

UCLA

UCLA Previously Published Works

Title

Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19

Permalink

<https://escholarship.org/uc/item/922199h2>

Journal

Genome Medicine, 15(1)

ISSN

1756-994X

Authors

Matuozzo, Daniela
Talouarn, Estelle
Marchal, Astrid
et al.

Publication Date

2023-04-01

DOI

10.1186/s13073-023-01173-8

Peer reviewed

RESEARCH

Open Access



Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19

Daniela Matuozzo^{1,2}, Estelle Talouarn^{1,2}, Astrid Marchal^{1,2}, Peng Zhang³, Jeremy Manry^{1,2}, Yoann Seeleuthner^{1,2}, Yu Zhang⁴, Alexandre Bolze⁵, Matthieu Chaldebas³, Baptiste Milisavljevic³, Adrian Gervais^{1,2}, Paul Bastard^{1,2,3,6}, Takaki Asano³, Lucy Bizien^{1,2}, Federica Barzaghi⁷, Hassan Abolhassani^{8,9}, Ahmad Abou Tayoun^{10,11}, Alessandro Aiuti^{12,13}, Ilad Alavi Darazam^{14,15}, Luis M. Allende¹⁶, Rebeca Alonso-Arias¹⁷, Andrés Augusto Arias^{3,18,19}, Gokhan Aytekin²⁰, Peter Bergman^{21,22}, Simone Bondesan²³, Yenan T. Bryceson²⁴, Ingrid G. Bustos²⁵, Oscar Cabrera-Marante²⁶, Sheila Carcel²⁷, Paola Carrera²³, Giorgio Casari^{28,29}, Khalil Chaïbi^{30,31}, Roger Colobran^{32,33,34}, Antonio Condino-Neto³⁵, Laura E. Covill²⁴, Ottavia M. Delmonte⁴, Loubna El Zein³⁶, Carlos Flores^{37,38,39,40}, Peter K. Gregersen⁴¹, Marta Gut⁴², Filomeen Haerynck⁴³, Rabih Halwani⁴⁴, Selda Hancerli⁴⁵, Lennart Hammarström⁸, Nevin Hatipoğlu⁴⁶, Adem Karbuza⁴⁷, Sevgi Keles⁴⁸, Christèle Kyheng⁴⁹, Rafael Leon-Lopez²⁷, Jose Luis Franco⁵⁰, Davood Mansouri^{51,52,53}, Javier Martinez-Picado^{54,55,56,57,58}, Ozge Metin Akcan⁴⁸, Isabelle Migeotte⁵⁹, Pierre-Emmanuel Morange^{60,61}, Guillaume Morelle⁴⁹, Andrea Martin-Nalda^{32,62,63}, Giuseppe Novelli^{64,65}, Antonio Novelli⁶⁶, Tayfun Ozcelik⁶⁷, Figen Palabiyik⁴⁶, Qiang Pan-Hammarström⁸, Rebeca Pérez de Diego⁶⁸, Laura Planas-Serra^{69,70}, Daniel E. Pleguezuelo¹⁶, Carolina Prando⁷¹, Aurora Pujol^{57,69,70}, Luis Felipe Reyes⁷², Jacques G. Rivière^{32,62,63}, Carlos Rodriguez-Gallego^{73,74}, Julian Rojas⁵⁰, Patrizia Rovere-Querini^{13,75}, Agatha Schlüter^{69,70}, Mohammad Shahrooei^{76,77}, Ali Sobh⁷⁸, Pere Soler-Palacin^{32,62,63}, Yacine Tandjaoui-Lambiotte⁷⁹, Imran Tipu⁸⁰, Cristina Tresoldi⁸¹, Jesus Troya⁸², Diederik van de Beek⁸³, Mayana Zatz⁸⁴, Pawel Zawadzki^{85,86}, Saleh Zaid Al-Muhsen⁸⁷, Mohammed Faraj Alosaimi⁸⁷, Fahad M. Alsohime⁸⁷, Hagit Baris-Feldman^{88,89}, Manish J. Butte⁹⁰, Stefan N. Constantinescu^{91,92,93,94}, Megan A. Cooper⁹⁵, Clifton L. Dalgard^{96,97}, Jacques Fellay^{98,99,100}, James R. Heath¹⁰¹, Yu-Lung Lau¹⁰², Richard P. Lifton^{103,104,105}, Tom Maniatis^{106,107}, Trine H. Mogensen^{108,109}, Horst von Bernuth¹¹⁰, Alban Lermine¹¹¹, Michel Vidaud¹¹¹, Anne Boland¹¹², Jean-François Deleuze¹¹², Robert Nussbaum¹¹³, Amanda Kahn-Kirby¹¹³, France Mentre¹¹⁴, Sarah Tubiana¹¹⁵,

†Jean-Laurent Casanova, Qian Zhang, Laurent Abel, and Aurélie Cobat contributed equally to this work.


*Correspondence:

Jean-Laurent Casanova
casanova@rockefeller.edu
Aurélie Cobat
aurelie.cobat@inserm.fr

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Guy Gorochov¹¹⁶, Florence Tubach¹¹⁷, Pierre Hausfater^{118,119}, COVID Human Genetic Effort, COVDeF Study Group, French COVID Cohort Study Group, CoV-Contact Cohort, COVID-STORM Clinicians, COVID Clinicians, Orchestra Working Group, Amsterdam UMC Covid-19 Biobank, NIAID-USUHS COVID Study Group, Isabelle Meyts¹²⁰, Shen-Ying Zhang^{1,2,3}, Anne Puel^{1,2,3}, Luigi D. Notarangelo¹²¹, Stephanie Boisson-Dupuis^{1,2,3}, Helen C. Su⁴, Bertrand Boisson^{1,2,3}, Emmanuelle Jouanguy^{1,2,3}, Jean-Laurent Casanova^{1,2,3,122*†}, Qian Zhang^{1,2,3†}, Laurent Abel^{1,2,3†} and Aurélie Cobat^{1,2,3*†} 

Abstract

Background We previously reported that impaired type I IFN activity, due to inborn errors of TLR3- and TLR7-dependent type I interferon (IFN) immunity or to autoantibodies against type I IFN, account for 15–20% of cases of life-threatening COVID-19 in unvaccinated patients. Therefore, the determinants of life-threatening COVID-19 remain to be identified in ~80% of cases.

Methods We report here a genome-wide rare variant burden association analysis in 3269 unvaccinated patients with life-threatening COVID-19, and 1373 unvaccinated SARS-CoV-2-infected individuals without pneumonia. Among the 928 patients tested for autoantibodies against type I IFN, a quarter (234) were positive and were excluded.

Results No gene reached genome-wide significance. Under a recessive model, the most significant gene with at-risk variants was *TLR7*, with an OR of 27.68 (95%CI 1.5–528.7, $P = 1.1 \times 10^{-4}$) for biochemically loss-of-function (bLOF) variants. We replicated the enrichment in rare predicted LOF (pLOF) variants at 13 influenza susceptibility loci involved in TLR3-dependent type I IFN immunity (OR = 3.70 [95%CI 1.3–8.2], $P = 2.1 \times 10^{-4}$). This enrichment was further strengthened by (1) adding the recently reported *TYK2* and *TLR7* COVID-19 loci, particularly under a recessive model (OR = 19.65 [95%CI 2.1–2635.4], $P = 3.4 \times 10^{-3}$), and (2) considering as pLOF branchpoint variants with potentially strong impacts on splicing among the 15 loci (OR = 4.40 [9%CI 2.3–8.4], $P = 7.7 \times 10^{-8}$). Finally, the patients with pLOF/bLOF variants at these 15 loci were significantly younger (mean age [SD] = 43.3 [20.3] years) than the other patients (56.0 [17.3] years; $P = 1.68 \times 10^{-5}$).

Conclusions Rare variants of TLR3- and TLR7-dependent type I IFN immunity genes can underlie life-threatening COVID-19, particularly with recessive inheritance, in patients under 60 years old.

Keywords Rare variants, COVID-19, Immunity, Type I interferon

Background

Clinical variability is high in unvaccinated individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranging from silent infection to lethal disease. In ~3% of cases, infection leads to critical COVID-19 pneumonia, requiring high-flow oxygen ($O_2 > 6$ L/min), mechanical ventilation (non-invasive or by intubation), or extracorporeal membrane oxygenation (ECMO) [1]. Advanced age is by far the strongest predictor of COVID-19 severity, with the risk of death doubling every 5 years of age from childhood onward [2, 3]. Men are also at greater risk of death than women [3–5]. Genome-wide (GW) association studies have identified several common loci associated with COVID-19 severity, the most significant being a region on chromosome 3p21.31 that was introduced by archaic introgression from Neanderthals [6–10]. The risk haplotype encompasses six genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*) and confers an estimated OR per copy of between 1.6 and 2.1, with higher

values for individuals under 60 years old [7, 11]. Twenty-four GW regions have been shown to be significantly associated with critical COVID-19 [10–12]. Four of these regions encompass genes involved in type I IFN immunity. The first, on chr12q24.13, containing protective variants, is also a Neanderthal haplotype [13] and includes the *OAS1*, *OAS2*, and *OAS3* cluster, these interferon-stimulated genes (ISGs) being required for the activation of antiviral RNaseL. The second, a region on chr21q22.1, includes *IFNAR2*. The third, a region on chr19p13.2, includes *TYK2*. The fourth, a region on chr9p21, includes *IFNA10*. However, common variants have a modest effect size and explain only a very small fraction of the clinical variability [6, 8]. This prompted us to search for rare variants conferring a stronger predisposition to life-threatening COVID-19.

Through a candidate approach focusing on influenza susceptibility genes, the COVID Human Genetics Effort (CHGE [14]) provided proof-of-concept that autosomal inborn errors of TLR3-dependent and -independent type

I interferon (IFN) immunity, including autosomal recessive (AR) deficiencies of *IFNAR1* or *IRF7*, can underlie critical COVID-19 [15]. Other children with AR *IFNAR1*, *IFNAR2*, *TBK1*, or *STAT2* deficiency were subsequently reported, as well as children with AR *TYK2* deficiency [16–20] (Fig. 1). Some other groups were unable to replicate these findings, but the variants were not tested biochemically and it is unclear whether recessive defects were considered [11, 21–23]. There may also be other reasons for their findings [1, 24], the most important being the age distribution of the case cohorts. The other case cohorts were much older than ours (mean age of 66 vs. 52 years) and we found that inborn errors of immunity (IEI) were more frequent in patients under 60 years old [25]. Consistently, we recently reported that ~10% of children with moderate, severe, or critical COVID-19 pneumonia had recessive inborn errors

of type I IFN immunity [19]. Moreover, older patients are more likely to carry pre-existing autoantibodies (auto-Abs) neutralizing type I IFN, which are found in about 15% of critical cases and up to 21% of patients over the age of 80 years [26, 27]. The presence of such auto-Abs has been replicated by at least 26 studies worldwide [28, 29], and we also recently showed that autoimmunity to type I IFNs is a strong common predictor of COVID-19 death in unvaccinated individuals, providing further evidence for the role of type I IFN immunity in life-threatening COVID-19 [29].

Using an unbiased X-wide gene burden test, we also identified X-linked recessive (XR) *TLR7* deficiency in 17 male patients aged 7–71 years with critical COVID-19 pneumonia, accounting for ~1% of cases in men (Fig. 1) [30]. Moreover, six of the 11 *TLR7* variants previously reported in patients from other studies were deleterious

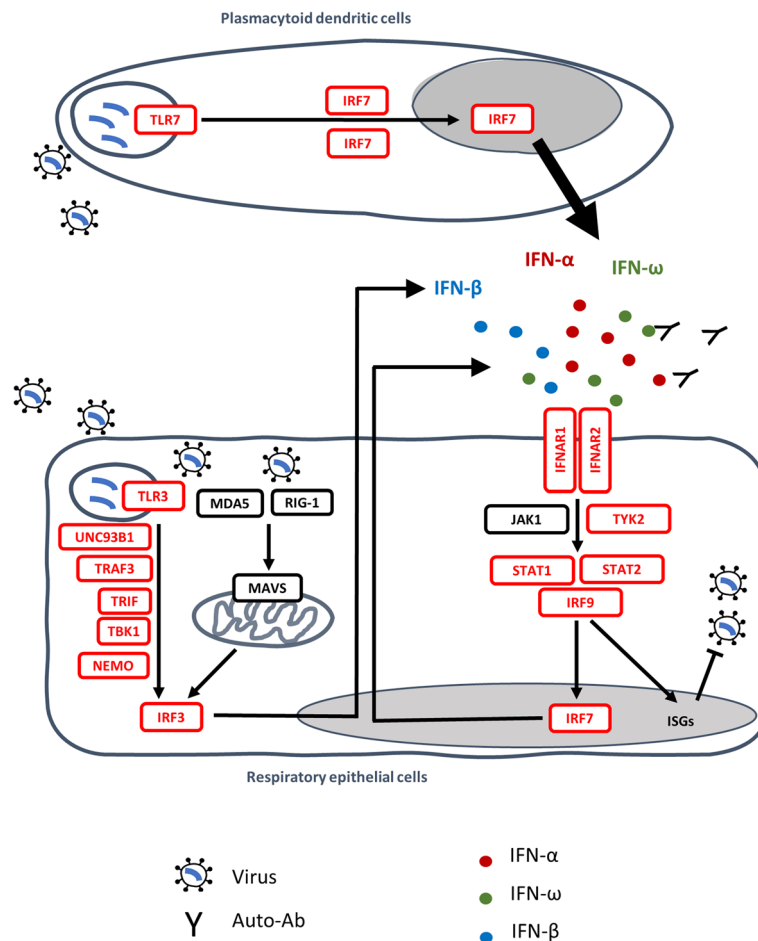


Fig. 1 Type I IFN immunity genes associated with life-threatening COVID-19. Inborn errors of type I IFN immunity and autoantibodies neutralizing type I IFNs (α , β , ω) underlie life-threatening COVID-19 pneumonia by interfering with type I IFN immunity in respiratory epithelial cells (RECs) and blood plasmacytoid dendritic cells (pDCs). SARS-CoV-2 infection can induce type I IFN production in a TLR3-dependent manner in tissue-resident RECs (which express TLR3 but not TLR7) and in a TLR7-dependent manner in circulating pDCs (which express TLR7 but not TLR3). *IRF7* is constitutively expressed in pDCs, at higher levels than in other cell types, whereas it is mostly induced by viral infection in RECs. Reported in red are the 13 genes (*IFNAR1*, *IFNAR2*, *IRF3*, *IRF7*, *IRF9*, *IKBK1*, *STAT1*, *STAT2*, *TBK1*, *TICAM1*, *TLR3*, *TRAF3*, and *UNC93B1*) investigated in a previous study [15]; *TYK2* and *TLR7* were subsequently shown to underlie severe COVID-19 [19, 30]

(carried by nine of 16 patients) [31–36], whereas the *TLR7* variants in other studies were not disclosed [21, 22]. *TLR3* senses viral dsRNA in respiratory epithelial cells, whereas *TLR7* senses ssRNA in plasmacytoid dendritic cells [25, 28]. Both pathways induce the production of type I IFNs. *TLR7* gain-of-function variants were recently shown to be associated with human systemic lupus erythematosus [37], providing an example of mirror genetic effects between infectious and inflammatory/autoimmune diseases [38]. Collectively, these findings suggest that type I IFNs are essential for protective immunity to SARS-CoV-2 in the respiratory tract, with insufficient type I IFN activity accounting for up to 15–20% of cases of life-threatening COVID-19. Despite this high proportion, the determinants of critical COVID-19 pneumonia remain to be identified in ~80% of cases. Here, we tested the hypotheses that other IEI may underlie critical COVID-19 pneumonia in at least some patients and that our initial findings could be replicated in a new cohort. With the CHGE, we performed a GW gene-based rare variant association analysis. This analysis was performed in both previously investigated patients who had not been screened at the GW level [15, 19, 30], and in newly recruited patients. We also tested the hypothesis that we could replicate our initial finding of an enrichment in pLOF variants of candidate type I IFN-related genes in newly recruited patients, given the controversy from other groups. We extended the analysis to two other type I IFN-related genes, *TLR7* and *TYK2*, that we had recently found to be associated with critical COVID-19 [19, 30], and to branchpoint (BP) variants with a potentially strong impact on the splicing of the 15 type I IFN-related genes [39]. Finally, we refined the analysis of the type I IFN-related genes by taking age, sex, and zygosity into account.

Methods

Cohort

Since the beginning of the pandemic, we have enrolled more than 9000 individuals with SARS-CoV-2 infection and broad clinical manifestations from all over the world through the COVID Human Genetic Effort (CHGE). In this study, we focused on 3503 patients with life-threatening COVID-19 and 1373 individuals with asymptomatic/mild infection. Life-threatening COVID-19 cases were defined as patients with pneumonia who developed critical disease, whether pulmonary with high-flow oxygen (>6 L/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. We screened for the presence of autoantibodies (auto-Abs) against type I IFNs in all patients for whom plasma was available ($N=928$), as previously described

[26, 27], and we excluded 234 patients who tested positive for auto-Abs as they already have a major risk factor for developing critical COVID-19 [29]. In total, 3269 patients with life-threatening COVID-19 were included in the analysis. Among those 3269 patients, 1301 had been included in previous studies restricted to a short list of 18 candidate genes [15, 19] or to the X chromosome [30], and 1968 had not been studied before. Controls were defined as individuals infected with SARS-CoV-2 who remained asymptomatic or pauci-symptomatic, with the presence of mild, self-healing, ambulatory disease ($N=1373$). The presence of infection was assessed on the basis of a positive PCR test and/or serological test and/or the presence of typical symptoms such as anosmia or ageusia after exposure to a confirmed COVID-19 case. Whole-exome ($N=2003$ cases and 866 controls) or whole-genome ($N=1266$ cases and 507 controls) sequencing was performed for the cases and controls, and high-quality variants were obtained from the sequencing data as detailed in the Additional file 1: Supplementary Methods.

Population stratification

Principal component analysis (PCA) was performed with PLINK v1.9 software [40] on a pruned subset of ~14,600 SNPs not in linkage disequilibrium (maximum r^2 value for linkage disequilibrium 0.4 between pairs of SNPs) with a minor allele frequency (MAF) > 1%, call rate > 99%, and P value for departure from Hardy–Weinberg equilibrium > 10^{-5} , as previously described [41]. Ethnic origin was inferred from the PCA as previously described [41].

Variant selection

For each gene, we considered several sets of candidate coding variants, defined according to (i) functional annotation: predicted loss-of-function (pLOF) variants only (including stop gain/lost, start lost, frameshift, or splice variants), or pLOF with missense and in-frame variants (MISSLOF); (ii) the gnomAD v2.1 allele frequency (AF): variants with a gnomAD allele frequency below 1%, 0.1%, or 0.01%; and (iii) Combined Annotation Dependent Depletion (CADD) score [42] for missense and in-frame variants: CADD score \geq mutation significance cut-off (MSC) for the corresponding gene [43] or all variants regardless of the CADD score. We considered nine sets of variants in total: (1) pLOF variants with gnomAD AF < 1%; (2) pLOF variants with gnomAD AF < 0.1%; (3) pLOF variants with gnomAD AF < 0.01%; (4) MISSLOF with CADD > MSC and gnomAD AF < 1%; (5) MISSLOF with CADD > MSC and gnomAD AF < 0.1%; (6) MISSLOF with CADD > MSC and gnomAD AF < 0.01%; (7) MISSLOF with gnomAD AF < 1%; (8) MISSLOF

with gnomAD AF < 0.1%; (9) MISSLOF with gnomAD AF < 0.01%.

Rare variant burden analysis

We performed a genome-wide gene-based rare variants burden analysis. For each gene, the genotypic information for candidate rare variants was summarized into a genetic score defined according to three genetic models: (1) co-dominant: samples were coded 2 if they carried at least one biallelic variant, 1 if they carried at least one monoallelic variant, and 0 otherwise; (2) heterozygous: samples were coded 1 if they carried at least one monoallelic variant and 0 otherwise; and (3) recessive: samples were coded 1 if they carried at least one biallelic variant and 0 otherwise. For the X chromosome, hemizygous males are considered to be equivalent to homozygous females. The association between the genetic score for each gene and the disease status was assessed with a logistic regression-based likelihood ratio test (LRT) from EPACTS (Efficient and Parallelizable Association Container Toolbox) [44] for the genome-wide burden analysis or R 3.6.0 [45] for the candidate type I IFN-related pathway. Firth's bias correction, with the `fast.logistf.fit` function of EPACTS or the `logistf` function of the R `logistf` package [46], was applied if the *P* value of the LRT was below 0.05. Analyses were adjusted for sex, age (in years), and the first five PCs of the PCA. In Firth's regression, a penalty term is assigned to the standard maximum likelihood function used to estimate the parameters of a logistic regression model when there are rare events or when complete separation exists [47]. With no covariates, this corresponds to adding 0.5 to every cell of a 2 by 2 table of allele counts versus case–control status. For a given gene and variant set, the burden test was not performed if the number of carriers across all samples was below 3.

