

## CORONAVIRUS

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

Takaki Asano<sup>1†</sup>, Bertrand Boisson<sup>1,2,3,\*†</sup>, Fanny Onodi<sup>4‡</sup>, Daniela Matuozzo<sup>2,3‡</sup>, Marcela Moncada-Velez<sup>1‡</sup>, Majistor Raj Luxman Maglorius Renkilraj<sup>2,3‡</sup>, Peng Zhang<sup>1‡</sup>, Laurent Meertens<sup>4‡</sup>, Alexandre Bolze<sup>5‡</sup>, Marie Materna<sup>2,3‡</sup>, Sarantis Korniotis<sup>6</sup>, Adrian Gervais<sup>2,3</sup>, Estelle Talouarn<sup>2,3</sup>, Benedetta Bigio<sup>1</sup>, Yoann Seeleuthner<sup>2,3</sup>, Kaya Bilguvar<sup>7</sup>, Yu Zhang<sup>8,9</sup>, Anna-Lena Neehus<sup>2,3</sup>, Masato Ogishi<sup>1</sup>, Simon J. Pelham<sup>1</sup>, Tom Le Voyer<sup>2,3</sup>, Jérémie Rosain<sup>2,3</sup>, Quentin Philippot<sup>2,3</sup>, Pere Soler-Palacín<sup>10,11,12</sup>, Roger Colobran<sup>12,13,14</sup>, Andrea Martin-Nalda<sup>10,11,12</sup>, Jacques G. Rivière<sup>10,11,12</sup>, Yacine Tandjaoui-Lambiotte<sup>15,16</sup>, Khalil Chaïbi<sup>17,18</sup>, Mohammad Shahrooei<sup>19,20</sup>, Ilad Alavi Darazam<sup>21,22</sup>, Nasrin Alipour Olyaei<sup>19,20</sup>, Davood Mansouri<sup>23,24,25</sup>, Nevin Hatipoğlu<sup>26</sup>, Figen Palabiyik<sup>26</sup>, Tayfun Ozcelik<sup>27</sup>, Giuseppe Novelli<sup>28</sup>, Antonio Novelli<sup>29</sup>, Giorgio Casari<sup>30,31</sup>, Alessandro Aiuti<sup>30,32</sup>, Paola Carrera<sup>31</sup>, Simone Bondesan<sup>31</sup>, Federica Barzaghi<sup>32</sup>, Patrizia Rovere-Querini<sup>30,33</sup>, Cristina Tresoldi<sup>34</sup>, Jose Luis Franco<sup>35</sup>, Julian Rojas<sup>35</sup>, Luis Felipe Reyes<sup>36</sup>, Ingrid G. Bustos<sup>36</sup>, Andres Augusto Arias<sup>1,35,37</sup>, Guillaume Morelle<sup>38</sup>, Christèle Kyheng<sup>38</sup>, Jesús Troya<sup>39</sup>, Laura Planas-Serra<sup>40,41</sup>, Agatha Schlüter<sup>40,41</sup>, Marta Gut<sup>42</sup>, Aurora Pujol<sup>40,41,43</sup>, Luis M. Allende<sup>44,45</sup>, Carlos Rodriguez-Gallego<sup>46,47</sup>, Carlos Flores<sup>48,49,50,51</sup>, Oscar Cabrera-Marante<sup>44</sup>, Daniel E. Pleguezuelo<sup>44</sup>, Rebeca Pérez de Diego<sup>52</sup>, Sevgi Keles<sup>53</sup>, Gokhan Aytekin<sup>54</sup>, Ozge Metin Akcan<sup>53</sup>, Yen-an T. Bryceson<sup>55</sup>, Peter Bergman<sup>56,57</sup>, Petter Brodin<sup>58</sup>, Daniel Smole<sup>59</sup>, C. I. Edvard Smith<sup>57,60</sup>, Anna-Carin Norlin<sup>57</sup>, Tessa M. Campbell<sup>55</sup>, Laura E. Covill<sup>55</sup>, Lennart Hammarström<sup>61</sup>, Qiang Pan-Hammarström<sup>61</sup>, Hassan Abolhassani<sup>61,62</sup>, Shrikant Mane<sup>63</sup>, Nico Marr<sup>64</sup>, Manar Ata<sup>64</sup>, Fatima Al Ali<sup>64</sup>, Taushif Khan<sup>64</sup>, Andrés N. Spaan<sup>1,65</sup>, Clifton L. Dalgard<sup>66,67</sup>, Paolo Bonfanti<sup>68</sup>, Andrea Biondi<sup>69</sup>, Sarah Tubiana<sup>70,71</sup>, Charles Burdet<sup>70,72</sup>, Robert Nussbaum<sup>73</sup>, Amanda Kahn-Kirby<sup>73</sup>, Andrew L. Snow<sup>74</sup>, COVID Human Genetic Effort<sup>5</sup>, COVID-STORM Clinicians<sup>5</sup>, COVID Clinicians<sup>5</sup>, Imagine COVID Group<sup>5</sup>, French COVID Cohort Study Group<sup>5</sup>, CoV-Contact Cohort<sup>5</sup>, Amsterdam UMC Covid-19 Biobank<sup>5</sup>, NIAID-USUHS COVID Study Group<sup>5</sup>, Jacinta Bustamante<sup>1,2,3,75</sup>, Anne Puel<sup>1,2,3</sup>, Stéphanie Boisson-Dupuis<sup>1,2,3</sup>, Shen-Ying Zhang<sup>1,2,3</sup>, Vivien Béziat<sup>1,2,3</sup>, Richard P. Lifton<sup>7,76||</sup>, Paul Bastard<sup>1,2,3||</sup>, Luigi D. Notarangelo<sup>8,9||</sup>, Laurent Abel<sup>1,2,3||</sup>, Helen C. Su<sup>8,9,77||</sup>, Emmanuelle Jouanguy<sup>1,2,3||</sup>, Ali Amara<sup>4||</sup>, Vassili Soumelis<sup>6,78||</sup>, Aurélie Cobat<sup>1,2,3||</sup>, Qian Zhang<sup>1,2,3||</sup>, Jean-Laurent Casanova<sup>1,2,3,79,\*||</sup>

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

## INTRODUCTION

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

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

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

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

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

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

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

†These authors contributed equally to this work.

‡These authors contributed equally to this work.

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

||These authors contributed equally to this work.

¶These authors contributed equally to this work.

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

## RESULTS

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

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

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

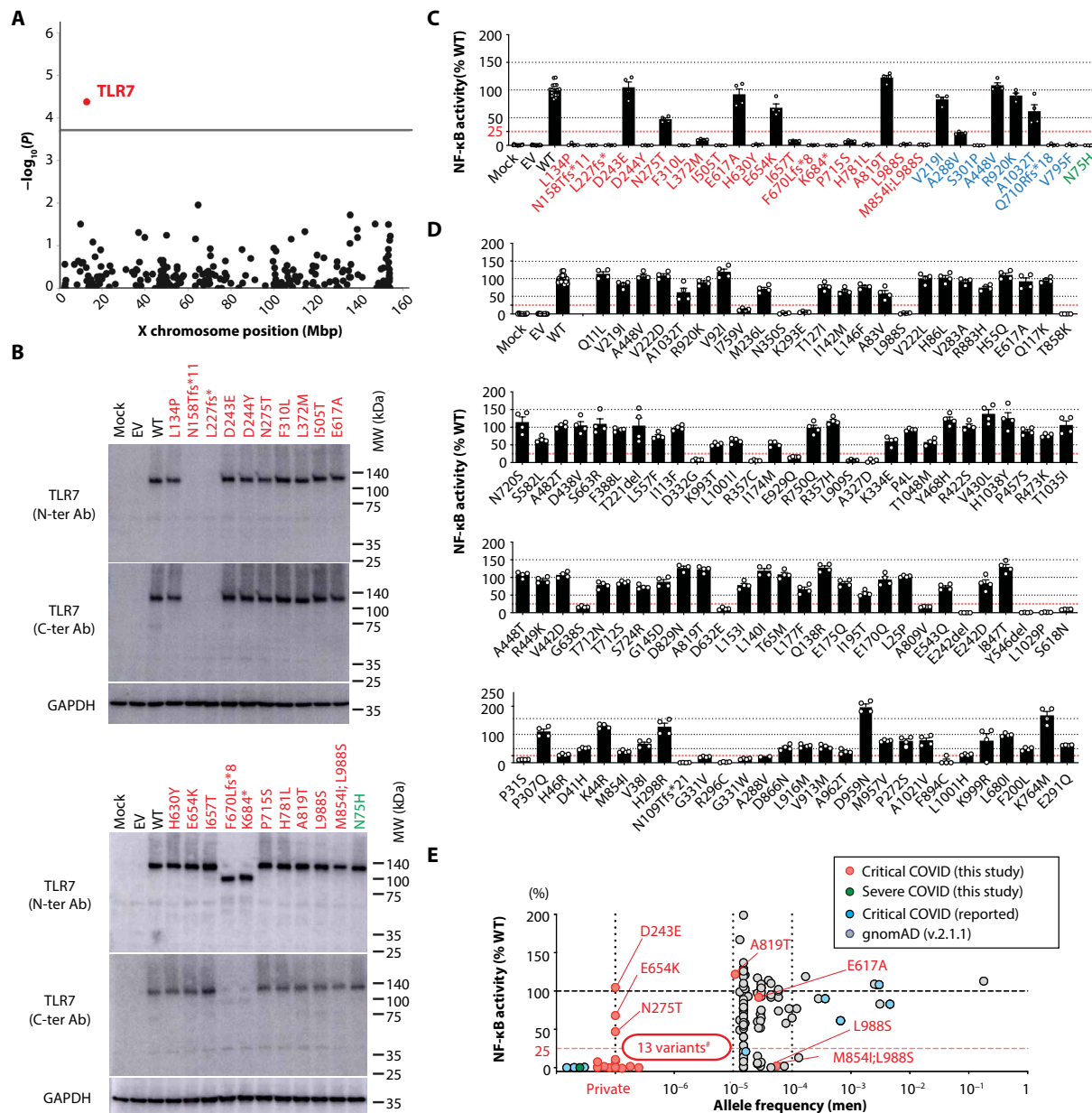
significant enrichment for coding nonsynonymous variants of the X-linked gene *TLR8* ( $P = 0.68$ ; table S2), the product of which, TLR8, is endosomal and can be stimulated by some synthetic TLR7 agonists, with an expression pattern and signaling pathway overlapping those of TLR7 (28, 29). Unlike TLR7,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

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

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

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

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



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

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

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



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

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

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

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

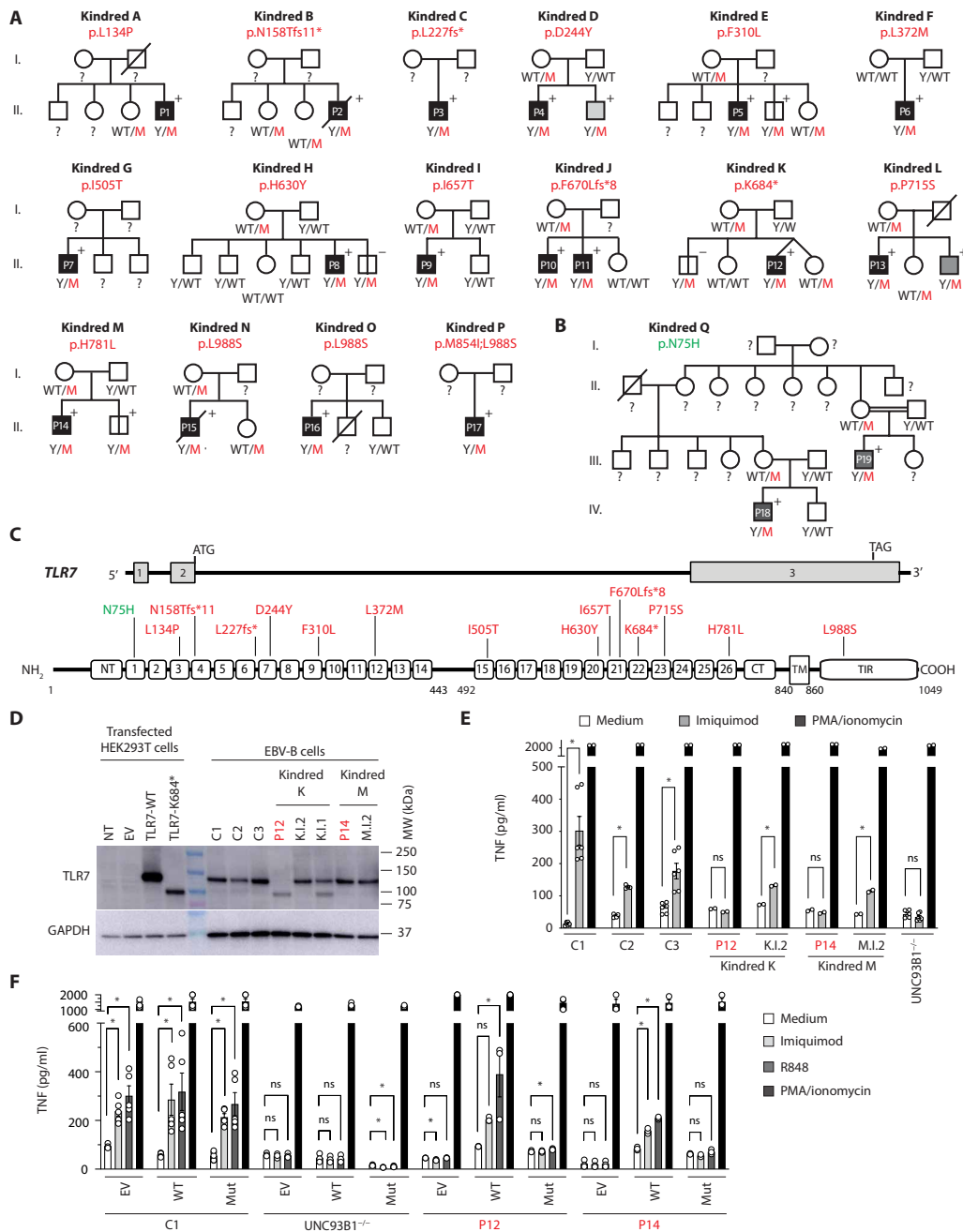
### High clinical penetrance of inherited *TLR7* deficiency in the patients' families

