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► **To cite this version:**

Qian Zhang, Paul Bastard, Zhiyong Liu, Jérémie Le Pen, Marcela Moncada-Velez, et al.. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*, 2020, 370 (6515), pp.eabd4570. 10.1126/science.abd4570 . hal-02950982

HAL Id: hal-02950982

<https://hal.science/hal-02950982>

Submitted on 26 May 2021

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RESEARCH ARTICLE SUMMARY

CORONAVIRUS

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

Qian Zhang *et al.*

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

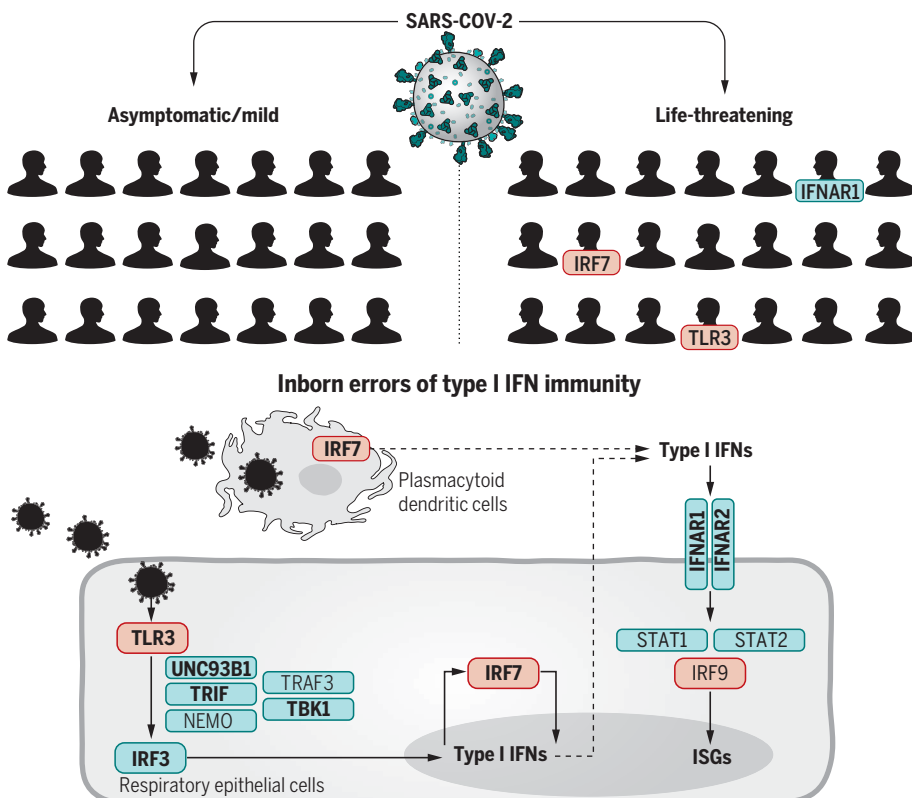
RATIONALE: We established the COVID Human Genetic Effort (www.covidhge.com) to test

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

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

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

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



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

The full author list and the list of affiliations is available in the full article online.