We used three analysis strategies: (1) joint analysis of all samples; (2) trans-ethnic meta-analysis: the analysis was stratified according to 7 inferred ancestry subgroups (African, North African, European, admixed American, Middle Eastern, South Asian, East Asian). For each subgroup, an ethnicity specific PCA was performed and used in the logistic regression model; and (3) trans-pipeline meta-analysis to account for heterogeneity due to the type of sequencing data: the analysis was stratified according to the type of data shared (FASTQ vs. VCF). Subgroup *P* values were subjected to further meta-analysis, accounting for the direction of the effect and sample size, with METAL [48].

Correction for multiple testing

For each gene, up to 9 burden tests were performed per genetic model. These tests were not independent; we therefore assessed the effective number of burden tests

Meff with a method adapted from that described by Patin et al. [49], based on the approach of Li and Ji [50]. This approach makes use of the variance of the eigenvalues of the observed statistics correlation matrix to estimate Meff. The Bonferroni-corrected threshold was then defined as 0.05/Meff.

Odds ratio (OR) equality for homozygous/hemizygous versus heterozygous carriers of pLOF variants at type I IFN genes

We investigated whether the odds of critical COVID-19 differed for carriers and non-carriers of pLOF variants at the type I IFN immunity loci as a function of zygosity (homozygous/hemizygous vs heterozygous). In the full sample, we used LRT to compare a full Firth bias-corrected logistic regression model including two different parameters for carriers of pLOF as a function of zygosity (alternative hypothesis) with a Firth bias-corrected logistic regression model including only one parameter for carriers of pLOF, not taking zygosity into account (null hypothesis). The analysis was performed with the R `logistf` package.

Biochemical characterization of TLR7 variants with a luciferase reporter assay

We tested the *TLR7* variants as previously described [30]. Briefly, *TLR7* variants were generated by site-directed mutagenesis. The WT or variant alleles were re-introduced into a Myc-DDK-pCMV6 vector (Origene). HEK293T cells, which have no endogenous *TLR7* expression, were transfected with 50 ng of Myc-DDK-pCMV6 vector, empty or containing the WT or a variant allele 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/Hygo) (Promega) reporter vector contains five copies of the NF-κB-responsive element (NF-κB-RE) linked to the luc2P luciferase reporter gene. After 24 h, 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 h. Relative luciferase activity was then determined by normalizing the values obtained against the firefly:Renilla luciferase signal ratio.

Results

Cohort description

Through the CHGE, we collected whole-exome sequencing (WES) or whole-genome sequencing (WGS) data for 3503 patients with life-threatening COVID-19 pneumonia (hereafter referred to as “patients”; see [Supplemental Methods](#)) and 1373 individuals with mild or asymptomatic

infection, i.e., without pneumonia (hereafter referred to as “controls”). In total, 928 of the 3503 patients were screened for the presence of auto-Abs against type I IFN [26, 27] (Supplemental Methods) and the 234 patients who tested positive were excluded from this analysis as they already have a major risk factor for the development of critical COVID-19 [29]. In total, 1301 of the 3269 remaining patients had been included in previous studies restricted to a short list of 18 candidate genes [15, 19] or to the X chromosome [30], and 1968 had not been studied before. The mean age (SD) of the patients was 55.7 (17.4) years, with a male-to-female ratio of 2.4 (Table 1). The controls were significantly younger than the patients ($P < 0.0001$), with a mean age (SD) of 43.8 years (20.1 years) and were more likely to be female ($P < 0.0001$; male-to-female ratio = 0.7). The patients and controls were of various ethnic origins, mostly of European and Middle Eastern ancestry, according to principal component analysis (PCA) (Fig. 2). Raw sequencing data were either centralized in the HGID laboratory and processed with the HGID pipeline (2492 cases and 870 controls) or processed separately by each sequencing hub (777 cases and 503 controls; See Supplemental Methods). A joint analysis was performed first on the combined sample of 3269 patients and 1373 controls. Given the heterogeneity of the cohort due to different

ancestries and processing pipelines, we also performed a trans-ethnic and a trans-pipeline meta-analysis; only results consistent across the three analyses are reported here (See Supplemental Methods).

Genome-wide analysis under a co-dominant model

We first performed a GW rare variant burden analysis on the 3269 patients with life-threatening COVID-19 and 1373 controls with asymptomatic/mild COVID-19 under a co-dominant model, using nine sets of variants (See Supplemental Methods). The QQ plots for the joint analysis of the samples revealed no systematic deviations from the null hypothesis, and the genomic inflation factors (λ) were close to 1 (Additional file 2: Table S1). In total, 18,064 genes were analyzed with at least one of the nine variant sets, resulting in an effective number of independent tests (Meff) for the joint analysis of 108,384, giving a Bonferroni-corrected significance threshold of 4.61×10^{-7} . No gene was found to be of GW significance (see the Manhattan plot in Fig. 3A, Additional file 2: Table S2). The gene with the strongest association was *TREH*, encoding the trehalase enzyme, which hydrolyses trehalose, with rare (gnomAD allele frequency [AF] $< 10^{-4}$) nonsynonymous variants associated with a lower risk of life-threatening COVID-19 (OR = 0.12 [95% CI 0.05–0.28], $P = 1.9 \times 10^{-6}$; Additional file 2: Table S3). In analyses of genes for which rare predicted loss-of-function (pLOF) variants were associated with an increase in the risk of life-threatening COVID-19 (Table 2), the strongest association was that for *NPC2*, for rare (gnomAD AF < 0.01) pLOF variants, with 28 heterozygous carriers among patients (0.9%), and four heterozygous carriers (0.3%) among controls (OR = 5.41 [95% CI 1.8–16.4], $P = 5.8 \times 10^{-4}$). *NPC2* encodes the Niemann-Pick disease type C2 protein and homozygous LOF mutations of this gene cause Niemann-Pick disease [51]. *NPC2* interacts with *NPC1*, which is also an essential endosomal receptor for the Ebola virus [52, 53]. Both *NPC1* and *NPC2* were implicated in the regulation of SARS-CoV-2 entry in a CRISPR screen [54]. The GW burden analysis under a dominant model yielded similar conclusions (Additional file 2: Table S3).

Genome-wide analysis under a recessive model

We then performed a GW screen under a recessive model (autosomal and X-linked). In total, 4511 genes were analyzed with at least one of the nine variant sets, resulting in 27,066 independent tests, giving a Bonferroni-corrected significance threshold of 1.85×10^{-6} . No gene reached GW significance (Fig. 3B). In analyses of genes with rare variants increasing the risk of life-threatening COVID-19, *TLR7* was, by two orders of

Table 1 Baseline characteristics of study participants

	Life-threatening COVID-19 n = 3269	Infected controls n = 1373	P value ^a
Sex , no. (%)			< 0.0001
Male	2314 (70.8%)	542 (39.5%)	
Female	955 (29.2%)	831 (60.5%)	
Age (years)			< 0.0001
Mean (SD)	55.74 (17.40)	43.83 (20.14)	
Median (range)	57 (0.08–99)	43 (0.08–105)	
Processing pipeline , no. (%)			< 0.0001
HGID laboratory	2492 (76.2%)	870 (63.4%)	
Other	777 (24.8%)	503 (36.6%)	
Ancestry , no. (%)			< 0.0001
European	1374 (42.0%)	960 (69.9%)	
Middle Eastern	483 (14.8%)	158 (11.5%)	
Admixed American	466 (14.3%)	109 (7.9%)	
North African	300 (9.2%)	24 (1.7%)	
South Asian	279 (8.5%)	36 (2.6%)	
Sub-Saharan African	234 (7.1%)	43 (3.1%)	
East Asian	133 (4.1%)	43 (3.1%)	

HGID Human Genetics of Infectious Diseases

^a Chi-squared tests were used to compare proportions, and *t* tests were used to compare the mean ages

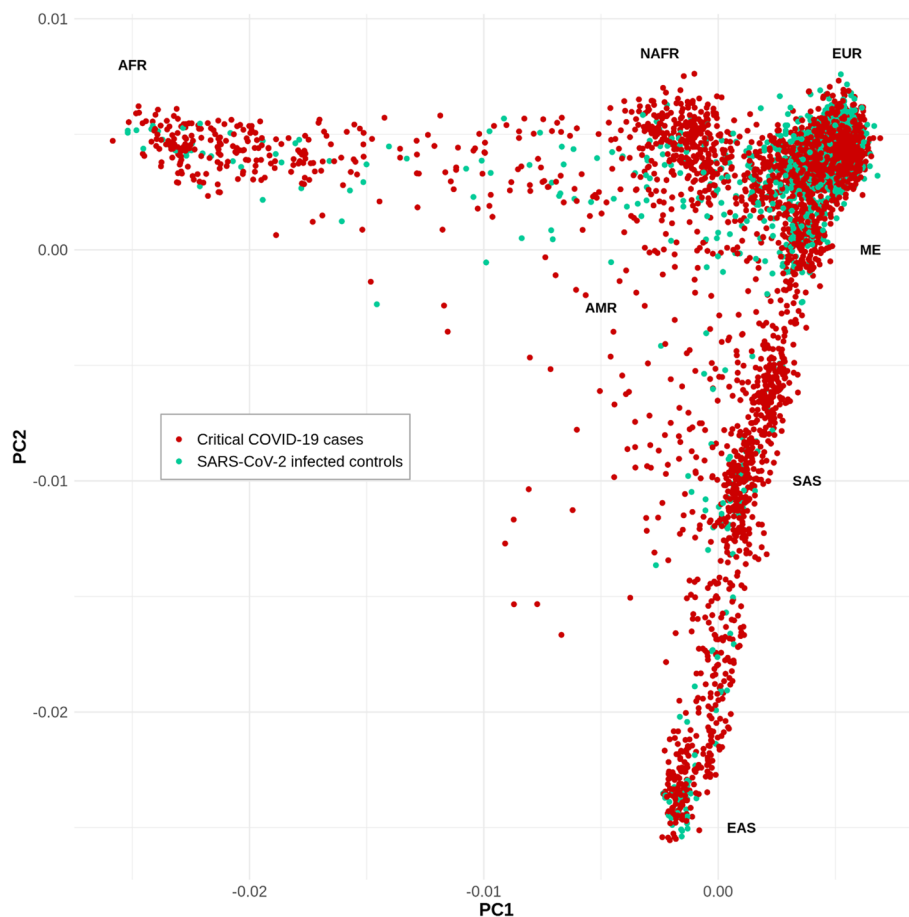


Fig. 2 Principal component analysis of patients with life-threatening COVID-19 (red) and SARS-CoV-2-infected controls (green). Principal component analysis (PCA) was performed with PLINK v1.9 software [40] on a pruned subset of ~14,600 exonic SNPs in linkage equilibrium (maximum r^2 value for linkage disequilibrium of 0.4 between pairs of SNPs) with a minor allele frequency (MAF) > 1%, call rate > 99% and P value for departure from Hardy–Weinberg equilibrium > 10^{-5} . Samples were of diverse ethnic origins, including European (EUR), admixed American (AMR), North African (NAFR), sub-Saharan African (AFR), Middle Eastern (ME), South Asian (SAS), and East Asian (EAS)

magnitude, the most significant gene, with 51 carriers (1.6%) of at least one rare (gnomAD AF < 0.01) missense or pLOF variant in patients versus two carriers (0.1%) in controls (OR = 8.41 [95% CI 1.9–35.5], $P = 8.95 \times 10^{-5}$) (Table 3). Most of the carriers were male, with only one carrier among the patients and one among the controls being female. The variants carried by the two controls were previously shown to be biochemically neutral [19, 30] (Additional file 2: Table S4). The 51 cases carried 33 different variants, 13 of which had been shown to be neutral; 16 were previously shown to be hypomorphic or amorphic [19, 30], and four were previously unknown. The four new variants were tested: one was found to be neutral and the other three were deleterious (Additional file 1: Fig S1). Restricting the analysis to biochemically proven LOF variants (bLOF) decreased the number of carriers (20 cases vs. 0 controls), but the association signal remained highly significant, with a much higher odds

ratio (OR = 27.68 [95% CI 1.5–528.7], $P = 1.08 \times 10^{-4}$) (Table 3). These findings confirm that *TLR7* is a critical COVID-19 susceptibility locus, responsible for 0.9% of critical cases in male patients.

Genome-wide gene-based analysis including common variants

Published GWAS identified a number of common variants associated with severe COVID-19 pneumonia [8, 10, 12, 55]. We then assessed the combined effect of common and rare candidate coding variants at the gene level, in a weighted burden approach [56], as detailed in the [Supplemental Methods](#). Briefly, for each individual, we calculated a genetic score by summing the number of minor alleles for each variant and weighting this sum by the frequency of the variant [57]. We then tested the association between this genetic score and case–control

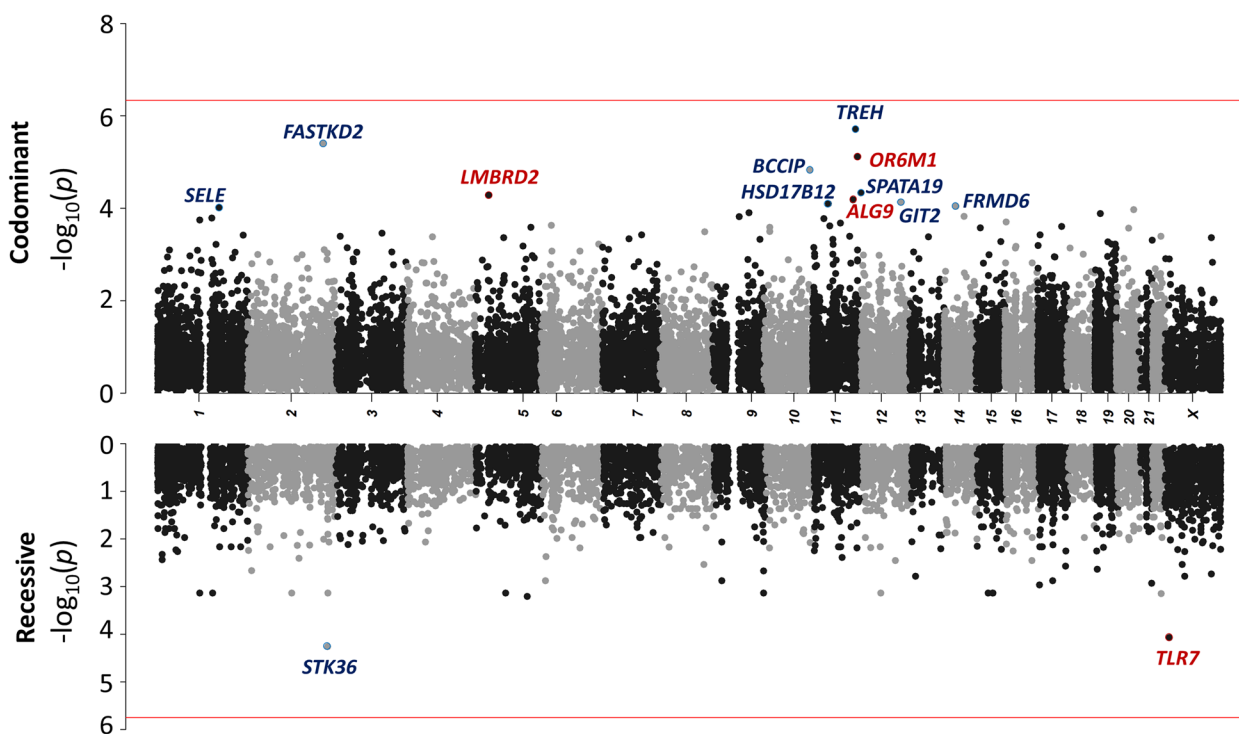


Fig. 3 Manhattan plot for genome-wide burden analysis under the co-dominant (top) and recessive (bottom) models. For each gene, the negative log-transformed p value of the joint analysis for the most significant variant set under a co-dominant (top) or recessive (bottom) model is plotted. For each gene, variant sets providing inconsistent results across the joint analysis, the trans-ethnic meta-analysis, and the trans-pipeline meta-analysis (i.e., $P < 0.001$ in the joint analysis and $P > 0.05$ in the trans-ethnic or trans-pipeline meta-analysis) were discarded. The red lines represent the significance threshold after Bonferroni correction to account for the total number of independent tests ($P = 4.61 \times 10^{-7}$ under a co-dominant model and 1.85×10^{-6} under a recessive model). The names of the top-ranked genes with a joint $P < 10^{-4}$ are shown in red for rare variants associated with an increase in the risk of critical COVID-19 and in blue otherwise

Table 2 Top results of the genome-wide burden analysis for rare pLOF variants increasing the risk of life-threatening COVID-19 under a co-dominant model

Chr	Gene	GnomAD AF threshold	No. carriers of at least one (no. homozygous) pLOF variant		Joint analysis		Trans-ethnic meta-analysis	Trans-pipeline meta-analysis
			Cases (n = 3269)	Controls (n = 1373)	OR[95%CI]	P value	P value	P value
14	<i>NPC2</i>	0.01	28 (0)	4 (0)	5.41[1.8–16.4]	5.8×10^{-4}	2.1×10^{-3}	3.3×10^{-4}
3	<i>DLEC1</i>	0.01	56 (0)	16 (0)	2.55[1.3–4.9]	3.6×10^{-3}	0.013	4.9×10^{-3}
13	<i>NEK5</i>	0.001	16 (0)	0 (0)	27.03[0.9–864.2]	4.0×10^{-3}	1.5×10^{-3}	0.011
5	<i>CCNI2</i>	0.01	19 (1)	1 (0)	7.15[1.2–43.1]	4.1×10^{-3}	4.1×10^{-3}	5.0×10^{-3}
22	<i>C22orf29</i>	0.001	13 (0)	0 (0)	15.6[0.8–315.8]	4.5×10^{-3}	7.9×10^{-3}	4.6×10^{-3}
20	<i>DLGAP4</i>	0.001	37 (0)	3 (0)	4.35[1.3–14.5]	4.8×10^{-3}	8.3×10^{-3}	0.011

Only genes with a P value $\leq 5 \times 10^{-3}$ in the joint analysis and P values < 0.05 in trans-ethnic and trans-pipeline meta-analyses are displayed
AF allele frequency

status in a logistic regression framework. As described above, we focused on pLOF only, pLOF and in-frame variants with $CADD > MSC$, or pLOF and in-frame variants without filtering on CADD score (Additional file 2:

Table S5). As in the analysis focusing on rare variants only, no gene reached genome-wide significance after correction for multiple testing in this analysis considering both rare and common variants. The top-ranked

Table 3 Top results of the genome-wide burden analysis for rare variants increasing the risk of life-threatening COVID-19 under a recessive model

Chr	Gene	Variant set	Type of variant	CADD > MSC ^a	GnomAD AF threshold	No. carriers of rare homo-/hemizygous variant	Joint analysis	Trans-ethnic meta-analysis	Trans-pipeline meta-analysis
						Cases (n = 3269)	Controls (n = 1373)	OR[95%CI]	P value
GW analysis									
X	TLR7	7	MISSLOF	FALSE	0.01	51	8.41 [1.9–35.5]	7.04×10^{-4}	2.66×10^{-4}
14	AHNAK2	5	MISSLOF	TRUE	0.001	37	4.45 [1.1–17.7]	2.15×10^{-3}	8.84×10^{-3}
Refined analysis on TLR7									
X	TLR7		bLOF	-	0.01	20	27.68[1.5–528.7]	1.1×10^{-4}	2.7×10^{-4}

Only genes with P values ≤ 0.01 in the joint analysis and P values < 0.05 in trans-ethnic and trans-pipeline meta-analyses are displayed
AF allele frequency

^a Combined Annotation Dependent Depletion (CADD) score [42] greater than the Mutation Significance Cut-off (MSC) for the corresponding gene. The MSC is defined for a given gene as the lower limit of the confidence interval (95%) of the CADD score of all its known pathogenic mutations [43]

gene, with consistent results across the joint analysis and the trans-ethnic and trans-pipeline meta-analyses, was *TREH*, with a protective effect against life-threatening COVID-19 of pLOF or nonsynonymous variants with a CADD score greater than the MSC (OR=0.85 [95%CI 0.78–0.91], $P=3.6 \times 10^{-6}$). Finally, we analyzed 20 candidate genes identified by GWAS for critical pneumonia in more detail [8, 10, 12, 55]. No significant association was detected for any of these genes (Additional file 2: Table S6), even with a relaxed Bonferroni threshold of 2.5×10^{-3} , accounting for the number of GWAS genes.