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

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

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

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



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

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

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

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

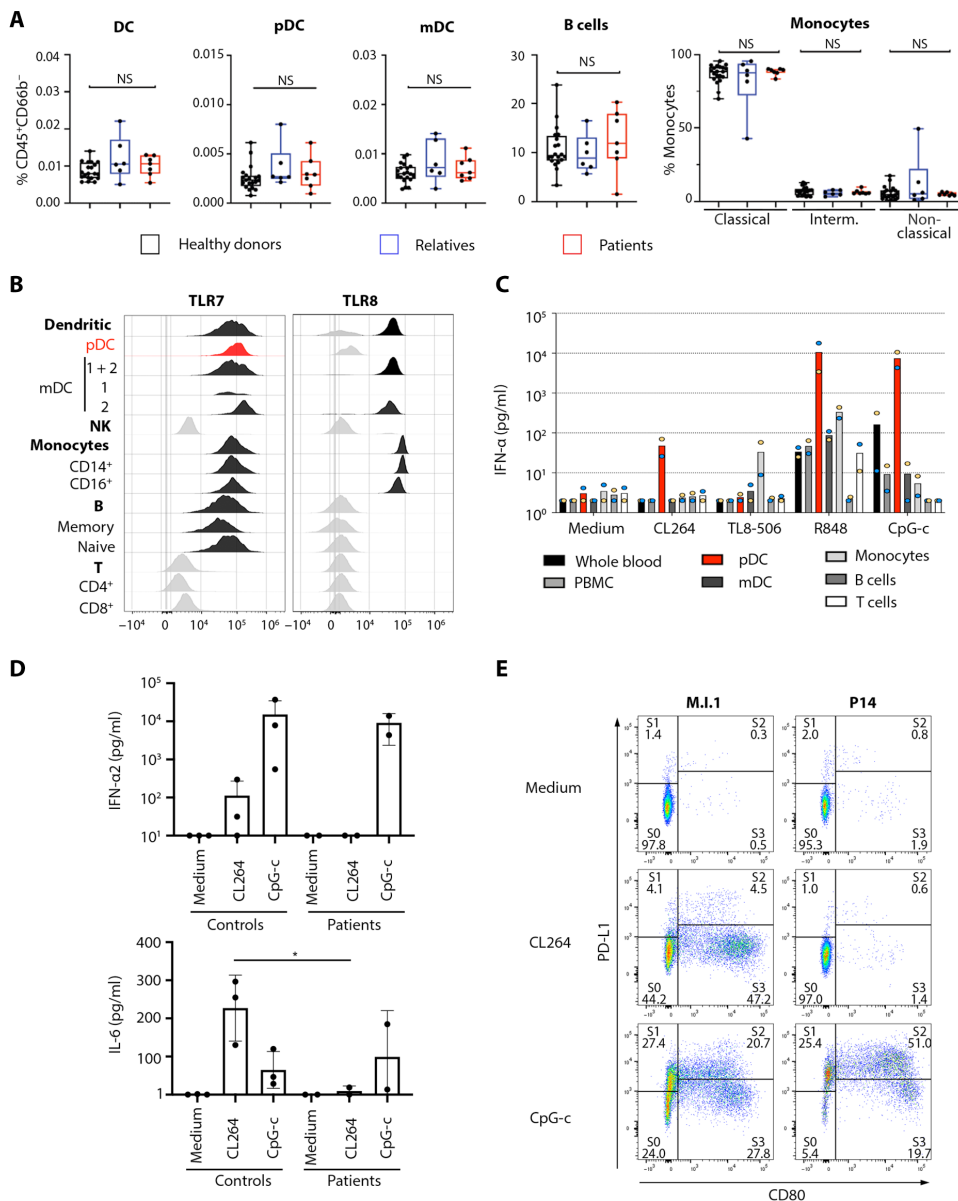
### The *TLR7*-mutated patients' myeloid cells, including pDCs, do not respond to *TLR7* agonists

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

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

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

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



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

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

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

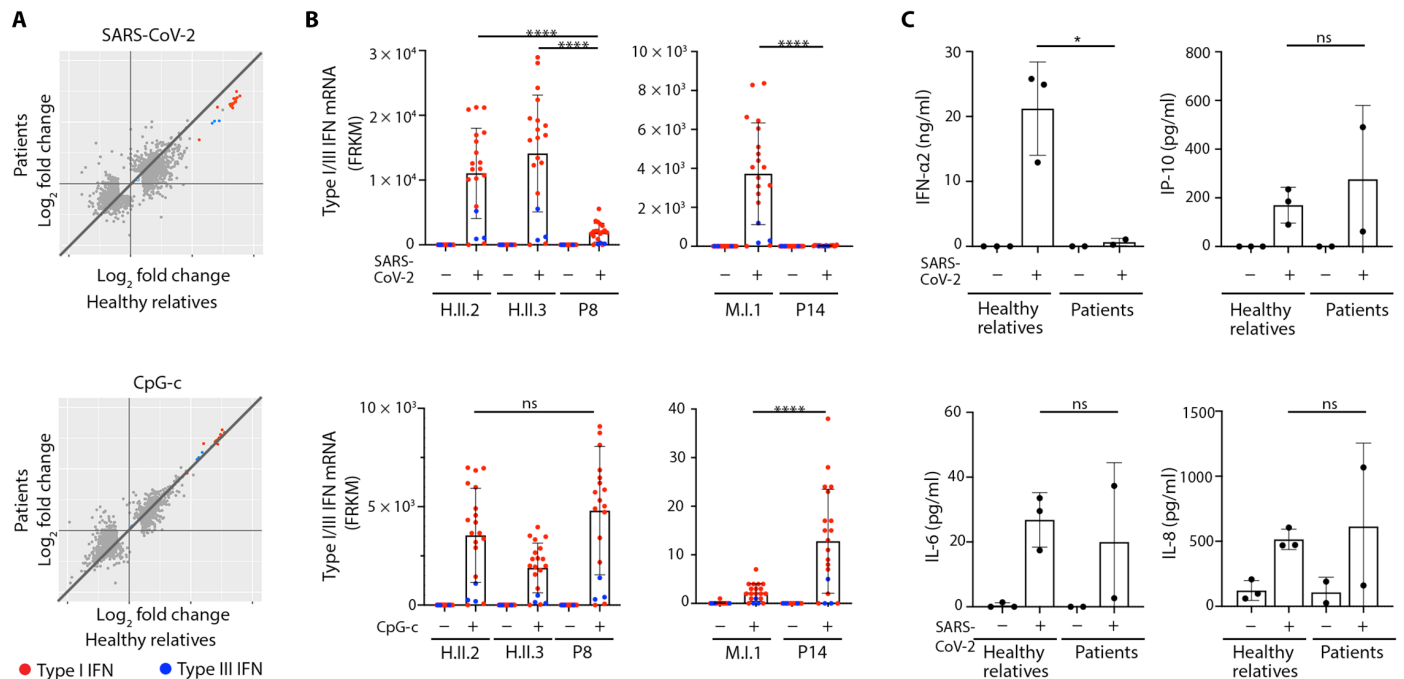
### DISCUSSION

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

type I IFNs in men than in women with critical COVID-19 pneumonia for patients over the age of 60 years (9).

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





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

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

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

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

## MATERIALS AND METHODS

### Study design

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

### Cohort recruitment and consent

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

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

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

### Next-generation sequencing

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

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

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

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

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

### Statistical analysis

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

### Cell culture

EBV-B cell lines derived from the patients were grown in complete RPMI 1640 (Life Technologies) supplemented with 10% heat-inactivated fetal bovine serum (FBS). HEK293T cells, derived from the HEK293 cell line, which expresses a mutant version of the SV40 large T antigen, were grown in complete Dulbecco's modified Eagle's medium (Life Technologies) supplemented with 10% FBS. Cells were incubated at 37°C in the presence of 5% CO<sub>2</sub>.

### Expression vectors and transfection experiments

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

### Western blotting

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

### Luciferase reporter assay

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

### RNA extraction and reverse transcription qPCR

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



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

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

### Stable transduction

The WT coding sequence of *TLR7* was inserted into pTRIP-CMV-puro-2A. For lentivirus production, HEK293T cells were transfected with 1.6  $\mu\text{g}$  of pTRIP-CMV-puro-2A-TLR7-WT (or mutant, K684\*), 0.2  $\mu\text{g}$  of pCMV-VSV-G (Addgene), 0.2  $\mu\text{g}$  of pXHB2 (NIH-AIDS Reagent 22 Program), and 1  $\mu\text{g}$  of psPAX2 (Addgene), with X-treme gene 9 (Roche), according to the manufacturer's instructions. Supernatants were harvested after 24 hours, and protamine sulfate (8  $\mu\text{g/ml}$ ) was added. The lentiviral suspension obtained was used to transduce  $2 \times 10^5$  EBV-B cells by spinoculation at 1200g for 2 hours. The transduced cells were selected by incubation on medium containing puromycin (1  $\mu\text{g/ml}$ ) for 2 days. The cells were then selected by incubation for a further 2 days on medium containing puromycin (2  $\mu\text{g/ml}$ ). During viral transduction, the cells were cultured with 5  $\mu\text{M}$  IRAK4 inhibitor (PF06650833) (Bio-Techne) to prevent cell death due to the overproduction of TLR7. Selected transduced cells were then stimulated with R848 (1  $\mu\text{g/ml}$ ) or imiquimod (5  $\mu\text{g/ml}$ ) for 24 hours without IRAK4 inhibitor. The supernatants were harvested after 24 hours of activation. ELISA determinations of TNF in cell culture supernatants were performed with a kit (Thermo Fisher Scientific), according to the manufacturer's instructions.

### VirScan analysis

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

### Deep immunophenotyping by mass cytometry (CyTOF)

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

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

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

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

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

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



**pDC activation**

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

**Flow cytometry analysis for human pDCs**

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

**RNA sequencing**

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

**Determination of secreted inflammatory cytokines**

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

**SUPPLEMENTARY MATERIALS**

www.science.org/doi/10.1126/sciimmunol.abl4348

Figs. S1 to S6

Tables S1 to S3

Data files S1 to S7

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

**REFERENCES AND NOTES**

- 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).
- Q. Zhang, P. Bastard, A. Bolze, E. Jouanguy, S. Y. Zhang; COVID Human Genetic Effort, A. Cobat, L. D. Notarangelo, H. C. Su, L. Abel, J. L. Casanova, Life-threatening COVID-19: Defective interferons unleash excessive inflammation. *Med* **1**, 14–20 (2020).
- M. O'Driscoll, G. Ribeiro Dos Santos, L. Wang, D. A. T. Cummings, A. S. Azman, J. Paireau, A. Fontanet, S. Cauchemez, H. Salje, Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* **590**, 140–145 (2021).
- E. P. Scully, J. Haverfield, R. L. Ursin, C. Tannenbaum, S. L. Klein, Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat. Rev. Immunol.* **20**, 442–447 (2020).
- M. J. Ciancanelli, S. X. Huang, P. Luthra, H. Garner, Y. Itan, S. Volpi, F. G. Lafaille, C. Trouillet, M. Schmolke, R. A. Albrecht, E. Israelsson, H. K. Lim, M. Casadio, T. Hermesh, L. Lorenzo, L. W. Leung, V. Pedergrana, B. Boisson, S. Okada, C. Picard, B. Ringuier, F. Troussier, D. Chaussabel, L. Abel, I. Pellier, L. D. Notarangelo, A. Garcia-Sastre, C. F. Basler, F. Geissmann, S. Y. Zhang, H. W. Snoeck, J. L. Casanova, Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science* **348**, 448–453 (2015).
- N. Hernandez, I. Melki, H. Jing, T. Habib, S. S. Y. Huang, J. Danielson, T. Kula, S. Drutman, S. Belkaya, V. Rattina, L. Lorenzo-Diaz, A. Boulai, Y. Rose, N. Kitabayashi, M. P. Rodero, C. Dumaine, S. Blanche, M. N. Lebras, M. C. Leung, L. S. Mathew, B. Boisson, S. Y. Zhang, S. Boisson-Dupuis, S. Giliani, D. Chaussabel, L. D. Notarangelo, S. J. Elledge, M. J. Ciancanelli, L. Abel, Q. Zhang, N. Marr, Y. J. Crow, H. C. Su, J. L. Casanova, Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. *J. Exp. Med.* **215**, 2567–2585 (2018).
- H. K. Lim, S. X. L. Huang, J. Chen, G. Kerner, O. Gilliaux, P. Bastard, K. Dobbs, N. Hernandez, N. Goudin, M. L. Hasek, E. J. Garcia Reino, F. G. Lafaille, L. Lorenzo, P. Luthra, T. Kochetkov, B. Bigio, S. Boucherit, F. Rozenberg, C. Vedrinne, M. D. Keller, Y. Itan, A. Garcia-Sastre, M. Celard, J. S. Orange, M. J. Ciancanelli, I. Meyts, Q. Zhang, L. Abel, L. D. Notarangelo, H. W. Snoeck, J. L. Casanova, S. Y. Zhang, Severe influenza pneumonitis in children with inherited TLR3 deficiency. *J. Exp. Med.* **216**, 2038–2056 (2019).
- 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. A. Arias, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbibi, L. Bonnet-Madin, K. Dorgham, N. Smith, W. M. Schneider, B. S. Razoogy, H. H. Hoffmann, E. Michailidis, L. Moens, J. E. Han, L. Lorenzo, L. Bizien, P. Meade, A. C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seeleuthner, J. Manry, C. Masson, Y. Schmitt, A. Schluter, 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. Almoufiri, S. Z. Al-Muhsen, F. Alosaime, S. Al Turki, R. Hasanato, D. van de Beek, A. Biondi, L. R. Betti, 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. Colkesen, T. Ozcelik, K. K. Yasar, S. Senoglu, S. N. Karabela, C. Rodriguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Laouenan; COVID-STORM 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. D. Milner, D. C. Vinh, T. H. Mogensen, N. Marr, A. N. Spaan, B. Boisson, S. Boisson-Dupuis, J. Bustamante, A. Puel, M. J. Ciancanelli, I. Meyts, T. Maniatis, V. Soumelis, A. Amara, M. Nussenzweig, A. Garcia-Sastre, F. Krammer, A. Pujol, D. Duffy, R. P. Lifton, S. Y. Zhang, G. Gorochov, V. Beziat, 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* **370**, eabd4570 (2020).
- P. Bastard, L. B. Rosen, Q. Zhang, E. Michailidis, H. H. Hoffmann, Y. Zhang, K. Dorgham, Q. Philippot, J. Rosain, V. Beziat, J. Manry, E. Shaw, L. Haljasmagi, P. Peterson, L. Lorenzo, L. Bizien, S. Trouillet-Assant, K. Dobbs, A. A. de Jesus, A. Belot, A. Kallaste, E. Catherineot, Y. Tandjaoui-Lambiotte, J. Le Pen, G. Kerner, B. Bigio, Y. Seeleuthner, R. Yang, A. Bolze, A. N. Spaan, O. M. Delmonte, M. S. Abers, A. Aiuti, G. Casari, V. Lampasona, L. Piemonti, F. Ciceri, K. Bilguvar, R. P. Lifton, M. Vasse, D. M. Smadja, M. Migaud, J. Hadjadj, B. Terrier, D. Duffy, L. Quintana-Murci, D. van de Beek, L. Roussel, D. C. Vinh, S. G. Tangye, F. Haerynck, D. Dalmau, J. Martinez-Picado, P. Brodin, M. C. Nussenzweig, S. Boisson-Dupuis,