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RESEARCH ARTICLE

CORONAVIRUS

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

Qian Zhang¹, Paul Bastard^{2,3*}, Zhiyong Liu^{1*}, J  r  mie Le Pen^{4*}, Marcela Moncada-Velez^{1*}, Jie Chen^{1*}, Masato Ogishi^{1*}, Ira K. D. Sabli^{5*}, Stephanie Hodeib^{5*}, Cecilia Korol^{2*}, J  r  mie Rosain^{2,3*}, Kaya Bilguvar^{6*}, Junqiang Ye^{7*}, Alexandre Bolze^{8*}, Benedetta Bigio^{1*}, Rui Yang^{1*}, Andr  s Augusto Arias^{1,9,10*}, Qinhu Zhou^{1*}, Yu Zhang^{11,12*}, Fanny Onodj¹³, Sarantis Korniotis¹³, L  a Karpf¹³, Quentin Philippot^{2,3}, Marwa Chbihi^{2,3}, Lucie Bonnet-Madin¹⁴, Karim Dorgham¹⁵, Nikaia Smith¹⁶, William M. Schneider⁴, Brandon S. Razoooky⁴, Hans-Heinrich Hoffmann⁴, Eleftherios Michailidis⁴, Leen Moens¹⁷, Ji Eun Han¹, Lazaro Lorenzo^{2,3}, Lucy Bizien^{2,3}, Philip Meade¹⁸, Anna-Lena Neehus^{2,3}, Aileen Camille Ugurbil¹, Aur  lien Corneau¹⁹, Gaspard Kerner^{2,3}, Peng Zhang¹, Franck Rapaport¹, Yoann Seeleuthner^{2,3}, Jeremy Manry^{2,3}, Cecile Masson²⁰, Yohann Schmitt²⁰, Agatha Schl  ter²¹, Tom Le Voyer^{2,3}, Taushif Khan²², Juan Li¹, Jacques Fellay^{23,24,25}, Lucie Roussel²⁶, Mohammad Shahrooei^{27,28}, Mohammed F. Alosaimi²⁹, Davood Mansouri^{30,31,32}, Haya Al-Saud³³, Fahd Al-Mulla³⁴, Feras Almourfi³³, Saleh Zaid Al-Muhsen³⁵, Fahad Alshohime²⁹, Saeed Al Turki^{36,37}, Rana Hasanato²⁹, Diederik van de Beek³⁸, Andrea Biondi³⁹, Laura Rachele Bettini³⁹, Mariella D'Angio³⁹, Paolo Bonfanti⁴⁰, Luisa Imberti⁴¹, Alessandra Sottini⁴¹, Simone Paghera⁴¹, Eugenia Quiros-Roldan⁴², Camillo Rossi⁴³, Andrew J. Oler⁴⁴, Miranda F. Tompkins⁴⁵, Camille Alba⁴⁵, Isabelle Vandernoot⁴⁶, Jean-Christophe Goffard⁴⁷, Guillaume Smits⁴⁶, Isabelle Migeotte⁴⁸, Filomeen Haerynck⁴⁹, Pere Soler-Palacin⁵⁰, Andrea Martin-Nalda⁵⁰, Roger Colobran⁵¹, Pierre-Emmanuel Morange⁵², Sevgi Keles⁵³, Fatma   lkesen⁵⁴, Tayfun Ozcelik⁵⁵, Kadriye Kart Yasar⁵⁶, Sevtaep Senoglu⁵⁶,   semi Nur Karabela⁵⁶, Carlos Rodr  guez-Gallego^{57,58}, Giuseppe Novelli⁵⁹, Sami Hraiech⁶⁰, Yacine Tandjaoui-Lambiotte^{61,62}, Xavier Duval^{63,64}, C  dric Laouenan^{63,64,65}, COVID-STORM Clinicians†, COVID Clinicians†, Imagine COVID Group†, French COVID Cohort Study Group†, CoV-Contact Cohort†, Amsterdam UMC Covid-19 Biobank†, COVID Human Genetic Effort†, NIAID-USUHS/TAGC COVID Immunity Group†, Andrew L. Snow⁶⁶, Clifton L. Dalgard^{45,67}, Joshua D. Milner⁶⁸, Donald C. Vinh²⁶, Trine H. Mogensen^{69,70}, Nico Marr^{22,71}, Andr  s N. Spaan^{1,72}, Bertrand Boisson^{1,2,3}, St  phanie Boisson-Dupuis^{1,2,3}, Jacinta Bustamante^{1,2,3,73}, Anne Puel^{1,2,3}, Michael J. Ciancanelli^{1,74}, Isabelle Meyts^{17,75}, Tom Maniatis^{7,76}, Vassili Soumelis^{13,77}, Ali Amara¹⁴, Michel Nussenzweig^{78,79}, Adolfo Garc  a-Sastre^{18,80,81,82}, Florian Kramer¹⁸, Aurora Pujol²¹, Darragh Duffy¹⁶, Richard P. Lifton^{83,84,85}†, Shen-Ying Zhang^{1,2,3}†, Guy Gorochov¹⁵†, Vivien B  ziat^{1,2,3}†, Emmanuelle Jouanguy^{1,2,3}†, Vanessa Sancho-Shimizu⁵†, Charles M. Rice⁴†, Laurent Abel^{1,2,3}†, Luigi D. Notarangelo^{11,12}  , Aur  lie Cobat^{1,2,3}  , Helen C. Su^{11,12}  , Jean-Laurent Casanova^{1,2,3,79,86}  ¶