Enrichment in rare pLOF variants at 13 type I IFN-related influenza susceptibility loci

Following on from our initial analysis [15], we also performed a candidate pathway enrichment analysis focusing on the 13 genes involved in Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (IRF7)-dependent type I IFN immunity to influenza virus (*IFNAR1*, *IFNAR2*, *IRF3*, *IRF7*, *IRF9*, *IKBKG*, *STAT1*, *STAT2*, *TBK1*, *TICAM1*, *TLR3*, *TRAF3*, and *UNC93B1*) (Fig. 1). We confirmed the significant enrichment in rare (gnomAD AF < 10^{-3}) pLOF variants at the 13 loci in patients with critical COVID-19, with 34 carriers among patients versus six among controls (OR=3.70 [95% CI 1.7–9.5], $P=2.1 \times 10^{-4}$ under a co-dominant

model; Table 4). We also estimated this p value in a simulation study taking 13 loci randomly selected from a set of genes with similar pLI and CoNeS values (see Additional file 1: Supplemental Methods); we obtained an empirical p value of 3.7×10^{-4} . Our cohort included 551 patients and 314 controls already screened for pLOF variants of the 13 genes included in our previous study [15] (Additional file 2: Table S7). The exclusion of these 551 cases and 314 controls resulted in a similar conclusion of enrichment in rare pLOF at the 13 loci (OR=3.21 [95% CI 1.3–8.2], $P=5.97 \times 10^{-3}$) formally replicating our initial association. Significant replication was also observed in the trans-ethnic ($P=0.01$) and the trans-pipeline ($P=0.009$) analyses. We found that 31 of the 34 carriers of pLOF variants were heterozygous, and three were homozygous: one for a frameshift variant of *IRF7* described in a previous study [15], one for a previously reported deletion spanning 4394 base pairs in *IFNAR1* [16, 19], and one for a previously unknown deletion spanning 6624 base pairs of *IFNAR1* (Additional file 2: Table S8). All the biallelic pLOF variants were found in patients. Consequently, the OR for homozygous carriers (OR=15.79 [95%CI 1.4–2170.4], $P=0.02$) was higher than that for heterozygous carriers (OR=3.11 [95%CI 1.4–8.6], $P=5.2 \times 10^{-3}$), but both were significant.

Table 4 Enrichment analysis of rare pLOF/bLOF variants in genes involved in type I IFN immunity

Gene set	Cohort	Model	No. carriers		Joint analysis		Trans-pipeline meta-analysis P value	Trans-ethnic meta-analysis P value
			Cases	Controls	P value	OR[95%CI]		
13 genes ^a	Samples independent of [15] ^b	Co-dominant	25	5	5.97×10^{-3}	3.21 [1.3–8.2]	9.15×10^{-3}	0.01
13 genes	Full ^c	Co-dominant	34	6	2.13×10^{-4}	3.70 [1.7–9.5]	7.45×10^{-4}	6.52×10^{-4}
13 genes	Full	Heterozygous only ^d	31	6	5.21×10^{-3}	3.11 [1.3–8.6]	7.88×10^{-3}	5.98×10^{-3}
13 genes	Full	Recessive	3	0	0.02	15.79 [1.4–2170.4]	0.05	0.03
13 genes + <i>TYK2</i>	Full	Co-dominant	37	7	1.40×10^{-4}	3.30 [1.6–7.8]	5.77×10^{-4}	5.64×10^{-4}
13 genes + <i>TYK2</i>	Full	Heterozygous only	32	7	0.02	2.53 [1.1–6.6]	0.03	0.02
13 genes + <i>TYK2</i>	Full	Recessive	5	0	3.36×10^{-3}	19.65 [2.1–2635.4]	9.84×10^{-3}	0.03
13 genes + <i>TYK2</i> + bLOF <i>TLR7</i>	Full	Co-dominant	57	9	1.27×10^{-7}	3.82 [2.0–7.2]	1.99×10^{-7}	2.20×10^{-6}
13 genes + <i>TYK2</i> + bLOF <i>TLR7</i>	Full	Heterozygous only	32	9	0.04	2.27 [1.0–5.2]	0.04	0.02
13 genes + <i>TYK2</i> + bLOF <i>TLR7</i>	Full	Recessive	25	0	4.69×10^{-7}	39.19 [5.2–5037.01]	2.39×10^{-6}	6.66×10^{-5}
13 genes + <i>TYK2</i> + bLOF <i>TLR7</i> + BP variants	Full	Co-dominant	67	9	7.7×10^{-8}	4.40 [2.3–8.4]	3.5×10^{-8}	6.5×10^{-7}

^a *IFNAR1*, *IFNAR2*, *IRF3*, *IRF7*, *IRF9*, *IKBKG*, *STAT1*, *STAT2*, *TBK1*, *TICAM1*, *TLR3*, *TRAF3* and *UNC93B1*

^b 2718 patients and 1059 controls newly recruited and not screened in [15]

^c The full cohort includes 3269 patients and 1373 controls

^d In this model, only subjects with heterozygous variants are considered as carriers

Inclusion of *TYK2* and *TLR7* genes and branchpoint variants

Since the publication of the aforementioned study [15], AR *TYK2* deficiency has been reported in children with COVID-19 pneumonia [19]. We identified two patients homozygous for a rare pLOF variant of *TYK2* already described in a previous study [19] and one patient and one control heterozygous for a rare pLOF variant (Additional file 2: Table S8). Adding these patients to the analysis gave very similar results under a co-dominant model (OR = 3.30 [95% CI 1.6–7.8], $P = 1.4 \times 10^{-4}$) and strengthened the evidence for association under a recessive model (OR = 19.65 [95% CI 2.1–2635.4], $P = 3.4 \times 10^{-3}$) (Table 4). An analysis of the rare pLOF variants at these 14 loci plus the bLOF variants of *TLR7* revealed highly significant enrichment (OR = 3.82 [95% CI 2.0–7.2], $P = 1.3 \times 10^{-7}$ under a co-dominant model). The effect was stronger for homozygous/hemizygous carriers (OR = 39.19 [95% CI 5.2–5037.01], $P = 4.7 \times 10^{-7}$) than for heterozygous carriers (OR = 2.27 [95% CI 1.0–5.2], $P = 0.04$), and these two ORs were significantly different ($P = 0.008$). We further screened the full cohort of cases and controls for intronic branchpoint (BP) variants, which might potentially have a strong impact on splicing and be considered pLOF variants, in the 15 type I IFN-related genes, with our new tool BPHunter [39]. We identified six branchpoint (BP) variants (Additional file 2: Table S9) carried in heterozygous state by 10 additional cases and no controls. Adding these BP variants to the analysis of the 15 type I IFN-related loci under a co-dominant model further strengthened the association signal (OR = 4.40 [2.3–8.4], $P = 7.7 \times 10^{-8}$) (Table 4).

Age and sex stratified analysis of the 15 type I IFN-related loci

Advanced age is the strongest risk factor for life-threatening COVID-19. Male individuals are also at higher risk than female individuals. As for the main GWAS hits [58, 59], we performed an analysis stratified for age and sex for the 15 type I IFN-related loci. The analysis stratified for sex revealed a much stronger association signal in male than in female individuals, as expected given the X-linked recessive mode of inheritance of *TLR7* deficiency (Additional file 2: Table S10). Nevertheless, the enrichment in rare pLOF variants at the 15 loci in female subjects remained significant under a co-dominant model ($P = 0.02$) and a recessive model ($P = 0.05$). The addition of the BP variants strengthened the association signal in female subjects under a co-dominant model ($P = 3.7 \times 10^{-3}$). In the analysis stratified for age, we assigned the cases to two age groups (under 60 years of age vs. 60 years and over), which we compared with all controls. We used an age cut-off of 60 years, which

was close to the median age of the cases, in accordance with the analyses performed in [7, 59]. The age stratified analysis revealed a strong impact of age, the genetic effect being restricted to younger cases (OR = 4.65 [2.4–9.0], $P = 2.2 \times 10^{-9}$, Additional file 2: Table S10). Accordingly, the 67 patients with critical COVID-19 carrying a rare pLOF or bLOF variant of one of the 15 genes were significantly younger than the remaining 3202 patients in the cohort (mean age [SD] in years: 43.68 [19.4] vs. 56.0 [17.3] years; $P = 2.3 \times 10^{-6}$), consistent with our previous reports that IEIs conferring a predisposition to life-threatening COVID-19 are more frequent in young patients [1, 15, 30]. Moreover, the homozygous/hemizygous carriers were significantly younger than the heterozygous carriers (35.2 [20.3] vs. 48.7 [17.1] years, $P = 0.008$, Additional file 1: Fig S2). Overall, these results clearly demonstrate that the search for additional rare variants conferring a strong predisposition to life-threatening COVID-19 benefits from focus on younger patients.

In-frame nonsynonymous variants at the 15 loci

We further screened our cohort for rare in-frame nonsynonymous variants with a gnomAD AF $< 10^{-3}$ at these type I IFN-related susceptibility loci. For the 13 initial loci, the enrichment disappeared when in-frame nonsynonymous variants were added to pLOF variants under a co-dominant model (OR = 1.08 [95% CI 0.9–1.3], $P = 0.42$) (Additional file 2: Table S11), whereas a non-significant trend persisted under the recessive model (OR = 5.02 [95% CI 0.7–52.7], $P = 0.06$). Focusing exclusively on in-frame variants decreased the strength of this trend considerably, with only eight homozygous carriers among patients and one among controls (OR = 1.14 [0.2–912.5], $P = 0.68$). Adding *TYK2* variants led to similar conclusions (Additional file 2: Table S11). We then added *TLR7* variants and considered the 15 loci together. Under a co-dominant model, the enrichment became non-significant when in-frame nonsynonymous variants were added (OR = 1.15 [1.0–1.4], $P = 0.09$), but enrichment remained significant under a recessive model (OR = 6.54 [2.4–24.8], $P = 5.3 \times 10^{-6}$; Additional file 2: Table S11). In analyses considering only rare in-frame homozygous/hemizygous nonsynonymous variants, the effect size was smaller, but the enrichment remained significant (OR = 3.52 [1.3–13.3], $P = 2.8 \times 10^{-3}$). In total, 41 patients carried a rare homozygous/hemizygous in-frame nonsynonymous variant at one of the 15 loci, and 16 of these variants (carried by 16 patients) were *TLR7* in-frame variants already shown to be bLOF. After excluding the *TLR7* bLOF variants, there was no residual significant enrichment in rare in-frame nonsynonymous variants in patients relative to controls, whatever the genetic model considered.

Discussion

In this exome-wide gene burden analysis for rare variants underlying critical COVID-19, no gene reached GW statistical significance after accounting for multiple testing. We used simulations to determine the power of our sample to detect an association at the 2.5×10^{-6} exome-wide significance threshold (Additional file 1: Fig S3); our sample had a power of more than 80% for detecting alleles with a carrier frequency of 5×10^{-3} in the general population and a relative risk of critical COVID-19 of at least 6. These results are consistent with those of two previous large exome-wide studies including more than 1000 critical cases and thousands of population-based controls that found no statistically significant autosomal gene burden associations at stringent significance thresholds accounting for the number of phenotypes and variant sets analyzed [11, 21]. However, under a recessive model, the strongest association—albeit not statistically significant at GW level—was obtained with the X-linked *TLR7* gene, for which association has consistently been reported across studies [21, 22, 30, 32], reaching the less conservative exome-wide significance threshold of 2.5×10^{-6} in some of these previous studies [21, 22]. It should be stressed that stringent correction for multiple testing, while necessary to avoid false positives, is a conservative strategy, and that the lack of formal statistical significance at a GW level does not preclude biological causality and medical significance. The burden of proof can be provided experimentally via biochemical, virological, and immunological experiments, as our previous studies of *TLR7* in which we showed that biochemically deleterious *TLR7* variants blunted the pDC-dependent sensing of SARS-CoV-2 and induction of type I IFN, thereby accounting for ~1% of critical pneumonia cases in men [30]. Additional genes may be found by restricting the association analysis to variants experimentally proven to be deleterious.

This analysis also confirms our previous findings of an enrichment in rare pLOF variants of 13 genes involved in TLR3- and IRF7-dependent type I IFN immunity to seasonal influenza virus in critical cases relative to controls with mild/asymptomatic infection [15]. These results were strengthened by the addition of *TYK2*, which was recently shown to underlie severe COVID-19 [19, 20], and *TLR7*, especially under a recessive model. We found that homozygous/hemizygous carriers of rare pLOF or bLOF variants at the 15 loci had a significantly higher risk of life-threatening COVID-19 than heterozygotes. This is consistent with the generally higher clinical penetrance of recessive than dominant IEI [1]. Overall, 1.7% of the patients with life-threatening COVID-19 carried a rare pLOF or bLOF variant at one of the 15 loci, these variants being homozygous/hemizygous in 0.8% of cases.

Adding the BP variants at the 15 loci increased the proportion of carriers among patients with life-threatening COVID-19 to 2.1%. One of the *STAT2* BP variants identified (2:56749159:T>A) has already been validated experimentally [39], but the effects of the five other BP variants identified require confirmation. The study of in-frame nonsynonymous variants might also increase this proportion, but would require the experimental characterization of all these variants. Indeed, in analyses restricted to rare in-frame nonsynonymous variants, we detected no significant enrichment in patients relative to controls. This result is not surprising, as we showed in a previous study [15] that less than 15% of the rare in-frame nonsynonymous variants at the 13 loci carried by cases initially studied were bLOF variants, whereas all the pLOF variants were found to be bLOF. Similar results were obtained for *TLR7*, with only 10 of 108 (9.2%) in-frame nonsynonymous variants observed in gnomAD being bLOF [30]. This high proportion of neutral variants strongly affects the power of burden tests and highlights the need for the experimental characterization of variants.

We also showed that patients carrying rare pLOF or bLOF variants of these 15 type I IFN-related genes were significantly younger than the remaining patients (mean age [SD] in years: 43.3 [20.3] vs. 56.0 [17.3] years). This was particularly true for homozygous/hemizygous carriers of rare pLOF or bLOF variants (35.2 [20.3] years), potentially accounting for the lack of replication of this finding by other studies including older patients [11, 21–23]. Consistent with this result, we recently found that ~10% of children hospitalized for COVID-19 pneumonia carry recessive inborn errors of type I IFN immunity [19]. In addition, older patients are more likely to carry auto-Abs against type I IFN, and unlike previous studies, we excluded patients carrying such antibodies from this analysis. None of the 234 patients with critical COVID-19 excluded from this study due to the presence of auto-Abs against type I IFN carried a rare pLOF variant of the 15 genes. Hence, samples in which the vast majority of patients are over the age of 60 years and of unknown status for auto-Abs against type I IFNs would have a much lower power to identify these rare inborn errors of type I IFN immunity.

Conclusions

Rare autosomal inborn errors of type I IFN-dependent immunity to influenza viruses can underlie critical forms of COVID-19, especially in subjects below 60 years of age, in addition to X-linked *TLR7* deficiency. The search for additional rare mutations conferring a strong predisposition to life-threatening COVID-19 should focus on young patients with critical COVID-19 without auto-Abs against type I IFNs.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13073-023-01173-8>.

Additional file 1: Supplementary Methods. **Fig S1.** 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 4 *TLR7* variants found in our cohort. After 24 h, transfected cells were left untreated or were treated by incubation with 1 µg/mL R848 for 24 h. 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. **Fig S2.** Age distribution as boxplot and violin plot of the critical COVID-19 cases according to the carrier status of pLOF/bLOF at 15 type I IFN-related loci. Mean age of the patients for each category is shown in red. WT was used to compare the means, showing a significant difference between non-carriers and carriers of heterozygous or homozygous/hemizygous variants ($P = 2.2 \times 10^{-6}$) and between heterozygous carriers and homozygous/hemizygous carriers ($P = 0.008$). **Fig S3.** Empirical power of our sample to detect an association at the 2.5×10^{-6} exome-wide significance threshold for various relative risks and proportion of carriers of at least one disease causing variant in the general population (PD), as estimated by simulation study ($N = 1000$ replicates).

Additional file 2: Table S1. Number of genes tested and Genomic inflation factor for each model and variant set. **Table S2.** Complete results of the genome-wide burden joint analysis, trans-pipeline meta-analysis and trans-ethnic meta-analysis on rare variants. **Table S3.** Best results of the genome-wide burden analysis on rare variants under a co-dominant and dominant model. **Table S4.** *TLR7* homozygous and hemizygous variants ($AF < 0.01$). **Table S5.** Results of the genome-wide burden analysis on common and rare variants under a co-dominant model. **Table S6.** Results of the genome-wide burden analyses for the candidate genes identified by GWAS under co-dominant model. **Table S7.** Characteristics of patients and controls in the full sample and according to the inclusion in the Zhang Q. et al., Science 2020 paper. **Table S8.** Carriers of rare pLOF/bLOF variants in genes involved in type I IFN immunity to influenza virus. **Table S9.** Branchpoint variants identified by BPHunter and characteristics of the carriers. **Table S10.** Age and sex stratified analysis for the 15 type I IFN-related loci. **Table S11.** Enrichment analysis of rare variants, including missense and inframe variants, in genes involved in type I IFN immunity in the full cohort of 3269 cases and 1373 controls. **Table S12.** pLI and CoNeS distribution of the analyzed genes.

Acknowledgements

We thank the patients and their families for agreeing to participate in our research. We thank all members of the consortia listed below:

Members of COVID Human Genetic Effort: Laurent Abel¹, Alessandro Aiuti², Saleh Al-Muhsen³, Fahd Al-Mulla⁴, Mark S. Anderson⁵, Evangelos Andreaskos⁶, Andrés A. Arias⁷, Hagit Baris Feldman⁸, Alexandre Belot⁹, Catherine M. Biggs¹⁰, Dusan Bogunovic¹¹, Alexandre Bolze¹², Anastasiia Bondarenko¹³, Ahmed A. Bousfiha¹⁴, Petter Brodin¹⁵, Yenan Bryceson¹⁶, Carlos D. Bustamante¹⁷, Manish J. Butte¹⁸, Giorgio Casari¹⁹, Samya Chakravorty²⁰, John Christodoulou²¹, Antonio Condino-Neto²², Stefan N. Constantinescu²³, Megan A. Cooper²⁴, Clifton L. Dalgard²⁵, Murkesh Desai²⁶, Beth A. Drolet²⁷, Jamila El Baghdadi²⁸, Sara Espinosa-Padilla²⁹, Jacques Fellay³⁰, Carlos Flores³¹, José Luis Franco⁷, Antoine Froidure³², Peter K. Gregersen³³, Filomeen Haerynck³⁴, David Hagin³⁵, Rabih Halwani³⁶, Lennart Hammarström³⁷, James R. Heath³⁸, Sarah E. Henrickson³⁹, Elena W. Y. Hsieh⁴⁰, Eystein Husebye⁴¹, Kohsuke Imai⁴², Yuval Itan⁴³, Erich D. Jarvis⁴⁴, Timokratis Karamitros⁴⁵, Kai Kisan⁴⁶, Cheng-Lung Ku⁴⁷, Yu-Lung Lau⁴⁸, Yun Ling⁴⁹, Carrie L. Lucas⁵⁰, Tom Maniatis⁵¹, Davood Mansouri⁵², László Maródi⁵³, Isabelle Meys⁵⁴, Joshua D. Milne⁵⁵, Kristina Mironska⁵⁶, Trine H. Mogensen⁵⁷, Tomohiro Morio⁵⁸, Lisa F. P. Ng⁵⁹, Luigi D. Notarangelo⁶⁰, Antonino Novelli⁶¹, Giuseppe Novelli⁶², Cliona O'Farrelly⁶³, Satoshi Okada⁶⁴, Tayfun Ozcelik⁶⁵, Qiang Pan-Hammarström³⁷, Rebeca Perez de Diego⁶⁶, Anna M. Planas⁶⁷, Carolina Prando⁶⁸, Aurora Pujol⁶⁹, Lluís Quintana-Murci⁷⁰, Laurent Renia⁵⁹, Igor Resnick⁷¹, Carlos Rodríguez-Gallego⁷², Vanessa Sanchez-Shimizu⁷³, Anna Sediva⁷⁴, Mikko R. J. Seppänen⁷⁵, Mohammed Shahronei⁷⁶, Anna Shcherbina⁷⁷, Ondrej Slaby⁷⁸, Andrew L. Snow⁷⁹, Pere Soler-Palacín⁸⁰,

Andrés N. Spaan⁸¹, Ivan Tancevski⁸², Stuart G. Tangye⁸³, Ahmad About Tayoun⁸⁴, Sathishkumar Ramaswamy⁸⁴, Stuart E. Turvey⁸⁵, Furkan Uddin⁸⁶, Mohammed J. Uddin⁸⁷, Diederik van de Beek⁸⁸, Donald C. Vinh⁸⁹, Horst von Bernuth⁹⁰, Mayana Zatz⁹¹, Pawel Zawadzki⁹², Helen C. Su⁶⁰, Jean-Laurent Casanova⁹³
¹INSERM U1163, University of Paris, Imagine Institute, Paris, France. ²San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, and Vita Salute San Raffaele University, Milan, Italy. ³Immunology Research Laboratory, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. ⁴Dasman Diabetes Institute, Department of Genetics and Bioinformatics, Dasman, Kuwait. ⁵Diabetes Center, University of California, San Francisco, San Francisco, CA, USA. ⁶Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ⁷Group of Primary Immunodeficiencies, Universidad de Antioquia UdeA, Medellín, Colombia. ⁸Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁹Pediatric Nephrology, Rheumatology, Dermatology, HFME, Hospices Civils de Lyon, National Referee Centre RAISE, and INSERM U1111, Université de Lyon, Lyon, France. ¹⁰Department of Pediatrics, British Columbia Children's Hospital, University of British Columbia, Vancouver, BC, Canada. ¹¹Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹²Helix, San Mateo, CA, USA. ¹³Shupyk National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹⁴Clinical Immunology Unit, Department of Pediatric Infectious Disease, CHU Ibn Rushd and LICIA, Laboratoire d'Immunologie Clinique, Inflammation et Allergie, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco. ¹⁵SciLifeLab, Department Of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden. ¹⁶Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden. ¹⁷Stanford University, Stanford, CA, USA. ¹⁸Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics and the Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, Los Angeles, CA, USA. ¹⁹Clinical Genomics, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy. ²⁰Department of Pediatrics and Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA. ²¹Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia. ²²Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil. ²³de Duve Institute and Ludwig Cancer Research, Brussels, Belgium. ²⁴Washington University School of Medicine, St. Louis, MO, USA. ²⁵Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ²⁶Bai Jerbai Wadia Hospital for Children, Mumbai, India. ²⁷School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. ²⁸Genetics Unit, Military Hospital Mohamed V, Rabat, Morocco. ²⁹Instituto Nacional de Pediatría (National Institute of Pediatrics), Mexico City, Mexico. ³⁰School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ³¹Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Faculty of Health Sciences, University of Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. ³²Pulmonology Department, Cliniques Universitaires Saint-Luc; Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium. ³³Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA. ³⁴Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPiG), PID Research Laboratory, Jeffrey Modell Diagnosis and Research Center, Ghent University Hospital, Ghent, Belgium. ³⁵Genetics Institute Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. ³⁶Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates. ³⁷Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. ³⁸Institute for Systems Biology, Seattle, WA, USA. ³⁹Department of Pediatrics, Division of Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁰Departments of Pediatrics, Immunology and Microbiology, University of Colorado, School of Medicine, Aurora, CO, USA. ⁴¹Department of Medicine, Haukeland University Hospital, Bergen, Norway. ⁴²Department of Community Pediatrics, Perinatal and Maternal