- C. Rodríguez-Gallego, G. Vogt, T. H. Mogensen, A. J. Oler, J. Gu, P. D. Burbelo, J. I. Cohen, A. Biondi, L. R. Bettini, M. D'Angio, P. Bonfanti, P. Rossignol, J. Mayaux, F. Rieux-Laucat, E. S. Husebye, F. Fusco, M. V. Ursini, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, R. Castagnoli, D. Montagna, A. Licari, G. L. Marseglia, X. Duval, J. Ghosh; 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; Co V-Contact Cohort; Amsterdam UMC Covid-Biobank; COVID Human Genetic Effort, J. S. Tsang, R. Goldbach-Mansky, K. Kisand, M. S. Lionakis, A. Puel, S. Y. Zhang, S. M. Holland, G. Gorochov, E. Jouanguy, C. M. Rice, A. Cobat, L. D. Notarangelo, L. Abel, H. C. Su, J. L. Casanova, Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **370**, eabd4585 (2020).
10. E. Y. Wang, T. Mao, J. Klein, Y. Dai, J. D. Huck, J. R. Jaycox, F. Liu, T. Zhou, B. Israelow, P. Wong, A. Coppi, C. Lucas, J. Silva, J. E. Oh, E. Song, E. S. Perotti, N. S. Zheng, S. Fischer, M. Campbell, J. B. Fournier, A. L. Wyllie, C. B. F. Vogels, I. M. Ott, C. C. Kalinich, M. E. Petrone, A. E. Watkins, I. T. Yale, C. Dela Cruz, S. F. Farhadian, W. L. Schulz, S. Ma, N. D. Grubaugh, A. I. Ko, A. Iwasaki, A. M. Ring, Diverse functional autoantibodies in patients with COVID-19. *Nature* **595**, 283–288 (2021).
  11. R. Koning, P. Bastard, J. L. Casanova, M. C. Brouwer, D. van de Beek; Amsterdam U.M.C. COVID-19 Biobank Investigators, Autoantibodies against type I interferons are associated with multi-organ failure in COVID-19 patients. *Intensive Care Med.* **47**, 704–706 (2021).
  12. J. Troya, P. Bastard, L. Planas-Serra, P. Ryan, M. Ruiz, M. de Carranza, J. Torres, A. Martinez, L. Abel, J. L. Casanova, A. Pujol, Neutralizing autoantibodies to type I IFNs in >10% of patients with severe COVID-19 pneumonia hospitalized in Madrid, Spain. *J. Clin. Immunol.* **41**, 914–922 (2021).
  13. G. David, M. Mehdi, B. Paul, P. Magali, S. Kahina, F. Nicole, P. Rémi, L. Christine, W. Thierry, C. Jean-Laurent, B. Alexandre, R. Jean-Christophe, T.-A. Sophie, Antibodies against type-I interferon: Detection and association with severe clinical outcome in COVID-19 patients. medRxiv 2021.2004.2002.21253262 [Preprint]. 5 April 2021. <https://doi.org/10.1101/2021.04.02.21253262>.
  14. M. G. P. van der Wijst, S. E. Vazquez, G. C. Hartoularos, P. Bastard, T. Grant, R. Bueno, D. S. Lee, J. R. Greenland, Y. Sun, R. Perez, A. Ogorodnikov, A. Ward, S. A. Mann, K. L. Lynch, C. Yun, D. V. Havlir, G. Chamie, C. Marquez, B. Greenhouse, M. S. Lionakis, P. J. Norris, L. J. Dumont, K. Kelly, P. Zhang, Q. Zhang, A. Gervais, T. L. Voyer, A. Whately, Y. Si, A. Byrne, A. J. Combes, A. A. Rao, Y. S. Song; UCSF COMET consortium, G. K. Fragiadakis, K. Kangelaris, C. S. Calfee, D. J. Erle, C. Hendrickson, M. F. Krummel, P. G. Woodruff, C. R. Langelier, J. L. Casanova, J. L. Derisi, M. S. Anderson, K. J. Ye, Longitudinal single-cell epitope and RNA-sequencing reveals the immunological impact of type 1 interferon autoantibodies in critical COVID-19. bioRxiv 2021.03.09.434529 [Preprint]. 10 March 2021. <https://doi.org/10.1101/2021.03.09.434529>.
  15. S. E. Vazquez, P. Bastard, K. Kelly, A. Gervais, P. J. Norris, L. J. Dumont, J. L. Casanova, M. S. Anderson, J. L. Derisi, Neutralizing autoantibodies to type I interferons in COVID-19 convalescent donor plasma. *J. Clin. Immunol.* **41**, 1169–1171 (2021).
  16. P. Bastard, E. Orlova, L. Sozaeva, R. Levy, A. James, M. M. Schmitt, S. Ochoa, M. Kareva, Y. Rodina, A. Gervais, T. Le Voyer, J. Rosain, Q. Philippot, A. L. Neehus, E. Shaw, M. Migaud, L. Bizien, O. Ekwali, S. Berg, G. Beccuti, L. Ghizzoni, G. Thiriez, A. Pavot, C. Goujard, M. L. Fremont, E. Carter, A. Rothenbuhler, A. Linglart, B. Mignot, A. Comte, N. Cheikh, O. Hermine, L. Breivik, E. S. Husebye, S. Humbert, P. Rohrlach, A. Coaquette, F. Vuoto, K. Faure, N. Mahlaoui, P. Kotnik, T. Battelino, K. Trebusak Podkrajsek, K. Kisand, E. M. N. Ferre, T. DiMaggio, L. B. Rosen, P. D. Burbelo, M. McIntyre, N. Y. Kann, A. Shcherbina, M. Pavlova, A. Kolodkina, S. M. Holland, S. Y. Zhang, Y. J. Crow, L. D. Notarangelo, H. C. Su, L. Abel, M. S. Anderson, E. Jouanguy, B. Neven, A. Puel, J. L. Casanova, M. S. Lionakis, Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J. Exp. Med.* **218**, e20210554 (2021).
  17. P. Bastard, E. Michailidis, H. H. Hoffmann, M. Chbihi, T. Le Voyer, J. Rosain, Q. Philippot, Y. Seeleuthner, A. Gervais, M. Materna, P. M. N. de Oliveira, M. L. S. Maia, A. P. Dinis Anjo Bom, T. Azamor, D. Araujo da Conceicao, E. Goudouris, A. Homma, G. Slesak, J. Schafer, B. Pulendran, J. D. Miller, R. Huits, R. Yang, L. B. Rosen, L. Bizien, L. Lorenzo, M. Chrabieh, L. V. Erazo, F. Rozenberg, M. M. Jeljeli, V. Beziat, S. M. Holland, A. Cobat, L. D. Notarangelo, H. C. Su, R. Ahmed, A. Puel, S. Y. Zhang, L. Abel, S. J. Seligman, Q. Zhang, M. R. MacDonald, E. Jouanguy, C. M. Rice, J. L. Casanova, Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. *J. Exp. Med.* **218**, e20202486 (2021).
  18. P. Bastard, A. Gervais, T. L. Voyer, J. Rosain, Q. Philippot, J. Manry, E. Michailidis, H.-H. Hoffmann, S. Eto, M. Garcia-Prat, L. Bizien, A. Parra-Martinez, R. Yang, L. Haljasmägi, M. Migaud, K. Särekannu, J. Maslovskaja, N. de Prost, Y. Tandjaoui-Lambiotte, C.-E. Luyt, B. Amador-Borrero, A. Gaudet, J. Poissy, P. Morel, P. Richard, F. Cognasse, J. Troya, S. Trouillet-Assant, A. Belot, K. Saker, P. Garçon, J. G. Rivière, J.-C. Lagier, S. Gentile, L. B. Rosen, E. Shaw, T. Morio, J. Tanaka, D. Dalmau, P.-L. Tharaux, D. Sene, A. Stephanian, B. Megarbane, V. Triantafyllia, A. Fekkar, J. R. Heath, J. L. Franco, J.-M. Anaya, J. Solé-Violán, L. Imberti, A. Biondi, P. Bonfanti, R. Castagnoli, O. M. Delmonte, Y. Zhang, A. L. Snow, S. M. Holland, C. Biggs, M. Moncada-Vélez, A. A. Arias, L. Lorenzo, S. Boucherit, B. Coulibaly, D. Anglicheau, A. M. Planas, F. Haerynck, S. Duvlis, R. L. Nussbaum, T. Ozcelik, S. Keles, A. A. Boussifha, J. E. Bakkouri, C. Ramirez-Santana, S. Paul, Q. Pan-Hammarström, L. Hammarström, A. Dupont, A. Kurolop, C. N. Metz, A. Aiuti, G. Casari, V. Lampasona, F. Ciceri, L. A. Barreiros, E. Dominguez-Garrido, M. Vidigal, M. Zatz, D. van de Beek, S. Sahanic, I. Tancevski, Y. Stepanovskyy, O. Boyarchuk, Y. Nukui, M. Tsumura, L. Vidaur, S. G. Tangye, S. Burrel, D. Duffy, L. Quintana-Murci, A. Klocperk, N. Y. Kann, A. Shcherbina, Y.-L. Lau, D. Leung, M. Coulangeat, J. Marlet, R. Koning, L. F. Reyes, A. Chauvineau-Grenier, F. Venet, G. Monneret, M. C. Nussenzweig, R. Arrestier, I. Boudhabay, H. Baris-Feldman, N. D. Hagin, J. Wauters, I. Meyts, A. H. Dyer, S. P. Kennelly, N. M. Bourke, R. Halwani, N. S. Sharif-Askari, K. Dorgham, J. Sallette, S. M. Sedkaoui, S. A. Khater, R. Rigo-Bonnin, F. Morandeira, L. Roussel, D. C. Vinh, S. R. Ostrowski, A. Condino-Neto, C. Prando, A. Bonradenko, A. N. Spaan, L. Gilardin, J. Fellay, S. Lyonnet, K. Bilguvar, R. P. Lifton, S. Mane; HGID Lab; COVID Clinicians; COVID-STORM Clinicians; NIAID Immune Response to COVID Group; NH-COVAIR Study Group; Danish CHGE; Danish Blood Donor Study; St. James's Hospital; SARS CoV2 Interest group; French COVID Cohort Study Group; Imagine COVID-Group; The Milieu Intérieur Consortium; CoV-Contact Cohort; Amsterdam UMC Covid-19; Biobank Investigators; COVID Human Genetic Effort; CONSTANCES cohort; 3C-Dijon Study; Cerba Health-Care; Etablissement du Sang study group, M. S. Anderson, B. Boisson, V. Béziat, S.-Y. Zhang, E. Vandreakos, O. Hermine, A. Pujol, P. Peterson, T. H. Mogensen, L. Rowen, J. Mond, S. Debette, X. de Lamballerie, X. Duval, F. Mentré, M. Zins, P. Soler-Palacin, R. Colobran, G. Gorochov, X. Solanich, S. Susen, J. Martinez-Picado, D. Raouf, M. Vasse, P. K. Gregersen, L. Piemonti, C. Rodríguez-Gallego, L. D. Notarangelo, H. C. Su, K. Kisand, S. Okada, A. Puel, E. Jouanguy, C. M. Rice, P. Tiberghien, Q. Zhang, A. Cobat, L. Abel, J.-L. Casanova, Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. *Sci. Immunol.*, ab14340 (2021).
  19. D. Firth, Bias reduction of maximum likelihood estimates. *Biometrika* **80**, 27–38 (1993).
  20. H. Hemmi, T. Kaisho, O. Takeuchi, S. Sato, H. Sanjo, K. Hoshino, T. Horiuchi, H. Tomizawa, K. Takeda, S. Akira, Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat. Immunol.* **3**, 196–200 (2002).
  21. S. S. Diebold, T. Kaisho, H. Hemmi, S. Akira, C. Reis e Sousa, Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science* **303**, 1529–1531 (2004).
  22. F. Heil, H. Hemmi, H. Hochrein, F. Ampenberger, C. Kirschning, S. Akira, G. Lipford, H. Wagner, S. Bauer, Species-specific recognition of single-stranded RNA via Toll-like receptor 7 and 8. *Science* **303**, 1526–1529 (2004).
  23. J. M. Lund, L. Alexopoulou, A. Sato, M. Karow, N. C. Adams, N. W. Gale, A. Iwasaki, R. A. Flavell, Recognition of single-stranded RNA viruses by Toll-like receptor 7. *Proc. Natl. Acad. Sci. U.S.A.* **101**, 5598–5603 (2004).
  24. B. Beutler, Inferences, questions and possibilities in Toll-like receptor signalling. *Nature* **430**, 257–263 (2004).
  25. M. Colonna, G. Trinchieri, Y. J. Liu, Plasmacytoid dendritic cells in immunity. *Nat. Immunol.* **5**, 1219–1226 (2004).
  26. M. Gilliet, W. Cao, Y. J. Liu, Plasmacytoid dendritic cells: Sensing nucleic acids in viral infection and autoimmune diseases. *Nat. Rev. Immunol.* **8**, 594–606 (2008).
  27. B. Reizis, Plasmacytoid dendritic cells: Development, regulation, and function. *Immunity* **50**, 37–50 (2019).
  28. A. T. Bender, E. Tzvetkov, A. Pereira, Y. Wu, S. Kasar, M. M. Przetak, J. Vlach, T. B. Niewold, M. A. Jensen, S. L. Okitsu, TLR7 and TLR8 differentially activate the IRF and NF- $\kappa$ B pathways in specific cell types to promote inflammation. *ImmunoHorizons* **4**, 93–107 (2020).
  29. K. Maeda, S. Akira, TLR7 Structure: Cut in Z-Loop. *Immunity* **45**, 705–707 (2016).
  30. J. Aluri, A. Bach, S. Kaviany, L. Chiquetto Paracatu, M. Kitcharoenakkul, M. A. Walkiewicz, C. D. Putnam, M. Shinawi, N. Saucier, E. M. Rizzi, M. T. Harmon, M. P. Keppel, M. Ritter, M. Similiuk, E. Kulm, M. Joyce, A. A. de Jesus, R. Goldbach-Mansky, Y. S. Lee, M. Cella, P. L. Kendall, M. C. Dinuer, J. J. Bednarski, C. Bemrich-Stolz, S. W. Canna, S. M. Abraham, M. M. Demczko, J. Powell, S. M. Jones, A. M. Scurlock, S. S. De Ravin, J. J. Bleesing, J. A. Connelly, V. K. Rao, L. G. Schuettel, M. A. Cooper, Immunodeficiency and bone marrow failure with mosaic and germline TLR8 gain of function. *Blood* **137**, 2450–2462 (2021).
  31. C. Uggetti, A. Lepellet, Y. J. Crow, Self-awareness: Nucleic acid-driven inflammation and the type I interferonopathies. *Annu. Rev. Immunol.* **37**, 247–267 (2019).
  32. B. Boisson, J. L. Casanova, TLR8 gain of function: A tall surprise. *Blood* **137**, 2420–2422 (2021).
  33. M. Uhlen, M. J. Karlsson, W. Zhong, A. Tebani, C. Pou, J. Mikes, T. Lakshminanth, B. Forsstrom, F. Edfors, J. Odeberg, A. Mardinoglu, C. Zhang, K. von Feilitzen, J. Mulder, E. Sjöstedt, A. Hober, P. Oksvold, M. Zwahlen, F. Ponten, C. Lindskog, A. Sivertsson, L. Fagerberg, P. Brodin, A genome-wide transcriptomic analysis of protein-coding genes in human blood cells. *Science* **366**, eaax9198 (2019).