Clinical outcome upon infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ranges from silent infection to lethal coronavirus disease 2019 (COVID-19). We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (IRF7)-dependent type I interferon (IFN) immunity to influenza virus in 659 patients with life-threatening COVID-19 pneumonia relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally defined LOF variants underlying autosomal-recessive or autosomal-dominant deficiencies in 23 patients (3.5%) 17 to 77 years of age. We show that human fibroblasts with mutations affecting this circuit are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already claimed at least 1 million lives, has been detected in at least 20 million people, and has probably infected at least another 200 million. The clinical manifestations range from silent infection to lethal disease, with an infection fatality rate of 0.1 to 0.9%. Three epidemiological factors increase the risk of severity: (i) increasing age, decade by decade, after the age of 50, (ii) being male,

and (iii) having various underlying medical conditions (1). However, even taking these factors into account, there is immense inter-individual clinical variability in each demographic category considered. Following on from our human genetic studies of other severe infectious diseases (2, 3), we established the COVID Human Genetic Effort (<https://www.covidhge.com>) to test the general hypothesis that in some patients, life-threatening coronavirus disease 2019 (COVID-19) may be

caused by monogenic inborn errors of immunity to SARS-CoV-2 with incomplete or complete penetrance (4). We enrolled 659 patients (74.5% men and 25.5% women, 13.9% of whom died) of various ancestries between 1 month and 99 years of age (Fig. 1A). These patients were hospitalized for life-threatening pneumonia caused by SARS-CoV-2 (critical COVID-19). We sequenced their whole genome ($N = 364$) or exome ($N = 295$), and principal component analysis (PCA) on these data confirmed their ancestries (Fig. 1B).

Candidate variants at 13 human loci that govern immunity to influenza virus

We first tested the specific hypothesis that inborn errors of Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (IRF7)-dependent type I interferon (IFN) immunity, which underlie life-threatening influenza pneumonia, may also underlie life-threatening COVID-19 pneumonia (5) (Fig. 2). We considered three loci previously shown to be mutated in patients with critical influenza pneumonia: *TLR3* (6), *IRF7* (7), and *IRF9* (8). We also considered 10 loci mutated in patients with other viral illnesses but directly connected to the three core genes conferring influenza susceptibility: *TICAMI/TRIF* (9), *UNC93B1* (10), *TRAF3* (11), *TBK1* (12), *IRF3* (13), and *NEMO/IKBKG* (14) in the TLR3-dependent type I IFN induction pathway, and *IFNARI* (15), *IFNAR2* (16), *STAT1* (17), and *STAT2* (18) in the IRF7- and IRF9-dependent type I IFN amplification pathway. We collected both monoallelic and biallelic nonsynonymous variants with a minor allele frequency (MAF) <0.001 at all 13 loci. Twelve of the 13 candidate loci are autosomal, whereas *NEMO* is X-linked. For the latter gene, we considered only a recessive model (19). Autosomal-dominant (AD) inheritance has not been proven for six of the 12 autosomal loci (*UNC93B1*, *IRF7*, *IFNARI*, *IFNAR2*, *STAT2*, and *IRF9*). Nevertheless, we considered heterozygous variants because none of the patients enrolled had been hospitalized for critical viral infections before COVID-19, raising the possibility that any underlying genetic defects that they might have display a lower penetrance for influenza and other viral illnesses than for COVID-19, which is triggered by a more virulent virus.