Medicine, Tokyo Medical and Dental University (TMDU), Tokyo, Japan. ⁴³Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁴⁴Laboratory of Neurogenetics of Language and Howard Hughes Medical Institute, Rockefeller University, New York, NY, USA. ⁴⁵Bioinformatics and Applied Genomics Unit, Hellenic Pasteur Institute, Athens, Greece. ⁴⁶Molecular Pathology, Department of Biomedicine, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia. ⁴⁷Chang Gung University, Taoyuan County, Taiwan. ⁴⁸Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong, China. ⁴⁹Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. ⁵⁰Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA. ⁵¹Columbia University Zuckerman Institute, New York, NY, USA. ⁵²Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRIITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁵³Primary Immunodeficiency Clinical Unit and Laboratory, Department of Dermatology, Venereology and Dermatocology, Semmelweis University, Budapest, Hungary. ⁵⁴Department of Pediatrics, University Hospitals Leuven; KU Leuven, Department of Microbiology, Immunology and Transplantation; Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium. ⁵⁵Department of Pediatrics, Columbia University Irving Medical Center, New York, NY, USA. ⁵⁶University Clinic for Children's Diseases, Department of Pediatric Immunology, Medical Faculty, University "St. Cyril and Methodij", Skopje, North Macedonia. ⁵⁷Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁵⁸Tokyo Medical and Dental University Hospital, Tokyo, Japan. ⁵⁹A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore, Singapore; Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore, Singapore. ⁶⁰National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. ⁶¹Laboratory of Medical Genetics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. ⁶²Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy. ⁶³Comparative Immunology Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland. ⁶⁴Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ⁶⁵Department of Molecular Biology and Genetics, Bilkent University, Bilkent-Ankara, Turkey. ⁶⁶Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ⁶⁷IBB-CSIC, IDIBAPS, Barcelona, Spain. ⁶⁸Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain; Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Barcelona, Spain. ⁷⁰Human Evolutionary Genetics Unit, CNRS U2000, Institut Pasteur, Paris, France; Human Genomics and Evolution, Collège de France, Paris, France. ⁷¹University Hospital St. Marina, Varna, Bulgaria. ⁷²Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁷³Department of Paediatric Infectious Diseases and Virology, Imperial College London, London, UK; Centre for Paediatrics and Child Health, Faculty of Medicine, Imperial College London, London, UK. ⁷⁴Department of Immunology, Second Faculty of Medicine Charles University, V Úvalu, University Hospital in Motol, Prague, Czech Republic. ⁷⁵Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Rare Diseases Center and Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. ⁷⁶Saeed Pathobiology and Genetics Lab, Tehran, Iran; Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. ⁷⁷Department of Immunology, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia. ⁷⁸Central European Institute of Technology and Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czech Republic. ⁷⁹Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁸⁰Pediatric Infectious Diseases and Immunodeficiencies Unit, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. ⁸¹St. Giles Laboratory of Human Genetics

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

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

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

Members of COVID Clinicians: Jorge Abad¹, Giulia Accordino², Cristian Achille³, Sergio Aguilera-Albesa⁴, Aina Aguiló-Cucurull⁵, Alessandro Aiuti⁶, Esra Akyüz Özkan⁷, İlad Alavi Darazam⁸, Jonathan Antonio Roblero Albuire⁹, Juan C. Aldave¹⁰, Miquel Alfonso Ramos¹¹, Taj Ali Khan¹², Anna Aliberti¹³, Seyed Alireza Nadji¹⁴, Gulsum Alkan¹⁵, Suzan A. Alkhatir¹⁶, Jerome Allardet-Servent¹⁷, Luis M. Allende¹⁸, Rebeca Alonso-Arias¹⁹, Mohammed S. Alshahrani²⁰, Laia Alsina²¹, Marie-Alexandra Alyanikian²², Blanca Amador Borrero²³, Zahir Amoura²⁴, Arnau Antolí²⁵, Romain Arrestier²⁶, Mélodie Aubert²⁷, Teresa Auguet²⁸, Iryna Avramenko²⁹, Gökhan Aytekin³⁰, Axelle Azot³¹, Seiamak Bahram³², Fanny Bajolle³³, Fausto Baldanti³⁴, Aurélie Baldolli³⁵, Maitte Ballester³⁶, Hagit Baris Feldman³⁷, Benoit Barrou³⁸, Federica Barzaghi³⁹, Sabrina Basso³⁹, Gulsum İclal Bayhan⁴⁰, Alexandre Belot⁴¹, Lilianna Bezrodnik⁴², Agurtzane Bilbao⁴³, Geraldine Blanchard-Rohner⁴⁴, Ignacio Blanco⁴⁵, Adeline Blandin-ières⁴⁶, Daniel Blázquez-Gamero⁴⁷, Alexandre Bleibtreu⁴⁸, Marketa Bloomfield⁴⁹, Mireia Bolívar-Prados⁵⁰, Anastasia Bondarenko⁵¹, Alessandro Borghesi⁵², Raphael Borie⁵², Elisabeth BotdHo-Nevers⁵³, Ahmed A. Bousfiha⁵⁴, Aurore Bousquet⁵⁵, David Boutolleau⁵⁶, Claire Bouvattier⁵⁷, Oksana Boyarchuk⁵⁸, Juliette Bravais⁵⁹, M. Luisa Briones⁶⁰, Marie-Eve Brunner⁶¹, Raffaele Bruno⁶², Maria Rita P. Bueno⁶³, Huda Bukhari⁶⁴, Jacinta Bustamante⁶³, Juan José Cáceres Agra⁶⁵, Ruggero Capra⁶⁶, Raphael Carapito⁶⁷, Maria Carrabba⁶⁸, Giorgio Casari⁶, Carlos Casasnovas⁶⁹, Marion Caseris⁷⁰, Irene Cassaniti³⁴, Martin Castelle⁷¹, Francesco Castelli⁷², Martin Castillo de Vera⁷³, Mateus V. Castro⁶³, Emilie Catherinot⁷⁴, Jale Bengi Celik⁷⁵, Alessandro Ceschi⁷⁶, Martin Chalumeau⁷⁷, Bruno Charbit⁷⁸, Matthew P. Cheng⁷⁹, Pèrè Clavé⁵⁰, Bonaventura Clotet⁸⁰, Anna Codina⁸¹, Yves Cohen⁸², Roger Colobran⁸³, Cloé Comarmond⁸⁴, Alain Combes⁸⁵, Patrizia Comolli³⁹, Angelo G. Corsico², Betul Sozeri⁸⁶, Taner Coşkun⁸⁶, Aleksandar Cvetkovski⁸⁷, Cyril Cyrus⁸⁸, David Dalmat⁸⁹, François Danion⁹⁰, David Ross Darley⁹¹, Vincent Das⁹², Nicolas Dauby⁹³, Stéphane Dauger⁹⁴, Paul De Munter⁹⁵, Loïc de Pontual⁹⁶, Amin Dehban⁹⁷, Geoffroy Delplançat⁹⁸, Alexandre Demoule⁹⁹, Isabelle Desguerre¹⁰⁰, Antonio Di Sabatino¹⁰¹, Jean-Luc Diehl¹⁰², Stephanie Dobbelaere¹⁰³, Elena Domínguez-Garrido¹⁰⁴, Clément Dubost¹⁰⁵, Olov Ekwall¹⁰⁶, Şefika Elmas Bozdemir¹⁰⁷, Marwa H. Elnagdy¹⁰⁸, Melike Emiroglu¹⁵, Akifumi Endo¹⁰⁹, Emine Hafize Erendiz¹¹⁰, Selma Erol Aytekin¹¹¹, Maria Pilar Etxart Lasa¹¹², Romain Euvrard¹¹³,

- Giovanna Fabio⁶⁸, Laurence Faivre¹¹⁴, Antonin Falck¹¹⁵, Muriel Fartoukh¹¹⁶, Morgane Faure¹¹⁷, Miguel Fernandez Arquer¹¹⁸, Ricard Ferrer¹¹⁹, Jose Ferreres¹²⁰, Carlos Flores¹²¹, Bruno Francois¹²², Victoria Fumadó¹²³, Kitty S. C. Fung¹²⁴, Francesca Fusco¹²⁵, Alenka Gagro¹²⁶, Blanca Garcia Solis¹²⁷, Pierre Garçon¹²⁸, Pascale Gaussem¹²⁸, Zeynep Gayretli¹²⁹, Juana Gil-Herrera¹³⁰, Laurent Gilardin¹³¹, Audrey Giraud Gatineau¹³², Mònica Girona-Alarcón¹³³, Karen Alejandra Cifuentes Godínez¹³⁴, Jean-Christophe Goffard¹³⁵, Nacho Gonzales¹³⁶, Luis I. Gonzalez-Granado¹³⁷, Rafaela González-Montelongo¹³⁸, Antoine Guerder¹³⁹, Belgün Gülhan¹⁴⁰, Victor Daniel Gumucio¹⁴¹, Leif Gunnar Hanitsch¹⁴², Jan Gunst¹⁴³, Marta Gut¹⁴⁴, Jérôme Hadjadj¹⁴⁵, Filomeen Haerynck¹⁴⁶, Rabih Halwani¹⁴⁷, Lennart Hammarström¹⁴⁸, Selda Hancerli¹⁴⁹, Tetyana Hariyan¹⁵⁰, Nevin Hatipoglu¹⁵¹, Deniz Heppckan¹⁵², Elisa Hernandez-Brito¹⁵³, Po-ki Ho¹⁵⁴, María Soledad Holanda-Peña¹⁵⁵, Juan P. Horcajada¹⁵⁶, Sami Hraiech¹⁵⁷, Linda Humbert¹⁵⁸, Ivan F. N. Hung¹⁵⁹, Alejandro D. Iglesias¹⁶⁰, Antonio Iñigo-Campos¹³⁸, Matthieu Jamme¹⁶¹, María Jesús Arranz⁸⁹, Marie-Thérèse Jimeno¹⁶², Iolanda Jordan¹³³, Saliha Kanik Yüsek¹⁶³, Yalcin Burak Kara¹⁶⁴, Aydin Karahan¹⁶⁵, Adem Karbuz¹⁶⁶, Kadriye Kart Yasar¹⁶⁷, Ozgur Kasapcopur¹⁶⁸, Kenichi Kashimada¹⁶⁹, Sevgi Keles¹¹¹, Yasemin Kendir Demirkol¹⁷⁰, Yasutoshi Kido¹⁷¹, Can Kizil¹⁷², Ahmet Osman Kılıç¹⁷³, Adam Koentz¹⁷⁴, Antonia Koutsoukou¹⁷⁵, Zbigniew J. Król¹⁷⁶, Hatem Ksouri¹⁷⁷, Paul Kuper¹⁷⁸, Arthur M. C. Kwan¹⁷⁹, Yat Wah M. Kwan¹⁸⁰, Janette S. Y. Kwok¹⁸¹, Jean-Christophe Lagier¹⁸², David S. Y. Lam¹⁸³, Vicky Lampropoulou¹⁸⁴, Fanny Lanternier¹⁸⁵, Yu-Lung Lau¹⁸⁶, Fleur Le Bourgeois⁹⁴, Yee-Sin Leo¹⁸⁷, Rafael Leon Lopez¹⁸⁸, Daniel Leung¹⁸⁶, Michael Levin¹⁸⁹, Michael Levy⁹⁴, Romain Lévy³³, Zhi Li⁷⁸, Daniele Lillieri³⁴, Edson Jose Adrian Bolanos Lima¹⁹⁰, Agnes Linglart¹⁹¹, Eduardo López-Collazo¹⁹², José M. Lorenzo-Salazar³⁸, Céline Louapre¹⁹³, Catherine Lubetzki¹⁹³, Kwok-Cheung Lung¹⁹⁴, Charles-Edouard Luyt¹⁹⁵, David C. Lye¹⁹⁶, Cynthia Magnone¹⁹⁷, Davood Mansouri¹⁹⁸, Enrico Marchioni¹⁹⁹, Carola Marioli², Majid Marjani²⁰⁰, Laura Marques²⁰¹, Jesus Marquez Pereira²⁰², Andrea Martín-Nalda²⁰³, David Martínez Pueyo²⁰⁴, Javier Martínez-Picado²⁰⁵, Iciar Marzana²⁰⁶, Carmen Mata-Martínez²⁰⁷, Alexis Mathian²⁴, Larissa R. B. Matos⁶³, Gail V. Matthews²⁰⁸, Julien Mayaux²⁰⁹, Raquel McLaughlin-García²¹⁰, Philippe Meersseman²¹¹, Jean-Louis Mège²¹², Armand Mekontso-Dessap²¹³, Isabelle Melki¹¹⁵, Federica Meloni², Jean-François Meritet²¹⁴, Paolo Merlani²¹⁵, Özge Metin Akcan²¹⁶, Isabelle Meys²¹⁷, Mehdi Mezidi²¹⁸, Isabelle Migeotte²¹⁹, Maude Millereux²²⁰, Matthieu Million²²¹, Tristan Mirault²²², Clotilde Mircher²²³, Mehdi Mirsaedi²²⁴, Yoko Mizoguchi²²⁵, Bhavi P. Modi²²⁶, Francesco Mojoli¹³, Elsa Moncomble²²⁷, Abián Montesdeoca Melián²²⁸, Antonio Morales Martínez²²⁹, Francisco Morandeira²³⁰, Pierre-Emmanuel Morange²³¹, Clémentine Mordacq¹⁵⁸, Guillaume Morelle²³², Stéphane J. Mouly²³³, Adrián Muñoz-Barrera¹³⁸, Cyril Nafati²³⁴, Shintaro Nagashima²³⁵, Yu Nakagama¹⁷¹, Bénédicte Neven²³⁶, João Farelle Neves²³⁷, Lisa F. P. Ng²³⁸, Yuk-Yung Ng²³⁹, hubert Nielly¹⁰⁵, Yeray Novoa Medina²¹⁰, Esmeralda Nuñez Cuadros²⁴⁰, Semsî Nur Karabela¹⁶⁷, J. Gonzalo Ocejón-Vinyals²⁴¹, Keisuke Okamoto¹⁰⁹, Mehdi Oualha³³, Amani Ouedrani²², Tayfun Özçelik²⁴², Aslinur Ozkaya-Parlakay¹⁴⁰, Michele Pagani¹³, Qiang Pan-Hammarström¹⁴⁸, Maria Papadaki²⁴³, Christophe Parizot²⁰⁹, Philippe Parola²⁴⁴, Tiffany Pascreau²⁴⁵, Stéphane Paul²⁴⁶, Estela Paz-Artal²⁴⁷, Sigifredo Pedraza²⁴⁸, Nancy Carolina González Pellecer¹³⁴, Silvia Pellegrini²⁴⁹, Rebeca Pérez de Diego¹²⁷, Xosé Luis Pérez-Fernández¹⁴¹, Aurélien Philippe²⁵⁰, Quentin Philippot¹¹⁶, Adrien Picod²⁵¹, Marc Pineton de Chambrun⁸⁵, Antonio Piralla³⁴, Laura Planas-Serra²⁵², Dominique Ploin²⁵³, Julien Poissy²⁵⁴, Géraldine Poncelet⁷⁰, Garyphallia Poulakou¹⁷⁵, Marie S. Pouletty²⁵⁵, Persia Pourshahnazar²⁵⁶, Jia Li Qiu-Chen²⁵⁷, Paul Quenrter²⁰⁹, Thomas Rambaud²⁵⁸, Didier Raoult²¹², Violette Raoult²⁵⁹, Anne-Sophie Rebillat²²³, Claire Redin²⁶⁰, Léa Resmini²⁶¹, Pilar Ricart²⁶², Jean-Christophe Richard²⁶³, Raúl Rigo-Bonnin²⁶⁴, Nadia rivet⁴⁶, Jacques G. Rivière²⁶⁵, Gemma Rocamora-Blanch²⁵, Mathieu P. Rodero²⁶⁶, Carlos Rodríguez²⁶⁷, Luis Antonio Rodríguez¹⁹⁰, Carlos Rodríguez-Gallego²⁶⁸, Agustí Rodríguez-Palmero²⁶⁹, Carolina Soledad Romero²⁷⁰, Anya Rothenbuhler²⁷¹, Damien Roux²⁷², Nikoletta Rovina¹⁷⁵, Flore Rozenberg²⁷³, Yvon Ruch⁹⁰, Montse Ruiz²⁷⁴, María Yolanda Ruiz del Prado²⁷⁵, Juan Carlos Ruiz-Rodríguez¹¹⁹, Joan Sabater-Riera¹⁴¹, Kai Saks²⁷⁶, Maria Salagianni¹⁸⁴, Oliver Sanchez²⁷⁷, Adrián Sánchez-Montalva²⁷⁸, Silvia Sánchez-Ramón²⁷⁹, Laire Schidrowski²⁸⁰, Agatha Schluter²⁵², Julien Schmidt²⁸¹, Matthieu Schmidt²⁸², Catharina Schuetz²⁸³, Cyril E. Schweitzer²⁸⁴, Francesco Scolari²⁸⁵, Anna Sediva²⁸⁶, Luis Seijo²⁸⁷, Analia Gisela Seminario⁴², Damien Sene²³, Piseth Seng²²¹, Sevtap Senoglu¹⁶⁷, Mikko Seppänen²⁸⁸, Alex Serra Llovich²⁸⁹, Mohammad Shahrooei⁹⁷, Anna Shcherbina²⁹⁰, Virginie Siguret²⁹¹, Eleni Siouti²⁹², David M. Smadja²⁹³, Nikaia Smith⁷⁸, Ali Sobh²⁹⁴, Xavier Solanich²⁵, Jordi Solé-Violán²⁹⁵, Catherine Soler²⁹⁶, Pere Soler-Palacín²⁹⁷, Betül Sözeri⁸⁶, Giulia Maria Stella², Yuriy Stepanovskiy²⁹⁸, Annabelle Stoclin²⁹⁹, Fabio Taccone²¹⁹, Yacine Tandjaoui-Lambiotte³⁰⁰, Jean-Luc Taupin³⁰¹, Simon J. Tavernier³⁰², Loreto Vidaur Tello¹¹², Benjamin Terrier³⁰³, Guillaume Thierry³⁰⁴, Christian Thorball²⁶⁰, Karolina Thorn³⁰⁵, Caroline Thumerelle¹⁵⁸, Imran Tipu³⁰⁶, Martin Tolstrup³⁰⁷, Gabriele Tomasoni³⁰⁸, Julie Toubiana⁷⁷, Josep Trenado Alvarez³⁰⁹, Vasiliki Triantafyllia³¹⁰, Sophie Trouillet-Assant³¹¹, Jesús Troya³¹², Owen T. Y. Tsang³¹³, Liina Tserel³¹⁴, Eugene Y. K. Tso³¹⁵, Alessandra Tucci³¹⁶, Şadiye Kübra Tüter Öz¹⁵, Matilde Valeria Ursini¹²⁵, Takanori Utsumi²²⁵, Yurdagül Uzunhan³¹⁷, Pierre Vabres³¹⁸, Juan Valencia-Ramos³¹⁹, Ana Maria Van Den Rym¹²⁷, Isabelle Vandernoot³²⁰, Valentina Velez-Santamaria³²¹, Silvia Patricia Zuniga Veliz³²⁴, Mateus C. Vidigal³²², Sébastien Viel²⁵³, Cédric Villain³²³, Marie E. Vilaire-Meunier²²³, Judit Villar-García³²⁴, Audrey Vincent⁵⁷, Guillaume Voirit³²⁶, Alla Volokha³²⁷, Fanny Vuotto¹⁵⁸, Els Wauters³²⁸, Joost Wauters³²⁹, Alan K. L. Wu³³⁰, Tak-Chiu Wu³³¹, Aysun Yahşi³³², Osman Yesilbas³³³, Mehmet Yildiz¹⁶⁸, Barnaby E. Young¹⁸⁷, Ufuk Yüselmiş³³⁴, Mayana Zatz⁶³, Marco Zecca³⁹, Valentina Zuccaro⁶², Jens Van Praet³³⁵, Bart N. Lambrecht³³⁶, Eva Van Braeckel³³⁶, Cédric Bosteels³³⁶, Levi Hoste³³⁷, Eric Hoste³³⁸, Fré Bauters³³⁶, Jozefien De Clercq³³⁶, Catherine Heijmans³³⁹, Hans Slabbynck³⁴⁰, Leslie Naesens³⁴¹, Benoit Florquin³⁴², Cécile Boulanger³⁴³, Dimitri Vanderlinden³⁴⁴
- ¹Germans Trias i Pujol University Hospital and Research Institute, Badalona, Barcelona, Spain. ²Respiratory Diseases Division, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy. ³Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ⁴Navarra Health Service Hospital, Pamplona, Spain. ⁵Jeffrey 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. ⁶Immunohematology Unit, San Raffaele Hospital, Milan, Italy. ⁷Öndokuz Mayıs University Medical Faculty Pediatrics, Samsun, Turkey. ⁸Department of Infectious Diseases, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁹Hospital Regional de Huehuetenango, "Dr. Jorge Vides de Molina," Huehuetenango, Guatemala. ¹⁰Hospital Nacional Edgardo Rebagliati Martines, Lima, Peru. ¹¹Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat Spain. ¹²Khyber Medical University, Khyber Pakhtunkhwa, Pakistan. ¹³Anesthesia and Intensive Care, Rianimazione I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ¹⁴Virology Research Center, National Institutes of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹⁵Department of Pediatrics, Division of Pediatric Infectious Diseases, Selcuk University Faculty of Medicine, Konya, Turkey. ¹⁶College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; Department of Pediatrics, King Fahad Hospital of the University, Al-Khobar, Saudi Arabia. ¹⁷Intensive Care Unit, Hôpital Européen, Marseille, France. ¹⁸Immunology Department, Hospital 12 de Octubre, Research Institute imas12, Complutense University, Madrid, Spain. ¹⁹Immunology Department, Asturias Central University Hospital, Biosanitary Research Institute of the Principality of Asturias (ISPA), Oviedo, Spain. ²⁰Emergency and Critical Care Medicine Departments, College of Medicine, Imam Abdulrahman Ben Faisal University, Dammam, Saudi Arabia. ²¹Clinical Immunology and Primary Immunodeficiencies Unit, Hospital Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, Barcelona, Spain; Universitat de Barcelona, Barcelona, Spain. ²²Department of Biological Immunology, Necker Hospital for Sick Children, AP-HP and INEM, Paris, France. ²³Internal Medicine Department, Hôpital Lariboisière, AP-HP, Paris, France; Université de Paris, Paris, France. ²⁴Internal Medicine Department, Pitié-Salpêtrière Hospital, Paris, France. ²⁵Department of Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²⁶Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, AP-HP, Créteil, France; Groupe de Recherche Clinique CARMAS, Faculté de Santé de Créteil, Université Paris Est Créteil, Créteil, France. ²⁷INSERM U1163, University of Paris, Imagine Institute, Paris, France and Pediatric Neurology Department, Necker-Enfants malades Hospital, AP-HP, Paris, France. ²⁸Hospital U. de Tarragona Joan XXIII. Universitat Rovira i Virgili (URV), IISPV, Tarragona, Spain. ²⁹Department of Propedeutics of Pediatrics and Medical Genetics, Danylo Haltsky Lviv National Medical University, Lviv, Ukraine. ³⁰Department of Immunology and Allergy, Konya City Hospital, Konya, Turkey. ³¹Private Practice, Paris, France. ³²INSERM U1109, University of Strasbourg, Strasbourg, France. ³³Necker Hospital for Sick Children, AP-HP, Paris, France. ³⁴Molecular Virology Unit, Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ³⁵Department of Infectious Diseases, CHU de Caen, Caen, France. ³⁶Consorcio Hospital General Universitario, Valencia, Spain. ³⁷Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ³⁸Department of Urology, Nephrology,

