest of the cohort, $p=0.024$), suggesting that the frequency of circulating anti-type I IFNs auto-Abs increases with age (Table 1 and Fig. 4B). However, auto-Abs were found in patients aged from 25 to 87 years (fig. S4B). PCA was performed on 49: 34 European, 5 North Africans, 1 sub-Saharan African, 2 patients from the Middle East, 2 South Asians, 1 East Asian, and 1 South American (Fig. 4C). Large-scale studies will be required to determine the frequency of such auto-Abs in humans of different sexes, ages, and ancestries. Finally, the presence of auto-Abs was associated with a poor outcome, with death occurring in 37 of the 101 patients (36.6%) (table S1).

Neutralizing auto-Abs to type I IFNs are causative of critical COVID-19

There are multiple lines of evidence to suggest that the neutralizing auto-Abs against type I IFNs observed in these 101 patients preceded infection with SARS-CoV-2 and accounted for the severity of disease. First, the two patients for whom testing was performed before COVID-19 were

found to have auto-Abs before infection. Second, three patients with APS-1 known to have neutralizing auto-Abs against type I IFN immunity before infection also had life-threatening COVID-19 (22) (supplementary methods). Third, we screened a series of 32 women with IP and found that a fourth of them had auto-Abs against type I IFNs, including one who developed critical COVID-19 (fig. S1C). Fourth, there is a marked bias in favor of men, suggesting that the production of auto-Abs against type I IFNs, whether driven by germ line or somatic genome, may be X-linked and therefore pre-existing to infection.

Moreover, IFN- α subtypes were undetectable during acute disease in the blood of patients with auto-Abs against IFN- α , suggesting a pre-existing or concomitant biological impact in vivo. It is also unlikely that patients could break self-tolerance and mount high titers of neutralizing IgG auto-Abs against type I IFN within only one, or even two weeks of infection. Finally, inborn errors of type I IFNs underlying life-threatening COVID-19 in other previously healthy adults, including autosomal recessive IFNAR1 deficiency, are reported in an accompanying paper (18). Collectively, these findings suggest that auto-Abs against type I IFNs are a cause, and not a consequence of severe SARS-CoV-2 infection, although their titers and affinity may be enhanced by the SARS-CoV-2-driven induction of type I IFNs. They also provide an explanation for the major sex bias seen in patients with life-threatening COVID-19, and perhaps also the increase in risk with age.

Conclusion

We report here that at least 10% of patients with life-threatening COVID-19 pneumonia have neutralizing auto-Abs against type I IFNs. With our accompanying description of patients with inborn errors of type I IFNs and life-threatening COVID-19 (18), this study highlights the crucial role of type I IFNs in protective immunity against SARS-CoV-2. These auto-Abs against type I IFNs were clinically silent until the patients were infected with SARS-CoV-2, which is a poor inducer of type I IFNs (28), suggesting that the small amounts of IFNs induced by the virus are important for protection against severe disease. The neutralizing auto-Abs against type I IFNs, like inborn errors of type I IFN production, tip the balance in favor of the virus, resulting in devastating disease, with insufficient, and even perhaps deleterious, innate and adaptive immune responses.

Our findings have direct clinical implications. First, SARS-CoV-2-infected patients can be screened to identify individuals with auto-Abs at risk of developing life-threatening pneumonia. Such patients recovering from life-threatening COVID-19 should also be excluded from donating convalescent plasma for ongoing clinical trial, or at least tested before their plasma donations are accepted (29).

Second, this unexpected finding paves the way for therapeutic intervention, including plasmapheresis, monoclonal Abs depleting plasmablasts, and the specific inhibition of type I IFN-reactive B cells (30). Finally, in this patient group, early treatment with IFN- α is unlikely to be beneficial. However, treatment with injected or nebulized IFN- β may have beneficial effects, as auto-Abs against IFN- β appear to be rare in patients with auto-Abs against type I IFNs.

Methods

Subjects and samples

We enrolled 987 patients with proven life-threatening (critical) COVID-19, 663 asymptomatic or pauci-symptomatic individuals with proven COVID-19, and 1127 healthy controls in this study. All subjects were recruited following protocols approved by local Institutional Review Boards (IRBs). All protocols followed local ethics recommendations and informed consent was obtained when required.

COVID-19 disease severity was assessed in accordance with the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. “Life-threatening COVID-19 pneumonia” is pneumonia in patients with critical disease, whether pulmonary, with mechanical ventilation (CPAP, BIPAP, intubation, high-flow oxygen), septic shock, or damage to any other organ requiring admission in the ICU. The individuals with asymptomatic or mild SARS-CoV-2 infection we individuals infected with SARS-CoV-2 who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia. The healthy controls were individuals who had not been exposed to SARS-CoV-2.

Plasma and serum samples from the patients and controls were frozen at -20°C immediately after collection. The fluid-phase luciferase immunoprecipitation systems (LIPS) assay was used to determine the levels of antibodies against the SARS-CoV-2 nucleoprotein and spike protein, as previously described (31).

Detection of anti-cytokine autoantibodies

Multiplex particle-based assay

Serum/plasma samples were screened for autoantibodies against 18 targets in a multiplex particle-based assay, in which magnetic beads with differential fluorescence were covalently coupled to recombinant human proteins. Patients with a fluorescence intensity (FI) of > 1500 for IFN- α 2, IFN- β , or > 1000 IFN- ω were tested for blocking activity; as were patients positive for another cytokine.

ELISA

Enzyme-linked immunosorbent assays (ELISA) was performed as previously described (5). In brief, ELISA plates

were coated with rhIFN- α , or rhIFN- ω and incubated with 1:50 dilutions of plasma samples from the patients or controls. A similar protocol was used when testing for 12 subtypes of IFN- α .

LIPS

Levels of autoantibodies against IFN- α subtypes were measured with luciferase-based immunoprecipitation assay (LIPS), as previously described (32). IFN- α 1, I IFN- α 2, I IFN- α 4, IFN- α 5, IFN- α 6, I IFN- α 7, IFN- α 8, IFN- α 10, IFN- α 14, IFN- α 16, IFN- α 17 and IFN- α 21 sequences were transfected in HEK293 cells and the IFN- α -luciferase fusion proteins were collected in the tissue culture supernatant. For autoantibody screening, serum samples were incubated with Protein G agarose beads and we then added 2×10^6 luminescence units (LU) of antigen and incubated. Luminescence intensity was measured. The results are expressed in arbitrary units (AU), as a fold-difference relative to the mean of the negative control samples.

Functional evaluation of anti-cytokine autoantibodies

The blocking activity of anti-IFN α and anti-IFN ω autoantibodies was determined by assessing STAT1 phosphorylation in healthy control cells following stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum/plasma.

We demonstrated that the IFN α/ω blocking activity observed was due to autoantibodies and not another plasma factor, by depleting IgG from the plasma with a protein G column. Without eluting the IgG, the flow-through fraction (IgG-depleted) was then collected and compared to total plasma in the phospho-STAT1 assay.

The blocking activity of anti-IFN γ , -GM-CSF, -IFN λ 1, -IFN λ 2, -IFN λ 3, -IL-6, -IL-10, -IL-12p70, -IL-22, -IL-17A, -IL-17F, -TNF α , and -TNF β antibodies was assessed with the assays outlined in the table in online supplementary materials, as previously reported (21).

For the neutralization of ISG induction, peripheral blood mononuclear cells (PBMCs) were left unstimulated or were stimulated for two hours with 10 ng/mL IFN α or 10 ng/mL IFN γ in a final volume of 100 μ L. Quantitative real-time PCR (RT-qPCR) was performed with Applied Biosystems *Taqman* assays for *CXCL10*, and the β -glucuronidase (GUS) housekeeping gene for normalization. Results are expressed according to the $\Delta\Delta C_t$ method, as described by the manufacturer's kit.

Phylogenetic reconstruction

Protein sequences were aligned with the online version of MAFFT v7.471 software (33), using the L-INS-i strategy (34) and the BLOSUM62 scoring matrix for amino-acid substitutions. Phylogenetic tree reconstruction was

performed by the neighbor-joining method (35), with the substitution model (36). Low-confidence branches (<50%) are likely to be due to gene conversion events between IFNA genes, as previously reported (24, 37). The tree was then visualized (38). Very similar results were obtained with the corresponding DNA sequences (37, 39).

Statistical analysis

Comparison of proportions were performed using a Fisher exact test, as implemented in R (<https://cran.r-project.org/>).

PCA was performed with Plink v1.9 software on whole-exome and whole-genome sequencing data with the 1000 Genomes (1kG) Project phase 3 public database as a reference.

Simoa

Serum-IFN α concentrations were determined with Simoa technology, as previously described (40, 41), with reagents and procedures obtained from Quanterix Corporation.

VSV assay

The seroneutralization assay was performed as previously described (42). In brief, the incubation of IFN- α 2 with Madin-Darby bovine kidney (MDBK) cells protects the cultured cells against the cytopathic effect of vesicular stomatitis virus (VSV). The titer of anti IFN alpha antibodies was defined as the last dilution causing 50% cell death.

SARS-CoV-2 experiment

SARS-CoV-2 strain USA-WA1/2020 was obtained from BEI Resources and amplified in Huh-7.5 hepatoma cells at 33°C. Viral titers were measured on Huh-7.5 cells in a standard plaque assay. Huh-7.5 cells (*H. sapiens*) were cultured. Plasma samples or a commercial anti-IFN- α 2 antibody were serially diluted and incubated with 20 pM recombinant IFN- α 2 for 1 hour at 37°C (starting concentration: plasma samples = 1/100 and anti-IFN- α 2 antibody = 1/1000). The cell culture medium was then removed and replaced with the plasma/antibody-IFN- α 2 mixture. The plates were incubated overnight and the plasma/antibody-IFN- α 2 mixture was removed by aspiration. The cells were washed once with PBS to remove potential anti-SARS-CoV-2-neutralizing antibodies and fresh medium was then added. Cells were then infected with SARS-CoV-2 by directly adding the virus to the wells. Cells infected at a high MOI were incubated at 37°C for 24 hours, whereas cells infected at a low MOI were incubated at 33°C for 48 hours. The cells were fixed with 7% formaldehyde, stained for SARS-CoV-2 with an anti-N antibody, imaged and analyzed as previously described (43).

Nanostring

For the NanoString assay, total RNA was extracted from

whole blood samples collected in PaxGene tubes. The expression of selected genes was determined by NanoString methods and a 28-gene type I IFN score was calculated (44).

REFERENCES AND NOTES

1. J.-L. Casanova, L. Abel, The human genetic determinism of life-threatening infectious diseases: Genetic heterogeneity and physiological homogeneity? *Hum. Genet.* **139**, 681–694 (2020). [doi:10.1007/s00439-020-02184-w](https://doi.org/10.1007/s00439-020-02184-w) Medline
2. R. Döffinger, M. R. Helbert, G. Barcenar-Morales, K. Yang, S. Dupuis, L. Ceron-Gutierrez, C. Espitia-Pinzon, N. Barnes, G. Bothamley, J.-L. Casanova, H. J. Longhurst, D. S. Kumararatne, Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. *Clin. Infect. Dis.* **38**, e10–e14 (2004). [doi:10.1086/380453](https://doi.org/10.1086/380453) Medline
3. C. Höfllich, R. Sabat, S. Rosseau, B. Temmesfeld, H. Slevogt, W.-D. Döcke, G. Grütz, C. Meisel, E. Halle, U. B. Göbel, H.-D. Volk, N. Suttrop, Naturally occurring anti-IFN-gamma autoantibody and severe infections with Mycobacterium chelonae and Burkholderia cocovenenans. *Blood* **103**, 673–675 (2004). [doi:10.1182/blood-2003-04-1065](https://doi.org/10.1182/blood-2003-04-1065) Medline
4. B. Kampmann, C. Hemingway, A. Stephens, R. Davidson, A. Goodsall, S. Anderson, M. Nicol, E. Schölvinc, D. Relman, S. Waddell, P. Langford, B. Sheehan, L. Sempile, K. A. Wilkinson, R. J. Wilkinson, S. Ress, M. Hibberd, M. Levin, Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-gamma. *J. Clin. Invest.* **115**, 2480–2488 (2005). [doi:10.1172/JCI19316](https://doi.org/10.1172/JCI19316) Medline
5. A. Puel, C. Picard, M. Lorrot, C. Pons, M. Chrabieh, L. Lorenzo, M. Mamani-Matsuda, E. Jouanguy, D. Gendrel, J.-L. Casanova, Recurrent staphylococcal cellulitis and subcutaneous abscesses in a child with autoantibodies against IL-6. *J. Immunol.* **180**, 647–654 (2008). [doi:10.4049/jimmunol.180.1.647](https://doi.org/10.4049/jimmunol.180.1.647) Medline
6. A. Puel, R. Döffinger, A. Natividad, M. Chrabieh, G. Barcenar-Morales, C. Picard, A. Cobat, M. Ouachée-Chardin, A. Toulon, J. Bustamante, S. Al-Muhsen, M. Al-Owain, P. D. Arkwright, C. Costigan, V. McConnell, A. J. Cant, M. Abinun, B. Polak, P.-F. Bougnères, D. Kumararatne, L. Marodi, A. Nahum, C. Roifman, S. Blanche, A. Fischer, C. Bodemer, L. Abel, D. Lilic, J.-L. Casanova, Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J. Exp. Med.* **207**, 291–297 (2010). [doi:10.1084/jem.20091983](https://doi.org/10.1084/jem.20091983) Medline
7. K. Kisand, A. S. Bøe Wolff, K. T. Podkrajsek, L. Tserel, M. Link, K. V. Kisand, E. Ersvær, J. Perheentupa, M. M. Erichsen, N. Bratanic, A. Meloni, F. Cetani, R. Perniola, B. Ergun-Longmire, N. Maclaren, K. J. E. Krohn, M. Pura, B. Schälke, P. Ströbel, M. I. Leite, T. Battelino, E. S. Husebye, P. Peterson, N. Willcox, A. Meager, Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J. Exp. Med.* **207**, 299–308 (2010). [doi:10.1084/jem.20091669](https://doi.org/10.1084/jem.20091669) Medline
8. C.-L. Ku, C.-Y. Chi, H. von Bernuth, R. Döffinger, Autoantibodies against cytokines: Phenocopies of primary immunodeficiencies? *Hum. Genet.* **139**, 783–794 (2020). [doi:10.1007/s00439-020-02180-0](https://doi.org/10.1007/s00439-020-02180-0) Medline
9. A. Isaacs, J. Lindenmann, Virus interference. I. The interferon. *Proc. R. Soc. Lond. B* **147**, 258–267 (1957). [doi:10.1098/rspb.1957.0048](https://doi.org/10.1098/rspb.1957.0048) Medline
10. A. Isaacs, J. Lindenmann, R. C. Valentine, Virus interference. II. Some properties of interferon. *Proc. R. Soc. Lond. B* **147**, 268–273 (1957). [doi:10.1098/rspb.1957.0049](https://doi.org/10.1098/rspb.1957.0049) Medline
11. I. Gresser, Wherefore interferon? *J. Leukoc. Biol.* **61**, 567–574 (1997). [doi:10.1002/jlb.61.5.567](https://doi.org/10.1002/jlb.61.5.567) Medline
12. H.-H. Hoffmann, W. M. Schneider, C. M. Rice, Interferons and viruses: An evolutionary arms race of molecular interactions. *Trends Immunol.* **36**, 124–138 (2015). [doi:10.1016/j.it.2015.01.004](https://doi.org/10.1016/j.it.2015.01.004) Medline
13. N. A. de Weerd, J. P. Vivian, S. S. Lim, S. U.-S. Huang, P. J. Hertzog, Structural integrity with functional plasticity: What type I IFN receptor polymorphisms reveal. *J. Leukoc. Biol.* **108**, 909–924 (2020). [doi:10.1002/jlb.2MR0420-152R](https://doi.org/10.1002/jlb.2MR0420-152R)
14. J. E. Darnell Jr., STATs and gene regulation. *Science* **277**, 1630–1635 (1997). [doi:10.1126/science.277.5332.1630](https://doi.org/10.1126/science.277.5332.1630) Medline
15. A. Vallbracht, J. Treuner, B. Flehmig, K. E. Joester, D. Niethammer, Interferon-neutralizing antibodies in a patient treated with human fibroblast interferon. *Nature* **289**, 496–497 (1981). [doi:10.1038/289496a0](https://doi.org/10.1038/289496a0) Medline