Enrichment of variants predicted to be LOF at the influenza susceptibility loci

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

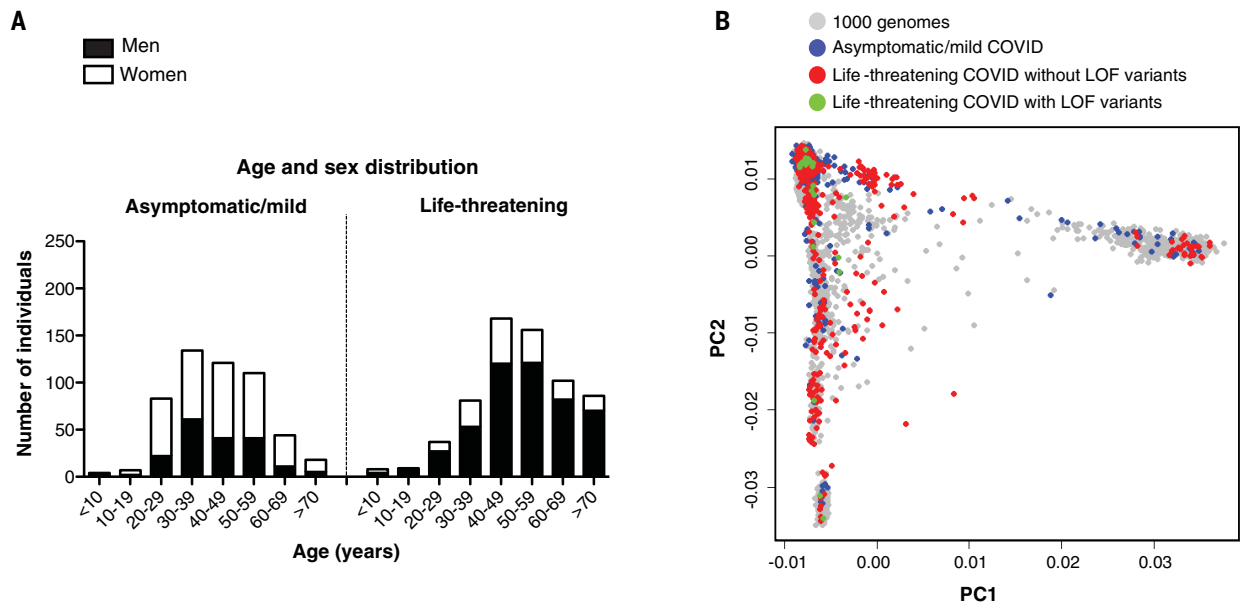


Fig. 1. Demographic and genetic data for the COVID-19 cohort. (A) Age and sex distribution of patients with life-threatening COVID-19. **(B)** PCA of patient (with or without LOF variants in the 13 candidate genes) and control cohorts (patients with mild or asymptomatic disease and individuals from the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

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for these 13 genes. Unexpectedly, one of these variants has been reported in patients with life-threatening influenza pneumonia (*TLR3* p.Pro554Ser) (6, 20) and another was shown to be both deleterious and dominant-negative

(*IFNAR1* p.Pro335del) (21). Nine of the 118 biallelic or monoallelic variants were predicted to be LOF (pLOF), whereas the remaining 109 were missense or in-frame indels (table S1). In a sample of 534 controls with asymptomatic

or mild SARS-CoV-2 infection, we found only one heterozygous pLOF variation with a MAF <0.001 at the 13 loci (*IRF7* p.Leu99fs). A PCA-adjusted burden test on the 12 autosomal loci revealed significant enrichment in pLOF variants in patients relative to controls [$P = 0.01$; odds ratio (OR) = 8.28; 95% confidence interval (CI) = 1.04 to 65.64] under an AD mode of inheritance. The same analysis performed on synonymous variants with a MAF <0.001 was not significant ($P = 0.19$), indicating that our ethnicity-adjusted burden test was well calibrated.

Experimentally deleterious alleles at the influenza susceptibility loci in 3.5% of patients

We tested these 118 variants experimentally in ad hoc overexpression systems. We found that 24 variants of eight genes were deleterious (including all the pLOF variants) because they were loss-of-expression, LOF, or severely hypomorphic: *TLR3* ($N = 4$ variants), *UNC93B1* ($N = 1$), *TICAM1* ($N = 3$), *TBK1* ($N = 2$), *IRF3* ($N = 2$), *IRF7* ($N = 8$), *IFNAR1* ($N = 3$), and *IFNAR2* ($N = 1$) (table S1, Fig. 3, and figs. S1 to S8). Consistently, heterozygous LOF variants of *IRF3* and *IRF7* were reported in single patients with life-threatening influenza pneumonia (22, 23). The remaining 94 variants were biochemically neutral. Twenty-three patients carried these 24 deleterious variants, resulting in four autosomal-recessive (AR) deficiencies (homozygosity or compound heterozygosity