34. C. Fallerini, S. Daga, S. Mantovani, E. Benetti, N. Picchiotti, D. Francisci, F. Pacioni, E. Schiaroli, M. Baldassarri, F. Fava, M. Palmieri, S. Ludovisi, F. Castelli, E. Quiros-Roldan, M. Vaghi, S. Rusconi, M. Siano, M. Bandini, O. Spiga, K. Capitani, S. Furini, F. Mari; GEN-COVID Multicenter Study, A. Renieri, M. U. Mondelli, E. Frullanti, Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: Findings from a nested case-control study. *eLife* **10**, e67569 (2021).
35. A. Simons, J. Schuurs-Hoeijmakers, G. van den Heuvel, T. Mantere, S. Kersten, R. C. van Deuren, M. Steehouwer, S. V. van Reijmersdal, M. Jaeger, T. Hofste, G. Astuti, J. C. Galbany, V. van der Schoot, H. van der Hoeven; Wanda Hagmolen Of Ten Have, E. Klijn, C. van den Meer, J. Fiddelaers, Q. de Mast, C. P. Bleeker-Rovers, L. A. B. Joosten, H. G. Yntema, C. Gilissen, M. Nelen, J. W. M. van der Meer, H. G. Brunner, M. G. Netea, F. L. van de Veerdonk, A. Hoischen, Presence of genetic variants among young men with severe COVID-19. *JAMA* **324**, 663–673 (2020).
36. A. Belkadi, V. Pederghana, A. Cobat, Y. Itan, Q. B. Vincent, A. Abhyankar, L. Shang, J. El Baghdadi, A. Bousfiha; Exome/Array Consortium, A. Alcais, B. Boisson, J. L. Casanova, L. Abel, Whole-exome sequencing to analyze population structure, parental inbreeding, and familial linkage. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 6713–6718 (2016).
37. M. Shodell, F. P. Siegal, Circulating, interferon-producing plasmacytoid dendritic cells decline during human ageing. *Scand. J. Immunol.* **56**, 518–521 (2002).
38. Y. Jing, E. Shaheen, R. R. Drake, N. Chen, S. Gravenstein, Y. Deng, Aging is associated with a numerical and functional decline in plasmacytoid dendritic cells, whereas myeloid dendritic cells are relatively unaltered in human peripheral blood. *Hum. Immunol.* **70**, 777–784 (2009).
39. M. V. Splunter, O. Perdijk, H. Fick-Brinkhof, E. G. Floris-Vollenbroek, B. Meijer, S. Brugman, H. F. J. Savelkoul, E. van Hoffen, R. J. Joost van Neerven, Plasmacytoid dendritic cell and myeloid dendritic cell function in ageing: A comparison between elderly and young adult women. *PLOS ONE* **14**, e0225825 (2019).
40. N. V. Giltiay, C. P. Chappell, X. Sun, N. Kolhatkar, T. H. Teal, A. E. Wiedeman, J. Kim, L. Tanaka, M. B. Buechler, J. A. Hamerman, T. Imanishi-Kari, E. A. Clark, K. B. Elkon, Overexpression of TLR7 promotes cell-intrinsic expansion and autoantibody production by transitional T1 B cells. *J. Exp. Med.* **210**, 2773–2789 (2013).
41. J. Lonsdale, J. Thomas, M. Salvatore, R. Phillips, E. Lo, S. Shad, R. Hasz, G. Walters, F. Garcia, N. Young, B. Foster, M. Moser, E. Karasik, B. Gillard, K. Ramsey, S. Sullivan, J. Bridge, H. Magazine, J. Syron, J. Fleming, L. Siminoff, H. Traino, M. Mosavel, L. Barker, S. Jewell, D. Rohrer, D. Maxim, D. Filkins, P. Harbach, E. Cortadillo, B. Berghuis, L. Turner, E. Hudson, K. Feenstra, L. Sobin, J. Robb, P. Branton, G. Korzeniewski, C. Shive, D. Tabor, L. Qi, K. Groch, S. Nampally, S. Buia, A. Zimmerman, A. Smith, R. Burges, K. Robinson, K. Valentino, D. Bradbury, M. Cosentino, N. Diaz-Mayoral, M. Kennedy, T. Engel, P. Williams, K. Erickson, K. Ardlie, W. Winckler, G. Getz, D. De Luca, D. M. Arthur, M. Kellis, A. Thomson, T. Young, E. Gelfand, M. Donovan, Y. Meng, G. Grant, D. Mash, Y. Marcus, M. Basile, J. Liu, J. Zhu, Z. Tu, N. J. Cox, D. L. Nicolae, E. R. Gamazon, H. K. Im, A. Konkashbaev, J. Pritchard, M. Stevens, T. Flutre, X. Wen, E. T. Dermitzakis, T. Lappalainen, R. Guigo, J. Monlong, M. Sammeth, D. Koller, A. Battle, S. Mostafavi, M. M. Carthy, M. Rivas, J. Maller, I. Rusyn, A. Nobel, F. Wright, A. Shabalina, M. Feolo, N. Sharopova, A. Sturcke, J. Paschal, J. M. Anderson, E. L. Wilder, L. K. Derr, E. D. Green, J. P. Struewing, G. Temple, S. Volpi, J. T. Boyer, E. J. Thomson, M. S. Guyer, C. Ng, A. Abdallah, D. Colantuoni, T. R. Insel, S. E. Koester, A. R. Little, P. K. Bender, T. Lehner, Y. Yao, C. C. Compton, J. B. Vaught, S. Sawyer, N. C. Lockhart, J. Demchok, H. F. Moore, The Genotype-Tissue Expression (GTEx) project. *Nat. Genet.* **45**, 580–585 (2013).
42. K. J. Travaglini, A. N. Nabhan, L. Penland, R. Sinha, A. Gillich, R. V. Sit, S. Chang, S. D. Conley, Y. Mori, J. Seita, G. J. Berry, J. B. Shrager, R. J. Metzger, C. S. Kuo, N. Neff, I. L. Weissman, S. R. Quake, M. A. Krasnow, A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature* **587**, 619–625 (2020).
43. M. Cella, D. Jarrossay, F. Facchetti, O. Aleardi, H. Nakajima, A. Lanzavecchia, M. Colonna, Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nat. Med.* **5**, 919–923 (1999).
44. F. P. Siegal, N. Kadowaki, M. Shodell, P. A. Fitzgerald-Bocarsly, K. Shah, S. Ho, S. Antonenko, Y. J. Liu, The nature of the principal type 1 interferon-producing cells in human blood. *Science* **284**, 1835–1837 (1999).
45. K. Honda, T. Taniguchi, IRFs: Master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. *Nat. Rev. Immunol.* **6**, 644–658 (2006).
46. F. Onodi, L. Bonnet-Madin, L. Meertens, L. Karpf, J. Poirot, S. Y. Zhang, C. Picard, A. Puel, E. Jouanguy, Q. Zhang, J. Le Goff, J. M. Molina, C. Delaugerre, J. L. Casanova, A. Amara, V. Soumelis, SARS-CoV-2 induces human plasmacytoid dendritic cell diversification via UNC93B and IRAK4. *J. Exp. Med.* **218**, (2021).
47. L. Cervantes-Barragan, A. Vanderheiden, C. J. Royer, M. E. Davis-Gardner, P. Ralfs, T. Chirkova, L. J. Anderson, A. Grakoui, M. S. Suthar, Plasmacytoid dendritic cells produce type I interferon and reduce viral replication in airway epithelial cells after SARS-CoV-2 infection. *bioRxiv* 2021.05.12.443948 [Preprint]. 13 March 2021. <https://doi.org/10.1101/2021.05.12.443948>.
48. S. G. Alculumbre, V. Saint-Andre, J. Di Domizio, P. Vargas, P. Sirven, P. Bost, M. Maurin, P. Maiuri, M. Wery, M. S. Roman, L. Savey, M. Touzot, B. Terrier, D. Saadoun, C. Conrad, M. Gilliet, A. Morillon, V. Soumelis, Diversification of human plasmacytoid dendritic cells in response to a single stimulus. *Nat. Immunol.* **19**, 63–75 (2018).
49. J. A. Kosmicki, J. E. Horowitz, N. Banerjee, R. Lanche, A. Marcketta, E. Maxwell, X. Bai, D. Sun, J. D. Backman, D. Sharma, F. S. P. Kury, H. M. Kang, C. O'Dushlaine, A. Yadav, A. J. Mansfield, A. H. Li, K. Watanabe, L. Gorski, S. E. McCarthy, A. E. Locke, S. Khalid, S. O'Keefe, J. Mbatchou, O. Chazara, Y. Huang, E. Kvikstad, A. O'Neill, P. Nioi, M. M. Parker, S. Petrovski, H. Runz, J. D. Szustakowski, Q. Wang, E. Wong, A. Cordova-Palamera, E. N. Smith, S. Szalma, X. Zheng, S. Esmaeli, J. W. Davis, Y.-P. Lai, X. Chen, A. E. Justice, J. B. Leader, T. Mirshahi, D. J. Carey, A. Verma, G. Sirugo, M. D. Ritchie, D. J. Rader, G. Povysil, D. B. Goldstein, K. Kiryluk, E. Pairo-Castineira, K. Rawlik, D. Pasko, S. Walker, A. Meynert, A. Kousathanas, L. Moutsianas, A. Tenesa, M. Caulfield, R. Scott, J. F. Wilson, J. K. Baillie, G. Butler-Laporte, T. Nakanishi, M. Lathrop, J. B. Richards, M. Jones, S. Balasubramanian, W. Salerno, A. R. Shuldiner, J. Marchini, J. D. Overton, L. Habegger, M. N. Cantor, J. G. Reid, A. Baras, G. R. Abecasis, M. A. R. Ferreira, Pan-ancestry exome-wide association analyses of COVID-19 outcomes in 586,157 individuals. *Am. J. Hum. Genet.* **108**, 1350–1355 (2021).
50. K. Yang, A. Puel, S. Zhang, C. Eidschinken, C. L. Ku, A. Casrouge, C. Picard, H. von Bernuth, B. Senechal, S. Plancoulaine, S. Al-Hajjar, A. Al-Ghoniaim, L. Marodi, D. Davidsson, D. Speert, C. Roifman, B. Z. Garty, A. Ozinsky, F. J. Barrat, R. L. Coffman, R. L. Miller, X. Li, P. Lebon, C. Rodriguez-Gallego, H. Chapel, F. Geissmann, E. Jouanguy, J. L. Casanova, Human TLR-7, -8, and -9-mediated induction of IFN-alpha/beta and -lambda is IRAK-4 dependent and redundant for protective immunity to viruses. *Immunity* **23**, 465–478 (2005).
51. C. L. Ku, H. von Bernuth, C. Picard, S. Y. Zhang, H. H. Chang, K. Yang, M. Chrabieh, A. C. Issekutz, C. K. Cunningham, J. Gallin, S. M. Holland, C. Roifman, S. Ehl, J. Smart, M. Tang, F. J. Barrat, O. Levy, D. McDonald, N. K. Day-Good, R. Miller, H. Takada, T. Hara, S. Al-Hajjar, A. Al-Ghoniaim, D. Speert, D. Sanlaville, X. Li, F. Geissmann, E. Vivier, L. Marodi, B. Z. Garty, H. Chapel, C. Rodriguez-Gallego, X. Bossuyt, L. Abel, A. Puel, J. L. Casanova, Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. *J. Exp. Med.* **204**, 2407–2422 (2007).
52. J. L. Casanova, L. Abel, L. Quintana-Murci, Human TLRs and IL-1Rs in host defense: Natural insights from evolutionary, epidemiological, and clinical genetics. *Annu. Rev. Immunol.* **29**, 447–491 (2011).
53. B. Boisson, The genetic basis of pneumococcal and staphylococcal infections: Inborn errors of human TLR and IL-1R immunity. *Hum. Genet.* **139**, 981–991 (2020).
54. L. B. Barreiro, M. Ben-Ali, H. Quach, G. Laval, E. Patin, J. K. Pickrell, C. Bouchier, M. Tichit, O. Neyrolles, B. Gicquel, J. R. Kidd, K. K. Kidd, A. Alcais, J. Ragimbeau, S. Pellegrini, L. Abel, J. L. Casanova, L. Quintana-Murci, Evolutionary dynamics of human Toll-like receptors and their different contributions to host defense. *PLOS Genet.* **5**, e1000562 (2009).
55. H. von Bernuth, C. Picard, Z. Jin, R. Pankla, H. Xiao, C. L. Ku, M. Chrabieh, I. B. Mustapha, P. Ghandil, Y. Camcioglu, J. Vasconcelos, N. Sirvent, M. Guedes, A. B. Vitor, M. J. Herrero-Mata, J. I. Arostegui, C. Rodrigo, L. Alsina, E. Ruiz-Ortiz, M. Juan, C. Fortuny, J. Yague, J. Anton, M. Pascal, H. H. Chang, L. Janniere, Y. Rose, B. Z. Garty, H. Chapel, A. Issekutz, L. Marodi, C. Rodriguez-Gallego, J. Banchereau, L. Abel, X. Li, D. Chaussabel, A. Puel, J. L. Casanova, Pyogenic bacterial infections in humans with MyD88 deficiency. *Science* **321**, 691–696 (2008).
56. C. Picard, A. Puel, M. Bonnet, C. L. Ku, J. Bustamante, K. Yang, C. Soudais, S. Dupuis, J. Feinberg, C. Fieschi, C. Elbim, R. Hitchcock, D. Lammis, G. Davies, A. Al-Ghoniaim, H. Al-Rayes, S. Al-Jumaah, S. Al-Hajjar, I. Z. Al-Mohsen, H. H. Frayha, R. Rucker, T. R. Hawn, A. Aderem, H. Tufenkeji, S. Haraguchi, N. K. Day, R. A. Good, M. A. Gougerot-Pocidalo, A. Ozinsky, J. L. Casanova, Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science* **299**, 2076–2079 (2003).
57. A. Casrouge, S. Y. Zhang, C. Eidschinken, E. Jouanguy, A. Puel, K. Yang, A. Alcais, C. Picard, N. Mahfoufi, N. Nicolas, L. Lorenzo, S. Plancoulaine, B. Senechal, F. Geissmann, K. Tabet, K. Hoebe, X. Du, R. L. Miller, B. Heron, C. Mignot, T. B. de Villemeur, P. Lebon, O. Dulac, F. Rozenberg, B. Beutler, M. Tardieu, L. Abel, J. L. Casanova, Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science* **314**, 308–312 (2006).
58. Y. J. Liu, Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. *Cell* **106**, 259–262 (2001).
59. M. Swiecki, M. Colonna, Unraveling the functions of plasmacytoid dendritic cells during viral infections, autoimmunity, and tolerance. *Immunol. Rev.* **234**, 142–162 (2010).
60. F. J. Barrat, L. Su, A pathogenic role of plasmacytoid dendritic cells in autoimmunity and chronic viral infection. *J. Exp. Med.* **216**, 1974–1985 (2019).
61. I. Sologuren, M. T. Martinez-Saavedra, J. Sole-Violan, E. de Borges de Oliveira Jr., E. Betancor, I. Casas, C. Oleaga-Quintas, M. Martinez-Gallo, S. Y. Zhang, J. Pestano, R. Colobran, E. Herrera-Ramos, C. Perez, M. Lopez-Rodriguez, J. J. Ruiz-Hernandez, N. Franco, J. M. Ferrer, C. Bilbao, M. Andujar-Sanchez, M. Alvarez-Fernandez, M. J. Ciancanelli, F. Rodriguez de Castro, J. L. Casanova, J. Bustamante, C. Rodriguez-Gallego, Lethal