16. A. Meager, K. Visvalingam, P. Peterson, K. Möll, A. Murumägi, K. Krohn, P. Eskelin, J. Perheentupa, E. Husebye, Y. Kadota, N. Willcox, Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLOS Med.* **3**, e289 (2006). [doi:10.1371/journal.pmed.0030289](https://doi.org/10.1371/journal.pmed.0030289) [Medline](#)
17. S. Panem, I. J. Check, D. Henriksen, J. Vilcek, Antibodies to alpha-interferon in a patient with systemic lupus erythematosus. *J. Immunol.* **129**, 1–3 (1982). [Medline](#)
18. Q. Zhang, P. Bastard, Z. Liu, J. Le Pen, M. Moncada-Velez, J. Chen, M. Ogishi, I. K. D. Sabli, S. Hodeib, C. Korol, J. Rosain, K. Bilguvar, J. Ye, A. Bolze, B. Bigio, R. Yang, A. Augusto Arias Sierra, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbihi, L. Bonnet-Madin, K. Dorgham, N. Smith, W. M. Schneider, B. S. Razoogy, H.-H. Hoffmann, E. Michailidis, L. Moens, J. E. Han, L. Lorenzo, L. Bizien, P. Meade, A.-L. Neehus, A. C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seeleuthner, J. Manry, C. Masson, Y. Schmitt, A. Schlüter, T. Le Voyer, T. Khan, J. Li, J. Fellay, L. Roussel, M. Shahrooei, M. F. Alosaimi, D. Mansouri, H. Al-Saud, F. Al-Mulla, F. Almourfi, S. Z. Al-Muhsen, F. Alshohime, S. Al Turki, R. Hasanato, D. van de Beek, A. Biondi, L. R. Bettini, M. D'Angio, P. Bonfanti, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, A. J. Oler, M. F. Tompkins, C. Alba, I. Vandernoot, J.-C. Goffard, G. Smits, I. Migeotte, F. Haerynck, P. Soler-Palacin, A. Martin-Nalda, R. Colobran, P.-E. Morange, S. Keles, F. Çölkesen, T. Özcelik, K. K. Yasar, S. Senoglu, Ş. N. Karabela, C. Rodríguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Laouenan, COVID-STORM Clinicians, COVID Clinicians, Imagine COVID group, French COVID Cohort Study Group, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, NIAID-USUHS/TAGC COVID Immunity Group, A. L. Snow, C. L. Dalgard, J. Milner, D. C. Vinh, T. H. Mogensen, N. Marr, A. N. Spaan, B. Boisson, S. Boisson-Dupuis, J. Bustamante, A. Puel, M. Ciancanelli, I. Meyts, T. Maniatis, V. Soumelis, A. Amara, M. Nussenzeig, A. García-Sastre, F. Krammer, A. Pujol, D. Duffy, R. Lifton, S.-Y. Zhang, G. Gorochoy, V. Béziat, E. Jouanguy, V. Sancho-Shimizu, C. M. Rice, L. Abel, L. D. Notarangelo, A. Cobat, H. C. Su, J.-L. Casanova, Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* **10.1126/science.abd4570** (2020). [doi:10.1126/science.abd4570](https://doi.org/10.1126/science.abd4570)
19. B. Pozzetto, K. E. Mogensen, M. G. Tovey, I. Gresser, Characteristics of autoantibodies to human interferon in a patient with varicella-zoster disease. *J. Infect. Dis.* **150**, 707–713 (1984). [doi:10.1093/infdis/150.5.707](https://doi.org/10.1093/infdis/150.5.707) [Medline](#)
20. J.-L. Casanova, I. Gresser, J. *Interferon Cytokine Res.* **39**, 317–320 (2019). [doi:10.1089/jir.2018.29015.mem](https://doi.org/10.1089/jir.2018.29015.mem)
21. J. E. Walter, L. B. Rosen, K. Csomos, J. M. Rosenberg, D. Mathew, M. Keszei, B. Ujhazi, K. Chen, Y. N. Lee, I. Tirosh, K. Dobbs, W. Al-Herz, M. J. Cowan, J. Puck, J. J. Bleesing, M. S. Grimley, H. Malech, S. S. De Ravin, A. R. Gennery, R. S. Abraham, A. Y. Joshi, T. G. Boyce, M. J. Butte, K. C. Nadeau, I. Balboni, K. E. Sullivan, J. Akhter, M. Adeli, R. A. El-Feky, D. H. El-Ghoneimy, G. Dbaibo, R. Wakim, C. Azzari, P. Palma, C. Cancrini, K. Capuder, A. Condino-Neto, B. T. Costa-Carvalho, J. B. Oliveira, C. Roifman, D. Buchbinder, A. Kumanovics, J. L. Franco, T. Niehues, C. Schuetz, T. Kuijpers, C. Yee, J. Chou, M. J. Masaad, R. Geha, G. Uzel, R. Gelman, S. M. Holland, M. Recher, P. J. Utz, S. K. Browne, L. D. Notarangelo, Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. *J. Clin. Invest.* **125**, 4135–4148 (2015). [doi:10.1172/JCI80477](https://doi.org/10.1172/JCI80477) [Medline](#)
22. G. Beccuti, L. Ghizzoni, V. Cambria, V. Codullo, P. Sacchi, E. Lovati, S. Mongodi, G. A. Iotti, F. Mojoli, A COVID-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy, Italy: Letter to the editor. *J. Endocrinol. Invest.* **43**, 1175–1177 (2020). [doi:10.1007/s40618-020-01323-4](https://doi.org/10.1007/s40618-020-01323-4) [Medline](#)
23. J.-L. Casanova, H. C. Su, COVID Human Genetic Effort, A Global Effort to Define the Human Genetics of Protective Immunity to SARS-CoV-2 Infection. *Cell* **181**, 1194–1199 (2020). [doi:10.1016/j.cell.2020.05.016](https://doi.org/10.1016/j.cell.2020.05.016) [Medline](#)
24. J. Manry, G. Laval, E. Patin, S. Fornarino, Y. Itan, M. Fumagalli, M. Sironi, M. Tichit, C. Bouchier, J.-L. Casanova, L. B. Barreiro, L. Quintana-Murci, Evolutionary genetic dissection of human interferons. *J. Exp. Med.* **208**, 2747–2759 (2011). [doi:10.1084/jem.20111680](https://doi.org/10.1084/jem.20111680) [Medline](#)
25. S. Trouillet-Assant, S. Viel, A. Gaymard, S. Pons, J.-C. Richard, M. Perret, M. Villard, K. Brengel-Pesce, B. Lina, M. Mezidi, L. Bitker, A. Belot, COVID HCL Study group, Type I IFN immunoprofiling in COVID-19 patients. *J. Allergy Clin. Immunol.* **146**, 206–208.e2 (2020). [doi:10.1016/j.jaci.2020.04.029](https://doi.org/10.1016/j.jaci.2020.04.029) [Medline](#)
26. H. Hadjadj, N. Yatim, L. Barnabei, A. Corneau, J. Boussier, N. Smith, H. Péré, B. Charbit, V. Bondet, C. Chenevier-Gobeaux, P. Breillat, N. Carlier, R. Gauzit, C. Morbieu, F. Pène, N. Marin, N. Roche, T.-A. Szwebel, S. H. Merklung, J.-M. Treluyer, D. Veyer, L. Mouthon, C. Blanc, P.-L. Tharaux, F. Rozenberg, A. Fischer, D. Duffy, F. Rieux-Laucat, S. Kernéis, B. Terrier, Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* **369**, 718–724 (2020). [doi:10.1126/science.abc6027](https://doi.org/10.1126/science.abc6027) [Medline](#)
27. A. Harris, J. Collins, D. Vetrie, C. Cole, M. Bobrow, X inactivation as a mechanism of selection against lethal alleles: Further investigation of incontinentia pigmenti and X linked lymphoproliferative disease. *J. Med. Genet.* **29**, 608–614 (1992). [doi:10.1136/jmg.29.9.608](https://doi.org/10.1136/jmg.29.9.608) [Medline](#)
28. D. Blanco-Melo, B. E. Nilsson-Payant, W.-C. Liu, S. Uhl, D. Hoagland, R. Möller, T. X. Jordan, K. Oishi, M. Panis, D. Sachs, T. T. Wang, R. E. Schwartz, J. K. Lim, R. A. Albrecht, B. R. tenOever, Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* **181**, 1036–1045.e9 (2020). [doi:10.1016/j.cell.2020.04.026](https://doi.org/10.1016/j.cell.2020.04.026) [Medline](#)
29. S. L. Klein, A. Pekosz, H.-S. Park, R. L. Ursin, J. R. Shapiro, S. E. Benner, K. Littlefield, S. Kumar, H. M. Naik, M. Betenbaugh, R. Shrestha, A. A. Wu, R. M. Hughes, I. Burgess, P. Caturegli, O. Laeyendecker, T. C. Quinn, D. J. Sullivan, S. Shoham, A. D. Redd, E. M. Bloch, A. Casadevall, A. A. R. Tobian, Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J. Clin. Invest.* **142**004 (2020). [doi:10.1172/JCI142004](https://doi.org/10.1172/JCI142004) [Medline](#)
30. T. T. Wang, J. V. Ravetch, Functional diversification of IgGs through Fc glycosylation. *J. Clin. Invest.* **129**, 3492–3498 (2019). [doi:10.1172/JCI130029](https://doi.org/10.1172/JCI130029) [Medline](#)
31. P. D. Burbelo, F. X. Riedo, C. Morishima, S. Rawlings, D. Smith, S. Das, J. R. Strich, D. S. Chertow, R. T. Davey Jr., J. I. Cohen, Sensitivity in Detection of Antibodies to Nucleocapsid and Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus 2 in Patients With Coronavirus Disease 2019. *J. Infect. Dis.* **222**, 206–213 (2020). [doi:10.1093/infdis/jiaa273](https://doi.org/10.1093/infdis/jiaa273) [Medline](#)
32. S. Meyer, M. Woodward, C. Hertel, P. Vlaicu, Y. Haque, J. Käner, A. Macagno, S. C. Onuoha, D. Fishman, H. Peterson, K. Metsküla, R. Uibo, K. Jääntti, K. Hokynar, A. S. B. Wolff, APECED patient collaborative, K. Krohn, A. Ranki, P. Peterson, K. Kisan, A. Hayday, AIRE-Deficient Patients Harbor Unique High-Affinity Disease-Ameliorating Autoantibodies. *Cell* **166**, 582–595 (2016). [doi:10.1016/j.cell.2016.06.024](https://doi.org/10.1016/j.cell.2016.06.024) [Medline](#)
33. K. Katoh, J. Rozewicki, K. D. Yamada, MAFFT online service: Multiple sequence alignment, interactive sequence choice and visualization. *Brief. Bioinform.* **20**, 1160–1166 (2019). [doi:10.1093/bib/bbx108](https://doi.org/10.1093/bib/bbx108) [Medline](#)
34. K. Katoh, K. Kuma, H. Toh, T. Miyata, MAFFT version 5: Improvement in accuracy of multiple sequence alignment. *Nucleic Acids Res.* **33**, 511–518 (2005). [doi:10.1093/nar/gki198](https://doi.org/10.1093/nar/gki198) [Medline](#)
35. N. Saitou, M. Nei, The neighbor-joining method: A new method for reconstructing phylogenetic trees. *Mol. Biol. Evol.* **4**, 406–425 (1987). [doi:10.1093/oxfordjournals.molbev.a040454](https://doi.org/10.1093/oxfordjournals.molbev.a040454) [Medline](#)
36. D. T. Jones, W. R. Taylor, J. M. Thornton, The rapid generation of mutation data matrices from protein sequences. *Comput. Appl. Biosci.* **8**, 275–282 (1992). [doi:10.1093/bioinformatics/8.3.275](https://doi.org/10.1093/bioinformatics/8.3.275) [Medline](#)
37. C. H. Woelk, S. D. W. Frost, D. D. Richman, P. E. Higley, S. L. Kosakovsky Pond, Evolution of the interferon alpha gene family in eutherian mammals. *Gene* **397**, 38–50 (2007). [doi:10.1016/j.gene.2007.03.018](https://doi.org/10.1016/j.gene.2007.03.018) [Medline](#)
38. M. V. Han, C. M. Zmasek, phyloXML: XML for evolutionary biology and comparative genomics. *BMC Bioinformatics* **10**, 356 (2009). [doi:10.1186/1471-2105-10-356](https://doi.org/10.1186/1471-2105-10-356) [Medline](#)
39. S. Pestka, C. D. Krause, M. R. Walter, Interferons, interferon-like cytokines, and their receptors. *Immunol. Rev.* **202**, 8–32 (2004). [doi:10.1111/j.0105-2896.2004.00204.x](https://doi.org/10.1111/j.0105-2896.2004.00204.x) [Medline](#)
40. D. M. Rissin, C. W. Kan, T. G. Campbell, S. C. Howes, D. R. Fournier, L. Song, T. Piech, P. P. Patel, L. Chang, A. J. Rivnak, E. P. Ferrell, J. D. Randall, G. K. Provuncher, D. R. Walt, D. C. Duffy, Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. *Nat. Biotechnol.* **28**, 595–599 (2010). [doi:10.1038/nbt.1641](https://doi.org/10.1038/nbt.1641) [Medline](#)
41. A. Mathian, S. Mouries-Martin, K. Dorgham, H. Devilliers, L. Barnabei, E. Ben Salah, F. Cohen-Aubart, L. Garrido Castillo, J. Haroche, M. Hie, M. Pineton de Chambrun, M. Miyara, D. Sterlin, M. Pha, D. Lê Thi Huong, F. Rieux-Laucat, F. Rozenberg, G. Gorochoy, Z. Amoura, Monitoring Disease Activity in Systemic Lupus