Transplantation, AHPH-SU, Sorbonne Université, INSERM U 1082, Paris, France.³⁹Cell Factory and Pediatric Hematology-Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.⁴⁰Yildirim Beyazit University, Faculty of Medicine, Ankara City Hospital, Children's Hospital, Ankara, Turkey.⁴¹University of Lyon, CIRI, INSERM U1111, National Referee Centre RAISE, Pediatric Rheumatology, HFME, Hospices Civils de Lyon, Lyon, France.⁴²Center for Clinical Immunology, CABA, Buenos Aires, Argentina.⁴³Cruces University Hospital, Bizkaia, Spain.⁴⁴Paediatric Immunology and Vaccinology Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.⁴⁵University Hospital and Research Institute "Germans Trias i Pujol," Badalona, Spain.⁴⁶Hematology, Georges Pompidou Hospital, AP-HP, Paris, France.⁴⁷Pediatric Infectious Diseases Unit, Instituto de Investigación Hospital 12 de Octubre (imas12), Hospital Universitario 12 de Octubre, Universidad Complutense, Madrid, Spain.⁴⁸Infectious disease Unit, Pitié-Salpêtrière Hospital, AP-AP, Paris, France.⁴⁹Department of Pediatrics, Thomayer's Hospital, first Faculty of Medicine, Charles University, Prague, Czech Republic; Department of Immunology, Motol University Hospital, Second Faculty of Medicine, Charles University, Prague, Czech Republic.⁵⁰Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain.⁵¹Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine.⁵²Service de Pneumologie, Hôpital Bichat, AP-HP, Paris, France.⁵³Department of Infectious Diseases, CIC1408, GIMAP CIRI INSERM U1111, University Hospital of Saint-Etienne, Saint-Etienne, France.⁵⁴Clinical Immunology Unit, Pediatric Infectious Disease Department, Faculty of Medicine and Pharmacy, Averroes University Hospital, LICIA Laboratoire d'immunologie clinique, d'inflammation et d'allergie, Hassani II University, Casablanca, Morocco.⁵⁵Bégin Military Hospital, St Mandé, France.⁵⁶Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), AP-HP, Hôpital Pitié Salpêtrière, Service de Virologie, Paris, France.⁵⁷Endocrinology Unit, AP-HP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France.⁵⁸Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.⁵⁹Pneumology Unit, Tenon Hospital, AP-HP, Paris, France.⁶⁰Department of Respiratory Diseases, Hospital Clínico y Universitario de Valencia, Valencia, Spain.⁶¹Intensive Care Unit, Réseau Hospitalier Neuchâtelois, Neuchâtel, Switzerland.⁶²Infectious Diseases Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.⁶³Human Genome and Stem Cell Research Center, University of São Paulo, São Paulo, Brazil.⁶⁴Department of Internal Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.⁶⁵Hospital Insular, Las Palmas de Gran Canaria, Spain.⁶⁶MS Center, Spedali Civili, Brescia, Italy.⁶⁷Laboratoire d'Immunorhéumatologie Moléculaire, plateforme GENOMAX, INSERM UMR_S 1109, Faculté de Médecine, ITI TRANSPLANTE NG, Université de Strasbourg, Strasbourg, France.⁶⁸Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.⁶⁹Neuromuscular Unit, Neurology Department, Hospital Universitari de Bellvitge-IDIBELL and CIBERER, Barcelona, Spain.⁷⁰Hôpital Robert Debré, Paris, France.⁷¹Pediatric Immunohematology Unit, Necker Enfants Malades Hospital, AP-HP, Paris, France.⁷²Department of Infectious and Tropical Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy.⁷³Doctoral Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain.⁷⁴Hôpital Foch, Suresnes, France.⁷⁵Selcuk University Faculty of Medicine, Department of Anesthesiology and Reanimation, Intensive Care Medicine Unit, Konya, Turkey.⁷⁶Division of Clinical Pharmacology and Toxicology, Institute of Pharmaceutical Sciences of Southern Switzerland, Ente Ospedaliero Cantonale and Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland.⁷⁷Necker Hospital for Sick Children, Paris University, AP-HP, Paris, France.⁷⁸Pasteur Institute, Paris, France.⁷⁹McGill University Health Centre, Montreal, Canada.⁸⁰University Hospital and Research Institute "Germans Trias i Pujol," IrsiCaixa AIDS Research Institute, UVic-UCC, Badalona, Spain.⁸¹Clinical Biochemistry, Pathology, Paediatric Neurology and Molecular Medicine Departments and Biobank, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Esplugues, Spain.⁸²AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; University Sorbonne Paris Nord, Bobigny, France; INSERM, U942, F-75010, Paris, France.⁸³Hospital Universitari Vall d'Hebron, Barcelona, Spain.⁸⁴Pitié-Salpêtrière Hospital, Paris, France.⁸⁵Service de médecine Intensive Réanimation, Groupe Hospitalier Pitié-Salpêtrière, Sorbonne Université, Paris, France.⁸⁶Umraniye Training and Research Hospital, Istanbul, Turkey.⁸⁷Faculty of Medical Sciences at University "Goce Delcev," Shtip, North Macedonia.⁸⁸Department of Biochemistry, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.⁸⁹Fundació Docència i Recerca Mutua Terrassa, Barcelona, Spain.⁹⁰Maladies Infectieuses et Tropicales, Nouvel Hôpital Civil, CHU Strasbourg, Strasbourg, France.⁹¹UNSW Medicine, St Vincent's Clinical School, Sydney, NSW, Australia; Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst, Sydney, NSW, Australia.⁹²Intensive Care Unit, Montreuil Hospital, Montreuil, France.⁹³CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium.⁹⁴Pediatric Intensive Care Unit, Robert-Debré University Hospital, AP-HP, Paris, France.⁹⁵General Internal Medicine, University Hospitals Leuven, Leuven, Belgium.⁹⁶Hôpital Jean Verdier, AP-HP, Bondy, France.⁹⁷Specialized Immunology Laboratory of Dr. Shahrooei, Sina Medical Complex, Ahvaz, Iran.⁹⁸Centre de génétique humaine, CHU Besançon, Besançon, France.⁹⁹Sorbonne Université médecine and AP-HP Sorbonne université site Pitié-Salpêtrière, Paris, France.¹⁰⁰Pediatric Neurology Department, Necker-Enfants Malades Hospital, AP-HP, Paris, France.¹⁰¹Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy.¹⁰²Intensive Care Unit, Georges Pompidou Hospital, AP-HP, Paris, France.¹⁰³Department of Pneumology, AZ Delta, Roeselare, Belgium.¹⁰⁴Molecular Diagnostic Unit, Fundación Rioja Salud, Logroño, La Rioja, Spain.¹⁰⁵Bégin Military Hospital, Saint Mandé, France.¹⁰⁶Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.¹⁰⁷Bursa City Hospital, Bursa, Turkey.¹⁰⁸Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University, Mansoura, Egypt.¹⁰⁹Tokyo Medical and Dental University, Tokyo, Japan.¹¹⁰Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey.¹¹¹Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey.¹¹²Intensive Care Medicine, Donostia University Hospital, Biodonostia Institute of Donostia, CIBER Enfermedades Respiratorias ISCIII, Donostia, Spain.¹¹³Internal Medicine, University Hospital Edouard Herriot, Hospices Civils de Lyon, Lyon, France.¹¹⁴Centre de Génétique, CHU Dijon, Dijon, France.¹¹⁵Robert Debré Hospital, Paris, France.¹¹⁶AP-HP Tenon Hospital, Paris, France.¹¹⁷Sorbonne Universités, UPMC University of Paris, Paris, France.¹¹⁸Department of Clinical Immunology, Hospital Clínico San Carlos, Madrid, Spain.¹¹⁹Intensive Care Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain; Shock, Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain.¹²⁰Intensive Care Unit, Hospital Clínico y Universitario de Valencia, Valencia, Spain.¹²¹Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Faculty of Health Sciences, University of Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain.¹²²CHU Limoges and INSERM CIC 1435 and UMR 1092, Limoges, France.¹²³Infectious Diseases Unit, Department of Pediatrics, Hospital Sant Joan de Déu, Barcelona, Spain; Institut de Recerca Sant Joan de Déu, Spain; Universitat de Barcelona (UB), Barcelona, Spain.¹²⁴Department of Pathology, United Christian Hospital, Hong Kong, China.¹²⁵Institute of Genetics and Biophysics "Adriano Buzzati-Traverso," IGB-CNR, Naples, Italy.¹²⁶Department of Pediatrics, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Josip Juraj Strossmayer University of Zagreb, Medical Faculty Osijek, Osijek, Croatia.¹²⁷Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain.¹²⁸Hematology, AP-HP, Hôpital Européen Georges Pompidou and INSERM UMR-S1140, Paris, France.¹²⁹Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Karadeniz Technical University, Trabzon, Turkey.¹³⁰Division of Immunology, Hospital General Universitario and Instituto de Investigación Sanitaria "Gregorio Marañón," Madrid, Spain.¹³¹Bégin Military Hospital, Bégin, France.¹³²Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, IHU Méditerranée Infection, Marseille, France, French Armed Forces Center for Epidemiology and Public Health (CESPA), Marseille, France.¹³³Pediatric Intensive Care Unit, Hospital Sant Joan de Déu, Barcelona, Spain.¹³⁴Gestión Integral en Salud, Guatemala.¹³⁵Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.¹³⁶Immunodeficiencies Unit, Research Institute Hospital, Madrid, Spain.¹³⁷Primary Immunodeficiencies Unit, Pediatrics, University Hospital 12 de Octubre, Madrid, Spain; School of Medicine Complutense University of Madrid, Madrid, Spain.¹³⁸Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain.¹³⁹Assistance Publique Hôpitaux de Paris, Paris, France.¹⁴⁰Ankara City Hospital, Ankara,

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

of Biochemistry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. ²⁴⁹Diabetes Research Institute, IRCCS San Raffaele Hospital, Milan, Italy. ²⁵⁰AP-HP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ²⁵¹AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; INSERM UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), University of Paris, Paris, France. ²⁵²Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona; CIBERER U759, ISCIII Madrid, Spain. ²⁵³Hospices Civils de Lyon, Lyon, France. ²⁵⁴Univ. Lille, INSERM U1285, CHU Lille, Pôle de médecine intensive-réanimation, CNRS, UMR 8576–Unité de Glycobiologie Structurale et Fonctionnelle, Lille, France. ²⁵⁵Department of General Pediatrics, Robert Debre Hospital, Paris, France. ²⁵⁶University of British Columbia, Vancouver, BC, Canada. ²⁵⁷Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain; Diagnostic Immunology Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ²⁵⁸AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; University Sorbonne Paris Nord, Bobigny, France. ²⁵⁹Centre Hospitalier de Saint-Denis, St Denis, France. ²⁶⁰Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ²⁶¹Paris Cardiovascular Center, PARCC, INSERM, Université de Paris, Paris, France. ²⁶²Germans Trias i Pujol Hospital, Badalona, Spain. ²⁶³Medical Intensive Care Unit, Hospital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France. ²⁶⁴Department of Clinical Laboratory, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²⁶⁵Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus., Barcelona, Spain. ²⁶⁶Université de Paris, CNRS UMR-8601, Paris, France; Team Chemistry and Biology, Modeling and Immunology for Therapy, CBMIT, Paris, France. ²⁶⁷Germans Trias i Pujol University Hospital and Research Institute, Badalona, Spain. ²⁶⁸Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ²⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), 08908 L'Hospitalet de Llobregat, Barcelona, Spain; University Hospital Germans Trias i Pujol, Badalona, Barcelona, Catalonia, Spain. ²⁷⁰Consorcio Hospital General Universitario, Valencia, Spain. ²⁷¹AP-HP Hôpitaux Universitaires Paris-Sud, Paris, France. ²⁷²Intensive Care Unit, Louis-Mourier Hospital, Colombes, France. ²⁷³Virology Unit, Université de Paris, Cochin Hospital, AP-HP, Paris, France. ²⁷⁴Neurometabolic Diseases Laboratory and CIBERER U759, Barcelona, Spain. ²⁷⁵Hospital San Pedro, Logroño, Spain. ²⁷⁶University of Tartu, Institute of Biomedicine and Translational Medicine, Tartu, Estonia. ²⁷⁷Respiratory Medicine, Georges Pompidou Hospital, AP-HP, Paris, France. ²⁷⁸Infectious Diseases Department, International Health Program of the Catalan Institute of Health (PROSICS), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain. ²⁷⁹Hospital Clínico San Carlos and IdSSC, Madrid, Spain. ²⁸⁰Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ²⁸¹AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France. ²⁸²Service de Médecine Intensive Réanimation, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France. ²⁸³Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. ²⁸⁴CHRU de Nancy, Hôpital d'Enfants, Vandoeuvre, France. ²⁸⁵Chair of Nephrology, University of Brescia, Brescia, Italy. ²⁸⁶Department of Immunology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic. ²⁸⁷Clínica Universidad de Navarra and Ciberes, Madrid, Spain. ²⁸⁸HUS Helsinki University Hospital, Children and Adolescents, Rare Disease Center, and Inflammation Center, Adult Immunodeficiency Unit, Majakka, Helsinki, Finland. ²⁸⁹Fundació Docència i Recerca Mutua Terrassa, Terrassa, Spain. ²⁹⁰D. Rogachev National Medical and Research Center of Pediatric Hematology, Oncology, Immunology, Moscow, Russia. ²⁹¹Haematology Laboratory, Lariboisière Hospital, University of Paris, Paris, France. ²⁹²Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ²⁹³INSERM U1140, University of Paris, European Georges Pompidou Hospital, Paris, France. ²⁹⁴Department of Pediatrics, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ²⁹⁵Intensive Care Medicine, Hospital Universitari de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ²⁹⁶CHU de Saint Etienne, Saint-Priest-en-Jarez, France. ²⁹⁷Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus. Universitat Autònoma de Barcelona (UAB),

Barcelona, Catalonia, Spain; EU, Barcelona, Spain. ²⁹⁸Department of Pediatric Infectious Diseases and Pediatric Immunology, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. ²⁹⁹Gustave Roussy Cancer Campus, Villejuif, France. ³⁰⁰Intensive Care Unit, Avicenne Hospital, AP-HP, Bobigny, France. ³⁰¹Laboratory of Immunology and Histocompatibility, Saint-Louis Hospital, Paris University, Paris, France. ³⁰²Center for Inflammation Research, Laboratory of Molecular Signal Transduction in Inflammation, VIB, Ghent, Belgium. ³⁰³Department of Internal Medicine, Université de Paris, INSERM, U970, PARCC, F-75015, Paris, France. ³⁰⁴Service de médecine intensive réanimation, CHU de Saint-Etienne, France. ³⁰⁵Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ³⁰⁶University of Management and Technology, Lahore, Pakistan. ³⁰⁷Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark. ³⁰⁸First Division of Anesthesiology and Critical Care Medicine, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ³⁰⁹Intensive Care Department, Hospital Universitari MutuaTerrassa, Universitat Barcelona, Terrassa, Spain. ³¹⁰Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ³¹¹International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France; Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France. ³¹²Infanta Leonor University Hospital, Madrid, Spain. ³¹³Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong, China. ³¹⁴University of Tartu, Institute of Clinical Medicine, Tartu, Estonia. ³¹⁵Department of Medicine, United Christian Hospital, Hong Kong, China. ³¹⁶Hematology Department, ASST Spedali Civili di Brescia, Brescia, Italy. ³¹⁷Pneumologie, Hôpital Avicenne, AP-HP, INSERM U1272, Université Sorbonne Paris Nord, Bobigny, France. ³¹⁸Dermatology Unit, Laboratoire GAD, INSERM UMR1231 LNC, Université de Bourgogne, Dijon, France. ³¹⁹University Hospital of Burgos, Burgos, Spain. ³²⁰Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ³²¹Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain. ³²²University of São Paulo, São Paulo, Brazil. ³²³CHU de Caen, Caen, France. ³²⁴Hospital del Mar–IMIM Biomedical Research Institute, Barcelona, Catalonia, Spain. ³²⁵Sorbonne Université, Service de Médecine Intensive Réanimation, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France. ³²⁷Pediatric Infectious Disease and Pediatric Immunology Department, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. ³²⁸Department of Pneumology, University Hospitals Leuven, Leuven, Belgium. ³²⁹Laboratory for Clinical Infectious and Inflammatory Disorders, Department of Microbiology, Immunology, and Transplantation, Leuven, Belgium. ³³⁰Department of Clinical Pathology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China. ³³¹Department of Medicine, Queen Elizabeth Hospital, Hong Kong, China. ³³²Ankara City Hospital, Children's Hospital, Ankara, Turkey. ³³³Division of Pediatric Infectious Disease, Department of Pediatrics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey. ³³⁴Health Sciences University, Lütfi Kırdar Kartal Education and Research Hospital, Istanbul, Turkey. ³³⁵Department of Nephrology and Infectiology, AZ Sint-Jan, Bruges, Belgium. ³³⁶Department of Pulmonology, Ghent University Hospital, Belgium. ³³⁷Department of Pediatric Pulmonology and Immunology, Ghent University Hospital, Ghent, Belgium. ³³⁸Department of Intensive Care Unit, Ghent University Hospital, Ghent, Belgium. ³³⁹Department of Pediatric Hemato-oncology, Jolimont Hospital, La Louvière, Belgium. ³⁴⁰Department of Pulmonology, ZNA Middelheim, Antwerp, Belgium. ³⁴¹Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium. ³⁴²Department of Pediatric Immunohemato-rheumatology, CHR Citadelle, Liège, Belgium. ³⁴³Department of Pediatric Hemato-oncology, UCL Louvain, Brussels, Belgium. ³⁴⁴Department of Pediatrics, Saint Luc, UCL Louvain, Brussels Belgium. ³⁴⁵Intensive Care Unit, Grand Hôpital de l'Est Francilien Site de Marne-La-Vallée, Jossigny, France.