- influenza in two related adults with inherited GATA2 deficiency. *J. Clin. Immunol.* **38**, 513–526 (2018).
62. D. C. Vinh, S. Y. Patel, G. Uzel, V. L. Anderson, A. F. Freeman, K. N. Olivier, C. Spalding, S. Hughes, S. Pittaluga, M. Raffeld, L. R. Sorbara, H. Z. Eloumi, D. B. Kuhns, M. L. Turner, E. W. Cowen, D. Fink, D. Long-Priel, A. P. Hsu, L. Ding, M. L. Paulson, A. R. Whitney, E. P. Sampaio, D. M. Frucht, F. R. DeLeo, S. M. Holland, Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. *Blood* **115**, 1519–1529 (2010).
  63. R. E. Dickinson, H. Griffin, V. Bigley, L. N. Reynard, R. Hussain, M. Haniffa, J. H. Lakey, T. Rahman, X. N. Wang, N. McGovern, S. Pagan, S. Cookson, D. McDonald, I. Chua, J. Wallis, A. Cant, M. Wright, B. Keavney, P. F. Chinnery, J. Loughlin, S. Hambleton, M. Santibanez-Koref, M. Collin, Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. *Blood* **118**, 2656–2658 (2011).
  64. M. Pasquet, C. Bellanne-Chantelot, S. Tavitian, N. Prade, B. Beaupain, O. Larochelle, A. Petit, P. Rohrlrich, C. Ferrand, E. Van Den Neste, H. A. Poirel, T. Lamy, M. Ouachee-Charidin, V. Mansat-De Mas, J. Corre, C. Recher, G. Plat, F. Bachelier, J. Donadieu, E. Delabesse, High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia. *Blood* **121**, 822–829 (2013).
  65. V. Bigley, U. Cytlak, M. Collin, Human dendritic cell immunodeficiencies. *Semin. Cell Dev. Biol.* **86**, 50–61 (2019).
  66. D. Gao, M. J. Ciancanelli, P. Zhang, O. Harschnitz, V. Bondet, M. Hasek, J. Chen, X. Mu, Y. Itan, A. Cobat, V. Sancho-Shimizu, B. Bigio, L. Lorenzo, G. Ciceri, J. McAlpine, E. Anguiano, E. Jouanguy, D. Chaussabel, I. Meyts, M. S. Diamond, L. Abel, S. Hur, G. A. Smith, L. Notarangelo, D. Duffy, L. Studer, J. L. Casanova, S. Y. Zhang, TLR3 controls constitutive IFN- $\beta$  antiviral immunity in human fibroblasts and cortical neurons. *J. Clin. Invest.* **131**, (2021).
  67. N. Kadowaki, S. Ho, S. Antonenko, R. W. Malefyt, R. A. Kastelein, F. Bazan, Y. J. Liu, Subsets of human dendritic cell precursors express different toll-like receptors and respond to different microbial antigens. *J. Exp. Med.* **194**, 863–869 (2001).
  68. K. Honda, Y. Ohba, H. Yanai, H. Negishi, T. Mizutani, A. Takaoka, C. Taya, T. Taniguchi, Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. *Nature* **434**, 1035–1040 (2005).
  69. Y. Wang, M. Swiecki, S. A. McCartney, M. Colonna, dsRNA sensors and plasmacytoid dendritic cells in host defense and autoimmunity. *Immunol. Rev.* **243**, 74–90 (2011).
  70. M. A. DePristo, E. Banks, R. Poplin, K. V. Garimella, J. R. Maguire, C. Hartl, A. A. Philippakis, G. del Angel, M. A. Rivas, M. Hanna, A. McKenna, T. J. Fennell, A. M. Kernytzky, A. Y. Sivachenko, K. Cibulskis, S. B. Gabriel, D. Altshuler, M. J. Daly, A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nat. Genet.* **43**, 491–498 (2011).
  71. H. Li, R. Durbin, Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754–1760 (2009).
  72. W. McLaren, L. Gil, S. E. Hunt, H. S. Riat, G. R. Ritchie, A. Thormann, P. Flicek, F. Cunningham, The Ensembl variant effect predictor. *Genome Biol.* **17**, 122 (2016).
  73. G. J. Xu, T. Kula, Q. Xu, M. Z. Li, S. D. Vernon, T. Ndung'u, K. Ruxrungtham, J. Sanchez, C. Brander, R. T. Chung, K. C. O'Connor, B. Walker, H. B. Larman, S. J. Elledge, Viral immunology. Comprehensive serological profiling of human populations using a synthetic human virome. *Science* **348**, aaa0698 (2015).
  74. P. Ewels, M. Magnusson, S. Lundin, M. Kaller, MultiQC: Summarize analysis results for multiple tools and samples in a single report. *Bioinformatics* **32**, 3047–3048 (2016).
  75. A. Dobin, C. A. Davis, F. Schlesinger, J. Drenkow, C. Zaleski, S. Jha, P. Batut, M. Chaisson, T. R. Gingeras, STAR: Ultrafast universal RNA-seq aligner. *Bioinformatics* **29**, 15–21 (2013).
  76. Y. Liao, G. K. Smyth, W. Shi, featureCounts: An efficient general purpose program for assigning sequence reads to genomic features. *Bioinformatics* **30**, 923–930 (2014).
  77. J. Harrow, A. Frankish, J. M. Gonzalez, E. Tapanari, M. Diekhans, F. Kokocinski, B. L. Aken, D. Barrell, A. Zadissa, S. Searle, I. Barnes, A. Bignell, V. Boychenko, T. Hunt, M. Kay, G. Mukherjee, J. Rajan, G. Despacio-Reyes, G. Saunders, C. Steward, R. Harte, M. Lin, C. Howald, A. Tanzer, T. Derrien, J. Chrast, N. Walters, S. Balasubramanian, B. Pei, M. Tress, J. M. Rodriguez, I. Ezkurdia, J. van Baren, M. Brent, D. Haussler, M. Kellis, A. Valencia, A. Reymond, M. Gerstein, R. Guigo, T. J. Hubbard, GENCODE: The reference human genome annotation for The ENCODE Project. *Genome Res.* **22**, 1760–1774 (2012).
  78. M. I. Love, W. Huber, S. Anders, Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol.* **15**, 550 (2014).
  79. M. D. Robinson, D. J. McCarthy, G. K. Smyth, edgeR: A Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics* **26**, 139–140 (2010).

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**Members of COVID Human Genetic Effort:** Laurent Abel<sup>1</sup>, Alessandro Aiuti<sup>2</sup>, Saleh Al-Muhsen<sup>3</sup>, Fahd Al-Mulla<sup>4</sup>, Mark S. Anderson<sup>5</sup>, Evangelos Andreaskos<sup>6</sup>, Andrés A. Arias<sup>7</sup>, Hagit Baris Feldman<sup>8</sup>, Alexandre Belot<sup>9</sup>, Catherine M. Biggs<sup>10</sup>, Dusan Bogunovic<sup>11</sup>, Alexandre Bolze<sup>12</sup>, Anastasiia Bondarenko<sup>13</sup>, Ahmed A. Bousfiha<sup>14</sup>, Petter Brodin<sup>15</sup>, Yenan Bryceson<sup>16</sup>, Carlos D. Bustamante<sup>17</sup>, Manish J. Butte<sup>18</sup>, Giorgio Casari<sup>19</sup>, Samya Chakravorty<sup>20</sup>, John Christodoulou<sup>21</sup>, Antonio Condino-Neto<sup>22</sup>, Stefan N. Constantinescu<sup>23</sup>, Megan A. Cooper<sup>24</sup>, Clifton L. Dalgard<sup>25</sup>, Murkesh Desai<sup>26</sup>, Beth A. Drollet<sup>27</sup>, Jamila El Baghdadi<sup>28</sup>, Sara Espinosa-Padilla<sup>29</sup>, Jacques Fellay<sup>30</sup>, Carlos Flores<sup>31</sup>, José Luis Franco<sup>32</sup>, Antoine Froidure<sup>32</sup>, Peter K. Gregersen<sup>33</sup>, Filomeen Haerynck<sup>34</sup>, David Hagin<sup>35</sup>, Rabih Halwani<sup>36</sup>, Lennart Hammarström<sup>37</sup>, James R. Heath<sup>38</sup>, Sarah E. Henrickson<sup>39</sup>, Elena W. Y. Hsieh<sup>40</sup>, Eysteine Husebye<sup>41</sup>, Kohsuke Imai<sup>42</sup>, Yuval Itan<sup>43</sup>, Erich D. Jarvis<sup>44</sup>, Timokratsis Karamitros<sup>45</sup>, Kai Kisand<sup>46</sup>, Cheng-Lung Ku<sup>47</sup>, Yu-Lung Lau<sup>48</sup>, Yun Ling<sup>49</sup>, Carrie L. Lucas<sup>50</sup>, Tom Maniatis<sup>51</sup>, Davoud Mansouri<sup>52</sup>, László Maródi<sup>53</sup>, Isabelle Meyts<sup>54</sup>, Joshua D. Milner<sup>55</sup>, Kristina Mironoska<sup>56</sup>, Trine H. Mogensen<sup>57</sup>, Tomohiro Morio<sup>58</sup>, Lisa F. P. Ng<sup>59</sup>, Luigi D. Notarangelo<sup>60</sup>, Antonio Novelli<sup>61</sup>, Giuseppe Novelli<sup>62</sup>, Cliona O'Farrelly<sup>63</sup>, Satoshi Okada<sup>64</sup>, Tayfun Ozcelik<sup>65</sup>, Qiang Pan-Hammarström<sup>37</sup>, Rebeca Perez de Diego<sup>66</sup>, Anna M. Planas<sup>67</sup>, Carolina Prando<sup>68</sup>, Aurora Pujol<sup>69</sup>, Lluís Quintana-Murci<sup>70</sup>, Laurent Renia<sup>59</sup>, Igor Resnick<sup>71</sup>, Carlos Rodriguez-Gallego<sup>72</sup>, Vanessa Sancho-Shimizu<sup>73</sup>, Anna Sediva<sup>74</sup>, Mikko R. J. Seppänen<sup>75</sup>, Mohammed Shahrooei<sup>76</sup>, Anna Shcherbina<sup>77</sup>, Ondrej Slaby<sup>78</sup>, Andrew L. Snow<sup>79</sup>, Pere Soler-Palacín<sup>80</sup>, Andrés N. Spaan<sup>81</sup>, Ivan Tancevski<sup>82</sup>, Stuart G. Tangye<sup>83</sup>, Ahmad Abou Tayoun<sup>84</sup>, Sathishkumar Ramaswamy<sup>84</sup>, Stuart E. Turvey<sup>85</sup>, Furkan Uddin<sup>86</sup>, Mohammed J. Uddin<sup>87</sup>, Diederik van de Beek<sup>88</sup>, Donald C. Vinh<sup>89</sup>, Horst von Bernuth<sup>90</sup>, Mayana Zatz<sup>91</sup>, Pawel Zawadzki<sup>92</sup>, Helen C. Su<sup>60</sup>, Jean-Laurent Casanova<sup>93</sup>

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

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

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

**Members of COVID-STORM Clinicians:** Giuseppe Foti<sup>1</sup>, Giacomo Bellani<sup>1</sup>, Giuseppe Citerio<sup>1</sup>, Ernesto Contro<sup>1</sup>, Alberto Pesci<sup>2</sup>, Maria Grazia Valsecchi<sup>3</sup>, Marina Cazzaniga<sup>4</sup>