- Erythematosus With Single-Molecule Array Digital Enzyme-Linked Immunosorbent Assay Quantification of Serum Interferon- α . *Arthritis Rheumatol.* **71**, 756–765 (2019). [doi:10.1002/art.40792](https://doi.org/10.1002/art.40792) [Medline](#)
42. P. Lebon, G. Ponsot, J. Aicardi, F. Goutières, M. Arthuis, Early intrathecal synthesis of interferon in herpes encephalitis. *Biomedicine* **31**, 267–271 (1979). [Medline](#)
43. D. F. Robbiani, C. Gaebler, F. Muecksch, J. C. C. Lorenzi, Z. Wang, A. Cho, M. Agudelo, C. O. Barnes, A. Gazumyan, S. Finkin, T. Hägglöf, T. Y. Oliveira, C. Viant, A. Hurlley, H.-H. Hoffmann, K. G. Millard, R. G. Kost, M. Cipolla, K. Gordon, F. Bianchini, S. T. Chen, V. Ramos, R. Patel, J. Dizon, I. Shimeliovich, P. Mendoza, H. Hartweger, L. Nogueira, M. Pack, J. Horowitz, F. Schmidt, Y. Weisblum, E. Michailidis, A. W. Ashbrook, E. Waltari, J. E. Pak, K. E. Huey-Tubman, N. Koranda, P. R. Hoffman, A. P. West Jr., C. M. Rice, T. Hatziioannou, P. J. Bjorkman, P. D. Bieniasz, M. Caskey, M. C. Nussenzweig, Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature* **584**, 437–442 (2020). [doi:10.1038/s41586-020-2456-9](https://doi.org/10.1038/s41586-020-2456-9) [Medline](#)
44. H. Kim, A. A. de Jesus, S. R. Brooks, Y. Liu, Y. Huang, R. VanTries, G. A. Montealegre Sanchez, Y. Rotman, M. Gadina, R. Goldbach-Mansky, Development of a Validated Interferon Score Using NanoString Technology. *J. Interferon Cytokine Res.* **38**, 171–185 (2018). [doi:10.1089/jir.2017.0127](https://doi.org/10.1089/jir.2017.0127) [Medline](#)
45. J. P. Ferreira, N. Girerd, E. Bozec, L. Mercière, A. Pizard, S. Bouali, E. Eby, C. Leroy, J.-L. Machu, J.-M. Boivin, Z. Lamiral, P. Rossignol, F. Zannad, Cohort Profile: Rationale and design of the fourth visit of the STANISLAS cohort: a familial longitudinal population-based cohort from the Nancy region of France. *Int. J. Epidemiol.* **47**, 395–395j (2018). [doi:10.1093/ije/dyx240](https://doi.org/10.1093/ije/dyx240)

ACKNOWLEDGMENTS

We thank the patients, their families, and healthy donors for placing their trust in us. We warmly thank the “French Incontinentia pigmenti” association for their help and support. We warmly thank Y. Nemirovskaya, D. Papandrea, M. Woollet, D. Liu, C. Rivalain and C. Patissier for administrative assistance; D. Kapogiannis (National Institute on Aging) for providing healthy donor samples and S. Xirasager, J. Barnett, X. Cheng, S. Weber, J. Danielson, B. Garabedian, and H. Matthews for their assistance in this study. We also thank R. Apps, B. Ryan, Y. Belkaid of the CHI for their assistance. We thank the CRB-Institut Jérôme Lejeune, CRB-BioJeL, Paris, France, for their assistance. We thank M.C. García Guerrero, I. Erkizia, E. Grau, M. Massanella from irsiCaixa AIDS Research Institute, Badalona, Spain and J. Guitart from the department of Clinical Genetics, University Hospital “Germans Trias i Pujol”, Badalona, Spain for providing samples; as well as J. Dalmat from irsiCaixa for assistance. **Funding:** The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercatus Center at George Mason University, the Yale Center for Mendelian Genomics and the GSP Coordinating Center funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956), the French National Research Agency (ANR) under the “Investments for the Future” program (ANR-10-IAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBED), the French Foundation for Medical Research (FRM) (EQU201903007798), the FRM and ANR GENCOV project, ANRS-COV05, the Square Foundation, *Grandir - Fonds de solidarité pour l'enfance*, the SCOR Corporate Foundation for Science, Institut National de la Santé et de la Recherche Médicale (INSERM) and the University of Paris. Samples from San Raffaele Hospital were obtained within the Covid-BioB project and healthcare personnel of San Raffaele Hospital, San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) clinical lab and clinical research Unit; funded by the Program Project COVID-19 OSR-UniSR and Fondazione Telethon. The French COVID Cohort study group was sponsored by Inserm and supported by the REACTing consortium and by a grant from the French Ministry of Health (PHRC 20-0424). The Cov-Contact Cohort was supported by the REACTing consortium, the French Ministry of Health, and the European Commission

(RECOVER WP 6). The “Milieu Intérieur” cohort was supported by was supported by the French Government’s *Investissement d’Avenir* Program, *Laboratoire d’Excellence* “Milieu Intérieur” Grant (ANR-10-LABX-69-01) (PI: L Quintana-Murci & D Duffy). The Simoa experiment was supported by the PHRC-20-0375 COVID-19 grant “DIGITAL COVID” (PI: G Gorochov). SGT is supported by a Leadership 3 Investigator Grant awarded by the National Health and Medical Research Council of Australia, and a COVID19 Rapid Response Grant awarded by UNSW Sydney. CRG and colleagues were supported by Instituto de Salud Carlos III (COV20_01333 and COV20_01334, Spanish Ministry of Science and Innovation-RTC-2017-6471-1; AEI/FEDER, UE), and Cabildo Insular de Tenerife (CGIEU0000219140 and “Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19”). SA and AB were supported by ANR-20-COVI-0064 (PI: A Belot). This work is supported by the French Ministry of Health “Programme Hospitalier de Recherche Clinique Inter régional 2013”, by the Contrat de Plan Etat-Lorraine and FEDER Lorraine, and a public grant overseen by the French National Research Agency (ANR) as part of the second “Investissements d’Avenir” program FIGHT-HF (reference: ANR-15-RHU-0004) and by the French PIA project “Lorraine Université d’Excellence”, reference ANR-15-IDEX-04-LUE (45) and biobanking is performed by the Biological Resource Center Lorrain BB-0033-00035. This study was supported by the Fonds IMMUNOV, for Innovation in Immunopathology and by a grant from the Agence National de la Recherche (ANR-flash Covid19 “AIROCovid” to FRL), and by the FAST Foundation (French Friends of Sheba Tel Hashomer Hospital). Work in the Laboratory of Virology and Infectious Disease was supported by NIH grants P01AI138398-S1, 2U19AI111825, and R01AI091707-10S1, a George Mason University Fast Grant, and the G. Harold and Leila Y. Mathers Charitable Foundation. The Amsterdam UMC Covid-19 Biobank was supported by grants of the Amsterdam Corona Research Fund, Dr. C.J. Vaillant Fund, and Netherlands Organization for Health Research and Development (ZonMw; NWO-Vici-Grant [grant number 918-19-627 to DvdB]). This work was also supported by the Division of Intramural Research of the National Institute of Dental Craniofacial Research and National Institute of Allergy and Infectious Diseases, National Institutes of Health, and by Regione Lombardia, Italy (project “Risposta immune in pazienti con COVID-19 e comorbidità”). The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense. JH holds an Institut Imagine MD-PhD fellowship from the Fondation Bettencourt-Schueller. JR is supported by the Inserm PhD program (“poste d’accueil Inserm”). PB was supported by the French Foundation for Medical Research (FRM, EA20170638020) and the MD-PhD program of the Imagine Institute (with the support of the Fondation Bettencourt-Schueller). We thank the Association “Turner et vous” for their help and support. Sample processing at IrsiCaixa was possible thanks to the crowdfunding initiative YoMeCorono. DCV is supported by the Fonds de la recherche en santé du Québec clinician-scientist scholar program. K. Kisand was supported by the Estonian Research Council grant PUT1367. We thank the GEN-COVID Multicenter Study (<https://sites.google.com/dbm.unisi.it/gen-covid>). We thank the NIAID Office of Cyber Infrastructure and Computational Biology, Bioinformatics and Computational Biosciences Branch (Contract HHSN316201300006W/HHSN27200002 to MSC, Inc) and Operations Engineering Branch for developing the HGRPO system to enable streamlined access to the data and the NCI Advanced Biomedical Computational Science (ABCS) for data transformation support. **Author contributions:** PB, LBR, QZ, EM, HHH, YZ, KD, QP, JR, VB, JM, ES, LH, PP, LL, LB, SA, KD, AADJ, AB, LP, DD, ESH, JST, RGM, KK, AP, SHZ, SMH, GG, EJ, CMR, LDN, HCS, JLC performed provided supervision of experiments, generated and analyzed data, and contributed to the manuscript by providing figures and tables. JLP, GK, BB, YS, RY, AB, KB, RL, MM, AC, LA, performed computational analysis of data. PB, AK, EC, YTL, ANS, OMD, MSA, AA, GC, VL, FC, MV, DMS, JH, BT, DD, LQM, DVB, LR, DCV, SGT, FH, DD, TM, PB, JMP, MCN, SBD, CRG, GV, AJO, JG, PDB, JC, AB, LRB, MDA, PB, PR, FRL, FF, MVU, LI, AS, SP, EQR, CR, RC, DM, AL, GLM, XD, JG, MSL, GG, evaluated and recruited patients to COVID and/or control cohorts of patients. PB, QZ, AC, EJ, LA and JLC wrote the manuscript. JLC supervised the project. All authors edited the manuscript. **Competing interests:** Helen Su is adjunct faculty at the University of Pennsylvania. Jean-Laurent Casanova is

listed as an inventor on patent application US 63/055,155 filed by The Rockefeller University that encompasses aspects of this publication. Richard Lifton is a non-executive director of Roche and its subsidiary Genentech. The authors declare no other competing interests. **Data and materials availability:** All data are available in the manuscript or in the supplementary materials. Plasma, cells, and genomic DNA are available from Dr. Jean-Laurent Casanova/Dr. Donald Vinh under a material agreement with Rockefeller University/Research Institute-McGill University Health Centre. Huh-7.5 cells are available upon request from Charles Rice under a material agreement with The Rockefeller University and Apath, LLC. Materials and reagents used are almost exclusively commercially available and non-proprietary. Requests for materials derived from human samples may be made available, subject to any underlying restrictions on such samples. Jean-Laurent Casanova can make material transfer agreements available through The Rockefeller University. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

HGID Lab

Andrés Augusto Arias^{1,3}, Bertrand Boisson^{1,2}, Soraya Boucherit², Jacinta Bustamante^{1,2}, Marwa Chbihi², Jie Chen¹, Maya Chrabieh², Tatiana Kochetkov¹, Tom Le Voyer², Dana Liu¹, Yelena Nemirovskaya¹, Masato Ogishi¹, Dominick Papandrea¹, Cécile Patissier², Franck Rapaport¹, Manon Roynard², Natasha Vladikine², Mark Woollett¹, Peng Zhang¹

¹St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University. ²Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children. ³School of Microbiology and Group of Primary Immunodeficiencies, University of Antioquia UdeA, Medellín, Colombia.

NIAID-USUHS Immune Response to COVID Group

Anuj Kashyap¹, Li Ding¹, Marita Bosticardo¹, Qinlu Wang², Sebastian Ochoa¹, Hui Liu¹, Samuel D. Chauvin³, Michael Stack¹, Galina Koroleva⁴, Neha Bansal⁵, Clifton L. Dalgard^{6,7}, Andrew L. Snow⁸

¹Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ²Bioinformatics and Computational Biosciences Branch, NIAID Office of Cyber Infrastructure and Computational Biology, NIAID, NIH, Bethesda, MD, USA. ³Laboratory of Immune System Biology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ⁴NIH Center for Human Immunology, NIH, Bethesda, MD, USA. ⁵Multiscale Systems Biology Section, Laboratory of Immune System Biology, NIAID, NIH, Bethesda, MD, USA. ⁶PRIMER, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁷Department of Anatomy, Physiology & Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁸Department of Pharmacology & Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.