Members of Orchestra Working Group: Laurent Abel¹, Matilda Berkell², Valerio Carelli³, Alessio Fiorentino³, Surbi Malhotra², Alessandro Mattiaccio³, Tommaso Pippucci³, Marco Seri³, Evelina Tacconelli⁴

¹Inserm, University Paris cité, Imagine Institute, Paris, France, ²University of Antwerp, Antwerp, Belgium, ³University of Bologna, Bologna, 40138, Italy, ⁴University of Verona, 37129 Verona, Italy

Members of French COVID Cohort Study Group: Laurent Abel¹, Claire Andrejak², François Angoulvant³, Delphine Bachelet⁴, Marie Bartoli⁵, Romain Basmaci⁶, Sylvie Behillil⁷, Marine Beluze⁸, Dehbia Benkerrou⁹, Krishna Bhavsar⁴, Lila Bouadma⁴, Sabelline Bouchez¹⁰, Maude Bouscambert¹¹, Minerva Cervantes-Gonzalez⁴, Anissa Chair⁴, Catherine Chirouze¹², Alexandra Coelho¹³, Camille Couffignal⁴, Sandrine Couffin-Cadiergues¹⁴, Eric d'Ortenzio⁵,

Marie-Pierre Debray⁴, Lauren Deconinck⁴, Dominique Deplanque¹⁵, Diane Descamps⁴, Mathilde Desvallée¹⁶, Alpha Diallo⁵, Alphonsine Diouf¹³, Céline Dorival⁹, François Dubos¹⁷, Xavier Duval⁴, Brigitte Elharrar¹⁸, Philippine Eloy⁴, Vincent Enouf⁷, Hélène Esperou¹⁴, Marina Esposito-Farese⁴, Manuel Etienne¹⁹, Eglantine Ferrand Devouge¹⁹, Nathalie Gault⁴, Alexandre Gaymard¹¹, Jade Ghosn⁴, Tristan Gigante²⁰, Morgane Gilg²⁰, Jérémie Guedj²¹, Alexandre Hocht¹³, Isabelle Hoffmann⁴, Ikram Houas¹⁴, Jean-Sébastien Hulot²², Salma Jaafoura¹⁴, Ouifya Kafif⁴, Florentia Kaguelidou²³, Sabrina Kali⁴, Antoine Khalil⁴, Coralie Khan¹⁶, Cédric Laouénan⁴, Samira Laribi⁴, Minh Le⁴, Quentin Le Hingrat⁴, Soizic Le Mestre⁵, Hervé Le Nagard²⁴, François-Xavier Lescuré⁴, Sophie Letrou⁴, Yves Levy²⁵, Bruno Lina¹¹, Guillaume Lingas²⁴, Jean-Christophe Lucet⁴, Denis Malvy²⁶, Marina Mambert¹³, France Mentré⁴, Amina Meziane⁹, Hugo Mouquet⁷, Jimmy Mullaert⁴, Nadège Neant²⁴, Duc Nguyen²⁶, Marion Noret²⁷, Saad Nseir¹⁷, Aurélie Papadopoulou¹⁴, Christelle Paul⁵, Nathan Peiffer-Smadja⁴, Thomas Perpoint²⁸, Ventzislava Petrov-Sanchez⁵, Gilles Peytavin⁴, Huong Pham⁴, Olivier Picone⁶, Valentine Piquard⁴, Oriane Puechal²⁹, Christian Rabaud³⁰, Manuel Rosa-Calatrava¹¹, Bénédicte Rossignol²⁰, Patrick Rossignol³⁰, Carine Roy⁴, Marion Schneider⁴, Richa Su⁴, Coralie Tardivon⁴, Marie-Capucine Tellier⁴, François Téoulou⁹, Olivier Terrier¹¹, Jean-François Timsit⁴, Christelle Tuai³¹, Sarah Tubiana⁴, Sylvie Van Der Werf⁷, Noémie Vanel³², Aurélie Veislinger³¹, Benoit Visseaux⁴, Aurélie Wiedemann²⁵, Yazdan Yazdanpanah⁴

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

Members of CoV-Contact Cohort: Loubna Alavoine¹, Sylvie Behillil², Charles Burdet³, Charlotte Charpentier⁴, Aline Dechanet⁵, Diane Descamps⁶, Xavier Duval⁷, Jean-Luc Ecobichon¹, Vincent Enouf⁸, Wahiba Frezouls¹, Nadhira Houhou⁹, Ouifya Kafif², Jonathan Lehacaut¹, Sophie Letrou¹, Bruno Lina⁹, Jean-Christophe Lucet¹⁰, Pauline Manchon⁵, Mariama Nouroudine¹, Valentine Piquard⁵, Caroline Quintin¹, Michael Thy¹¹, Sarah Tubiana¹, Sylvie van der Werf⁸, Valérie Vignali¹, Benoit Visseaux¹⁰, Yazdan Yazdanpanah¹⁰, Abir Chahine¹², Nawal Waucquier¹², Maria-Claire Migaud¹², Dominique Deplanque¹², Félix Djossou¹³, Mayka Mergeay-Fabre¹⁴, Aude Lucarelli¹⁵, Magalie Demar¹³, Léa Bruneau¹⁶, Patrick Gérardin¹⁷, Adrien Maillot¹⁶, Christine Payet¹⁸, Bruno Laviolle¹⁹, Fabrice Laine¹⁹, Christophe Paris¹⁹, Mireille Desille-Dugast¹⁹, Julie Fouchard¹⁹, Denis Malvy²⁰, Duc Nguyen²⁰, Thierry Pistone²⁰, Pauline Perreau²⁰, Valérie Gissot²¹, Carole L. E. Goas²¹, Samatha Montagne²², Lucie Richard²³, Catherine Chirouze²⁴, Kévin Bouiller²⁴, Maxime Desmarests²⁵, Alexandre Meunier²⁶, Marilou Bourgeois²⁶, Benjamin Lefèvre²⁷, Hélène Jeulin²⁸, Karine Legrand²⁹, Sandra Lomazzi³⁰, Bernard Tardy³¹, Amandine Gagneux-Brunon³², Frédérique Bertholon³³, Elisabeth Botelhou-Nevers³², Kouakam Christelle³⁴, Leturque Nicolas³⁴, Layidé Roufai³⁴, Karine Amat³⁵, Sandrine Couffin-Cadiergues³⁴, Hélène Espérou³⁶, Samia Hendou³⁴

¹Centre d'Investigation Clinique, INSERM CIC 1425, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ²Institut Pasteur, Paris, France. ³Université de Paris, IAME, INSERM U1137, Paris, France; Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁴Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁵Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁶IAME INSERM U1140, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ⁷Centre d'Investigation Clinique, INSERM CIC 1425, AP-HP, IAME, Paris University, Paris, France. ⁸Institut Pasteur, U3569 CNRS, Université de Paris, Paris, France. ⁹Virpath Laboratory, International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS U5308, ENS, UCBL, Lyon, France. ¹⁰IAME INSERM U1138, Hôpital Bichat Claude Bernard, AP-HP, Paris, France. ¹¹Center for Clinical Investigation, Assistance Publique-Hôpitaux de Paris, Bichat-Claude Bernard University Hospital, Paris, France. ¹²Centre d'Investigation Clinique, INSERM CIC 1403, Centre Hospitalo universitaire

de Lille, Lille, France. ¹³Service des maladies infectieuses, Centre Hospitalo universitaire de Cayenne, Guyane, France. ¹⁴Centre d'Investigation Clinique, INSERM CIC 1424, Centre Hospitalier de Cayenne, Cayenne, Guyane Française. ¹⁵Service Hôpital de jour Adulte, Centre Hospitalier de Cayenne, Guyane, France. ¹⁶Centre d'Investigation Clinique, INSERM CIC 1410, Centre Hospitalo universitaire de la Réunion, La Réunion, France. ¹⁷Centre d'Investigation Clinique, INSERM CIC 1410, CHU Reunion, Saint-Pierre, Reunion Island. ¹⁸Centre d'Investigation Clinique, INSERM CIC 1410, Centre de Ressources Biologiques, Centre Hospitalo universitaire de la Réunion, La Réunion, France. ¹⁹Centre d'Investigation Clinique, INSERM CIC 1414, Centre Hospitalo universitaire de Rennes, Rennes, France. ²⁰Service des maladies infectieuses, Centre Hospitalo universitaire de Bordeaux, Bordeaux, France. ²¹Centre d'Investigation Clinique, INSERM CIC 1415, CHRU Tours, Tours, France. ²²CRBT, Centre Hospitalo universitaire de Tours, Tours, France. ²³Pole de Biologie Médicale, Centre Hospitalo universitaire de Tours, Tours, France. ²⁴Service des maladies infectieuses, Centre Hospitalo universitaire de Besançon, Besançon, France. ²⁵Service des maladies infectieuses, Centre d'Investigation Clinique, INSERM CIC1431, Centre Hospitalier Universitaire de Besançon, Besançon, France. ²⁶Centre de Ressources Biologiques-Filière Microbiologique de Besançon, Centre Hospitalier Universitaire, Besançon, France. ²⁷Université de Lorraine, CHRU-Nancy and APEMAC, Infectious and Tropical Diseases, Nancy, France. ²⁸Laboratoire de Virologie, CHRU de Nancy Brabois, Vandoeuvre-lès-Nancy, France. ²⁹INSERM CIC-EC 1433, Centre Hospitalo universitaire de Nancy, Nancy, France. ³⁰Centre de ressources Biologiques, Centre Hospitalo universitaire de Nancy, Nancy, France. ³¹Centre d'Investigation Clinique, INSERM CIC 1408, Centre Hospitalo universitaire de Saint Etienne, Saint Etienne, France. ³²Service des maladies infectieuses, Centre Hospitalo universitaire de Saint Etienne, Saint Etienne, France. ³³Service des maladies infectieuses, CRB⁴²-BTK, Centre Hospitalo Universitaire de Saint Etienne, Saint Etienne, France. ³⁴Pole Recherche Clinique, INSERM, Paris, France. ³⁵IMEA Fondation Léon M'Ba, Paris, France. ³⁶INSERM Clinical Research Department, Paris, France.

Members of the COVIDeF study group: Serge Bureau¹, Yannick Vacher¹, Anne Gysembergh-Houal¹, Lauren Demerville¹, Abba Chachoua¹, Sebastien Abad², Radhiya Abassi³, Abdelrafie Abdellaoui³, Abdelkrim Abdelmalek⁴, Hedy Abdoul⁵, Helene Abergel⁶, Fariza Aboud⁷, Sophie Abgrall⁸, Noemie Abisror⁴, Marylise Adechian⁹, Nordine Aderdour⁹, Hakeem Farid Admane⁴, Frederic Adnet², Sara Afritt⁵, Helene Agostini¹⁰, Claire Aguilar¹¹, Sophie Agut¹², Tommaso Francesco Aiello¹³, Marc Ait Kaci¹⁴, Hafid Ait Oufella⁴, Gokula Ajeenthiravasan¹⁵, Virginie Alauzy³, Fanny Alby-Laurent¹¹, Lucie Allard², Marie-Alexandra Alyanaki¹¹, Blanca Amador Borrero⁷, Sabrina Amam⁶, Lucile Amrouche¹¹, Marc Andronikof¹⁶, Dany Anglicheau¹¹, Nadia Anguel⁹, Djillali Annane¹⁵, Mohammed Aounzou³, Caroline Aparicio⁷, Gladys Aratus⁴, Jean-Benoit Arlet¹⁴, Jeremy Arzoine³, Elisabeth Aslangul¹³, Mona Assefi³, Adeline Aubry³, Laetitia Audiffred⁴, Etienne Audureau¹⁷, Christelle Nathalie Auger⁵, Jean-Charles Auregan⁸, Celine Awotar¹¹, Sonia Ayllon Milla⁵, Delphine Azan⁵, Laurene Azemar⁷, Billal Azzougouen⁷, Marwa Bachir Elrufai¹², Aida Badi⁷, Prissile Bakouboula¹¹, Coline Balcerowiak³, Fanta Balde¹², Elodie Baldvina¹⁷, Eliane-Flore Bangamingo¹⁸, Amandine Baptiste³, Fanny Baran-Marszak², Caroline Barau¹⁷, Nathalie Barget¹⁹, Flore Baronnet³, Romain Barthelemy⁷, Jean-Luc Baudel⁴, Camille Baudry², Elodie Baudry⁹, Laurent Beaugerie², Adel Belamri³, Nicolas Belaube¹², Rhida Bellilita³, Pierre Bellassen³, Rawan Belmokhtar², Isabel Beltran⁶, Ruben Benainou², Mourad Benallaoua², Robert Benamouzig², Amélie Benbara¹⁹, Jaouad Benhida³, Anis Benkhelouf³, Jihene Benlagha¹⁸, Chahinez Benmostafa¹⁴, Skander Benothmane¹⁸, Miassa Bentifraouine², Laurence Berard⁴, Quentin Bernier³, Enora Berti¹⁷, Astrid Bertier⁹, Laure Berton⁷, Simon Bessis¹⁵, Alexandra Beurton²⁰, Céline Bianco⁴, Clara Bianquis³, Frank Bidar³, Philippe Blanche⁵, Clarisse Blayau¹², Alexandre Bleibtreu³, Emmanuelle Blin¹², Coralie Bloch-Queyrat², Marie-Christophe Boissier², Diane Bollens⁴, Marion Bolzoni⁴, Rudy pierre Bompard¹², Nicolas Bonnet², Justine Bonnouvrier⁴, Shirmonecrystal Botha³, Wissam Boucenna⁴, Fatima Bouchama³, Olivier Bouchaud², Hanane Bouchghoul¹⁷, Taoueslylia Boudjebba¹², Noel Boudjema¹⁷, Catherine Bouffard⁶, Adrien Bougle³, Meriem Bouguerra³, Leila Bouras⁷, Agnes Bourcier³, Anne Bourgarit Durand¹⁹, Anne Bourrier⁴, Fabrice Bouscarat⁶, Diane Bouvy², Nesrine Bouziri³, Ons Bouzrara³, Sarah Bribrier⁹, Delphine Brugier³, Melanie Brunel¹¹, Eida Bui⁴, Anne Buisson²¹, Iryna Bukreyeva⁹, Côme Bureau²⁰, Jacques Cadranet¹², Johann Cailhol², Ruxandra Calin¹², Clara Campos Vega¹¹, Pauline Canavaggio³, Marta Cancellà³, Delphine Cantin²², Albert Cao³, Lionel Carbillon¹⁹, Nicolas Carlier⁵, Clementine Cassard³, Guilaine Castor⁷, Marion Cauchy⁷, Olivier Cha⁴, Benjamin Chaigne², Salima Challal², Karine Champion⁷, Patrick Chariot¹⁹, Julie Chas¹², Simon Chauveau², Anthony Chauvin⁷, Clement Chauvin¹⁸, Nathalie Chavart¹¹,

Kamélia Chebbout³, Mustapha Cherai³, Ilaria Cherubini³, Amelie Chevalier⁵, Thibault Chiarabini⁴, Thierry Chinet¹⁰, Richard Chocron¹⁴, Pascaline Choinier¹², Juliette Chommeloux³, Christophe Choquet⁶, Laure Choupeaux¹¹, Benjamin Chousterman⁷, Dragosmaris Cioan⁸, Ada Clarke⁵, Gaëlle Clavere²³, Florian Clavier³, Karine Clement³, Sebastien Clerc¹⁴, Yves Cohen², Fleur Cohen³, Adrien Cohen²³, Audrey Coilly²⁴, Hester Colboc²⁵, Pauline Colin³, Magalie Collet⁷, Chloé Comarmond⁷, Emeline Combanco⁵, Alain Combes³, Celine Comparon², Jean-Michel Constantin³, Hugues Cordel², Anne-Gael Cordier⁹, Adrien Costantini¹⁰, Nathalie Costedoat Chalumeau⁵, Camille Couffignal⁶, Doriane Coupeau⁴, Alain Creange¹⁷, Yannick Cuvillier Lamarre²², Charlène Da Silveira⁶, Sandrine Dautheville Guibal El Kayani¹², Nathalie De Castro¹⁸, Yann De Rycke³, Lucie Del Pozo¹⁹, Quentin Delannoy³, Mathieu Delay¹², Robin Delleris³, Juliette Delforge¹³, Laëtitia Delphine³, Noemie Demare², Sophie Demeret³, Alexandre Demoule³, Aurore Deniau², François Depret¹⁸, Sophie Derolez², Ouda Derradj⁹, Nawal Derridj¹⁰, Vincent Descamps⁶, Lydia Deschamps⁶, Celine Desconclois⁸, Cyrielle Desnos³, Karine Desongins¹⁸, Robin Dhote², Benjamin Diallo¹², Morgane Didier², Myriam Diemer⁷, Stephane Diez⁹, Juliette Djadi-Prat¹⁴, Fatima-Zohra Djamouri Monnory¹², Siham Djebara³, Naoual Djebra², Minette Djietcheu¹⁸, Hadjer Djillali⁴, Nouara Djouadi⁴, Severine Donneger¹⁹, Catarina Dos Santos⁵, Nathalie Dournout², Martin Dres²⁰, Laura Droctove³, Marie Drogrey³, Margot Dropy³, Elodie Drouet⁴, Valérie Dubosq¹², Evelyne Dubreucq¹², Estelle Dubus³, Boris Duchemann², Thibault Duchenois⁵, Emmanuel Dudoignon¹⁸, Romain Duffau¹⁹, Florence Dumas⁵, Clara Duran¹⁰, Emmanuelle Duron²⁴, Antoine Durrah¹⁷, Claudine Duvivier¹¹, Nathan Ebstein², Jihane El Khalifa⁶, Alexandre Elabbadi¹², Caroline Elie¹¹, Gabriel Ernotte³, Anne Esling¹¹, Martin Etienne⁹, Xavier Eyer⁷, Muriel Sarah Fartoukh¹², Takoua Fayali³, Marion Fermaut¹⁹, Arianna Fiorentino⁴, Souha Fliss², Marie-Céline Fournier⁷, Benjamin Fournier¹¹, Héléne Francois¹², Olivia Freynet⁵, Yvann Frigout¹⁴, Isaure Fromont⁷, Axelle Fuentes⁶, Thomas Furet³, Joris Galand⁷, Marc Garnier⁴, Agnes Gaubert³, Stéphane Gaudry², Samuel Gaugain⁷, Damien Gauthier³, Maxime Gautier⁷, Sophie Georgin-Lavialle¹², Daniela Geromin¹⁴, Mohamed Ghalayini², Bijan Ghaleh¹⁷, Myriam Ghezal²¹, Aude Gibelin¹², Linda Gimeno³, Benoit Girard⁵, Bénédicte Giroux Leprieur², Doryan Gomes¹⁸, Elisabete Gomes-Pires¹¹, Guy Gorochov³, Anne Gouge¹⁸, Amel Gouja¹⁷, Helene Goulet¹², Sylvain Goupil¹¹, Jeanne Goupil De Bouille², Julien Gras⁷, Segolene Greffe¹⁰, Lamiæ Grimaldi⁹, Paul Guedeney³, Bertrand Guidet⁴, Matthias Guillo¹⁸, Mariechristelle Guczynski²⁶, Tassadit Hadjam⁷, Didier Haguenauer¹³, Soumeia Hammal³, Nadjib Hammoudi³, Olivier Hanon²³, Anarole Harrois⁹, Pierre Hausfater³, Coraline Hautem¹⁴, Guillaume Hekimian³, Nicholas Heming¹⁵, Olivier Hermine¹¹, Sylvie Ho³, Marie Houllier⁹, Benjamin Huot⁷, Tessa Huscenot⁷, Wafa Ibn Saïed¹², Ghilias Ikherbane³, Meriem Imarazene¹¹, Patrick Ingiliz², Lina Iratni¹⁷, Stephane Jaureguiberry⁹, Jean-Francois Jean-Marc¹⁰, Deleena Jeyarajasingham¹⁸, Pauline Jouany¹⁴, Veronique Jouis⁷, Clement Jourdain⁷, Oufiya Kafir⁶, Rim Kallala²⁴, Sandrine Katsahian¹⁴, Lilil Kelesyan²⁷, Vixra Keo³, Flora Ketz²¹, Warda Khamis⁵, Enfel Khelili³, Mehdi Khellaf⁷, Christy Gaëlla Kotokpo Youkou¹⁰, Ilias Kounis²⁴, Gaelle Kpalma³, Jessica Krause⁴, Vincent Labbe¹², Karine Lacombe⁴, Jean-Marc Lacorte³, Anne Gaëlle Lafont⁴, Emmanuel Lafont¹¹, Lynda Lagha²⁷, Lionel Lamhaut¹¹, Aymeric Lancelot³, Cecilia Landman⁴, Fanny Lanternier¹¹, Cecile Larcheveque³, Caroline Lascoux Combe¹⁸, Ludovic Lassel¹², Benjamin Laverdant¹², Christophe Lavergne¹⁸, Jean-Rémi Lavillegrand⁴, Pompilia Lazreanu⁷, Loïc Le Guennec³, Lamia Leberre⁴, Claire Leblanc¹⁹, Marion Leboyer²⁸, François Lecomte⁵, Marine Lecorre³, Romain Leenhardt⁴, Marylou Lefebvre⁴, Bénédicte Lefebvre⁴, Paul Legendre⁵, Anne Leger³, Laurence Legros²⁴, Justyna Legrosse³, Sébastien Lehuunghia⁵, Julien Lemarec³, Jeremie Leporrier-Ext¹¹, Manon Lesoin⁵, Hubert Lesur²⁴, Vincent Levy², Albert Levy¹⁴, Edwige Lopes⁷, Amanda Lopes⁷, Vanessa Lopez¹¹, Julien Lopinto¹², Olivier Lortholary¹¹, Badr Louadah⁷, Bénédicte Loze¹⁸, Marie-Laure Lucas²², Axelle Lucasamichi⁸, Liem Binh Luong⁵, Arouna Magazimama-Ext⁷, David Maingret⁷, Lakhdar Mameri¹⁸, Philippe Manivet⁷, Cylia Mansouri⁴, Estelle Marcuati⁶, Jonathan Marey⁵, Nathalie Marin⁵, Clémence Mairois³, Olivier Martin², Lou Martineau⁷, Cannelle Martinez-Lopez¹⁵, Pierre Martyniuck⁴, Pauline Mary De Farcy²⁹, Nessrine Marzouk¹², Rafik Masmoudi¹⁴, Alexandre Mebazaa⁷, Frédéric Mechaï², Fabio Mecozzi¹¹, Chamseddine Mediouni¹⁰, Bruno Megarbane⁷, Mohamed Meghadecha²², Élodie Mejean¹², Arsene Mekinian⁴, Nour Mekki Abdelhadi⁶, Rania Mekni³, Thinhinan Sabrina Meliti³, Breno Melo Lima¹⁸, Paris Meng¹², Soraya Merbah³, Fadila Messani², Yasmine Messaoudi³, Baboo-irwingsingh Mewasingh¹², Lydia Meziane³, Carole Michelot-Burger¹¹, Françoise Mignot¹⁸, Fadi Hillary Minka⁷, Makoto Miyara³, Pierre Moine¹⁵, Jean-Michel Molina¹⁸, Anaïs Montegnies-Boulet⁵, Alexandra Monti²¹, Claire Montlahuc¹⁸, Anne-Lise Montout³, Alexandre Moores⁵, Caroline Morbieu², Helene Mortelette¹⁴, Stéphane Mouly⁷, Rosita Muzaffar¹⁸, Cherifa