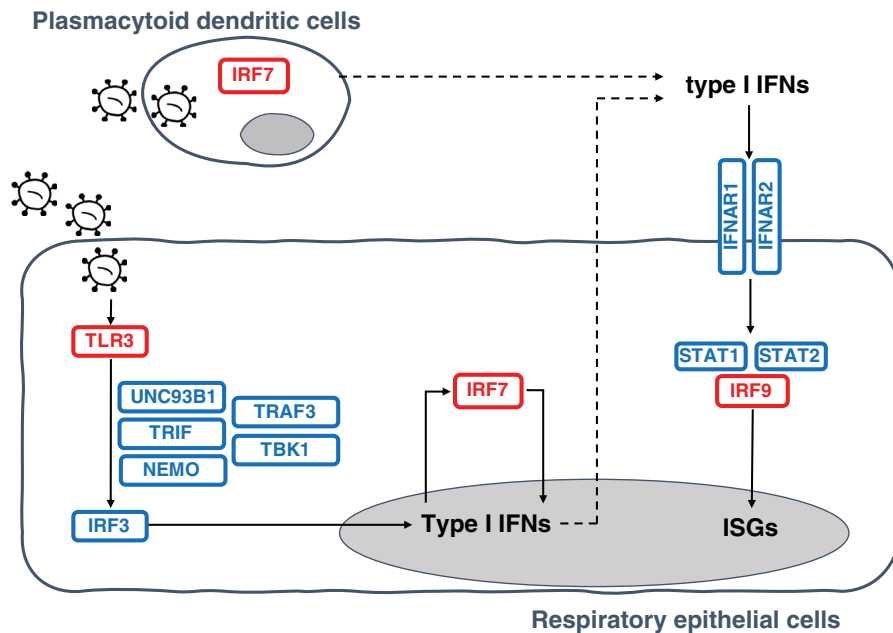


Fig. 2. Illustration of TLR3- and IRF7-dependent type I IFN production and amplification circuit. Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia with incomplete penetrance; deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. Type I IFNs also induce themselves. ISGs, interferon-stimulated genes.

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

Gene	Inheritance	Genetic form	Genotype	Gender	Age [years]	Ancestry/residence	Outcome
<i>TLR3</i>	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
<i>TLR3</i>	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
<i>TLR3</i>	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
<i>TLR3</i>	AD	Known	p.Met870Val/WT	M	56	Colombia/Spain	Survived
<i>UNC93B1</i>	AD	New	p.Glu96*/WT	M	48	Venezuela/Spain	Survived
<i>TICAM1</i>	AD	Known	p.Thr41le/WT	M	49	Italy	Survived
<i>TICAM1</i>	AD	Known	p.Ser60Cys/WT	F	61	Vietnam/France	Survived
<i>TICAM1</i>	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
<i>TBK1</i>	AD	Known	p.Phe24Ser/WT	F	46	Venezuela/Spain	Survived
<i>TBK1</i>	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
<i>IRF3</i>	AD	Known	p.Glu49del/WT	F	23	Bolivia/Spain	Survived
<i>IRF3</i>	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
<i>IRF7</i>	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italy/Belgium	Survived
<i>IRF7</i>	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
<i>IRF7</i>	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
<i>IRF7</i>	AD	New	p.Gln185*/WT	M	44	France	Survived
<i>IRF7</i>	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
<i>IRF7</i>	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
<i>IRF7</i>	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
<i>IFNAR1</i>	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
<i>IFNAR1</i>	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
<i>IFNAR1</i>	AD	New	p.Pro335del/WT	F	23	China/Italy	Survived
<i>IFNAR2</i>	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