COVID Clinicians

Jorge Abad¹, Sergio Aguilera-Albesa², Ozge Metin Akcan³, Ilad Alavi Darazam⁴, Juan C. Aldave⁵, Miquel Alfonso Ramos⁶, Seyed Alireza Nadi⁷, Gulsum Alkan⁸, Jerome Alardet-Servent⁹, Luis M. Allende¹⁰, Laia Alsina¹¹, Marie-Alexandra Alyanaki¹², Blanca Amador-Borrero¹³, Zahir Amoura¹⁴, Arnau Antolí¹⁵, Sevket Arslan¹⁶, Sophie Assant¹⁷, Terese August¹⁸, Axelle Azot¹⁹, Fanny Bajolle²⁰, Aurélie Baldoli²¹, Maite Ballester²², Hagit Baris Feldman²³, Benoit Barrou²⁴, Alexandra Beurton²⁵, Agurtzane Bilbao²⁶, Geraldine Blanchard-Rohner²⁷, Ignacio Blanco¹, Adeline Blandinières²⁸, Daniel Blazquez-Gamero²⁹, Marketa Bloomfield³⁰, Mireia Bolivar-Prados³¹, Raphael Borie³², Ahmed A. Bousfiha³³, Claire Bouvattier³⁴, Oksana Boyarchuk³⁵, Maria Rita P. Bueno³⁶, Jacinta Bustamante²⁰, Juan José Cáceres Agra³⁷, Semra Camli³⁸, Ruggero Capra³⁹, Maria Carabba⁴⁰, Carlos Casasnovas⁴¹, Marion Caseris⁴², Martin Castelle⁴³, Francesco Castelli⁴⁴, Martín Castillo de Vera⁴⁵, Mateus V. Castro³⁶, Emilie Catherinot⁴⁶, Martin Chalumeau⁴⁷, Bruno Charbit⁴⁸, Matthew P. Cheng⁴⁹, Père Clavé³¹, Bonaventura Clotet⁵⁰, Anna Codina⁵¹, Fatih Colkesen⁵², Fatma Colkesen⁵³, Roger Colobran⁵⁴, Cléo

Comarmond⁵⁵, Angelo G. Corsico⁵⁶, David Dalmay⁵⁷, David Ross Darley⁵⁸, Nicolas Dauby⁵⁹, Stéphane Dauger⁶⁰, Loïc de Pontual⁶¹, Amin Dehban⁶², Geoffroy Delplancq⁶³, Alexandre Demoule⁶⁴, Antonio Di Sabatino⁶⁵, Jean-Luc Diehl⁶⁶, Stephanie Dobbelaere⁶⁷, Sophie Durand⁶⁸, Waleed Eldars⁶⁹, Mohamed Elgamal⁷⁰, Marwa H. Elnagdy⁷¹, Melike Emiroglu⁷², Emine Hafize Erdeniz⁷³, Selma Erol Aytekin⁷⁴, Romain Euvrard⁷⁵, Recep Evcen⁷⁶, Giovanna Fabio⁴⁰, Laurence Faivre⁷⁷, Antonin Falck⁴², Muriel Fartoukh⁷⁸, Morgane Faure⁷⁹, Miguel Fernandez Arquer⁸⁰, Carlos Flores⁸¹, Bruno Francois⁸², Victoria Fumadó⁸³, Francesca Fusco⁸⁴, Blanca Garcia Solis⁸⁵, Pascale Gaussem⁸⁶, Juana Gil-Herrera⁸⁷, Laurent Gilardin⁸⁸, Monica Girona Alarcon⁸⁹, Mónica Girona-Alarcón⁸⁹, Jean-Christophe Goffard⁹⁰, Funda Gök⁹¹, Rafaela González-Montelongo⁹², Antoine Guerder⁹³, Yahya Gul⁹⁴, Sukru Nail Guner⁹⁴, Marta Gut⁹⁵, Jérôme Hadjadj⁹⁶, Filomeen Haerynck⁹⁷, Rabih Halwan⁹⁸, Lennart Hammarström⁹⁹, Nevin Hatipoğlu¹⁰⁰, Elisa Hernandez-Brito¹⁰¹, María Soledad Holanda-Peña¹⁰², Juan Pablo Horcajada¹⁰³, Sami Hraiech¹⁰⁴, Linda Humbert¹⁰⁵, Alejandro D. Iglesias¹⁰⁶, Antonio Íñigo-Campos⁹², Matthieu Jammé¹⁰⁷, María Jesús Arranz¹⁰⁸, Iolanda Jordan¹⁰⁹, Fikret Kanat¹¹⁰, Hasan Kapakli¹¹¹, Iskender Kara¹¹², Adem Karbuz¹¹³, Kadriye Kart Yasar¹¹⁴, Sevgi Keles¹¹⁵, Yasemin Kendir Demirkol¹¹⁶, Adam Klocperk¹¹⁷, Zbigniew J. Król¹¹⁸, Paul Kuentz¹¹⁹, Yat Wah M. Kwan¹²⁰, Jean-Christophe Lagier¹²¹, Yu-Lung Lau¹²², Fleur Le Bourgeois⁶⁰, Yee-Sin Leo¹²³, Rafael Leon Lopez¹²⁴, Daniel Leung¹²², Michael Levin¹²⁵, Michael Levy⁶⁰, Romain Lévy²⁰, Zhi Li⁴⁸, Agnes Lingart¹²⁶, José M. Lorenzo-Salazar⁹², Céline Louapre¹²⁷, Catherine Lubetzk¹²⁷, Charles-Edouard Luyt¹²⁸, David C. Lye¹²⁹, Davood Mansouri¹³⁰, Majid Marjani¹³¹, Jesus Marquez Pereira¹³², Andrea Martin¹³³, David Martínez Pueyo¹³⁴, Javier Martínez-Picado¹³⁵, Iciar Marzana¹³⁶, Alexis Mathian¹⁴, Larissa R. B. Matos³⁶, Gail V. Matthews¹³⁷, Julien Mayaux¹³⁸, Jean-Louis Mège¹³⁹, Isabelle Melki¹⁴⁰, Jean-François Meritet¹⁴¹, Ozge Metin¹⁴², Isabelle Meyts¹⁴³, Mehdi Mezidi¹⁴⁴, Isabelle Migeotte¹⁴⁵, Maude Millereux¹⁴⁶, Tristan Mirault¹⁴⁷, Clotilde Mircher⁶⁸, Mehdi Mirsaedi¹⁴⁸, Abián Montesdeoca Melián¹⁴⁹, Antonio Morales Martinez¹⁵⁰, Pierre Morange¹⁵¹, Demence Mordacq¹⁰⁵, Guillaume Morelle¹⁵², Stéphane Mouly¹³, Adrián Muñoz-Barrera⁹², Cyril Nafati¹⁵³, João Farelle Neves¹⁵⁴, Lisa F. P. Ng¹⁵⁵, Yeray Novoa Medina¹⁵⁶, Esmeralda Nuñez Cuadros¹⁵⁷, J. Gonzalo Ochoa-Vinyals¹⁵⁸, Zerrin Orbak¹⁵⁹, Mehdi Oualha²⁰, Tayfun Özçelik¹⁶⁰, Qiang Pan Hammarström¹⁶¹, Christophe Parizot¹³⁸, Tiffany Pascreau¹⁶², Estela Paz-Artal¹⁶³, Sandra Pellegrini¹⁶⁴, Rebeca Pérez de Diego⁸⁵, Aurélien Philippe¹⁶⁴, Quentin Philippot⁷⁸, Laura Planas-Serra¹⁶⁵, Dominique Ploin¹⁶⁶, Julien Poissy¹⁶⁷, Géraldine Poncelet⁴², Marie Pouletty¹⁶⁸, Paul Quentric¹³⁸, Didier Raoult¹³⁹, Anne-Sophie Rebillat⁶⁸, Ismail Reisli¹⁶⁹, Pilar Ricart¹⁷⁰, Jean-Christophe Richard¹⁷¹, Nadia Rivet²⁸, Jacques G. Rivière¹⁷², Gemma Rocamora Blanch¹⁵, Carlos Rodrigo¹, Carlos Rodríguez-Gallego¹⁷³, Agustí Rodríguez-Palmero¹⁷⁴, Carolina Soledad Romero¹⁷⁵, Anya Rothenbuhler¹⁷⁶, Flore Rozenberg¹⁷⁷, Maria Yolanda Ruiz del Prado¹⁷⁸, Joan Sabater Riera¹⁵, Oliver Sanchez¹⁷⁹, Silvia Sánchez-Ramón¹⁸⁰, Agatha Schluter¹⁶⁵, Matthieu Schmidt¹⁸¹, Cyril E. Schweitzer¹⁸², Francesco Scolari¹⁸³, Anna Sediva¹⁸⁴, Luis M. Seijo¹⁸⁵, Damien Sene¹³, Sevtap Senoglu¹¹⁴, Mikko Seppänen¹⁸⁶, Alex Serra Ilovich¹⁸⁷, Mohammad Shahrinei¹⁸⁸, David Smadja¹⁸⁸, Ali Sobh¹⁸⁹, Xavier Solanich Moreno¹⁵, Jordi Solé-Violán¹⁹⁰, Catherine Soler¹⁹¹, Pere Soler-Palacin¹³³, Yuri Stepanovskiy¹⁹², Annabelle Stoclin¹⁹³, Fabio Taccone¹⁴⁵, Yacine Tandjaoui-Lambiotte¹⁹⁴, Jean-Luc Taupin¹⁹⁵, Simon J. Tavernier¹⁹⁶, Benjamin Terrier¹⁹⁷, Caroline Thumerelle¹⁰⁵, Gabriele Tomasoni¹⁹⁸, Julie Toubiana⁴⁷, Josep Trenado Alvarez¹⁹⁹, Sophie Trouillet-Assant²⁰⁰, Jesús Troya²⁰¹, Alessandra Tucci²⁰², Matilde Valeria Ursini⁸⁴, Yurdagul Uzunhan²⁰³, Pierre Vabres²⁰⁴, Juan Valencia-Ramos²⁰⁵, Ana Maria Van Den Rym⁸⁵, Isabelle Vandernoot²⁰⁶, Hulya Vatansev²⁰⁷, Valentina Vélez-Santamaria⁴¹, Sébastien Viel¹⁶⁶, Cédric Vilain²⁰⁸, Marie E. Vilaire⁶⁸, Audrey Vincent³⁴, Guillaume Voiriot²⁰⁹, Fanny Vuotto¹⁰⁵, Alper Yosunkaya⁹¹, Barnaby E. Young¹²³, Fatih Yucel²¹⁰, Faheer Zannad²¹¹, Mayana Zatz³⁶, Alexandre Belot^{212*}

¹University Hospital and Research Institute "Germans Trias i Pujol", Badalona, Spain. ²Navarra Health Service Hospital, Pamplona, Spain. ³Division of Pediatric Infectious Diseases, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁴Department of Infectious Diseases, Lohman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁵Hospital Nacional Edgardo Rebagliatti Martins, Lima, Peru. ⁶Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain. ⁷Virology Research Center, National Institutes of Tuberculosis and Lung diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁸Division of Pediatric Infectious Diseases, Faculty of Medicine, Selcuk University, Konya, Turkey. ⁹Intensive care unit, Hôpital Européen, Marseille, France. ¹⁰Immunology Department, University Hospital 12 de Octubre. Research Institute imas12. Complutense University, Madrid, Spain. ¹¹Hospital Sant Joan de Déu, Barcelona, Spain. ¹²Department of Biological Immunology, Necker Hospital for Sick Children, APHP and INEM, Paris, France. ¹³Internal

medicine department, Hôpital Lariboisière, APHP, Université de Paris, Paris, France. ¹⁴Internal medicine department, Pitié-Salpêtrière Hospital, Paris, France. ¹⁵Hospital Universitari de Bellvitge, Barcelona, Spain. ¹⁶Division of Clinical Immunology and Allergy, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ¹⁷Joint Research Unit, Hospices Civils de Lyon-bio Mérieux, Hospices Civils de Lyon, Lyon Sud Hospital, Lyon, France. ¹⁸Hospital U. de Tarragona Joan XXIII. Universitat Rovira i Virgili (URV), IISPV, Tarragona, Spain. ¹⁹Private practice, Paris, France. ²⁰Necker Hospital for Sick Children, AP-HP, Paris, France. ²¹Department of Infectious Diseases, CHU de Caen, Caen, France. ²²Consorcio Hospital General Universitario, Valencia, Spain. ²³The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ²⁴Dept Urology, Nephrology, Transplantation, APHP-SU, Sorbonne Université, INSERM U1082, Paris, France. ²⁵Service de Médecine Intensive-Réanimation et Pneumologie, APHP Hôpital Pitié-Salpêtrière, Paris, France. ²⁶Cruces University Hospital, Bizkaia, Spain. ²⁷Paediatric Immunology and Vaccinology Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland. ²⁸Hematology, Georges Pompidou Hospital, APHP, Paris, France. ²⁹Pediatric Infectious Diseases Unit, Instituto de Investigación 12 de Octubre (imas12), Hospital Universitario 12 de Octubre, Madrid, Spain. ³⁰Department of Immunology, Motol University Hospital, 2nd Faculty of Medicine, Charles University, Department of Pediatrics, Thomayer's Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic. ³¹Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain. ³²Service de Pneumologie, Hôpital Bichat, APHP, Paris, France. ³³Clinical 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. ³⁴Endocrinology unit, APHP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ³⁵Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. ³⁶Human Genome and stem-cell research center- University of São Paulo, São Paulo, Brazil. ³⁷Hospital Insular, Las Palmas de Gran Canaria, Spain. ³⁸Division of Critical Care Medicine, Department of Anesthesiology and Reanimation, Konya State Hospital, Konya, Turkey. ³⁹MS Center, Spedali Civili, Brescia, Italy. ⁴⁰Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. ⁴¹Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain. ⁴²Hôpital Robert Debré, Paris, France. ⁴³Pediatric Immuno-hematology Unit, Necker Enfants Malades Hospital, AP-HP, Paris, France. ⁴⁴Department of Infectious and Tropical Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ⁴⁵Doctoral Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁴⁶Hôpital Foch, Suresnes, France. ⁴⁷Necker Hospital for Sick Children, Paris University, AP-HP, Paris, France. ⁴⁸Pasteur Institute, Paris, France. ⁴⁹McGill University Health Centre, Montreal, Canada. ⁵⁰University Hospital and Research Institute "Germans Trias i Pujol", IrsiCaixa AIDS Research Institute, UVIC-UCC, Badalona, Spain. ⁵¹Clinical Biochemistry, Pathology, Paediatric Neurology and Molecular Medicine Departments and Biobank, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Esplugues, Spain. ⁵²Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁵³Department of Infectious Diseases and Clinical Microbiology, Konya Training and Research Hospital, Konya, Turkey. ⁵⁴Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁵⁵Pitié-Salpêtrière Hospital, Paris, France. ⁵⁶Respiratory Diseases Division, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy. ⁵⁷Fundació Docència i Recerca Mútua Terrassa, Barcelona, Spain. ⁵⁸UNSW Medicine, St Vincent's Clinical School; Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst, Sydney, Australia. ⁵⁹CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium. ⁶⁰Pediatric Intensive Care Unit, Robert-Debré University Hospital, APHP, Paris, France. ⁶¹Sorbonne Paris Nord, Hôpital Jean Verdier, APHP, Bondy, France. ⁶²Specialized Immunology Laboratory of Dr. Shahrooei, Sina Medical Complex, Ahvaz, Iran. ⁶³Centre de génétique humaine, CHU Besançon, Besançon, France. ⁶⁴Sorbonne Université médecine and APHP Sorbonne université site Pitié-Salpêtrière, Paris, France. ⁶⁵Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. ⁶⁶Intensive Care unit, Georges Pompidou Hospital, APHP, Paris, France. ⁶⁷Department of Pneumology, AZ Delta, Roeselare, Belgium. ⁶⁸Institut Jérôme Lejeune, Paris, France. ⁶⁹Department of Microbiology and Immunology, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ⁷⁰Department of Chest, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ⁷¹Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine,