Iness Nacerddine³, Marine Nadal¹², Hajer Nadi³, Kladoum Nassarmadj⁷, Pierre Natella¹⁷, Sandrine Ndingamondze³, Stefan Neraal⁵, Caroline Nguyen⁶, Bao N'Guyen³, Isabelle Nion Larmurier⁴, Luc Niomenyengue¹⁴, Nicolas Noel⁹, Hilario Nunes², Edris Omar³, Zineb Ouazene⁴, Elise Ouedraogo², Wassila Ouelaa³, Anissa Oukhedouma³, Yasmina Ould Amara³, Herve Oya³, Johanna Oziel², Thomas Padilla³, Elena Paillaud²⁶, Solenne Paiva³, Beatrice Parfait⁵, Perrine Parize¹¹, Christophe Parizot³, Antoine Parrot¹², Arthur Pavot⁹, Laetitia Peaudecerf⁵, Frédéric Pene⁵, Marion Pepin¹⁰, Julie Pernet³, Claire Pernin⁷, Mylène Petit², Olivier Peyrony¹⁸, Marie-Pierre Pietri²², Olivia Pietri⁴, Marc Pineton De Chambrun³, Michelle Pinson¹³, Claire Pintado¹⁸, Valentine Piquard⁶, Christine Pires³, Benjamin Planquette¹⁴, Sandrine Poirier⁸, Anne-Laure Pomel⁸, Stéphanie Pons³, Diane Ponscarne¹⁸, Anne Roux⁴, Claire Rouzard⁹, Valérie Pourcher³, Anne Pouvart¹¹, Florian Prever⁴, Miresta Previlon¹⁸, Margot Prevost³, Marie-Julie Provoost⁷, Cyril Quemeneur³, Cédric Rafat¹², Agathe Rami⁷, Brigitte Ranque¹⁴, Maurice Raphael⁹, Jean Herle Raphaelen¹¹, Anna Rastoin⁷, Mathieu Raux³, Amani Rebai², Michael Reby²⁵, Alexis Regent⁵, Asma Regrag¹⁴, Matthieu Resche-Rigon¹⁸, Quentin Ressaire¹⁸, Christian Richard⁹, Mariacarine Richard³, Maxence Robert³, Benjamin Rohaut³, Camille Rolland-Debord¹², Jacques Ropers³, Anne-Marie Roque-Afonso²⁴, Charlotte Rosso³⁰, Mélanie Rousseaux⁴, Nabila Rousseaux³, Swasti Roux²⁶, Lorène Roux⁴, Claire Rouzard¹¹, Antoine Rozes³, Emma Rubenstein⁷, Jean-Marc Sabate², Sheila Sabet¹², Sophie-Caroline Sacleux²⁴, Nathalie Saldenberg Kermanach², Faouzi Saliba²⁴, Dominique Salmon²², Laurent Savale³¹, Guillaume Savary³, Rebecca Sberro¹¹, Anne Scemla¹¹, Frederic Schlemmer¹⁷, Mathieu Schwartz⁷, Saïd Sedfi³, Samia Sefir-Kribel⁵, Philippe Seksik⁴, Pierre Sellier⁷, Agathe Selves³, Nicole Sembach¹⁴, Luca Semerano², Marie-Victoire Senat⁹, Damien Sene⁷, Alexandra Serris¹¹, Lucile Sese², Naima Sghiouar¹⁵, Johanna Sigaux², Martin Siguier¹², Johanne Silvain³, Noémie Simon³, Tabassome Simon⁴, Lina Innes Skandri², Miassa Slimani², Aurélie Snauwaert⁶, Harry Sokol⁴, Heithem Soliman⁴, Nisrine Soltani⁹, Benjamin Soyer⁷, Gabriel Steg⁶, Lydia Suarez⁷, Tali-Anne Szwebel⁵, Kossi Taffame³, Yacine Tandraoui-Lambiotte², Claire Tantet², Mariagrazia Tateo¹⁸, Igor Theodose¹⁸, Pierre clement Thiebaud⁴, Caroline Thomas⁴, Kelly Tiercelet¹⁸, Julie Tisserand⁹, Carole Tomczak¹⁸, Krystel Torelino³, Fatima Touam-Ext¹¹, Lilia Toumi¹¹, Gustave Toury¹⁴, Mireille Toy-Miou³, Olivia Tran Dinh Thanh Lien⁷, Alexy Trandinh⁶, Jean-Marc Treluyer⁵, Baptiste Tringue⁷, Jennifer Truchot⁷, Florence Tubach³, Sarah Tubiana⁶, Simone Tunesi¹⁹, Matthieu Turpin¹², Agathe Turpin³, Tomas Urbina⁴, Rafael Usubillaga Narvaez²², Yurdagül Uzunhan², Prabakar Vaithinadaayar²⁷, Arnaud Valent¹⁸, Maelle Valentian¹², Nadia Valin⁴, Héléne Vallet⁴, Marina Vaz³, Miguel-Alejandro Vazquezibarra⁷, Benoit Vedie¹⁴, Laetitia Velly³, Céline Verstuyft⁹, Cedric Viallette³, Eric Vicaut⁷, Dorothee Vignes⁸, Damien Vimperc¹¹, Myriam Virlovet⁹, Guillaume Voirot¹², Lena Voisot²¹, Emmanuel Weiss²⁷, Nicolas Weiss³, Anaïs Winchenne², Youri Yordanov⁴, Lara Zafrani¹⁸, Mohamad Zaidan⁹, Wisssem Zaidi⁴, Cathia Zak¹², Aida Zarhrate-Ghouli³, Ouassila Zatout⁶, Suzanne Zeino⁹, Michel Zeitouni³, Naïma Zemirli³, Lorene Zerah³, Ounsa Zia³, Marianne Zioli¹⁹, Oceane Zolario⁴, Julien Zuber¹¹

¹DRCI-APHP, Paris, France, ²Hôpital Avicenne, Bobigny, France, ³Hôpital Pitié-Salpêtrière, Paris, France, ⁴Hôpital Saint-Antoine, Paris, France, ⁵Hôpital Cochin, Paris, France, ⁶Hôpital Bichat, Paris, France, ⁷Hôpital Lariboisière, Paris, France, ⁸Hôpital Antoine Bécclère, Clamart, France, ⁹Hôpital Kremlin Bicêtre, Le Kremlin-Bicêtre, France, ¹⁰Hôpital Ambroise-Paré, Boulogne Billancourt, France, ¹¹Hôpital Necker Enfants malades, Paris, France, ¹²Hôpital Tenon, Paris, France, ¹³Hôpital Louis Mourier, Colombes, France, ¹⁴Hôpital Européen Georges Pompidou, Paris, France, ¹⁵Hôpital Raymond Poincaré, Garches, France, ¹⁶Hôpital Antoine Bécclère, Calmart, France, ¹⁷Hôpital Henri Mondor, Créteil, France, ¹⁸Hôpital Saint Louis, Paris, France, ¹⁹Hôpital Jean Verdier, Bondy, France, ²⁰Université Paris-Sorbonne, Hôpital Pitié-Salpêtrière, INSERM, Paris, France, ²¹Hôpital Charles Foix, Ivry-sur-Seine, France, ²²Hôpital Hôtel Dieu, Paris, France, ²³Hôpital Broca, Paris, France, ²⁴Hôpital Paul-Brousse, Villejuif, France, ²⁵Hôpital Rothschild, Paris, France, ²⁶Hôpital Corentin Celton, Issy-les-Moulineaux, France, ²⁷Hôpital Beaujon, Clichy, France, ²⁸Hôpital Albert Chenevier, Créteil, France, ²⁹Hôpital Sainte-Périne, Paris, France, ³⁰Université Paris-Sorbonne, Hôpital Pitié-Salpêtrière, INSERM, CNRS, Paris, France, ³¹Université Paris-Saclay, Hôpital Kremlin Bicêtre, INSERM, Le Kremlin-Bicêtre, France

Members of Amsterdam UMC Covid-19 Biobank: Michiel van Agtmael², Anne Geke Algera¹, Brent Appelman², Frank van Baarle¹, Diane Bax³, Martijn Beudel⁴, Harm Jan Bogaard⁵, Marije Bomers², Peter Bonta⁵, Lieuwe Bos¹, Michela Botta¹, Justin de Brabander², Godelieve de Bree², Sanne de Bruin¹, David T. P. Buis¹, Marianna Bugiani⁵, Esther Bulle¹, Osoul Chouchane² Alex Cloherty³, Mirjam Dijkstra¹², Dave A. Dongelmans¹, Romein W. G. Dujardin¹, Paul Elbers¹, Lucas Fleuren¹, Suzanne Geerlings² Theo Geijtenbeek³, Armand Girbes¹, Bram Goorhuis², Martin P. Grobusch², Florianne Hafkamp³, Laura Hagens¹, Jorg

Hamann⁷, Vanessa Harris², Robert Hemke⁸, Sabine M. Hermans², Leo Heunks¹, Markus Hollmann⁶, Janneke Horn¹, Joppe W. Hovius², Menno D. de Jong⁹, Rutger Koning⁴, Endry H. T. Lim¹, Niels van Mourik¹, Jeaninne Nellen², Esther J. Nossent⁵, Frederique Paulus¹, Edgar Peters², Dan A. I. Pina-Fuentes⁴, Tom van der Poll², Benedikt Preckel⁶, Jan M. Prins², Jorinde Raasveld¹, Tom Reijnders², Maurits C. F. J. de Rotte¹², Michiel Schinkel², Marcus J. Schultze¹, Femke A. P. Schrauwen¹², Alex Schuurmans¹⁰, Jaap Schuurmans¹, Kim Sigaloff¹, Marleen A. Slim¹², Patrick Smeele⁵, Marry Smit¹, Cornelis S. Stijns², Willelme Stijls¹, Charlotte Teunissen¹¹, Patrick Thorat¹, Anissa M. Tsonas¹, Pieter R. Tuinman², Marc van der Valk², Denise Veelo⁶, Carolien Volleman¹, Heder de Vries¹, Lonkeke A. Vught¹², Michèle van Vugt², Dorien Wouters¹², A. H. (Kooos) Zwinderman¹³, Matthijs C. Brouwer⁴, W. Joost Wiersinga², Alexander P. J. Vlaar¹, Diederik van de Beek⁴

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

Members of NIAID-USUHS COVID Study Group: Miranda F. Tompkins¹, Camille Alba¹, Andrew L. Snow², Daniel N. Hupalo¹, John Rosenberger¹, Gauthaman Sukumar¹, Matthew D. Wilkerson¹, Xijun Zhang¹, Justin Lack³, Andrew J. Oler⁴, Kerry Dobbis⁵, Ottavia M. Delmonte⁵, Jeffrey J. Danielson⁵, Andrea Biondi⁶, Laura Rachele Bettini⁶, Mariella D'Angio⁶, Ilaria Beretta⁷, Luisa Imberti⁸, Alessandra Sottini⁸, Virginia Quaresima⁸, Eugenia Quiros-Roldan⁹, Camillo Rossi¹⁰

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

Authors' contributions

D Matuozzo, ET, AM, JM, YS, YZ, A Bolze, MC, BM, P Zhang, LA, and AC performed computational analysis. D Matuozzo, AG, P Bastard, TA, LB, I Meyts, SYZ, A Puel, SBD, BB, EJ, and QZ performed or supervised experiments, generated and analyzed data, and contributed to the manuscript by providing figures and tables. P Bastard, FB, HA, AAT, AA, IAD, LMA, RAA, AAA, GA, P Bergman, SB, YTB, IGB, OCM, SC, PC, GC, KC, RC, CAN, OMD, LEZ, CF, PKG, MG, FH, RH, SH, LH, NH, AK, SK, CK, RLL, JLF, D Mansouri, JMP, OMA, I Migeotte, PEM, GM, AMN, GN, AN, TO, FP, QPH, RP, LPS, DEP, CP, A Pujol, LFR, JGR, CRG, JR, PRQ, MS, A Sobh, PSP, YTL, IT, CT, JT, MZ, P Zawadzki, SZAM, MFA, FMA, HBF, MJB, SNC, MAC, CLD, JF, JRH, YLL, RPL, TM, THM, HVB, AL, MV, A Boland, JFD, FM, ST, GG, FT, PH, LDN, and HCS evaluated and recruited patients and /or controls. CRG, CF, A Schlüter, MS, MZ, P Zawadzki, SZAM, HBF, MJB, SNC, MAC, CLD, JF, JRH, YLL, RPL, TM, THM, HVB, AL, MV, A Boland, JFD, RN, and AKK performed sequencing. D Matuozzo, BB, JLC, QZ, LA, and AC wrote the manuscript. JLC, QZ, LA and AC supervised the project. All the authors edited the manuscript. All authors read and approved the final manuscript.

Funding

The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI088364 and R01AI63029), the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercatus Center at George Mason University, the Yale Center for Mendelian Genomics and the GSP Coordinating Center funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956), the Yale High Performance Computing Center (S10OD018521), the Fisher Center for Alzheimer's Research Foundation, the JPB Foundation, the Meyer Foundation, the French National Research Agency (ANR) under the "Investments for the Future" program (ANR-10-IJAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID), the French Foundation for Medical Research (FRM) (EQU201903007798), the ANR GenMISC (ANR-21-COVR-039), the ANRS-COV05, ANR GENVIR (ANR-20-CE93-003) ANR AABIFNCOV (ANR-20-CO11-0001) projects, the ANR-RHU program COVIF-ERON (ANR-21-RHUS-08), the European Union's Horizon 2020 research and innovation program under grant agreement No. 824110 (EASI-genomics), the HORIZON-HLTH-2021-DISEASE-04 program under grant agreement 01057100 (UNDINE), the Square Foundation, Grandir—Fonds de solidarité pour l'enfance, Fondation du Souffle, the SCOR Corporate Foundation for Science, the Battersea & Bowery Advisory Group, The French Ministry of Higher Education, Research, and Innovation (MESRI-COVID-19), Institut National de la Santé et de la Recherche Médicale (INSERM), REACTing-INSERM and the University of Paris Cité. The study was supported by the ORCHESTRA project, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 10101616. P Bastard was supported by the MD-PhD program of the Imagine Institute (with the support of the Fondation Bettencourt-Schueller). The French COVID Cohort study group was sponsored by INSERM and supported by the REACTing consortium and by a grant from the French Ministry of Health (Grant PHRC 20-0424). The Cov-Contact Cohort was supported by the REACTing consortium, the French Ministry of Health, and the European Commission (Grant RECOVER WP 6). The COVIDeF study was supported by the French Ministry of Health, Fondation AP-HP et Programme Hospitalier de Recherche Clinique (PHRC COVID-19-20-0048) and was sponsored by APHP. Y.Z., O.M.D., L.D.N., H.C.S. are supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, NIH. G.N. and A.N. are supported by Regione Lazio (Research Group Projects 2020) No. A0375-2020-36663, GecoBiomark. I Meyts is a Senior Clinical Investigator at the Research Foundation – Flanders, and is supported by the CSL Behring Chair of Primary Immunodeficiencies, by the KU Leuven C1 Grant C16/18/007, by a VIB GC PID Grant, by the FWO Grants G0C8517N, G0B5120N and G0E8420N and by the Jeffrey Modell Foundation. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 948959). This work is supported by the Swiss National Science Foundation (grant # 310030L_197721 to JF). This work is supported by ERN-RITA. The Canarian Sequencing Hub is funded by Instituto de Salud Carlos III (COV20_01333, and COV20_01334, and PI20/00876) and Spanish Ministry of Science and Innovation (RTC-2017-6471-1; AEI/FEDER, UE), co-financed by the European Regional Development Funds, "A way of making Europe" from the European Union, and Cabildo Insular de Tenerife (CGIEU0000219140 and "Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19"). This work was funded, at least in part, by grant AJF202059 from Al Jalila Foundation, Dubai, United Arab Emirates. Sample processing at IrsiCaixa was possible thanks to the crowdfunding initiative YoMeCorono. We thank I Erkizia, E Grau, M Massanella, and J Guitart from the IrsiCaixa and Hospital Germans Trias i Pujol (Badalona, Spain) for sample collection, handling and processing.

Availability of data and materials

Data supporting the findings of this study are available within the manuscript and supplemental files. The whole-genome sequencing data of anonymized patients recruited through the National Institutes of Health (NIH) and sequenced at the National Institute of Allergy and Infectious Diseases (NIAID) through the Uniformed Services University of the Health Sciences (USUHS)/ the American Genome Center (TAGC) are available under dbGaP submission phs002245.v1. Other patients were not consented to share the raw WES/WGS data files beyond the research and clinical teams.

Declarations

Ethics approval and consent to participate

All the enrolled participants provided written informed consent for participation and were recruited 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 CORONA lab). STORM-Health care workers were enrolled in the STUDIO OsseRazionale sullo screening dei lavoratori ospedalieri per COVID-19 (STORM-HCW) study, with approval from the local institutional review board (IRB) obtained on June 18, 2020. Patients and relatives from San Raffaele Hospital (Milan) were enrolled in COVID-BioB/Gene-COVID protocols and, for additional studies, TIGET-06, with the approval of the local ethics committee. Patients and relatives from Rome were enrolled in Protocol no. 50/20 (Tor Vergata University Hospital). Informed consent was obtained from each patient. For the patients enrolled in the COVIDeF Study Group (ClinicalTrials.gov NCT04352348), ethics approval was obtained from the Comité de Protection des Personnes Ile de France XI (ID RCB, 2020-A00754-35). For patients enrolled in Spain, the study was approved by the Committee for Ethical Research of the Infanta Leonor University Hospital, code 008–20; the Committee for Ethical Research of the 12 de Octubre University Hospital, 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 the 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).

Consent for publication

Not applicable.

Competing interests

RN and AKK are employees of Invitae and hold equities in the company. RPL is a member of the board of directors of Roche and its subsidiary Genentech. I Meys holds a chair in Primary Immunodeficiencies and receives research grant from CSL Behring, paid to KUL. JLC reported a patent to PCT/US2021/042741 pending. FT is head of the Centre de Pharmacopépidémiologie (Cephepi) of the Assistance Publique – Hôpitaux de Paris and of the Clinical Research Unit of Pitié-Salpêtrière hospital, both these structures have received unrestricted research funding and grants for the research projects handled and fees for consultant activities from a large number of pharmaceutical companies, that have contributed indiscriminately to the salaries of its employees. FT is not employed by these structures and did not receive any personal remuneration from these companies. The remaining authors declare that they have no competing interests.