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

**Members of COVID Clinicians:** Jorge Abad<sup>1</sup>, Giulia Accordini<sup>2</sup>, Cristian Achille<sup>3</sup>, Sergio Aguilera-Albesa<sup>4</sup>, Aina Aguiló-Cucurull<sup>5</sup>, Alessandro Aiuti<sup>6</sup>, Esra Akyüz Özkan<sup>7</sup>, Ilad Alavi Darazam<sup>8</sup>, Jonathan Antonio Roblero Albisures<sup>9</sup>, Juan C. Aldave<sup>10</sup>, Miquel Alfonso Ramos<sup>11</sup>, Taj Ali Khan<sup>12</sup>, Anna Aliberti<sup>13</sup>, Seyed Alireza Nadjil<sup>14</sup>, Gulsum Alkan<sup>15</sup>, Suzan A. Alkhatir<sup>16</sup>, Jerome Allardet-Servent<sup>17</sup>, Luis M. Allende<sup>18</sup>, Rebeca Alonso-Arias<sup>19</sup>, Mohammed S. Alshahrani<sup>20</sup>, Laia Alsina<sup>21</sup>, Marie-Alexandra Alyanakian<sup>22</sup>, Blanca Amador Borrero<sup>23</sup>, Zahir Amoura<sup>24</sup>, Arnau Antolí<sup>25</sup>, Romain Arrestier<sup>26</sup>, Mélodie Aubart<sup>27</sup>, Teresa August<sup>28</sup>, Iryna Avramenko<sup>29</sup>, Gökhan Aytekin<sup>30</sup>, Axelle Azot<sup>31</sup>, Seiamak Bahram<sup>32</sup>, Fanny Bajolle<sup>33</sup>, Fausto Baldanti<sup>34</sup>, Aurélie Baldolli<sup>35</sup>, Maite Ballester<sup>36</sup>, Hagit Baris Feldman<sup>37</sup>, Benoit Barrou<sup>38</sup>, Federica Barzagh<sup>39</sup>, Sabrina Basso<sup>39</sup>, Gulsum Iclal Bayhan<sup>40</sup>, Alexandre Belot<sup>41</sup>, Liliana Bezrodnik<sup>42</sup>, Agurtzane Bilbao<sup>43</sup>, Geraldine Blanchard-Rohner<sup>44</sup>, Ignacio Blanco<sup>45</sup>, Adeline Blandinières<sup>46</sup>, Daniel Blázquez-Gamero<sup>47</sup>, Alexandre Bleibtreu<sup>48</sup>, Marketa Bloomfield<sup>49</sup>, Mireia Bolivar-Prados<sup>50</sup>, Anastasia Bondarenko<sup>51</sup>, Alessandro Borghesi<sup>52</sup>, Raphael Borie<sup>52</sup>, Elisabeth Botdhalo-Nevers<sup>53</sup>, Ahmed A. Bousfiha<sup>54</sup>, Aurore Bousquet<sup>55</sup>, David Boutolleau<sup>56</sup>, Claire Bouvattier<sup>57</sup>, Oksana Boyarchuk<sup>58</sup>, Juliette Bravais<sup>59</sup>, M. Luisa Briones<sup>60</sup>, Marie-Eve Brunner<sup>61</sup>, Raffaele Bruno<sup>62</sup>, Maria Rita P. Bueno<sup>63</sup>, Huda Bukhari<sup>64</sup>, Jacinta Bustamante<sup>65</sup>, Juan José Cáceres Agra<sup>65</sup>, Ruggero Capra<sup>66</sup>, Raphael Carapito<sup>67</sup>, Maria Carrabba<sup>68</sup>, Giorgio Casari<sup>69</sup>, Carlos Casasnovas<sup>69</sup>, Marion Caseris<sup>70</sup>, Irene Cassaniti<sup>34</sup>, Martin Castelle<sup>71</sup>, Francesco Castelli<sup>72</sup>, Martín Castillo de Vera<sup>73</sup>, Mateus V. Castro<sup>63</sup>, Emilie Catherine<sup>74</sup>, Jale Bengi Celik<sup>75</sup>, Alessandro Ceschi<sup>76</sup>, Martin Chalumeau<sup>77</sup>, Bruno Charbit<sup>78</sup>, Matthew P. Cheng<sup>79</sup>, Pèrre Clavé<sup>50</sup>, Bonaventura Clotet<sup>80</sup>, Anna Codina<sup>81</sup>, Yves Cohen<sup>82</sup>, Roger Colobran<sup>83</sup>, Cloé Comarmond<sup>84</sup>, Alain Combes<sup>85</sup>, Patrizia Comolli<sup>39</sup>, Angelo G. Corsico<sup>2</sup>, Taner Coşkun<sup>86</sup>, Aleksandar Cvetkovski<sup>87</sup>, Cyril Cyrus<sup>88</sup>, David Dalmau<sup>89</sup>, François Danion<sup>90</sup>, David Ross Darley<sup>91</sup>, Vincent Das<sup>92</sup>, Nicolas Dauby<sup>93</sup>, Stéphane Dauger<sup>94</sup>, Paul De Munter<sup>95</sup>, Loïc de Pontual<sup>96</sup>, Amin Dehban<sup>97</sup>, Geoffroy Delplanche<sup>98</sup>, Alexandre Demoule<sup>99</sup>, Isabelle Desguerre<sup>100</sup>, Antonio Di Sabatino<sup>101</sup>, Jean-Luc Diehl<sup>102</sup>, Stephanie Dobbela<sup>103</sup>, Elena Domínguez-Garrido<sup>104</sup>, Clément Dubost<sup>105</sup>, Olov Ekwali<sup>106</sup>, Şefika Elmas Bozdemir<sup>107</sup>, Marwa H. Elhagdy<sup>108</sup>, Melike Emiroglu<sup>15</sup>, Akifumi Endo<sup>109</sup>, Emine Hafize Erdeniz<sup>110</sup>, Selma Erol Aytekin<sup>111</sup>, Maria Pilar Etxart Lasa<sup>112</sup>, Romain Euvrard<sup>113</sup>, Giovanna Fabio<sup>68</sup>, Laurence Faivre<sup>114</sup>, Antonin Falck<sup>115</sup>, Muriel Fartoukh<sup>116</sup>, Morgane Faure<sup>117</sup>, Miguel Fernandez Arquer<sup>118</sup>, Ricard Ferrer<sup>119</sup>, Jose Ferreres<sup>120</sup>, Carlos Flores<sup>121</sup>, Bruno Francois<sup>122</sup>, Victoria Fumadó<sup>123</sup>, Kitty S. C. Fung<sup>124</sup>, Francesca Fusco<sup>125</sup>, Alenka Gagro<sup>126</sup>, Blanca García Solis<sup>127</sup>, Pierre Garçon<sup>345</sup>, Pascale Gaussem<sup>128</sup>, Zeynep Gayretli<sup>129</sup>, Juana Gil-Herrera<sup>130</sup>, Laurent Gilibert<sup>131</sup>, Audrey Giraud Gateau<sup>132</sup>, Mónica Girona-Alarcón<sup>133</sup>, Karen Alejandra Cifuentes Godínez<sup>134</sup>, Jean-Christophe Goffard<sup>135</sup>, Nacho Gonzales<sup>136</sup>, Luis I. Gonzalez-Granado<sup>137</sup>, Rafaela González-Montelongo<sup>138</sup>, Antoine Guerdet<sup>139</sup>, Belgin Gülhan<sup>140</sup>, Victor Daniel Gumucio<sup>141</sup>, Leib Gunnar Hanitsch<sup>142</sup>, Jan Gunst<sup>143</sup>, Marta Gut<sup>144</sup>, Jérôme Hadjadj<sup>145</sup>, Filomeen Haeruyck<sup>146</sup>, Rabi Halwani<sup>147</sup>, Lennart Hammarström<sup>148</sup>, Selda Hanceli<sup>149</sup>, Tetyana Hariyan<sup>150</sup>, Nevin Hatipoglu<sup>151</sup>, Deniz Heppekcan<sup>152</sup>, Elisa Hernandez-Brito<sup>153</sup>, Po-ki Ho<sup>154</sup>, María Soledad Holanda-Peña<sup>155</sup>,

Juan P. Horcajada<sup>156</sup>, Sami Hraiech<sup>157</sup>, Linda Humbert<sup>158</sup>, Ivan F. N. Hung<sup>159</sup>, Alejandro D. Iglesias<sup>160</sup>, Antonio Íñigo-Campos<sup>138</sup>, Matthieu Jamme<sup>161</sup>, María Jesús Arranz<sup>89</sup>, Marie-Thérèse Jimeno<sup>162</sup>, Iolanda Jordan<sup>133</sup>, Saliha Kanik Yüsek<sup>163</sup>, Yalcin Kara<sup>164</sup>, Aydin Karahan<sup>165</sup>, Adem Kurbuz<sup>166</sup>, Kadriye Kart Yasar<sup>167</sup>, Ozgur Kasapcopur<sup>168</sup>, Kenichi Kashimada<sup>169</sup>, Sevgi Keles<sup>111</sup>, Yasemin Kendir Demirkol<sup>170</sup>, Yasutoshi Kido<sup>171</sup>, Can Kizil<sup>172</sup>, Ahmet Osman Kiliç<sup>173</sup>, Adam Klocperk<sup>174</sup>, Antonia Koutsoukou<sup>175</sup>, Zbigniew J. Król<sup>176</sup>, Hatem Ksour<sup>177</sup>, Paul Kuentz<sup>178</sup>, Arthur M. C. Kwan<sup>179</sup>, Yat Wah M. Kwan<sup>180</sup>, Janette S. Y. Kwok<sup>181</sup>, Jean-Christophe Lagier<sup>182</sup>, David S. Y. Lam<sup>183</sup>, Vicky Lampropoulou<sup>184</sup>, Fanny Lantermier<sup>185</sup>, Yu-Lung Lau<sup>186</sup>, Fleur Le Bourgeois<sup>94</sup>, Yee-Sin Leo<sup>187</sup>, Rafael Leon Lopez<sup>188</sup>, Daniel Leung<sup>186</sup>, Michael Levin<sup>189</sup>, Michael Levy<sup>94</sup>, Romain Lévy<sup>33</sup>, Zhi Li<sup>78</sup>, Daniele Lillieri<sup>84</sup>, Edson Jose Adrian Bolanos Lima<sup>190</sup>, Agnes Linglart<sup>191</sup>, Eduardo López-Collazo<sup>192</sup>, José M. Lorenzo-Salazar<sup>198</sup>, Céline Louapre<sup>193</sup>, Catherine Lubetzki<sup>193</sup>, Kwok-Cheung Lung<sup>194</sup>, Charles-Edouard Luyt<sup>195</sup>, David C. Lye<sup>196</sup>, Cynthia Magnone<sup>197</sup>, Davood Mansouri<sup>198</sup>, Enrico Marchioni<sup>199</sup>, Carola Marioli<sup>2</sup>, Majid Marjani<sup>200</sup>, Laura Marques<sup>201</sup>, Jesus Marquez Pereira<sup>202</sup>, Andrea Martin-Nalda<sup>203</sup>, David Martínez Pueyo<sup>204</sup>, Javier Martínez-Picado<sup>205</sup>, Iciar Marzana<sup>206</sup>, Carmen Mata-Martínez<sup>207</sup>, Alexis Mathian<sup>24</sup>, Larissa R. B. Matos<sup>63</sup>, Gail V. Matthews<sup>208</sup>, Julien Mayaux<sup>209</sup>, Raquel McLaughtin-García<sup>210</sup>, Philippe Meersseman<sup>211</sup>, Jean-Louis Mège<sup>212</sup>, Armand Mekontso-Dessap<sup>213</sup>, Isabelle Melki<sup>115</sup>, Federica Meloni<sup>2</sup>, Jean-François Meritet<sup>214</sup>, Paolo Merlani<sup>215</sup>, Özge Metin Akan<sup>216</sup>, Isabelle Meys<sup>217</sup>, Mehdi Mezidi<sup>218</sup>, Isabelle Migeotte<sup>219</sup>, Maude Millereux<sup>220</sup>, Matthieu Million<sup>221</sup>, Tristan Miralet<sup>222</sup>, Clotilde Mircher<sup>223</sup>, Mehdi Mirsaedi<sup>224</sup>, Yoko Mizoguchi<sup>225</sup>, Bhavi P. Modi<sup>26</sup>, Francesco Mojoli<sup>13</sup>, Elsa Moncomble<sup>227</sup>, Abián Montesdeoca Melián<sup>228</sup>, Antonio Morales Martínez<sup>229</sup>, Francisco Morandeira<sup>230</sup>, Pierre-Emmanuel Morange<sup>231</sup>, Cléemence Mordacq<sup>158</sup>, Guillaume Morelle<sup>232</sup>, Stéphane J. Mouly<sup>233</sup>, Adrián Muñoz-Barrera<sup>138</sup>, Cyril Nafati<sup>234</sup>, Shintaro Nagashima<sup>235</sup>, Yu Nakagama<sup>171</sup>, Bénédicte Neven<sup>236</sup>, João Farela Neves<sup>237</sup>, Lisa F. P. Ng<sup>238</sup>, Yuk-Yung Ng<sup>239</sup>, hubert Nielly<sup>105</sup>, Yeras Novoa Medina<sup>210</sup>, Esmeralda Nuñez Cuadros<sup>240</sup>, J. Gonzalo Ocejo-Vinyals<sup>241</sup>, Keisuke Okamoto<sup>109</sup>, Mehdi Oualha<sup>33</sup>, Amani Ouedrani<sup>22</sup>, Tayfun Özçelik<sup>242</sup>, Aslinur Ozkaya-Parlakay<sup>140</sup>, Michele Paganì<sup>13</sup>, Qiang Pan-Hammarström<sup>148</sup>, Maria Papadaki<sup>243</sup>, Christophe Parizot<sup>209</sup>, Philippe Parola<sup>244</sup>, Tiffany Pascreau<sup>245</sup>, Stéphane Paul<sup>246</sup>, Estela Paz-Artal<sup>247</sup>, Sigifredo Pedraza<sup>248</sup>, Nancy Carolina González Pellecer<sup>134</sup>, Silvia Pellegrini<sup>249</sup>, Rebeca Pérez de Diego<sup>127</sup>, Xosé Luis Pérez-Fernández<sup>141</sup>, Aurélien Philippe<sup>250</sup>, Quentin Philippot<sup>116</sup>, Adrien Picod<sup>251</sup>, Marc Pinotet de Chambrun<sup>85</sup>, Antonio Piralla<sup>34</sup>, Laura Planas-Serra<sup>252</sup>, Dominique Ploin<sup>253</sup>, Julien Poisy<sup>254</sup>, Géraldine Poncelet<sup>70</sup>, Garyphalla Poulakou<sup>175</sup>, Marie S. Pouletty<sup>255</sup>, Persia Pourshahzari<sup>256</sup>, Jia Li Qiu-Chen<sup>257</sup>, Paul Quentric<sup>209</sup>, Thomas Rambaud<sup>258</sup>, Didier Raoult<sup>212</sup>, Violette Raoult<sup>259</sup>, Anne-Sophie Rebillat<sup>223</sup>, Claire Redin<sup>260</sup>, Léa Resmini<sup>261</sup>, Pilar Ricart<sup>262</sup>, Jean-Christophe Richard<sup>263</sup>, Raül Rigo-Bonnin<sup>264</sup>, Nadia rivet<sup>46</sup>, Jacques G. Rivière<sup>265</sup>, Gemma Rocamora-Blanch<sup>25</sup>, Mathieu P. Rodero<sup>266</sup>, Carlos Rodrigo<sup>267</sup>, Luis Antonio Rodriguez<sup>190</sup>, Carlos Rodriguez-Gallego<sup>268</sup>, Agustí Rodriguez-Palmero<sup>269</sup>, Carolina Soledad Romero<sup>270</sup>, Anya Rothenbuhler<sup>271</sup>, Damien Roux<sup>272</sup>, Nikolettta Rovina<sup>175</sup>, Flore Rozenberg<sup>273</sup>, Yvon Ruch<sup>90</sup>, Montse Ruiz<sup>274</sup>, María Yolanda Ruiz del Prado<sup>275</sup>, Juan Carlos Ruiz-Rodríguez<sup>119</sup>, Joan Sabater-Riera<sup>141</sup>, Kai Saks<sup>276</sup>, Maria Salagianni<sup>184</sup>, Oliver Sanchez<sup>277</sup>, Adrián Sánchez-Montalvá<sup>278</sup>, Silvia Sánchez-Ramón<sup>279</sup>, Laire Schidlowski<sup>280</sup>, Agatha Schluter<sup>252</sup>, Julien Schmidt<sup>281</sup>, Matthieu Schmidt<sup>282</sup>, Catharina Schuetz<sup>283</sup>, Cyril E. Schweitzer<sup>284</sup>, Francesco Scolari<sup>285</sup>, Anna Sediva<sup>167</sup>, Luis Seijo<sup>287</sup>, Analia Gisela Seminario<sup>42</sup>, Damien Sene<sup>23</sup>, Piseth Seng<sup>221</sup>, Sevptan Senoglu<sup>167</sup>, Mikko Seppänen<sup>288</sup>, Alex Serra Llovich<sup>289</sup>, Mohammad Shahrooee<sup>97</sup>, Anna Shcherbina<sup>290</sup>, Virginie Siguret<sup>291</sup>, Eleni Siouti<sup>292</sup>, David M. Smađja<sup>293</sup>, Niklas Smith<sup>78</sup>, Ali Sobh<sup>294</sup>, Xavier Solanich<sup>25</sup>, Jordi Solé-Violán<sup>295</sup>, Catherine Soler<sup>296</sup>, Pere Soler-Palacin<sup>297</sup>, Betül Sözer<sup>86</sup>, Giulia Maria Stella<sup>2</sup>, Yuriy Stepanovskiy<sup>298</sup>, Annabelle Stodion<sup>299</sup>, Fabio Taccone<sup>219</sup>, Yacine Tandjaoui-Lambiotte<sup>300</sup>, Jean-Luc Taupin<sup>301</sup>, Simon J. Tavernier<sup>302</sup>, Loreto Vidaur Tello<sup>112</sup>, Benjamin Terrier<sup>303</sup>, Guillaume Thier<sup>304</sup>, Christian Thorbal<sup>260</sup>, Karolina Thoren<sup>305</sup>, Caroline Thumerelle<sup>158</sup>, Imran Tipu<sup>306</sup>, Martin Tolstrup<sup>307</sup>, Gabriele Tomasoni<sup>308</sup>, Julie Toubiana<sup>77</sup>, Josep Trenado Alvarez<sup>309</sup>, Vasiliki Triantafyllia<sup>310</sup>, Sophie Trouillet-Assant<sup>311</sup>, Jesús Troya<sup>312</sup>, Owen T. Y. Tsang<sup>313</sup>, Liina Tserel<sup>314</sup>, Eugene Y. K. Tso<sup>315</sup>, Alessandra Tucci<sup>316</sup>, Şadiye Kübra Tüter Öz<sup>15</sup>, Matilde Valeria Ursini<sup>125</sup>, Takanori Utsumi<sup>225</sup>, Yurdagül Uzunhan<sup>317</sup>, Pierre Vabres<sup>318</sup>, Juan Valencia-Ramos<sup>319</sup>, Ana Maria Van Den Rym<sup>127</sup>, Isabelle Vandernoot<sup>320</sup>, Valentina Velez-Santamaría<sup>321</sup>, Silvia Patricia Zuniga Veliz<sup>324</sup>, Mateus C. Vidigal<sup>322</sup>, Sébastien Viel<sup>253</sup>, Cédric Vilain<sup>323</sup>, Marie E. Vilaire-Meunier<sup>223</sup>, Judit Villar-García<sup>324</sup>, Audrey Vincent<sup>57</sup>, Guillaume Vogt<sup>325</sup>, Guillaume Voiriot<sup>326</sup>, Alla Volokha<sup>327</sup>, Fanny Vuotto<sup>158</sup>, Els Wauters<sup>328</sup>, Joost Wauters<sup>329</sup>, Alan K. L. Wu<sup>330</sup>, Tak-Chiu Wu<sup>331</sup>, Aysun Yahşi<sup>332</sup>, Osman Yesilbas<sup>333</sup>, Mehmet Yildiz<sup>168</sup>, Barnaby E. Young<sup>187</sup>, Ufuk Yükselmis<sup>334</sup>, Mayana Zatz<sup>63</sup>, Marco Zecca<sup>39</sup>, Valentina Zuccaro<sup>62</sup>, Jens Van Praet<sup>335</sup>, Bart N. Lambrecht<sup>336</sup>, Eva Van Braeckel<sup>336</sup>, Cédric Boesteels<sup>336</sup>, Levi Hoste<sup>337</sup>, Eric Hoste<sup>338</sup>, Fré Barts<sup>338</sup>, Jozefien De Clerck<sup>336</sup>, Catherine Heijmans<sup>339</sup>, Hans Slabbynck<sup>340</sup>, Leslie Naesens<sup>341</sup>, Benoît Florin<sup>342</sup>, Cécile Boulanger<sup>343</sup>, Dimitri Vanderlinden<sup>344</sup>