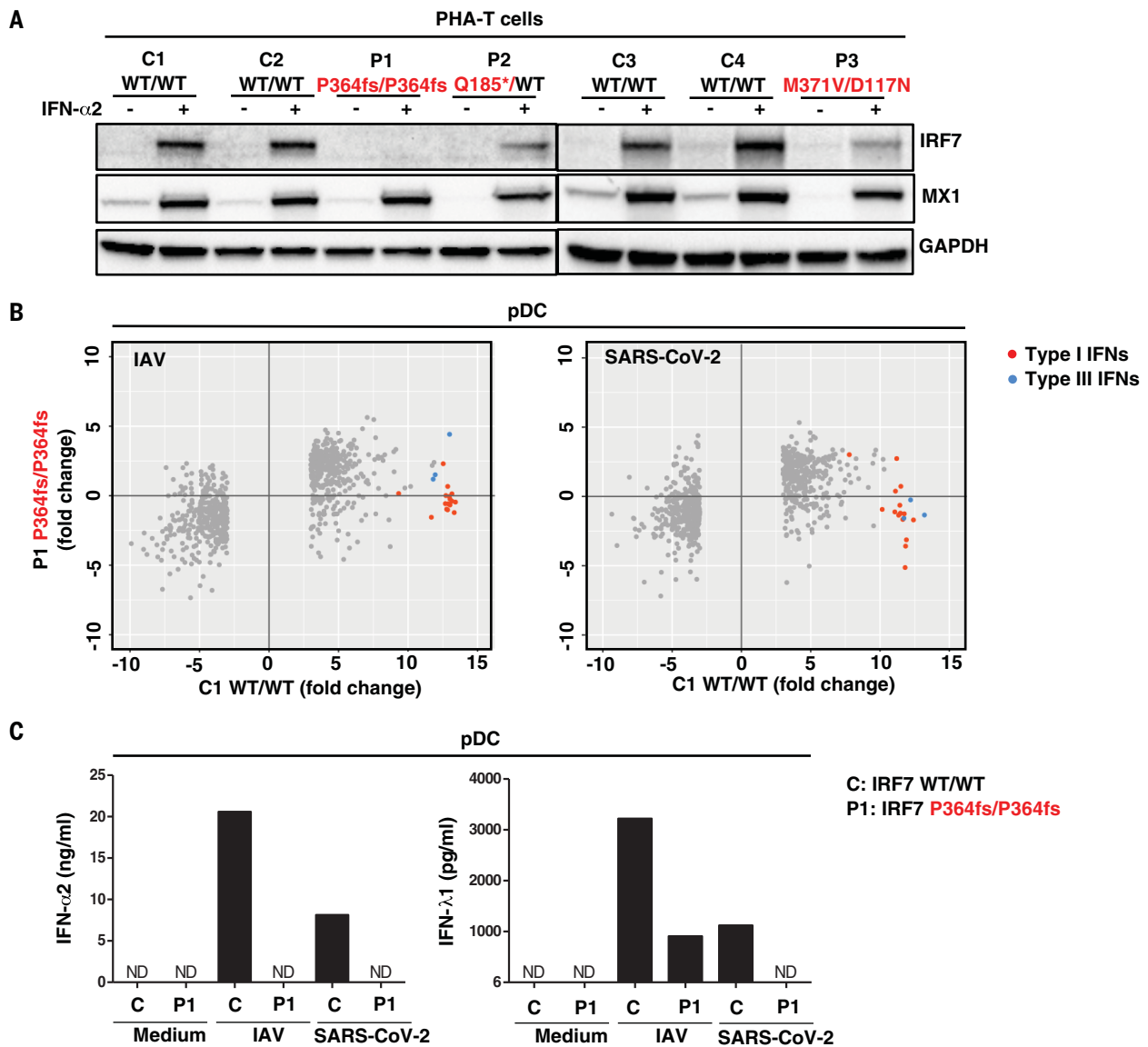


Fig. 4. Type I IFN responses in patient cells defective for IRF7. (A) Levels of the IRF7 protein in PHA-T cells from two patients with AR IRF7 deficiency (P1 and P3), one patient with AD IRF7 deficiency (P2), and four healthy donors (C1 to C4). Cells were either left untreated or stimulated with IFN- α 2 for 24 hours, and protein levels were measured by Western blotting. MX1 was used as a positive control for IFN- α 2 treatment. (B) pDCs isolated from an AR IRF7-deficient patient (P1) and a healthy donor (C1) were either left untreated or

infected with influenza A virus (IAV) or SARS-CoV-2, and RNA-seq was performed. Genes with expression >2.5-fold higher or lower in C1 after infection are plotted as the fold change in expression. Red dots are type I IFN genes; blue dots are type III IFN genes. (C) pDCs isolated from healthy donor C and IRF7-deficient patient (P1) were either left untreated (Medium) or infected with IAV or SARS-CoV-2, and the production of IFN- α 2 and IFN- λ 1 was measured by CBA and ELISA, respectively, on the supernatant. ND, not detected.

for *IRF7*; homozygosity for *IFNAR1*) and 19 AD deficiencies. These 23 patients did not carry candidate variants at the other 417 loci known to underlie inborn errors of immunity (table S2) (24–26). These findings suggest that at least 23 (3.5%) unrelated patients of the 659 patients tested suffered from a deficiency at one of eight loci among the 13 tested: four patients with a known AR disorder (*IRF7* or *IFNAR1*) (7, 15), 11 with a known AD disorder (*TLR3*, *TICAM1*, *TBKI*, or *IRF3*) (6, 9, 12, 13, 20), and eight with a previously unknown AD genetic disorder (*UNC93B1*, *IRF7*, *IFNAR1*, or *IFNAR2*).