Author details

¹Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Paris, France. ²University Paris Cité, Imagine Institute, Paris, France. ³St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. ⁴Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, Bethesda, MD, USA. ⁵Helix, San Mateo, CA, USA. ⁶Pediatric Hematology-Immunology and Rheumatology Unit, Necker Hospital for Sick Children, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. ⁷Department of Paediatric Immunohematology, IRCCS San Raffaele Scientific Institute, Milan, Italy. ⁸Department of Biosciences and Nutrition, Karolinska Institute, Stockholm, Sweden. ⁹Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children’s Medical Center, Tehran, Iran. ¹⁰Genomics Center

of Excellence, Al Jalila Children’s Specialty Hospital, Dubai, United Arab Emirates. ¹¹Center for Genomic Discovery, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates. ¹²San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute, Milan, Italy. ¹³Vita-Salute San Raffaele University, Milan, Italy. ¹⁴Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹⁵Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹⁶Immunology Department, University Hospital 12 de Octubre, Research Institute imas12 and Complutense University, Madrid, Spain. ¹⁷Immunology Department, Hospital Universitario Central de Asturias; Health Research Institute of Principality of Asturias, Oviedo, Spain. ¹⁸Department of Microbiology and Parasitology, Primary Immunodeficiencies Group, School of Medicine, University of Antioquia UdeA, 050010 Medellín, Colombia. ¹⁹School of Microbiology, University of Antioquia UdeA, 050010 Medellín, Colombia. ²⁰Department of Internal Medicine, Division of Allergy and Immunology, Konya City Hospital, Konya, Turkey. ²¹Department of Infectious Diseases, The Immunodeficiency Unit, Karolinska University Hospital, Stockholm, Sweden. ²²Department of Laboratory Medicine, Division of Clinical Immunology, Stockholm, Sweden. ²³Clinical Genomics, IRCCS San Raffaele Scientific Institute, Milan, Italy. ²⁴Department of Medicine, Centre for Hematology and Regenerative Medicine, Karolinska Institute, Stockholm, Sweden. ²⁵Universidad de La Sabana, Chia, Colombia. ²⁶Institute of Biomedical Research of IdiPAZ, University Hospital “La Paz”, Madrid, Spain. ²⁷Unidad de Gestión Clínica de Cuidados Intensivos, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofía, Universidad de Córdoba (UCO), Córdoba, Spain. ²⁸Division of Genetics and Cell Biology, Genome-Phenome Relationship, San Raffaele Hospital, Milan, Italy. ²⁹School of Medicine, Vita-Salute San Raffaele University, Milan, Italy. ³⁰Intensive Care Unit Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Bobigny, France. ³¹Common and Rare Kidney Diseases, Sorbonne University, INSERM UMR-S 1155, Paris, France. ³²Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain. ³³Translational Immunology Research Group, Vall d’Hebron Research Institute (VHIR), Vall d’Hebron University Hospital (HUVH), Vall d’Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ³⁴Genetics Department, Immunology Division, Vall d’Hebron University Hospital (HUVH), Vall d’Hebron Barcelona Hospital Campus, Autonomous University of Barcelona (UAB), Barcelona, Catalonia, Spain. ³⁵Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil. ³⁶Biology Department, Lebanese University, Beirut, Lebanon. ³⁷Genomics Division, Institute of Technology and Renewable Energies (ITER), Santa Cruz de Tenerife, Spain. ³⁸CIBER de Enfermedades Respiratorias, Carlos III Health Institute, Madrid, Spain. ³⁹Research Unit, University Hospital of Ntra. Sra. de Candelaria, Santa Cruz de Tenerife, Spain. ⁴⁰Faculty of Health Sciences, University of Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁴¹Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA. ⁴²CNAG-CRG, Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology (BIST), Barcelona, Spain. ⁴³Department of Internal Diseases and Pediatrics, Primary Immune Deficiency Research Laboratory, Centre for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Centre, Ghent, Belgium. ⁴⁴Research Institute for Medical and Health Sciences, University of Sharjah, Sharjah, United Arab Emirates. ⁴⁵Department of Pediatrics (Infectious Diseases), Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey. ⁴⁶Pediatric Infectious Diseases Unit, Bakirkoy Dr Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ⁴⁷Department of Pediatric Infectious Disease, Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey. ⁴⁸Meram Medical Faculty, Pediatric Infectious Diseases Department, Necmettin Erbakan University, Konya, Turkey. ⁴⁹Department of General Paediatrics, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, University of Paris Saclay, Le Kremlin-Bicêtre, France. ⁵⁰Primary Immunodeficiencies Group, Department of Microbiology and Parasitology, School of Medicine, University of Antioquia UDEA, Medellín 050010, Colombia. ⁵¹The Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁵²Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁵³Pediatric Respiratory Diseases

Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ⁵⁴IrsiCaixa AIDS Research Institute and Institute for Health Science Research Germans Trias I Pujol (IGTP), Badalona, Spain. ⁵⁵Institute for Health Science Research Germans Trias I Pujol (IGTP), Badalona, Spain. ⁵⁶Department of Infectious Diseases and Immunity, University of Vic–Central University of Catalonia, Vic, Spain. ⁵⁷Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain. ⁵⁸Consorcio Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain. ⁵⁹Centre de Génétique Humaine de L'Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium. ⁶⁰Laboratory of Haematology, La Timone Hospital, Marseille, France. ⁶¹C2VN, INSERM, INRAE, Aix-Marseille University, Marseille, France. ⁶²Pediatric Infectious Diseases and Immunodeficiencies Unit, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus, Autonomous University of Barcelona (UAB), Barcelona, Catalonia, Spain. ⁶³Infection and Immunity in 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. ⁶⁴Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy. ⁶⁵IRCCS Neuromed, Pozzilli, Italy. ⁶⁶Laboratory of Medical Genetics, Translational Cytogenomics Research Unit, Bambino Gesù Children Hospital, IRCCS, Rome, Italy. ⁶⁷Department of Molecular Biology and Genetics, Bilkent University, Ankara, Turkey. ⁶⁸Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, University Hospital "La Paz", Madrid, Spain. ⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Catalonia, Spain. ⁷⁰Center for Biomedical Research On Rare Diseases (CIBERER), ISCIII, Madrid, Spain. ⁷¹Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ⁷²Universidad de La Sabana, Chía, Colombia. ⁷³Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁷⁴Department of Clinical Sciences, University of Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁷⁵Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy. ⁷⁶Specialized Immunology Laboratory of Dr Shahrooei, Sina Medical Complex, Ahvaz, Iran. ⁷⁷Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. ⁷⁸Department of Pediatrics, Mansoura University Children's Hospital, Mansoura University Faculty of Medicine, Mansoura, Egypt. ⁷⁹Hypoxia and Lung, INSERM U1272, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Bobigny, France. ⁸⁰Department of Life Sciences, School of Science, University of Management and Technology, Lahore, Pakistan. ⁸¹Division of Immunology, Transplantation and Infectious Diseases, IRCCS Ospedale San Raffaele, Milan, Italy. ⁸²Department of Internal Medicine, Infanta Leonor University Hospital, Madrid, Spain. ⁸³Department of Neurology, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, Netherlands. ⁸⁴Biosciences Institute, University of São Paulo, São Paulo, Brazil. ⁸⁵Gordion Bioscience Inc, Cambridge, MA, USA. ⁸⁶Faculty of Physics, Adam Mickiewicz University, Poznan, Poland. ⁸⁷Department of Pediatrics, Immunology Research Laboratory, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. ⁸⁸The Genetics Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. ⁸⁹Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁹⁰Departments of Pediatrics and Microbiology, Immunology, and Molecular Genetics, Division of Immunology, Allergy, and Rheumatology, University of California Los Angeles, Los Angeles, CA, USA. ⁹¹Ludwig Institute for Cancer Research, Brussels, Belgium. ⁹²SIGN Unit, de Duve Institute, Université Catholique de Louvain, Brussels, Belgium. ⁹³WELBIO (Walloon Excellence in Life Sciences and Biotechnology), Brussels, Belgium. ⁹⁴Nuffield Department of Medicine, Ludwig Institute for Cancer Research, Oxford University, Oxford, UK. ⁹⁵Department of Pediatrics, Division of Rheumatology/Immunology, Washington University in St. Louis, St. Louis, MO, USA. ⁹⁶The American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, USA. ⁹⁷Department of Anatomy, Physiology & Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁹⁸School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland. ⁹⁹Swiss Institute of Bioinformatics, Lausanne, Switzerland. ¹⁰⁰Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ¹⁰¹Institute for Systems Biology, Seattle, WA, USA. ¹⁰²Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China. ¹⁰³Laboratory of Genetics and Genomics,

The Rockefeller University, New York, NY, USA. ¹⁰⁴Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. ¹⁰⁵Yale Center for Genome Analysis, Yale School of Medicine, New Haven, CT, USA. ¹⁰⁶Zukerman Mind Brain Behavior Institute, Columbia University, New York, NY, USA. ¹⁰⁷New York Genome Center, New York, NY, USA. ¹⁰⁸Department of Biomedicine, Aarhus University, Aarhus, Denmark. ¹⁰⁹Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark. ¹¹⁰Department of Paediatric Respiratory Medicine, Immunology, and Critical Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany. ¹¹¹Laboratoire de Biologie Médicale Multisites Seqoia, MG2025, MG2025 Paris, France. ¹¹²Université Paris-Saclay, CEA, Centre National de Recherche en Génomique Humaine (CNRGH), Evry, France. ¹¹³Invitae, San Francisco, CA, USA. ¹¹⁴Unité de Recherche Clinique, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France. ¹¹⁵Centre d'Investigation Clinique, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France. ¹¹⁶Sorbonne Université, INSERM Centre d'immunologie et des Maladies Infectieuses, CIMI-Paris, Département d'immunologie Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France. ¹¹⁷Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Pitié Salpêtrière, Département de Santé Publique, Unité de Recherche Clinique PSL-CFX, CIC-1901, Paris, France. ¹¹⁸Emergency Department, Hôpital Pitié-Salpêtrière, APHP-Sorbonne Université, Paris, France. ¹¹⁹GRC-14 BIOFAST Sorbonne Université, UMR INSERM 1135, CIMI, Sorbonne Université, Paris, France. ¹²⁰Department of Microbiology, Immunology and Transplantation, Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium. ¹²¹Laboratory of Host Defenses, NIAID, National Institutes of Health, Bethesda, MA, USA. ¹²²Howard Hughes Medical Institute, New York, NY, USA.

Received: 15 September 2022 Accepted: 10 March 2023

Published online: 05 April 2023

References

- Zhang Q, Bastard P, Covid Human Genetic Effort, Cobat A, Casanova JL. Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature*. 2022;603:587–98.
- Covid Forecasting Team. Variation in the COVID-19 infection-fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis. *Lancet*. 2022;399:1469–88.
- O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature*. 2021;590:140–5.
- Bennett TD, Moffitt RA, Hajagos JG, Amor B, Anand A, Bissell MM, et al. Clinical characterization and prediction of clinical severity of SARS-CoV-2 infection among US adults using data from the US National COVID Cohort Collaborative. *JAMA Netw Open*. 2021;4:e2116901.
- Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature*. 2020;588:315–20.
- Initiative CHG. Mapping the human genetic architecture of COVID-19. *Nature*. 2021;600:472–7.
- Nakanishi T, Pigazzini S, Degenhardt F, Cordioli M, Butler-Laporte G, Maya-Miles D, et al. Age-dependent impact of the major common genetic risk factor for COVID-19 on severity and mortality. *J Clin Invest*. 2021;131. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/34597274>. [Cited 2022 Apr 29].
- Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in COVID-19. *Nature*. 2021;591:92–8.
- Zeberg H, Paabo S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature*. 2020;587:610–2.
- Initiative CHG. A first update on mapping the human genetic architecture of COVID-19. *Nature*. 2022;608:E1–10.
- Kousathanas A, Pairo-Castineira E, Rawlik K, Stuckey A, Odhams CA, Walker S, et al. Whole-genome sequencing reveals host factors underlying critical COVID-19. *Nature*. 2022;607:97–103.
- Namkoong H, Eda Hiro R, Takano T, Nishihara H, Shirai Y, Sonehara K, et al. DOCK2 is involved in the host genetics and biology of severe COVID-19. *Nature*. 2022;609:754–60.
- Zeberg H, Paabo S. A genomic region associated with protection against severe COVID-19 is inherited from Neandertals. *Proc Natl Acad Sci U A*. 2021;118:e2026309118.

14. Casanova JL, Su HC, Covid Human Genetic Effort. A Global Effort to Define the Human Genetics of Protective Immunity to SARS-CoV-2 Infection. *Cell*. 2020;181:1194–9.
15. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020;370:eabd4570.
16. Abolhassani H, Landegren N, Bastard P, Materna M, Modaresi M, Du L, et al. Inherited IFNAR1 deficiency in a child with both critical COVID-19 pneumonia and multisystem inflammatory syndrome. *J Clin Immunol*. 2022;42:471–83.
17. Khanmohammadi S, Rezaei N, Khazaei M, Shirvani A. A case of autosomal recessive interferon alpha/beta receptor alpha chain (IFNAR1) deficiency with severe COVID-19. *J Clin Immunol*. 2022;42:19–24.
18. Schmidt A, Peters S, Knaus A, Sabir H, Hamsen F, Maj C, et al. TBK1 and TNFRSF13B mutations and an autoinflammatory disease in a child with lethal COVID-19. *NPJ Genom Med*. 2021;6:55.
19. Zhang Q, Matuozzo D, Le Pen J, Lee D, Moens L, Asano T, et al. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. *J Exp Med*. 2022;219:e20220131.
20. Ogishi M, Arias A, Yang R, Han JE, Zhang P, Rinchai D, et al. Impaired IL-23-dependent induction of IFN- γ underlies mycobacterial disease in patients with inherited TYK2 deficiency. *J Exp Med*. 2022;219(10):e20220094. <https://doi.org/10.1084/jem.20220094>.
21. Butler-Laporte G, Povysil G, Kosmicki JA, Cirulli ET, Drivas T, Furini S, et al. Exome-wide association study to identify rare variants influencing COVID-19 outcomes: Results from the Host Genetics Initiative. *PLoS Genet*. 2022;18:e1010367.
22. Kosmicki JA, Horowitz JE, Banerjee N, Lanche R, Marcketta A, Maxwell E, et al. Pan-ancestry exome-wide association analyses of COVID-19 outcomes in 586,157 individuals. *Am J Hum Genet*. 2021;108:1350–5.
23. Povysil G, Butler-Laporte G, Shang N, Wang C, Khan A, Alaamery M, et al. Rare loss-of-function variants in type I IFN immunity genes are not associated with severe COVID-19. *J Clin Invest*. 2021;131. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/34043590>. [Cited 2022 Apr 29].
24. Zhang Q, Cobat A, Bastard P, Notarangelo LD, Su HC, Abel L, et al. Association of rare predicted loss-of-function variants of influenza-related type I IFN genes with critical COVID-19 pneumonia. *J Clin Invest*. 2021;131. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/34166232>. [Cited 2022 Apr 29].
25. Casanova JL, Abel L. Mechanisms of viral inflammation and disease in humans. *Science*. 2021;374(6571):1080–6. <https://doi.org/10.1126/science.abj7965>
26. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370:eabd4585.
27. Bastard P, Gervais A, Le Voyer T, Rosain J, Philippot Q, Manry J, et al. 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*. 2021;6:eabl4340.
28. Casanova JL, Abel L. From rare disorders of immunity to common determinants of infection: following the mechanistic thread. *Cell*. 2022;185:3086–103.
29. Manry J, Bastard P, Gervais A, Le Voyer T, Rosain J, Philippot Q, et al. The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies. *Proc Natl Acad Sci U A*. 2022;119:e2200413119.
30. Asano T, Boisson B, Onodi F, Matuozzo D, Moncada-Velez M, Maglorius Renkilaraj MRL, et al. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. *Sci Immunol*. 2021;6:eabl4348.
31. van der Made CI, Netea MG, van der Veerdonk FL, Hoischen A. Clinical implications of host genetic variation and susceptibility to severe or critical COVID-19. *Genome Med*. 2022;14:96.
32. Fallerini C, Daga S, Mantovani S, Benetti E, Picchiotti N, Francisci D, et al. Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study. *Elife*. 2021;10:e67569.
33. Mantovani S, Daga S, Fallerini C, Baldassarri M, Benetti E, Picchiotti N, et al. Rare variants in Toll-like receptor 7 results in functional impairment and downregulation of cytokine-mediated signaling in COVID-19 patients. *Genes Immun*. 2022;23:51–6.
34. Pessoa NL, Bentes AA, de Carvalho AL, de Souza Silva TB, Alves PA, de Sousa Reis EV, et al. Case report: hepatitis in a child infected with SARS-CoV-2 presenting toll-like receptor 7 Gln11Leu single nucleotide polymorphism. *Virology*. 2021;18:180.
35. Solanich X, Vargas-Parra G, van der Made CI, Simons A, Schuurs-Hoeijmakers J, Antoli A, et al. Genetic screening for TLR7 variants in young and previously healthy men with severe COVID-19. *Front Immunol*. 2021;12:719115.
36. van der Made CI, Simons A, Schuurs-Hoeijmakers J, van den Heuvel G, Mantere T, Kersten S, et al. Presence of genetic variants among young men with severe COVID-19. *JAMA*. 2020;324:663–73.
37. Brown GJ, Canete PF, Wang H, Medhavy A, Bones J, Roco JA, et al. TLR7 gain-of-function genetic variation causes human lupus. *Nature*. 2022;605:349–56.
38. Barreiro LB, Quintana-Murci L. From evolutionary genetics to human immunology: how selection shapes host defence genes. *Nat Rev Genet*. 2010;11:17–30.
39. Zhang P, Philippot Q, Ren W, Lei WT, Li J, Stenson PD, et al. Genome-wide detection of human variants that disrupt intronic branchpoints. *Proc Natl Acad Sci*. 2022;119:e2211194119.
40. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–75.
41. Belkadi A, Pedergrana V, Cobat A, Itan Y, Vincent QB, Abhyankar A, et al. Whole-exome sequencing to analyze population structure, parental inbreeding, and familial linkage. *Proc Natl Acad Sci U A*. 2016;113:6713–8.
42. Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Res*. 2019;47:D886–94.
43. Itan Y, Shang L, Boisson B, Ciancanelli MJ, Markle JG, Martinez-Barricarte R, et al. The mutation significance cutoff: gene-level thresholds for variant predictions. *Nat Methods*. 2016;13:109–10.
44. Efficient and Parallelizable Association Container Toolbox (EPACTS). Available from: <https://genome.sph.umich.edu/wiki/EPACTS>.
45. R Core Team. R: A language and environment for statistical computing. Vienna, Austria; 2022. Available from: <https://www.R-project.org/>.
46. Heinze G, Ploner M, Jiricka L. logistf: Firth's Bias-Reduced Logistic Regression. R package version 1.24.1.; Available from: <https://CRAN.R-project.org/package=logistf>.
47. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80:27.
48. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26:2190–1.
49. Patin E, Kutalik Z, Guernon J, Bibert S, Nalpas B, Jouanguy E, et al. Genome-wide association study identifies variants associated with progression of liver fibrosis from HCV infection. *Gastroenterology*. 2012;143:1244–1252 e12.
50. Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Hered Edinb*. 2005;95:221–7.
51. Verot L, Chikh K, Freydiere E, Honore R, Vanier MT, Millat G. Niemann-Pick C disease: functional characterization of three NPC2 mutations and clinical and molecular update on patients with NPC2. *Clin Genet*. 2007;71:320–30.
52. Carette JE, Raaben M, Wong AC, Herbert AS, Obernosterer G, Mulherkar N, et al. Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. *Nature*. 2011;477:340–3.
53. Zhao Y, Ren J, Harlos K, Stuart DI. Structure of glycosylated NPC1 luminal domain C reveals insights into NPC2 and Ebola virus interactions. *FEBS Lett*. 2016;590:605–12.
54. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, et al. A genome-wide CRISPR screen identifies host factors that regulate SARS-CoV-2 entry. *Nat Commun*. 2021;12:961.
55. Ostendorf BN, Patel MA, Bilanovic J, Hoffmann H-H, Carrasco SE, Rice CM, et al. Common human genetic variants of APOE impact murine COVID-19 mortality. *Nature*. 2022;611:346–51.

56. Curtis D. A weighted burden test using logistic regression for integrated analysis of sequence variants, copy number variants and polygenic risk score. *Eur J Hum Genet.* 2019;27:114–24.
57. Curtis D. A rapid method for combined analysis of common and rare variants at the level of a region, gene, or pathway. *Adv Appl Bioinforma Chem.* 2012;5:1–9. <https://doi.org/10.2147/AABC.S33049>.
58. Karlsen TH. Understanding COVID-19 through genome-wide association studies. *Nat Genet.* 2022;54:368–9.
59. Degenhardt F, Ellinghaus D, Juzenas S, Lerga-Jaso J, Wendorff M, Maya-Miles D, et al. Detailed stratified GWAS analysis for severe COVID-19 in four European populations. *Hum Mol Genet.* 2022;31:3945–66.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