Mansoura University, Mansoura, Egypt. ⁷²Faculty of Medicine, Division of Pediatric Infectious Diseases, Selcuk University, Konya, Turkey. ⁷³Division of Pediatric Infectious Diseases, Ondokuz Mayıs University, Samsun, Turkey. ⁷⁴Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. ⁷⁵Centre Hospitalier Fleyriat, Bourg-en-Bresse, France. ⁷⁶Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁷⁷Centre de Génétique, CHU Dijon, Dijon, France. ⁷⁸APHP Tenon Hospital, Paris, France. ⁷⁹Sorbonne Universités, UPMC University of Paris, Paris, France. ⁸⁰Department of Clinical Immunology, Hospital Clínico San Carlos, Madrid, Spain. ⁸¹Genomics 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. ⁸²CHU Limoges and Inserm CIC 1435 & UMR 1092, Limoges, France. ⁸³Infectious 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. ⁸⁴Institute of Genetics and Biophysics 'Adriano Buzzati-Traverso', IGB-CNR, Naples, Italy. ⁸⁵Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ⁸⁶Hematology, APHP, Hôpital Européen Georges Pompidou and Inserm UMR-S1140, Paris, France. ⁸⁷Hospital General Universitario and Instituto de Investigación Sanitaria "Gregorio Marañón", Madrid, Spain. ⁸⁸Bégin military Hospital, Bégin, France. ⁸⁹Pediatric Intensive Care Unit, Hospital Sant Joan de Déu, Barcelona, Spain. ⁹⁰Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ⁹¹Division of Critical Care Medicine, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁹²Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain. ⁹³Assistance Publique Hôpitaux de Paris, Paris, France. ⁹⁴Division of Allergy and Immunology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ⁹⁵CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST); Universitat Pompeu Fabra (UPF), Barcelona, Spain. ⁹⁶Department of Internal Medicine, National Reference Center for Rare Systemic Autoimmune Diseases, AP-HP, APHP-CUP, Hôpital Cochin, Paris, France. ⁹⁷Ghent University Hospital, Ghent, Belgium. ⁹⁸Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, UAE. ⁹⁹Department of Biosciences and Nutrition, SE14183, Huddinge, Karolinska Institutet, Stockholm, Sweden. ¹⁰⁰Pediatric Infectious Diseases Unit, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹⁰¹Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁰²IntensiveCare Unit, Marqués de Valdecilla Hospital, Santander, Spain. ¹⁰³Hospital del Mar, Parc de Salut Mar, Barcelona, Spain. ¹⁰⁴Intensive care unit, APHM, Marseille, France. ¹⁰⁵CHU Lille, Lille, France. ¹⁰⁶Department of Pediatrics, Columbia University, New York, NY, USA. ¹⁰⁷Centre hospitalier intercommunal Poissy Saint Germain en Laye, Poissy, France. ¹⁰⁸Division of Respiratory Diseases, Fundació Docència i Recerca Mútua Terrassa, Barcelona, Spain. ¹⁰⁹Hospital Sant Joan de Déu, Kids Corona Platform, Barcelona, Spain. ¹¹⁰Selcuk University, Faculty of Medicine, Chest Diseases Department, Konya, Turkey. ¹¹¹Division of Allergy and Immunology, Balikesir Ataturk City Hospital, Balikesir, Turkey. ¹¹²Division of Critical Care Medicine, Selcuk University, Faculty of Medicine, Konya, Turkey. ¹¹³Division of Pediatric Infectious Diseases, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey. ¹¹⁴Departments of Infectious Diseases and Clinical Microbiology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹¹⁵Meram Medical Faculty, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ¹¹⁶Health Sciences University, Umraniye Education and Research Hospital, Istanbul, Turkey. ¹¹⁷Department of Immunology, 2nd Faculty of Medicine, Charles University and University Hospital in Motol, Prague, Czech Republic. ¹¹⁸Central Clinical Hospital of Ministry of the Interior and Administration in Warsaw, Warsaw, Poland. ¹¹⁹Oncobiologie Génétique Bioinformatique, PC Bio, CHU Besançon, Besançon, France. ¹²⁰Paediatric Infectious Disease Unit, Hospital Authority Infectious Disease Center, Princess Margaret Hospital, Hong Kong (Special Administrative Region), China. ¹²¹Aix Marseille Univ, IRD, MEPHI, IHU Méditerranée Infection, Marseille, France. ¹²²Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China. ¹²³National Centre for Infectious Diseases, Singapore. ¹²⁴Hospital Universitario Reina Sofía, Cordoba, Spain. ¹²⁵Imperial College, London, England. ¹²⁶Endocrinology and diabetes for

children, AP-HP, Bicêtre Paris-Saclay hospital, Le Kremlin-Bicêtre, France. ¹²⁷Neurology unit, APHP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹²⁸Intensive care unit, APHP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹²⁹National Centre for Infectious Diseases; Tan Tock Seng Hospital; Yong Loo Lin School of Medicine; Lee Kong Chian School of Medicine, Singapore. ¹³⁰Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹³¹Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹³²Hospital Sant Joan de Déu and University of Barcelona, Barcelona, Spain. ¹³³Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain. ¹³⁴Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain. ¹³⁵IrsiCaixa AIDS Research Institute, ICREA, UVic-UCC, Research Institute "Germans Trias i Pujol", Badalona, Spain. ¹³⁶Department of Laboratory, Cruces University Hospital, Barakaldo, Bizkaia, Spain. ¹³⁷University of New South Wales, Australia. ¹³⁸APHP Pitié-Salpêtrière Hospital, Paris, France. ¹³⁹Aix-Marseille University, APHM, Marseille, France. ¹⁴⁰Robert Debré Hospital, Paris, France. ¹⁴¹APHP Cohin Hospital, Paris, France. ¹⁴²Necmettin Erbakan University Meram Faculty of Medicine Department of Pediatric Infectious Diseases, Konya, Turkey. ¹⁴³University Hospitals Leuven, Leuven, Belgium. ¹⁴⁴Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Lyon, France. ¹⁴⁵Hôpital Erasme, Brussels, Belgium. ¹⁴⁶CH Gonesse, Gonesse, France. ¹⁴⁷Vascular Medicine, Georges Pompidou Hospital, APHP, Paris, France. ¹⁴⁸Division of Pulmonary and Critical Care, University of Miami, Miami, USA. ¹⁴⁹Guanarteme Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁵⁰Regional University Hospital of Malaga, Malaga, Spain. ¹⁵¹Aix-Marseille Université, Marseille, France. ¹⁵²Department of General Paediatrics, Hôpital Bicêtre, AP-HP, University of Paris Saclay, Le Kremlin-Bicêtre, France. ¹⁵³CHU de La Timone, Marseille, France. ¹⁵⁴Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal. ¹⁵⁵Infectious Diseases Horizontal Technology Centre, A*STAR; Singapore Immunology Network, A*STAR, Singapore. ¹⁵⁶Department of Pediatrics, Complejo Hospitalario Universitario Insular-Materno-Infantil, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁵⁷Regional University Hospital of Malaga, Málaga, Spain. ¹⁵⁸Hospital Universitario Marqués de Valdecilla, Santander, Spain. ¹⁵⁹Ataturk University Medical Faculty, Erzurum, Turkey. ¹⁶⁰Bilkent University, Department of Molecular Biology and Genetics, Ankara, Turkey. ¹⁶¹Department of Laboratory Medicine, Karolinska Institutet, SE14186, Stockholm, Sweden. ¹⁶²L'Hôpital Foch, Suresnes, France. ¹⁶³Department of Immunology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain. ¹⁶⁴APHP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ¹⁶⁵Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona; CIBERER U759, ISCIII Madrid, Spain. ¹⁶⁶Hospices Civils de Lyon, Lyon, France. ¹⁶⁷Université de Lille, Inserm U1285, CHU Lille, Paris, France. ¹⁶⁸Département of General Pediatrics, University Hospital Robert Debré, APHP, Paris, France. ¹⁶⁹Necmettin Erbakan University, Konya, Turkey. ¹⁷⁰Germans Trias i Pujol Hospital, Badalona, Spain. ¹⁷¹Medical intensive care unit. Hôpital de la Croix-Rousse. Hospices Civils de Lyon, Lyon, France. ¹⁷²Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus., Barcelona, Spain. ¹⁷³Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain, EU. University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ¹⁷⁴Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona, Spain. ¹⁷⁵Consorcio Hospital General Universitario, Valencia, Spain. ¹⁷⁶APHP Hôpitaux Universitaires Paris-Sud, Paris, France. ¹⁷⁷Virology unit, Université de Paris, Cohin Hospital, APHP, Paris, France. ¹⁷⁸Hospital San Pedro, Logroño, Spain. ¹⁷⁹Respiratory medicine, Georges Pompidou Hospital, APHP, Paris, France. ¹⁸⁰Dept. Immunology, Hospital Clínico San Carlos, Madrid, Spain. ¹⁸¹Service de Médecine Intensive Réanimation, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France. ¹⁸²CHRU de Nancy, Hôpital d'Enfants, Vandoeuvre, France. ¹⁸³Chair of Nephrology, University of Brescia, Brescia, Italy. ¹⁸⁴Department of Immunology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic. ¹⁸⁵Clínica Universidad de Navarra, Madrid, Spain. ¹⁸⁶HUS Helsinki University Hospital, Children and Adolescents, Rare Disease Center, and Inflammation Center, Adult Immunodeficiency Unit, Majakka, Helsinki, Finland. ¹⁸⁷Fundació Docència i Recerca Mútua Terrassa, Terrassa, Spain. ¹⁸⁸Hôpital Européen Georges Pompidou,

Paris, France. ¹⁸⁹Department of Pediatrics, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ¹⁹⁰Critical Care Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁹¹CHU de Saint Etienne, Saint-Priest-en-Jarez, France. ¹⁹²Shupyk National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹⁹³Gustave Roussy Cancer Campus, Villejuif, France. ¹⁹⁴Intensive Care Unit, Avicenne Hospital, APHP, Bobigny, France. ¹⁹⁵Laboratory of Immunology and Histocompatibility, Saint-Louis Hospital, Paris University, Paris, France. ¹⁹⁶Department of Internal Diseases and Pediatrics, Primary Immune Deficiency Research Lab, Centre for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent, Belgium. ¹⁹⁷Department of Internal Medicine, Université de Paris, INSERM, U970, PARCC, F-75015, Paris, France. ¹⁹⁸First Division of Anesthesiology and Critical Care Medicine, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ¹⁹⁹Intensive Care Department, Hospital Universitari MutuaTerrassa, Universitat Barcelona, Terrassa, Spain. ²⁰⁰Hospices Civils de Lyon, Lyon Sud Hospital, Lyon, France. ²⁰¹Infanta Leonor University Hospital, Madrid, Spain. ²⁰²Hematology Department, ASST Spedali Civili di Brescia, Brescia, Italy. ²⁰³Pneumologie, Hôpital Avicenne, APHP, INSERM U1272, Université Sorbonne Paris Nord, Bobigny, France. ²⁰⁴Dermatology unit, Laboratoire GAD, INSERM UMR1231 LNC, université de Bourgogne, Dijon, France. ²⁰⁵University Hospital of Burgos, Burgos, Spain. ²⁰⁶Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ²⁰⁷Department of Chest Diseases, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey. ²⁰⁸CHU de Caen, Caen, France. ²⁰⁹Sorbonne Université, Service de Médecine Intensive Réanimation, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France. ²¹⁰General Intensive Care Unit, Konya Training and Research Hospital, Konya, Turkey. ²¹¹CHU de Nancy, Nancy, France. ²¹²University of Lyon, CIRI, INSERM U1111, National referee centre RAISE, Pediatric Rheumatology, HFME, Hospices Civils de Lyon, Lyon, France. *Leader of the COVID-clinicians group.

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 IT. ²Department of Pneumology, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza IT. ³Center of Bioinformatics and Biostatistics, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza IT. ⁴Phase I Research Center, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza IT.

Imagine COVID Group

Christine Bole-Feyso¹, Stanislas Lyonnet^{1*}, Cécile Masson¹, Patrick Nitschke¹, Aurore Pouliet¹, Yoann Schmitt¹, Frederic Tores¹, Mohammed Zarhrate¹

¹Imagine Institute, Université de Paris, INSERM UMR 1163, Paris, France. *Leader of the Imagine COVID group.