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

We tested cells from patients with selected genotypes and showed that PHA-driven T cell blasts (PHA-T cells) from patients with AR or AD IRF7 deficiency had low levels of IRF7 expression (Fig. 4A). We then isolated circulating plasmacytoid dendritic cells (pDCs) from a patient with AR IRF7 deficiency (fig. S9A) (7). These cells were present in normal proportions (fig. S9B), but they did not produce any detectable type I or III IFNs in response to SARS-CoV-2, as analyzed by cytometric bead

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

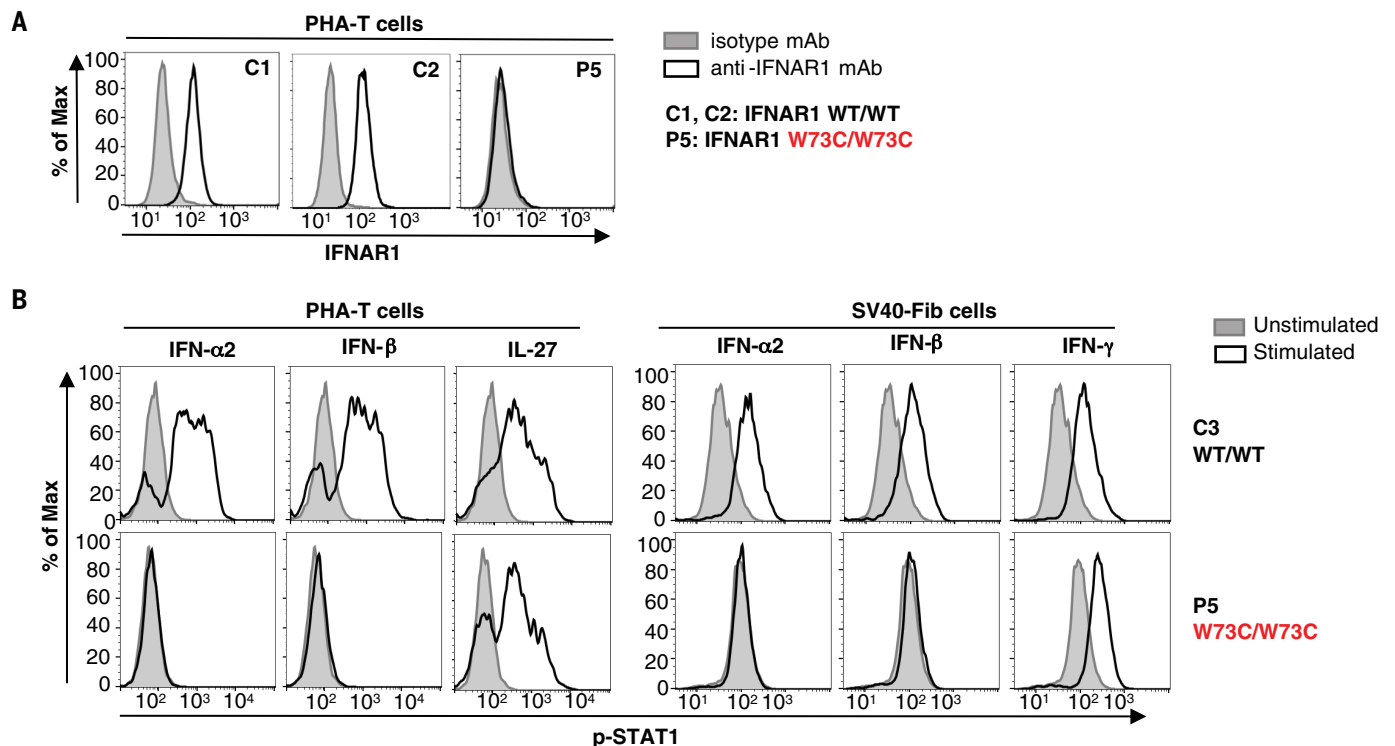


Fig. 5. Type I IFN responses in patient cells defective for IFNAR1. (A) FACS staining of IFNAR1 on the surface of PHA-T cells from a patient with AR IFNAR1 deficiency (P5) and healthy donors (C1 and C2). (B) PHA-T cells and SV40-Fib from a patient with AR IFNAR1 deficiency (P5) and a healthy donor (C3)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