<sup>1</sup>Germans Trias i Pujol University Hospital and Research Institute, Badalona, Barcelona, Spain. <sup>2</sup>Respiratory Diseases Division, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy. <sup>3</sup>Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. <sup>4</sup>Navarra Health Service Hospital, Pamplona, Spain. <sup>5</sup>Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain; Immunology Division, Genetics Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain. <sup>6</sup>Immunohematology Unit, San Raffaele Hospital,

Milan, Italy. <sup>7</sup>Ondokuz Mayıs University Medical Faculty Pediatrics, Samsun, Turkey.

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

1109, Faculté de Médecine, ITI TRANSPLANTEX NG, Université de Strasbourg, Strasbourg, France. <sup>68</sup>Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. <sup>69</sup>Neuromuscular Unit, Neurology Department, Hospital Universitari de Bellvitge-IDIBELL and CIBERER, Barcelona, Spain. <sup>70</sup>Hôpital Robert Debré, Paris, France. <sup>71</sup>Pediatric Immunohematology Unit, Necker Enfants Malades Hospital, AP-HP, Paris, France. <sup>72</sup>Department of Infectious and Tropical Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. <sup>73</sup>Doctoral Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. <sup>74</sup>Hôpital Foch, Suresnes, France. <sup>75</sup>Selcuk University Faculty of Medicine, Department of Anesthesiology and Reanimation, Intensive Care Medicine Unit, Konya, Turkey. <sup>76</sup>Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale and Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland. <sup>77</sup>Necker Hospital for Sick Children, Paris University, AP-HP, Paris, France. <sup>78</sup>Pasteur Institute, Paris, France. <sup>79</sup>McGill University Health Centre, Montreal, Canada. <sup>80</sup>University Hospital and Research Institute "Germans Trias i Pujol," IrsiCaixa AIDS Research Institute, Uvic-UCC, Badalona, Spain. <sup>81</sup>Clinical Biochemistry, Pathology, Paediatric Neurology and Molecular Medicine Departments and Biobank, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Esplugues, Spain. <sup>82</sup>AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; University Sorbonne Paris Nord, Bobigny, France; INSERM, U942, F-75010, Paris, France. <sup>83</sup>Hospital Universitari Vall d'Hebron, Barcelona, Spain. <sup>84</sup>Pitié-Salpêtrière Hospital, Paris, France. <sup>85</sup>Service de médecine Intensive Réanimation, Groupe Hospitalier Pitié-Salpêtrière, Sorbonne Université, Paris, France. <sup>86</sup>Umraniye Training and Research Hospital, Istanbul, Turkey. <sup>87</sup>Faculty of Medical Sciences at University "Goce Delcev," Shtip, North Macedonia. <sup>88</sup>Department of Biochemistry, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. <sup>89</sup>Fundació Docència i Recerca Mutua Terrassa, Barcelona, Spain. <sup>90</sup>Maladies Infectieuses et Tropicales, Nouvel Hôpital Civil, CHU Strasbourg, Strasbourg, France. <sup>91</sup>UNSW Medicine, St Vincent's Clinical School, Sydney, NSW, Australia; Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst, Sydney, NSW, Australia. <sup>92</sup>Intensive Care Unit, Montreuil Hospital, Montreuil, France. <sup>93</sup>CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium. <sup>94</sup>Pediatric Intensive Care Unit, Robert-Debré University Hospital, AP-HP, Paris, France. <sup>95</sup>General Internal Medicine, University Hospitals Leuven, Leuven, Belgium. <sup>96</sup>Hôpital Jean Verdier, AP-HP, Bondy, France. <sup>97</sup>Specialized Immunology Laboratory of Dr. Shahrooie, Sina Medical Complex, Ahvaz, Iran. <sup>98</sup>Centre de génétique humaine, CHU Besançon, Besançon, France. <sup>99</sup>Sorbonne Université médecine and AP-HP Sorbonne université site Pitié-Salpêtrière, Paris, France. <sup>100</sup>Pediatric Neurology Department, Necker-Enfants Malades Hospital, AP-HP, Paris, France. <sup>101</sup>Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. <sup>102</sup>Intensive Care Unit, Georges Pompidou Hospital, AP-HP, Paris, France. <sup>103</sup>Department of Pneumology, AZ Delta, Roeselare, Belgium. <sup>104</sup>Molecular Diagnostic Unit, Fundación Rioja Salud, Logroño, La Rioja, Spain. <sup>105</sup>Bégin Military Hospital, Saint Mandé, France. <sup>106</sup>Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. <sup>107</sup>Bursa City Hospital, Bursa, Turkey. <sup>108</sup>Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University, Mansoura, Egypt. <sup>109</sup>Tokyo Medical and Dental University, Tokyo, Japan. <sup>110</sup>Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey. <sup>111</sup>Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. <sup>112</sup>Intensive Care Medicine, Donostia University Hospital, Biodonostia Institute of Donostia, CIBER Enfermedades Respiratorias ISCIII, Donostia, Spain. <sup>113</sup>Internal Medicine, University Hospital Edouard Herriot, Hospices Civils de Lyon, Lyon, France. <sup>114</sup>Centre de Génétique, CHU Dijon, Dijon, France. <sup>115</sup>Robert Debré Hospital, Paris, France. <sup>116</sup>AP-HP Tenon Hospital, Paris, France. <sup>117</sup>Sorbonne Universités, UPMC University of Paris, Paris, France. <sup>118</sup>Department of Clinical Immunology, Hospital Clínico San Carlos, Madrid, Spain. <sup>119</sup>Intensive Care Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain; Shock, Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. <sup>120</sup>Intensive Care Unit, Hospital Clínico y Universitario de Valencia, Valencia, Spain. <sup>121</sup>Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristóbal de La Laguna, Spain, Santa Cruz de Tenerife, Spain. <sup>122</sup>CHU Limoges and INSERM CIC 1435 and UMR 1092, Limoges, France. <sup>123</sup>Infectious 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. <sup>124</sup>Department of Pathology, United Christian Hospital, Hong Kong, China. <sup>125</sup>Institute of Genetics and Biophysics "Adriano Buzzati-Traverso," IGB-CNR, Naples, Italy. <sup>126</sup>Department of Pediatrics, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Josip Juraj Strossmayer University of Osijek, Medical Faculty Osijek, Osijek, Croatia. <sup>127</sup>Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. <sup>128</sup>Hematology, AP-HP, Hôpital Européen Georges Pompidou and INSERM UMR-S1140, Paris, France. <sup>129</sup>Faculty of Medicine, Department of Pediatrics, Division of



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



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

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

**Members of Imagine COVID Group:** Jean-Philippe Annereau<sup>1</sup>, Luis Briseño-Roa<sup>1</sup>, Olivier Gribouval<sup>2</sup>, Anna Pelet<sup>2</sup>

<sup>1</sup>Medetia Pharmaceuticals, Paris, France. <sup>2</sup>Imagine Institute, Université de Paris, INSERM UMR 1163, Paris, France.

**Members of French COVID Cohort Study Group:** Laurent Abel<sup>1</sup>, Claire Andrejak<sup>2</sup>,

François Angoulant<sup>3</sup>, Delphine Bachelet<sup>4</sup>, Marie Bartoli<sup>5</sup>, Romain Basmaci<sup>6</sup>, Sylvie Behillil<sup>7</sup>, Marine Beluze<sup>8</sup>, Dehbia Benkerrou<sup>9</sup>, Krishna Bhavsar<sup>4</sup>, Lila Bouadma<sup>4</sup>, Sabelline Bouchez<sup>10</sup>, Maude Bouscambert<sup>11</sup>, Minerva Cervantes-Gonzalez<sup>4</sup>, Anissa Chair<sup>4</sup>, Catherine Chirouze<sup>12</sup>, Alexandra Coelho<sup>13</sup>, Camille Couffignal<sup>4</sup>, Sandrine Couffin-Cadriegues<sup>14</sup>, Eric d'Ortenzio<sup>5</sup>, Marie-Pierre Debray<sup>4</sup>, Lauren Deconinck<sup>4</sup>, Dominique Deplanque<sup>15</sup>, Diane Descamps<sup>4</sup>, Mathilde Desvallée<sup>16</sup>, Alpha Diallo<sup>5</sup>, Alphonsine Diour<sup>13</sup>, Céline Dorival<sup>9</sup>, François Dubos<sup>17</sup>, Xavier Duval<sup>4</sup>, Brigitte Elharrar<sup>18</sup>, Philippine Eloy<sup>4</sup>, Vincent Enouf<sup>7</sup>, Héléne Esperou<sup>14</sup>, Marina Esposito-Farese<sup>4</sup>, Manuel Etienne<sup>19</sup>, Eglantine Ferrand Devouge<sup>19</sup>, Nathalie Gault<sup>4</sup>, Alexandre Gaymard<sup>11</sup>, Jade Ghosn<sup>4</sup>, Tristan Gigante<sup>20</sup>, Morgane Gilg<sup>20</sup>, Jérémie Guedj<sup>21</sup>, Alexandre Hocin<sup>13</sup>, Isabelle Hoffmann<sup>4</sup>, Ikram Houas<sup>14</sup>, Jean-Sébastien Hulot<sup>22</sup>, Salma Jaafoura<sup>14</sup>, Ouifia Kafif<sup>2</sup>, Florentia Kaguelidou<sup>23</sup>, Sabrina Kali<sup>2</sup>, Antoine Khalil<sup>4</sup>, Coralie Khan<sup>16</sup>, Cédric Lauouenan<sup>4</sup>, Samira Laribi<sup>4</sup>, Minh Le<sup>4</sup>, Quentin Le Hingrat<sup>4</sup>, Soizic Le Mestre<sup>5</sup>, Hervé Le Nagard<sup>24</sup>, François-Xavier Lescure<sup>4</sup>, Sophie Letrou<sup>4</sup>, Yves Levy<sup>25</sup>, Bruno Lina<sup>11</sup>, Guillaume Lingas<sup>24</sup>, Jean Christophe Lucet<sup>4</sup>, Denis Malvy<sup>26</sup>, Marina Mambert<sup>13</sup>, France Mentré<sup>4</sup>, Amina Meziane<sup>9</sup>, Hugo Mouquet<sup>7</sup>, Jimmy Mullaert<sup>4</sup>, Nadège Neant<sup>24</sup>, Duc Nguyen<sup>26</sup>, Marion Noret<sup>27</sup>, Saad Nseir<sup>17</sup>, Aurélie Papadopoulou<sup>14</sup>, Christelle Paul<sup>5</sup>, Nathan Peiffer-Smadja<sup>4</sup>, Thomas Perpoint<sup>28</sup>, Ventsislava Petrov-Sanchez<sup>2</sup>, Gilles Peytavin<sup>4</sup>, Huong Pham<sup>4</sup>, Olivier Piconé<sup>9</sup>, Valentine Piquard<sup>4</sup>, Oriane Poüchal<sup>29</sup>, Christian Rabaud<sup>30</sup>, Manuel Rosa-Calatrava<sup>11</sup>, Bénédicte Rossignol<sup>20</sup>, Patrick Ruessing<sup>30</sup>, Carine Roy<sup>4</sup>, Marion Schneider<sup>4</sup>, Richa Su<sup>4</sup>, Coralie Tardivon<sup>4</sup>, Marie-Capucine Tellier<sup>4</sup>, François Téoulé<sup>9</sup>, Olivier Terrier<sup>11</sup>, Jean-François Timsit<sup>4</sup>, Christelle Tual<sup>31</sup>, Sarah Tubiana<sup>4</sup>, Sylvie Van Der Werf<sup>2</sup>, Noémie Vanel<sup>32</sup>, Aurélie Veislinger<sup>31</sup>, Benoit Visseaux<sup>4</sup>, Aurélie Wiedemann<sup>25</sup>, Yazdan Yazdanpanah<sup>4</sup>

<sup>1</sup>INSERM UMR 1163, Paris, France. <sup>2</sup>CHU Amiens, Amiens, France. <sup>3</sup>Hôpital Necker, Paris, France. <sup>4</sup>Hôpital Bichat, Paris, France. <sup>5</sup>ANRS, Paris, France. <sup>6</sup>Hôpital Louis Mourier, Colombes, France. <sup>7</sup>Pasteur Institute, Paris, France. <sup>8</sup>F-CRIN Partners Platform, Paris, France. <sup>9</sup>INSERM UMR 1136, Paris, France. <sup>10</sup>CHU Nantes, France. <sup>11</sup>INSERM UMR 1111, Lyon, France. <sup>12</sup>CHRU Jean Minjoz, Besançon, France. <sup>13</sup>INSERM UMR 1018, Paris, France. <sup>14</sup>INSERM Sponsor, Paris, France. <sup>15</sup>Centre d'Investigation Clinique, INSERM CIC 1403, Centre Hospitalo universitaire de Lille, Lille, France. <sup>16</sup>INSERM UMR 1219, Bordeaux, France. <sup>17</sup>CHU Lille, Lille, France. <sup>18</sup>CHI de Créteil, Créteil, France. <sup>19</sup>CHU Rouen, Rouen, France. <sup>20</sup>F-CRIN INI-CRCT, Nancy, France. <sup>21</sup>Université de Paris, INSERM, IAME, F-75018 Paris, France. <sup>22</sup>Hôpital Européen Georges Pompidou, Paris, France. <sup>23</sup>Hôpital Robert Debré, Paris, France. <sup>24</sup>INSERM UMR 1137, Paris, France. <sup>25</sup>Vaccine Research Institute (VRI), INSERM UMR 955, Créteil, France. <sup>26</sup>CHU Bordeaux, Bordeaux, France. <sup>27</sup>RENARC, Annecy, France. <sup>28</sup>CHU Lyon, Lyon, France. <sup>29</sup>REACTing, Paris, France. <sup>30</sup>CHU Nancy, Nancy, France. <sup>31</sup>INSERM CIC-1414, Rennes, France. <sup>32</sup>Hôpital la Timone, Marseille, France.