French COVID Cohort Study Group

Laurent Abel¹, Claire Andrejak², François Angoulvant³, Delphine Bachelet⁴, Romain Basmaci⁵, Sylvie Behillil⁶, Marine Beluze⁷, Dehbia Benkerrou⁸, Krishna Bhavsar⁴, François Bompard⁹, Lila Bouadma⁴, Maude Bouscambert¹⁰, Mireille Caralp¹¹, Minerva Cervantes-Gonzalez¹², Anissa Chair⁴, Alexandra Coelho¹³, Camille Couffignal⁴, Sandrine Couffin-Cardiergues¹⁴, Eric D'ortenzio¹², Charlene Da Silveira⁴, Marie-Pierre Debray⁴, Dominique Deplanque¹⁵, Diane Descamps¹⁶, Mathilde Desvallées¹⁷, Alpha Diallo¹⁸, Alphonsine Diouf¹³, Céline Dorival⁸, François Dubos¹⁹, Xavier Duval⁴, Philippine Eloy⁴, Vincent V. E. Enouf²⁰, Hélène Esperou²¹, Marina Esposito-Faresse⁴, Manuel Etienne²², Nadia Ettalhaoui⁴, Nathalie Gault⁴, Alexandre Gaymard¹⁰, Jade Ghosn⁴, Tristan Gigante²³, Isabelle Gorenne⁴, Jérémie Guedj²⁴, Alexandre Hocin¹³, Isabelle Hoffmann⁴, Salma Jaafoura²¹, Ouifia Kafif⁴, Florentia Kaguelidou²⁵, Sabina Kali⁴, Antoine Khalil⁴, Coralie Khan¹⁷, Cédric Laouénan⁴, Samira Laribi⁴, Minh Le⁴, Quentin Le Hingrat⁴, Soizic Le Mestre¹⁸, Hervé Le Nagard²⁴, François-Xavier Lescure⁴, Yves Lévy²⁶, Claire Levy-Marchal²⁷, Bruno Lina¹⁰, Guillaume Lingas²⁴, Jean Christophe Lucet⁴, Denis Malvy²⁸, Marina Mambert¹³, France Mentré⁴, Noémie Mercier¹⁸, Amina Meziane⁸, Hugo Mouquet²⁰, Jimmy Mullaert⁴, Nadège Neant²⁴, Marion Noret²⁹, Justine Pages³⁰, Aurélie Papadopoulos²¹, Christelle Paul¹⁸, Nathan Peiffer-Smadja⁴, Ventzislava Petrov-Sanchez¹⁸, Gilles Peytavin⁴, Olivier Picone³¹, Oriane Puéchal¹²,

Manuel Rosa-Calatrava¹⁰, Bénédicte Rossignol²³, Patrick Rossignol³², Carine Roy⁴, Marion Schneider⁴, Caroline Semaille¹², Nassima Si Mohammed⁴, Lysa Tagherset⁴, Coralie Tardivon⁴, Marie-Capucine Tellier⁴, François Téoulé⁸, Olivier Terrier¹⁰, Jean-François Timsit⁴, Théo Treoux⁴, Christelle Tual³³, Sarah Tubiana⁴, Sylvie van der Werf³⁴, Noémie Vanel³⁵, Aurélie Veislinger³³, Benoit Visseaux¹⁶, Aurélie Wiedemann²⁶, Yazdan Yazdanpanah³⁶

¹Inserm UMR 1163, Paris, France. ²CHU Amiens, France. ³Hôpital Necker, Paris, France. ⁴Hôpital Bichat, Paris, France. ⁵Hôpital Louis Mourier, Colombes, France. ⁶Institut Pasteur, Paris, France. ⁷F-CRIN Partners Platform, AP-HP, Université de Paris, Paris, France. ⁸Inserm UMR 1136, Paris, France. ⁹Drugs for Neglected Diseases initiative, Geneva, Switzerland. ¹⁰Inserm UMR 1111, Lyon, France. ¹¹Inserm Transfert, Paris, France. ¹²REACTing, Paris, France. ¹³Inserm UMR 1018, Paris, France. ¹⁴Inserm, Pôle Recherche Clinique, France. ¹⁵CIC 1403 Inserm-CHU Lille, Paris, France. ¹⁶Université de Paris, IAME, INSERM UMR 1137, AP-HP, University hospital Bichat Claude Bernard, Virology, F-75018 Paris, France. ¹⁷Inserm UMR 1219, Bordeaux, France. ¹⁸ANRS, Paris, France. ¹⁹CHU Lille, France. ²⁰Pasteur Institute, Paris, France. ²¹Inserm sponsor, Paris, France. ²²Rouen - SMIT, France. ²³FCRIN INI-CRCT, Nancy, France. ²⁴Inserm UMR 1137, Paris, France. ²⁵Centre d'Investigation Clinique, Inserm CIC1426, Hôpital Robert Debré, Paris, France. ²⁶Inserm UMR 955, Créteil, France; Vaccine Research Institute (VRI), Paris, France. ²⁷F-CRIN INI-CRCT, Paris, France. ²⁸Bordeaux - SMIT, France. ²⁹RENARCI, Annecy, France. ³⁰Hôpital Robert Debré, Paris, France. ³¹Colombes - Louis Mourier - Gynécologie, France. ³²University of Lorraine, Plurithematic Clinical Investigation Centre Inserm CIC-P; 1433, Inserm U1116, CHRU Nancy Hopitaux de Brabois, F-CRIN INI-CRCT; (Cardiovascular and Renal Clinical Trialists), Nancy, France. ³³Inserm CIC-1414, Rennes, France. ³⁴Institut Pasteur, UMR 3569 CNRS, Université de Paris, Paris, France. ³⁵Hôpital la timone, Marseille, France. ³⁶Paris - Bichat - SMIT, France.

The Milieu Intérieur Consortium

Laurent Abel¹, Andres Alcover², Hugues Aschard², Kalla Astrom³, Philippe Bousso², Pierre Bruhns², Ana Cumano², Caroline Demangel², Ludovic Deriano², James Di Santo², Françoise Dromer², Gérard Eberl², Jost Enninga², Jacques Fellay⁴, Ivo Gomperts-Boneca², Milena Hasan², Serge Hercberg⁵, Olivier Lantz⁶, Hugo Mouquet², Etienne Patin², Sandra Pellegrini², Stanislas Pol⁷, Antonio Rausell⁸, Lars Rogge², Anavaj Sakuntabhai², Olivier Schwartz², Benno Schwikowski², Spencer Shorte², Frédéric Tangy², Antoine Toubert⁹, Mathilde Touvier¹⁰, Marie-Noëlle Ungeheuer², Matthew L. Albert^{11*}, Daragh Duffy^{2*}, Lluís Quintana-Murci^{2*}

¹INSERM U1163, University of Paris, Imagine Institute, Paris, France. ²Pasteur Institute, Paris, France. ³Lund University, Lund, Sweden. ⁴EPFL, Lausanne, Switzerland. ⁵Université Paris 13, Paris, France. ⁶Curie Institute, Paris, France. ⁷Cochin Hospital, Paris, France. ⁸INSERM UMR 1163 – Institut Imagine. ⁹Hôpital Saint-Louis, Paris, France. ¹⁰Université Paris 13, Paris, France. ¹¹In Situ. *Co-coordinators of the Milieu Intérieur Consortium. Additional information can be found at: <https://www.pasteur.fr/labex/milieu-interieur>.

CoV-Contact Cohort

Loubna Alavoine¹, Karine K. A. Amat², Sylvie Behillil³, Julia Bielicki⁴, Patricia Brujning⁵, Charles Burdet⁶, Eric Caumes⁷, Charlotte Charpentier⁸, Bruno Coignard⁹, Yolande Costa¹, Sandrine Couffin-Cardièrgues¹⁰, Florence Damond⁸, Aline Dechanet¹¹, Christelle Delmas¹⁰, Diane Descamps⁸, Xavier Duval¹, Jean-Luc Ecobichon¹, Vincent Enouf³, Hélène Espérou¹⁰, Wahiba Frezouls¹, Nadhira Houhou¹¹, Emila Ilic-Habensuss¹, Ouifiya Kaffil¹¹, John Kikoine¹¹, Quentin Le Hingrat⁸, David Lebeaux¹², Anne Leclercq¹, Jonathan Lehacaut¹, Sophie Letrou¹, Bruno Lina¹³, Jean-Christophe Lucet¹⁴, Denis Malvy¹⁵, Pauline Manchon¹¹, Milica Mandic¹, Mohamed Meghadecha¹⁶, Justina Motiejunaite¹⁷, Mariama Nouroudine¹, Valentine Piquard¹¹, Andreea Postolache¹¹, Caroline Quintin¹, Jade Rexach¹, Layidé Roufai¹⁰, Zaven Terzian¹¹, Michael Thy¹⁸, Sarah Tubiana¹, Sylvie van der Werf³, Valérie Vignali¹, Benoit Visseaux⁸, Yazdan Yazdanpanah¹⁴

¹Centre d'Investigation Clinique, Inserm CIC 1425, Hôpital Bichat Claude Bernard, APHP, Paris, France. ²IMEA Fondation Léon M'Ba, Paris, France. ³Institut Pasteur, UMR 3569 CNRS, Université de Paris, Paris, France. ⁴University of Basel Children's Hospital. ⁵Julius Center for Health Sciences and Primary Care, Utrecht. ⁶Université de Paris, IAME, Inserm UMR 1137, F-75018, Paris, France, Hôpital Bichat Claude Bernard, APHP, Paris, France. ⁷Hôpital Pitié Salpêtrière, APHP, Paris. ⁸Université de Paris, IAME, INSERM UMR 1137, AP-HP, University hospital Bichat Claude Bernard, Virology,

F-75018 Paris, France. ⁹Santé Publique France, Saint Maurice, France. ¹⁰Pole Recherche Clinique, Inserm, Paris France. ¹¹Hôpital Bichat Claude Bernard, APHP, Paris, France. ¹²APHP, Paris, France. ¹³Virpath Laboratory, International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. ¹⁴IAME Inserm UMR 1138, Hôpital Bichat Claude Bernard, APHP, Paris, France. ¹⁵Service des Maladies Infectieuses et Tropicales; Groupe Pellegrin-Place Amélie-Raba-Léon, BORDEAUX. ¹⁶Hôpital Hotel Dieu, APHP, Paris, France. ¹⁷Service des explorations fonctionnelles, Hôpital Bichat- Claude Bernard, APHP, Paris, France. ¹⁸Center for Clinical Investigation, Assistance Publique-Hôpitaux de Paris, Bichat-Claude Bernard University Hospital.

Amsterdam UMC Covid-19 Biobank

Michiel van Agtmael¹, Anne Geke Algera², Frank van Baarle², Diane Bax³, Martijn Beudel⁴, Harm Jan Bogaard⁵, Marije Bomers¹, Lieuwe Bos², Michela Botta², Justin de Brabander⁶, Godelieve Bree⁶, Matthijs C. Brouwer⁴, Sanne de Bruin², Marianna Bugiani⁷, Esther Bulle², O. Chouchane¹, Alex Cloherty³, Paul Elbers², Lucas Fleuren², Suzanne Geerlings¹, Bart Geerts⁸, Theo Geijtenbeek⁹, Armand Girbes², Bram Goorhuis¹, Martin P. Grobusch¹, Florianne Hafkamp⁹, Laura Hagens², Jorg Hamann¹⁰, Vanessa Harris¹, Robert Hemke¹¹, Sabine M. Hermans¹, Leo Heunks², Markus Hollmann⁸, Janneke Horn², Joppe W. Hovius¹, Menno de Jong¹², Rutger Koning⁴, Mourik van Mourik², Jeanine Nellen¹, Frederique Paulus², Edgar Peters¹, Tom van der Poll¹, Benedikt Preckel¹⁸, Jan M. Prins¹, Jorinde Raasveld², Tom Reijnders¹, Michiel Schinkel¹, Marcus Schultz², Alex Schuurman¹³, Kim Sigaloff¹, Marry Smit², Cornelis S. Stijns¹, Willemke Stijlma², Charlotte Teunissen¹⁴, Patrick Thorat², Anissa Tsonas², Marc van der Valk¹, Denise Veelo⁸, Alexander P. J. Vlaar¹⁵, Heder de Vries², Michèle van Vugt¹, W. Joost Wiersinga¹, Dorien Wouters¹⁶, A. H. (Koo) Zwiderman¹⁷, Diederik van de Beek^{18*}

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

COVID Human Genetic Effort

Laurent Abel¹, Alessandro Aiuti², Saleh Al Muhsen³, Fahd Al-Mulla⁴, Mark S. Anderson⁵, Andrés Augusto Arias⁶, Hagit Baris Feldman⁷, Dusan Bogunovic⁸, Alexandre Bolze⁹, Anastasiia Bondarenko¹⁰, Ahmed A. Bousfiha¹¹, Petter Brodin¹², Yenan Bryceson¹², Carlos D. Bustamante¹³, Manish Butte¹⁴, Giorgio Casari¹⁵, Samya Chakravorty¹⁶, John Christodoulou¹⁷, Elizabeth Cirulli⁹, Antonio Condino Neto¹⁸, Megan A. Cooper¹⁹, Clifton L. Dalgard²⁰, Joseph L. DeRisi²¹, Murkesh Desai²², Beth A. Drolet²³, Sara Espinosa²⁴, Jacques Fellay²⁵, Carlos Flores²⁶, Jose Luis Franco²⁷, Peter K. Gregersen²⁸, Filomeen Haerynck²⁹, David Hagin³⁰, Rabih Halwani³¹, Jim Heath³², Sarah E. Henrickson³³, Elena Hsieh³⁴, Kohsuke Imai³⁵, Yuval Itan⁸, Timokratis Karamitros³⁶, Kai Kisand³⁷, Cheng-Lung Ku³⁸, Yu-Lung Lau³⁹, Yun Ling⁴⁰, Carrie L. Lucas⁴¹, Tom Maniatis⁴², Davoud Mansouri⁴³, Laszlo Marodi⁴⁴, Isabelle Meyts⁴⁵, Joshua Milner⁴⁶, Kristina Mironska⁴⁷, Trine Mogensen⁴⁸, Tomohiro Morio⁴⁹, Lisa P. Ng⁵⁰, Luigi D. Notarangelo⁵¹, Giuseppe Novelli⁵², Antonio Novelli⁵³, Cliona O'Farrelly⁵⁴, Satoshi Okada⁵⁵, Tayfun Ozelik⁵⁶, Rebecca Perez de Diego⁵⁷, Anna M. Planas⁵⁸, Carolina Prando⁵⁹, Aurora Pujol⁶⁰, Lluís Quintana-Murci⁶¹, Laurent Renia⁶², Alessandra Renier⁶³, Carlos Rodríguez-Gallego⁶⁴, Vanessa Sancho-Shimizu⁶⁵, Vijay Sankaran⁶⁶, Kelly Schiabor Barrett⁹, Mohammed Shahrooei⁶⁷, Andrew Snow⁶⁸, Pere Soler-Palacín⁶⁹, Andrés N. Spaan⁷⁰, Stuart Tangye⁷¹, Stuart Turvey⁷², Furkan Uddin⁷³, Mohammed J. Uddin⁷⁴, Diederik van de Beek⁷⁵, Sara E. Vazquez⁷⁶, Donald C. Vinh⁷⁷, Horst von Bernuth⁷⁸, Nicole Washington⁹, Pawel Zawadzki⁷⁹, Helen C. Su^{51*}, Jean-Laurent Casanova^{80*}

¹INSERM U1163, University of Paris, Imagine Institute, Paris, France. ²San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, Milan, Italy. ³King Saud University, Riyadh, Saudi Arabia. ⁴Kuwait University, Kuwait City, Kuwait. ⁵University of California, San Francisco, San Francisco, CA, USA. ⁶Universidad de Antioquia, Group of Primary Immunodeficiencies, Antioquia, Colombia. ⁷The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁸Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁹Helix, San Mateo, CA, USA. ¹⁰Shupyk National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹¹Clinical immunology unit, pediatric infectious disease department, Faculty of Medicine and Pharmacy, Averroes University Hospital. LICIA Laboratoire d'immunologie clinique, d'inflammation et d'allergie, Hassani I University, Casablanca, Morocco. ¹²Karolinska Institute, Stockholm, Sweden. ¹³Stanford University, Stanford, CA, USA. ¹⁴University of California, Los Angeles, CA, USA. ¹⁵Medical Genetics, IRCCS Ospedale San Raffaele, Milan, Italy. ¹⁶Emory, Atlanta, GA, USA. ¹⁷Murdoch Children's Research Institute, Victoria, Australia. ¹⁸University of São Paulo, São Paulo, Brazil. ¹⁹Washington University School of Medicine, St. Louis, MO, USA. ²⁰The American Genome Center; Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ²¹University of California San Francisco; Chan Zuckerberg Biohub, San Francisco, CA, United States. ²²Bai Jerbai Wadia Hospital for Children, Mumbai, India. ²³School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. ²⁴Instituto Nacional de Pediatría (National Institute of Pediatrics), Mexico City, Mexico. ²⁵Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland. ²⁶Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Canarian Health System, Santa Cruz de Tenerife, Spain. ²⁷University of Antioquia, Medellín, Colombia. ²⁸Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA. ²⁹Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPiG), PID research lab, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Edegem, Belgium. ³⁰The Genetics Institute Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. ³¹Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, UAE. ³²Institute for Systems Biology, Seattle, WA, USA. ³³Children's Hospital of Philadelphia, Philadelphia, PA, USA. ³⁴Anschutz Medical Campus, Aurora, CO, USA. ³⁵Riken, Tokyo, Japan. ³⁶Hellenic Pasteur Institute, Athens, Greece. ³⁷University of Tartu, Tartu, Estonia. ³⁸Chang Gung University, Taoyuan County, Taiwan. ³⁹The University of Hong Kong, Hong Kong, China. ⁴⁰Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. ⁴¹Yale School of Medicine, New Haven, CT, USA. ⁴²New York Genome Center, New York, NY, USA. ⁴³Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁴⁴Semmelweis University Budapest, Budapest, Hungary. ⁴⁵KU Leuven, Department of Immunology, Microbiology and Transplantation, Leuven, Belgium. ⁴⁶Columbia University Medical Center, New York, NY, USA. ⁴⁷University Clinic for Children's Diseases, Skopje, North Macedonia. ⁴⁸Aarhus University, Aarhus, Denmark. ⁴⁹Tokyo Medical & Dental University Hospital, Tokyo, Japan. ⁵⁰Singapore Immunology Network, Singapore. ⁵¹National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. ⁵²Bambino Gesù Children's Hospital, Rome, Italy; Dept. Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy. ⁵³Bambino Gesù Children's Hospital, Rome, Italy, Rome, Italy, Italy. ⁵⁴Trinity College, Dublin, Ireland. ⁵⁵Hiroshima University, Hiroshima, Japan. ⁵⁶Bilkent University, Ankara, Turkey. ⁵⁷Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid ²⁸⁰⁴⁶, Spain, EU, Madrid, Spain, Spain. ⁵⁸IBB-CSIC, IDIBAPS, Barcelona, Spain. ⁵⁹Faculdades Pequeno Príncipe e Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ⁶⁰Neurometabolic Diseases Laboratory, IDIBELL- Hospital Duran I Reynals; Catalan Institution for Research and Advanced Studies (ICREA); CIBERER U759, ISCiii Madrid Spain, Barcelona, Spain. ⁶¹Institut Pasteur (CNRS UMR2000) and Collège de France, Paris, France. ⁶²Infectious Diseases Horizontal Technology Center and Singapore Immunology Network, Agency for Science Technology (A*STAR), Singapore. ⁶³University of Siena, Siena, Italy. ⁶⁴Hospital Universitario de Gran Canaria Dr Negrín, Canarian Health System, Canary Islands, Spain. ⁶⁵Imperial College London, London, UK. ⁶⁶Boston Children's Hospital, Harvard Medical School, Boston, MA, USA. ⁶⁷Saeed Pathobiology and Genetic Lab, Tehran, Iran. ⁶⁸Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD, USA. ⁶⁹Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁷⁰University Medical Center Utrecht, Amsterdam, Netherlands. ⁷¹Garvan Institute of Medical Research, Sydney, Australia. ⁷²The University of British Columbia, Vancouver, Canada. ⁷³Holy Family Red Crescent Medical College; Centre for Precision Therapeutics, NeuroGen Children's Healthcare; Genetics and Genomic Medicine

Centre, NeuroGen Children's Healthcare, Dhaka, Bangladesh. ⁷⁴Mohammed Bin Rashid University of Medicine and Health Sciences, College of Medicine, Dubai, UAE; The Centre for Applied Genomics, Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada, Dhaka, Bangladesh. ⁷⁵Amsterdam UMC, Amsterdam, Netherlands. ⁷⁶University of California, San Francisco, San Francisco, CA, United States. ⁷⁷McGill University Health Centre, Montreal, Canada. ⁷⁸Charité - Berlin University Hospital Center, Berlin, Germany. ⁷⁹Molecular Biophysics Division, Faculty of Physics, A. Mickiewicz University, Uniwersytetu Poznańskiego 2, Poznań, Poland. ⁸⁰Rockefeller University, Howard Hughes Medical Institute, Necker Hospital, New York, NY, USA. *Leaders of the COVID Human Genetic Effort.

SUPPLEMENTARY MATERIALS

science.sciencemag.org/cgi/content/full/science.abd4585/DC1

Supplementary Materials and Methods

Figs. S1 to S4

Tables S1 to S3

Data S1

22 June 2020; accepted 16 September 2020

Published online 24 September 2020

10.1126/science.abd4585

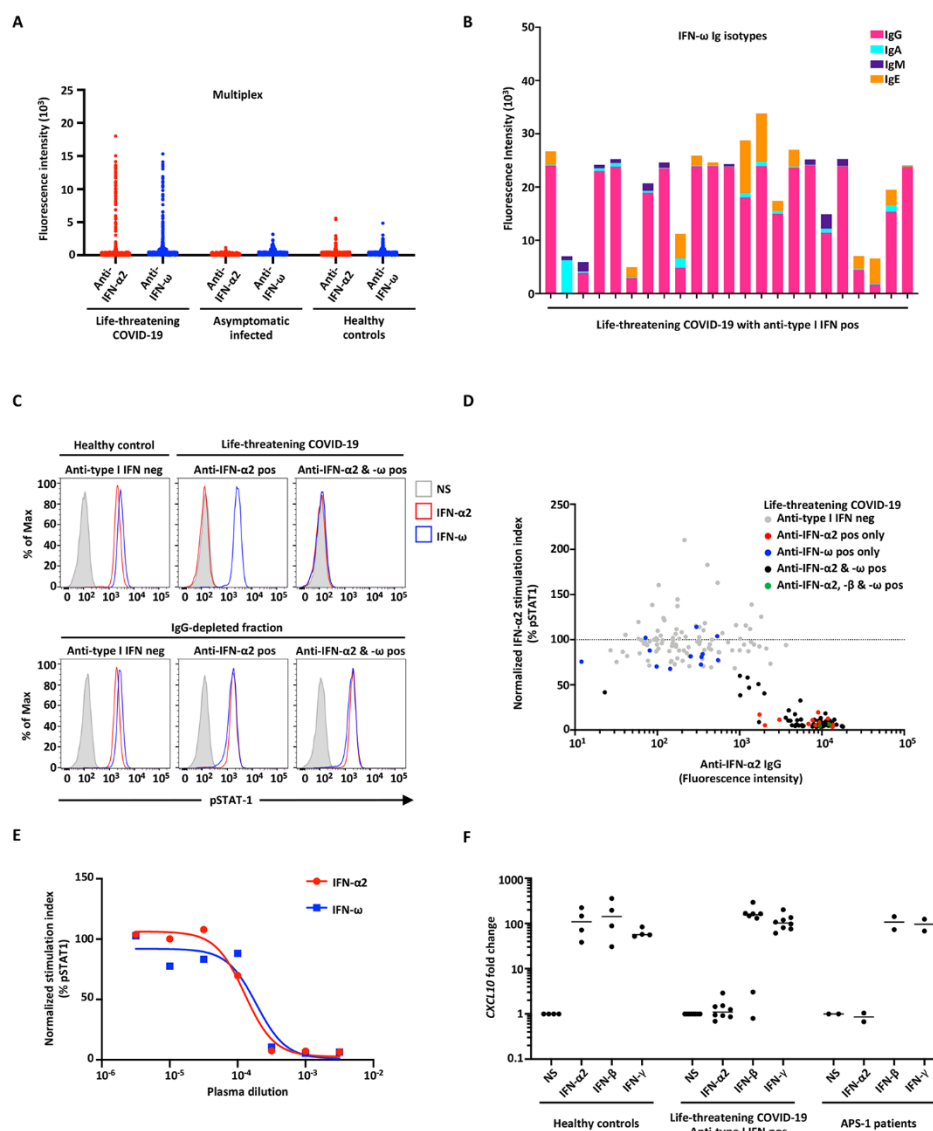


Fig. 1. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19. (A) Multiplex particle-based assay for auto-Abs against IFN-α2 and IFN-ω in patients with life-threatening COVID-19 (N=782), or asymptomatic or mild SARS-CoV-2 infection (N=443), and in healthy controls not infected with SARS-CoV2 (N=1160). (B) Anti-IFN-ω Ig isotypes in 23 patients with life-threatening COVID-19 and auto-Abs to type I IFNs. (C) Representative FACS plots depicting IFN-α2- or IFN-ω-induced pSTAT1 in healthy control cells (gated on CD14⁺ monocytes) in the presence of 10% healthy control or anti-IFN-α2/ω- auto-Abs-containing patient plasma (top panel) or an IgG-depleted plasma fraction (bottom panel). (D) Plot of anti-IFN-α2 auto-Ab levels against their neutralization capacity. The stimulation index (stimulated/unstimulated conditions) for the plasma from each was normalized against that of healthy control plasma from the same experiment. Spearman's rank correlation coefficient = -0.6805, *p*-value < 0.0001. (E) IC₅₀ curves representing IFN-α2- and IFN-ω-induced pSTAT1 levels in healthy donor cells in the presence of serial dilutions of patient plasma. The stimulation index (stimulated/unstimulated conditions) for patient plasma was normalized against that of 10% healthy control plasma. IFN-α2: IC₅₀ = 0.016%, R² = 0.985; IFN-ω: IC₅₀ = 0.0353%, R² = 0.926. (F) Neutralizing effect on CXCL10 induction after stimulation with IFN-α2, IFN-β or IFN-γ, of plasma from healthy controls (N=4), patients with life-threatening COVID-19 and auto-Abs against IFN-α2 (N=8) and APS-1 patients (N=2).

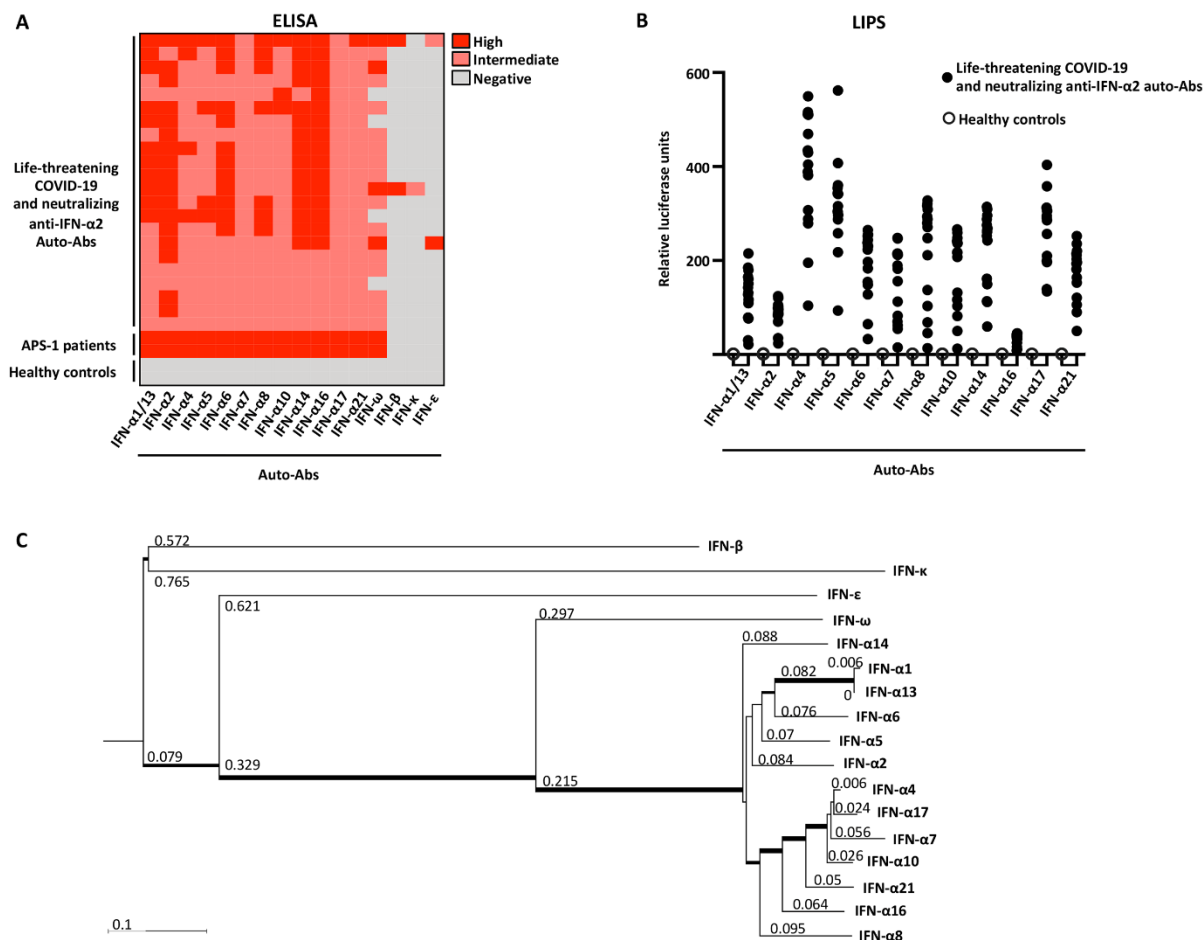


Fig. 2. Auto-Abs against the different type I IFN subtypes. (A) Enzyme-linked immunosorbent assay (ELISA) for auto-Abs against the 13 different IFN- α subtypes, IFN- ω , - β , - κ , and - ϵ in patients with life-threatening COVID-19 and auto-Abs against IFN- α 2 ($N=22$), APS-1 patients ($N=2$) and healthy controls ($N=2$). (B) Luciferase-based immunoprecipitation assay (LIPS) for the 12 different IFN- α subtypes tested in patients with auto-Abs against IFN- α 2 ($N=22$), and healthy controls ($N=2$). (C) Neighbor-joining phylogenetic tree of the 17 human type I IFN proteins. Horizontal branches are drawn to scale (bottom left, number of substitutions per site). Thinner, intermediate and thicker internal branches have bootstrap support $<50\%$, ≥ 50 and $>80\%$, respectively. The bootstrap value for the branch separating IFN- ω from all IFN- α is 100%.