**Members of CoV-Contact Cohort:** Loubna Alavoine<sup>1</sup>, Sylvie Behillil<sup>2</sup>, Charles Burdet<sup>3</sup>, Charlotte Charpentier<sup>4</sup>, Aline Dechanet<sup>5</sup>, Diane Descamps<sup>6</sup>, Xavier Duval<sup>7</sup>, Jean-Luc Ecobichon<sup>1</sup>, Vincent Enouf<sup>8</sup>, Wahiba Frezouls<sup>1</sup>, Nadhira Houhou<sup>5</sup>, Ouifia Kafif<sup>2</sup>, Jonathan Lehacaut<sup>1</sup>, Sophie Letrou<sup>1</sup>, Bruno Lina<sup>9</sup>, Jean-Christophe Lucet<sup>10</sup>, Pauline Manchon<sup>5</sup>, Mariama Nourouline<sup>1</sup>,

Valentine Piquard<sup>5</sup>, Caroline Quintin<sup>1</sup>, Michael Thy<sup>11</sup>, Sarah Tubiana<sup>1</sup>, Sylvie van der Werf<sup>8</sup>, Valérie Vignali<sup>1</sup>, Benoit Visseaux<sup>10</sup>, Yazdan Yazdanpanah<sup>10</sup>, Abir Chahine<sup>12</sup>, Nawal Waucquier<sup>12</sup>, Maria-Claire Migaud<sup>12</sup>, Dominique Deplanque<sup>12</sup>, Félix Djossou<sup>13</sup>, Mayka Mergeay-Fabre<sup>14</sup>, Aude Lucarelli<sup>15</sup>, Magalie Demar<sup>13</sup>, Léa Bruneau<sup>16</sup>, Patrick Gérardin<sup>17</sup>, Adrien Maillot<sup>16</sup>, Christine Payet<sup>18</sup>, Bruno Laviolle<sup>19</sup>, Fabrice Laine<sup>19</sup>, Christophe Paris<sup>19</sup>, Mireille Desille-Dugast<sup>19</sup>, Julie Fouchard<sup>19</sup>, Denis Malvy<sup>20</sup>, Duc Nguyen<sup>20</sup>, Thierry Pistone<sup>20</sup>, Pauline Perreau<sup>20</sup>, Valérie Gissot<sup>21</sup>, Carole L. E. Goas<sup>21</sup>, Samatha Montagne<sup>22</sup>, Lucie Richard<sup>23</sup>, Catherine Chirouze<sup>24</sup>, Kévin Bouiller<sup>24</sup>, Maxime Desmaretz<sup>25</sup>, Alexandre Meunier<sup>26</sup>, Benjamin Lefèvre<sup>27</sup>, Hélène Jeulin<sup>28</sup>, Karine Legrand<sup>29</sup>, Sandra Lomazzi<sup>30</sup>, Bernard Tardy<sup>31</sup>, Amandine Gagneux-Brunon<sup>32</sup>, Frédérique Bertholon<sup>33</sup>, Elisabeth Botelho-Nevers<sup>32</sup>, Kouakam Christelle Kouakam Christelle<sup>34</sup>, Leturque Nicolas Leturque Nicolas<sup>34</sup>, Layidé Roufai<sup>34</sup>, Karine Amat<sup>35</sup>, Sandrine Couffin-Cadiegues<sup>34</sup>, Héléne Espérou<sup>36</sup>, Samia Hendou<sup>34</sup>

<sup>1</sup>Centre d'Investigation Clinique, INSERM CIC 1425, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. <sup>2</sup>Institut Pasteur, Paris, France. <sup>3</sup>Université de Paris, IAME, INSERM U1137, Paris, France; Hôpital Bichat Claude Bernard, AP-HP, Paris, France. <sup>4</sup>Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. <sup>5</sup>Hôpital Bichat Claude Bernard, AP-HP, Paris, France. <sup>6</sup>IAME INSERM U1140, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. <sup>7</sup>Centre d'Investigation Clinique, INSERM CIC 1425, AP-HP, IAME, Paris University, Paris, France. <sup>8</sup>Institut Pasteur, U3569 CNRS, Université de Paris, Paris, France. <sup>9</sup>Virpath Laboratory, International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS U5308, ENS, UCBL, Lyon, France. <sup>10</sup>IAME INSERM U1138, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. <sup>11</sup>Center for Clinical Investigation, Assistance Publique-Hôpitaux de Paris, Bichat-Claude Bernard University Hospital, Paris, France. <sup>12</sup>Centre d'Investigation Clinique, INSERM CIC 1403, Centre Hospitalo universitaire de Lille, Lille, France. <sup>13</sup>Service des maladies infectieuses, Centre Hospitalo universitaire de Cayenne, Guyane, France. <sup>14</sup>Centre d'Investigation Clinique, INSERM CIC 1424, Centre Hospitalier de Cayenne, Cayenne, Guyane Française. <sup>15</sup>Service Hôpital de jour Adulte, Centre Hospitalier de Cayenne, Guyane, France. <sup>16</sup>Centre d'Investigation Clinique, INSERM CIC 1410, Centre Hospitalo universitaire de la Réunion, La Réunion, France. <sup>17</sup>Centre d'Investigation Clinique, INSERM CIC 1410, CHU Reunion, Saint-Pierre, Reunion Island. <sup>18</sup>Centre d'Investigation Clinique, INSERM CIC 1410, Centre de Ressources Biologiques, Centre Hospitalo universitaire de la Réunion, La Réunion, France. <sup>19</sup>Centre d'Investigation Clinique, INSERM CIC 1414, Centre Hospitalo universitaire de Rennes, Rennes, France. <sup>20</sup>Service des maladies infectieuses, Centre Hospitalo universitaire de Bordeaux, Bordeaux, France. <sup>21</sup>Centre d'Investigation Clinique, INSERM CIC 1415, CHRU Tours, Tours, France. <sup>22</sup>CRBT, Centre Hospitalo universitaire de Tours, Tours, France. <sup>23</sup>Pole de Biologie Médicale, Centre Hospitalo universitaire de Tours, Tours, France. <sup>24</sup>Service des maladies infectieuses, Centre Hospitalo universitaire de Besançon, Besançon, France. <sup>25</sup>Service des maladies infectieuses, Centre d'investigation clinique, INSERM CIC1431, Centre Hospitalier Universitaire de Besançon, Besançon, France. <sup>26</sup>Centre de Ressources Biologiques-Filière Microbiologique de Besançon, Centre Hospitalier Universitaire, Besançon, France. <sup>27</sup>Université de Lorraine, CHRU-Nancy and APEMAC, Infectious and Tropical Diseases, Nancy, France. <sup>28</sup>Laboratoire de Virologie, CHRU de Nancy Brabois, Vandoeuvre-lès-Nancy, France. <sup>29</sup>INSERM CIC-EC 1433, Centre Hospitalo universitaire de Nancy, Nancy, France. <sup>30</sup>Centre de ressources Biologiques, Centre Hospitalo universitaire de Nancy, Nancy, France. <sup>31</sup>Centre d'Investigation Clinique, INSERM CIC 1408, Centre Hospitalo universitaire de Saint Etienne, Saint Etienne, France. <sup>32</sup>Service des maladies infectieuses, Centre Hospitalo universitaire de Saint Etienne, Saint Etienne, France. <sup>33</sup>Service des maladies infectieuses, CRB<sup>42</sup>-BTK, Centre Hospitalo Universitaire de Saint Etienne, Saint Etienne, France. <sup>34</sup>Pole Recherche Clinique, INSERM, Paris, France. <sup>35</sup>IMEA Fondation Léon M'Ba, Paris, France. <sup>36</sup>INSERM Clinical Research Department, Paris, France.

**Members of Amsterdam UMC Covid-19 Biobank:** Michiel van Agtmael<sup>2</sup>, Anne Geke Algera<sup>1</sup>, Brent Appelman<sup>2</sup>, Frank van Baarle<sup>1</sup>, Diane Bax<sup>3</sup>, Martijn Beudel<sup>4</sup>, Harm Jan Bogaard<sup>5</sup>, Marije Bomers<sup>2</sup>, Peter Bonta<sup>5</sup>, Lieuwe Bos<sup>1</sup>, Michela Botta<sup>1</sup>, Justin de Brabander<sup>2</sup>, Godelieve de Bree<sup>2</sup>, Sanne de Bruin<sup>1</sup>, David T. P. Buis<sup>1</sup>, Marianna Bugiani<sup>5</sup>, Esther Bulle<sup>1</sup>, Osoul Chouchane<sup>2</sup>, Alex Cloherty<sup>3</sup>, Mirjam Dijkstra<sup>12</sup>, Dave A. Dongelmans<sup>1</sup>, Romein W. G. Dujardin<sup>1</sup>, Paul Elbers<sup>1</sup>, Lucas Fleuren<sup>1</sup>, Suzanne Geerlings<sup>2</sup>, Theo Geijtenbeek<sup>3</sup>, Armand Girbes<sup>1</sup>, Bram Goorhuis<sup>2</sup>, Martin P. Grobusch<sup>2</sup>, Florianne Hafkamp<sup>3</sup>, Laura Hagens<sup>1</sup>, Jorg Hamann<sup>7</sup>, Vanessa Harris<sup>2</sup>, Robert Hemke<sup>3</sup>, Sabine M. Hermans<sup>2</sup>, Leo Heunks<sup>1</sup>, Markus Hollmann<sup>6</sup>, Janneke Horn<sup>1</sup>, Joppe W. Hovius<sup>2</sup>, Menno D. de Jong<sup>9</sup>, Rutger Koning<sup>4</sup>, Endry H. T. Lim<sup>1</sup>, Niels van Mourik<sup>1</sup>, Jeaninne Nellen<sup>2</sup>, Esther J. Nossent<sup>2</sup>, Frederique Paulus<sup>1</sup>, Edgar Peters<sup>2</sup>, Dan A. I. Pina-Fuentes<sup>6</sup>, Tom van der Poll<sup>2</sup>, Benedikt Preckel<sup>6</sup>, Jan M. Prins<sup>2</sup>, Jorinde Raasveld<sup>1</sup>, Tom Reijnders<sup>2</sup>, Maurits C. F. J. de Rotte<sup>12</sup>, Michiel Schinkel<sup>2</sup>, Marcus J. Schultz<sup>1</sup>, Femke A. P. Schrauwen<sup>12</sup>, Alex Schuurmans<sup>10</sup>, Jaap Schuurmans<sup>1</sup>, Kim Sigaloff<sup>1</sup>, Marleen A. Slim<sup>12</sup>, Patrick Smeele<sup>5</sup>, Marry Smit<sup>1</sup>, Cornelis S. Stijns<sup>2</sup>, Willemke Stijlma<sup>1</sup>, Charlotte Teunissen<sup>11</sup>, Patrick Thorat<sup>1</sup>, Anissa M. Tsonas<sup>1</sup>, Pieter R. Tuinman<sup>2</sup>, Marc van der Valk<sup>2</sup>, Denise Veelo<sup>6</sup>, Carolien Volleman<sup>1</sup>, Heder de Vries<sup>1</sup>, Lonneke A. Vught<sup>12</sup>,

Michèle van Vugt<sup>2</sup>, Dorien Wouters<sup>12</sup>, A. H. (Koo) Zwinderman<sup>13</sup>, Matthijs C. Brouwer<sup>4</sup>, W. Joost Wiersinga<sup>2</sup>, Alexander P. J. Vlaar<sup>1</sup>, Diederik van de Beek (d.vandebeek@amsterdamumc.nl)<sup>4</sup>

<sup>1</sup>Department of Intensive Care, Amsterdam UMC, Amsterdam, Netherlands. <sup>2</sup>Department of Infectious Diseases, Amsterdam UMC, Amsterdam, Netherlands. <sup>3</sup>Experimental Immunology, Amsterdam UMC, Amsterdam, Netherlands. <sup>4</sup>Department of Neurology, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, Netherlands. <sup>5</sup>Department of Pulmonology, Amsterdam UMC, Amsterdam, Netherlands. <sup>6</sup>Department of Anesthesiology, Amsterdam UMC, Amsterdam, Netherlands. <sup>7</sup>Amsterdam UMC Biobank Core Facility, Amsterdam UMC, Amsterdam, Netherlands. <sup>8</sup>Department of Radiology, Amsterdam UMC, Amsterdam, Netherlands. <sup>9</sup>Department of Medical Microbiology, Amsterdam UMC, Amsterdam, Netherlands. <sup>10</sup>Department of Internal Medicine, Amsterdam UMC, Amsterdam, Netherlands. <sup>11</sup>Neurochemical Laboratory, Amsterdam UMC, Amsterdam, Netherlands. <sup>12</sup>Department of Clinical Chemistry, Amsterdam UMC, Amsterdam, Netherlands. <sup>13</sup>Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, Amsterdam, Netherlands.

**Members of NIAID-USUHS COVID Study Group:** Miranda F. Tompkins<sup>1</sup>, Camille Alba<sup>1</sup>, Andrew L. Snow<sup>2</sup>, Daniel N. Hupalo<sup>1</sup>, John Rosenberger<sup>1</sup>, Gauthaman Sukumar<sup>1</sup>, Matthew D. Wilkerson<sup>1</sup>, Xijun Zhang<sup>1</sup>, Justin Lack<sup>3</sup>, Andrew J. Oler<sup>4</sup>, Kerry Dobbs<sup>5</sup>, Ottavia M. Delmonte<sup>5</sup>, Jeffrey J. Danielson<sup>5</sup>, Andrea Biondi<sup>6</sup>, Laura Rachele Bettini<sup>6</sup>, Mariella D'Angio<sup>6</sup>, Ilaria Beretta<sup>7</sup>, Luisa Imberti<sup>8</sup>, Alessandra Sottini<sup>8</sup>, Virginia Quaresima<sup>8</sup>, Eugenia Quiros-Roldan<sup>9</sup>, Camillo Rossi<sup>10</sup>

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

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