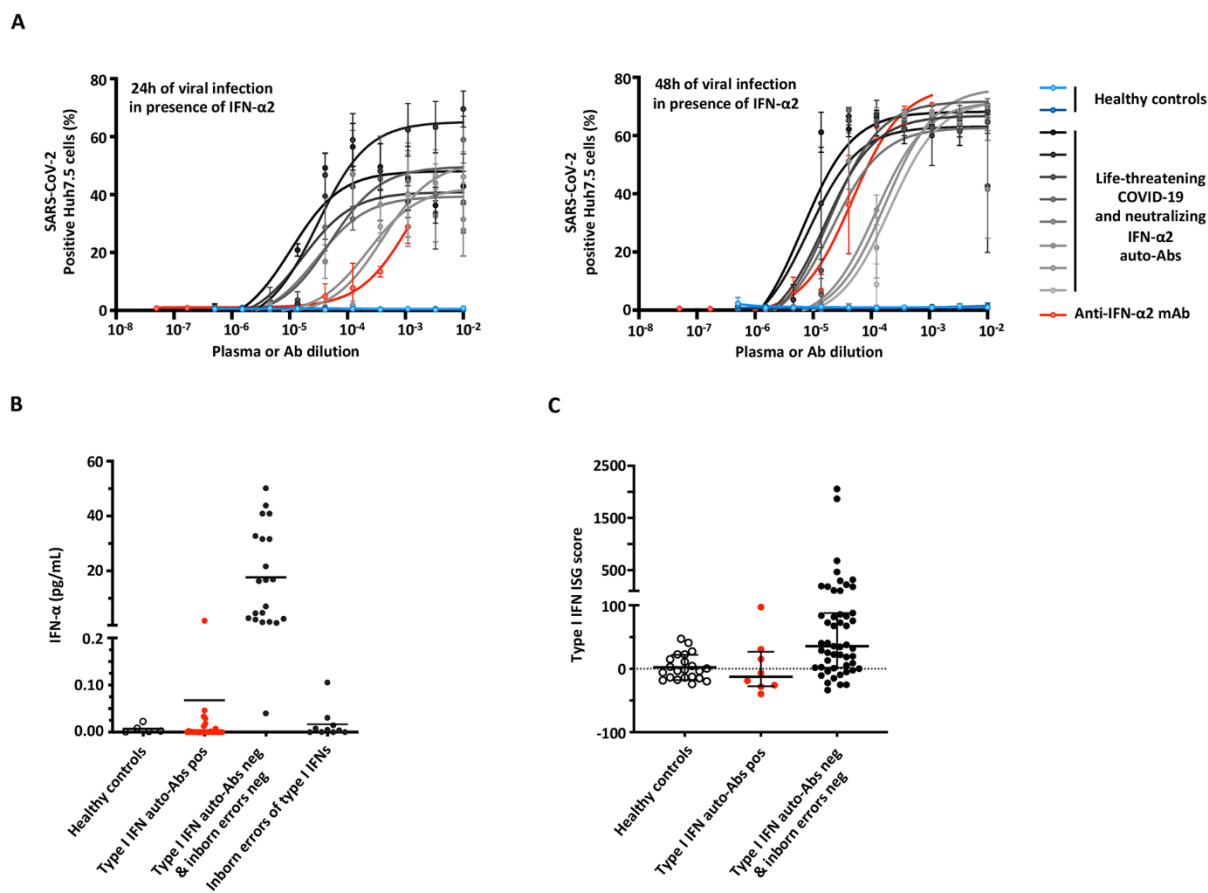


Fig. 3. Enhanced SARS-CoV-2 replication, despite the presence of IFN- α 2, in the presence of plasma from patients with auto-Abs against IFN- α . (A) SARS-CoV-2 replication, measured 24h (left panel) and 48h (right panel) after infection, in Huh7.5 cells treated with IFN- α 2 in the presence of plasma from patients with life-threatening COVID-19 and neutralizing auto-Abs against IFN- α 2 ($N=8$); a commercial anti-IFN- α 2 antibody; or control plasma ($N=2$). (B) IFN- α levels in the plasma or serum of patients with neutralizing Auto-Abs ($N=41$), healthy controls ($N=5$), COVID-19 patients without auto-Abs ($N=21$) and patients with life-threatening COVID-19 and loss-of-function (LOF) variants ($N=10$) as assessed by Simoa ELISA. (C) z-scores for type I IFN gene responses in whole blood of COVID-19 patients with ($N=8$) or without neutralizing Auto-Abs ($N=51$), or healthy uninfected controls ($N=22$). The median $\pm$ interquartile range is shown. Z-scores were significantly lower for patients with neutralizing auto-Abs compared with patients without auto-Abs (Mann-Whitney test, $p=0.01$).

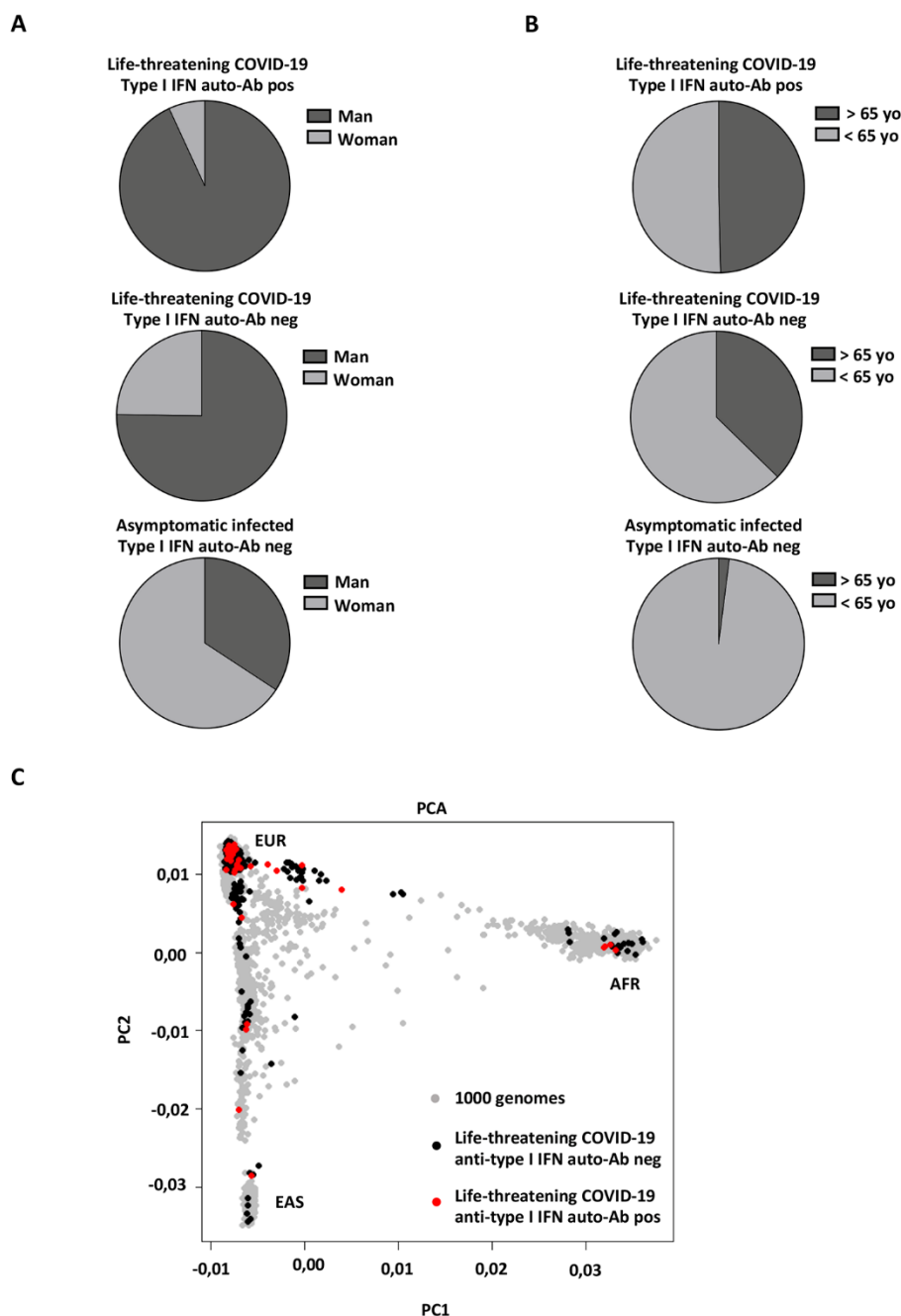


Fig. 4. Demographic and ethnic information about the patients and controls. (A) Gender distribution in patients with life-threatening COVID-19 and auto-Abs to type I IFNs, patients with life-threatening COVID-19 and without auto-Abs to type I IFNs and individuals with asymptomatic or mild SARS-CoV-2. **(B)** Age distribution in patients with life-threatening COVID-19 and auto-Abs to type I IFNs, patients with life-threatening COVID-19 and without auto-Abs to type I IFNs and individuals with asymptomatic or mild SARS-CoV-2. **(C)** Principal component analysis (PCA) on 49 patients with life-threatening COVID-19 and auto-Abs against type 1 IFNs.

Table 1. Sex and age distribution of patients with critical COVID-19 with and without autoAbs.
 Age and sex of the patients and controls, and information about auto-Abs against IFN- α 2 and IFN- ω by age and sex. OR: odds ratio.

Life-threatening COVID-19	N total	N auto-Abs positive (%)	OR [95% CI]	p-value*
Sex				
Female	226	6 (2.7%)	1	2.5 10 ⁻⁶
Male	761	95 (12.5%)	5.22 [2.27-14.80]	
Age				
<65 years	602	51 (8.5%)	1	0.024
≥65 years	385	50 (13.0%)	1.61 [1.04 - 2.49]	

*p-value were derived from Fisher's exact test, as implemented in R (<https://cran.r-project.org/>).

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard, Lindsey B. Rosen, Qian Zhang, Eleftherios Michailidis, Hans-Heinrich Hoffmann, Yu Zhang, Karim Dorgham, Quentin Philippot, Jérémie Rosain, Vivien Béziat, Jérémy Manry, Elana Shaw, Liis Haljasmägi, Pärt Peterson, Lazaro Lorenzo, Lucy Bizien, Sophie Trouillet-Assant, Kerry Dobbs, Adriana Almeida de Jesus, Alexandre Belot, Anne Kallaste, Emilie Catherinot, Yacine Tandjaoui-Lambiotte, Jeremie Le Pen, Gaspard Kerner, Benedetta Bigio, Yoann Seeleuthner, Rui Yang, Alexandre Bolze, Andrés N. Spaan, Ottavia M. Delmonte, Michael S. Abers, Alessandro Aiuti, Giorgio Casari, Vito Lampasona, Lorenzo Piemonti, Fabio Ciceri, Kaya Bilguvar, Richard P. Lifton, Marc Vasse, David M. Smadja, Mélanie Migaud, Jérôme Hadjadj, Benjamin Terrier, Darragh Duffy, Luis Quintana-Murci, Diederik van de Beek, Lucie Roussel, Donald C. Vinh, Stuart G. Tangye, Filomeen Haerynck, David Dalmau, Javier Martinez-Picado, Petter Brodin, Michel C. Nussenzweig, Stéphanie Boisson-Dupuis, Carlos Rodríguez-Gallego, Guillaume Vogt, Trine H. Mogensen, Andrew J. Oler, Jingwen Gu, Peter D. Burbelo, Jeffrey Cohen, Andrea Biondi, Laura Rachele Bettini, Mariella D'Angio, Paolo Bonfanti, Patrick Rossignol, Julien Mayaux, Frédéric Rieux-Laucat, Eystein S. Husebye, Francesca Fusco, Matilde Valeria Ursini, Luisa Imberti, Alessandra Sottini, Simone Paghera, Eugenia Quiros-Roldan, Camillo Rossi, Riccardo Castagnoli, Daniela Montagna, Amelia Licari, Gian Luigi Marseglia, Xavier Duval, Jade Ghosn, HGID Lab, NIAID-USUHS Immune Response to COVID Group, COVID Clinicians, COVID-STORM Clinicians, Imagine COVID Group, French COVID Cohort Study Group, The Milieu Intérieur Consortium, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, John S. Tsang, Raphaela Goldbach-Mansky, Kai Kisand, Michail S. Lionakis, Anne Puel, Shen-Ying Zhang, Steven M. Holland, Guy Gorochov, Emmanuelle Jouanguy, Charles M. Rice, Aurélie Cobat, Luigi D. Notarangelo, Laurent Abel, Helen C. Su and Jean-Laurent Casanova

published online September 24, 2020

ARTICLE TOOLS

<http://science.sciencemag.org/content/early/2020/09/23/science.abd4585>

SUPPLEMENTARY MATERIALS

<http://science.sciencemag.org/content/suppl/2020/09/24/science.abd4585.DC1>

RELATED CONTENT

<http://stm.sciencemag.org/content/scitransmed/12/559/eabc3103.full>
<http://stm.sciencemag.org/content/scitransmed/12/550/eabc3539.full>
<http://stm.sciencemag.org/content/scitransmed/12/564/eabd5487.full>
<http://stm.sciencemag.org/content/scitransmed/12/555/eabc9396.full>

REFERENCES

This article cites 45 articles, 9 of which you can access for free
<http://science.sciencemag.org/content/early/2020/09/23/science.abd4585#BIBL>

PERMISSIONS

<http://www.sciencemag.org/help/reprints-and-permissions>

Use of this article is subject to the [Terms of Service](#)

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.

Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works. Distributed under a Creative Commons Attribution License 4.0 (CC BY).