IFNAR1, all of which were previously transduced with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2). SARS-CoV-2 infection levels were higher in mutant cells than in cells from healthy donors, and transduction of WT *IRF7* or *IFNAR1* rescued their defects (Fig. 6). Collectively, these findings showed that AR *IRF7* deficiency impaired the production of type I IFN by pDCs stimulated with SARS-CoV-2, whereas AR and AD deficiencies of TLR3 or AR deficiency of IFNAR1 impaired fibroblast-intrinsic type I IFN immunity to SARS-CoV2. They also suggest that heterozygosity for LOF variations at the other five mutated loci also underlie life-threatening COVID-19.

Impaired production of type I IFNs in patients in vivo

We tested whether these genotypes impaired the production of type I IFN in vivo during the course of SARS-CoV-2 infection. We measured the levels of the 13 types of IFN- α in the blood of patients during the acute phase of COVID-19. We found that 10 of the 23 patients with mutations for whom samples were available (one with AR *IRF7* deficiency, four with AD *IRF7* deficiency, one with AD TLR3 deficiency, two with AD *TBK1* deficiency, one with AR *IFNAR1* deficiency, and one with AD *TICAM1* deficiency) had serum IFN- α levels <1 pg/ml

(Fig. 7). By contrast, previously published cohorts of patients hospitalized with unexplained, severe COVID-19 had various serum IFN- α levels, significantly higher than our 10 patients [one-way analysis of variance (ANOVA), $P = 1.4 \times 10^{-7}$; Fig. 7] (27, 28). Another 29 patients from our cohort displaying auto-antibodies (auto-Abs) against type I IFNs, reported in an accompanying paper, had undetectable levels of serum IFN- α (29). Moreover, none of the 23 patients with LOF mutations of the eight genes had detectable auto-Abs against type I IFNs (29), strongly suggesting that the two mechanisms of disease are similar but independent. Excluding patients with auto-Abs against type I IFN from the burden test of pLOF variants at the 12 autosomal loci strengthened the association signal ($P = 0.007$; OR = 8.97; 95% CI = 1.13 to 71.09).

Inborn errors of TLR3- and IRF7-dependent type I immunity underlie critical COVID-19

Collectively, our data suggest that at least 23 of the 659 patients with life-threatening COVID-19 pneumonia studied had known (six disorders) or new (four disorders) genetic defects at eight loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs. This discovery reveals the essential role of both the double-stranded RNA sensor TLR3 and type I IFN cell-intrinsic immunity in the

control of SARS-CoV-2 infection in the lungs, consistent with their previously documented roles in pulmonary immunity to influenza virus (5–8). These genotypes were silent until infection with SARS-CoV-2. The most thought-provoking examples are the AR deficiencies of *IRF7* and *IFNAR1*. AR *IRF7* deficiency was diagnosed in two individuals aged 49 and 50 years, and AR *IFNAR1* deficiency was diagnosed in two individuals aged 26 and 38 years, and none of the four patients had a prior history of life-threatening infections (Table 1). One patient with *IRF7* deficiency was tested and was seropositive for several common viruses, including various influenza A and B viruses (figs. S10 and S11). These genetic defects therefore display incomplete penetrance for influenza respiratory distress and only manifested clinically upon infection with the more virulent SARS-CoV-2.

Conclusion

The AR form of *IFNAR1* deficiency highlights the importance of type I IFN production relative to type III IFN production, which is also impaired by defects of TLR3, *IRF7*, and *IRF9* (5). This conclusion is also supported by our accompanying report of neutralizing auto-Abs against type I IFNs, but not type III IFNs, in other patients with life-threatening COVID-19 pneumonia (29). Inborn errors of TLR3- and

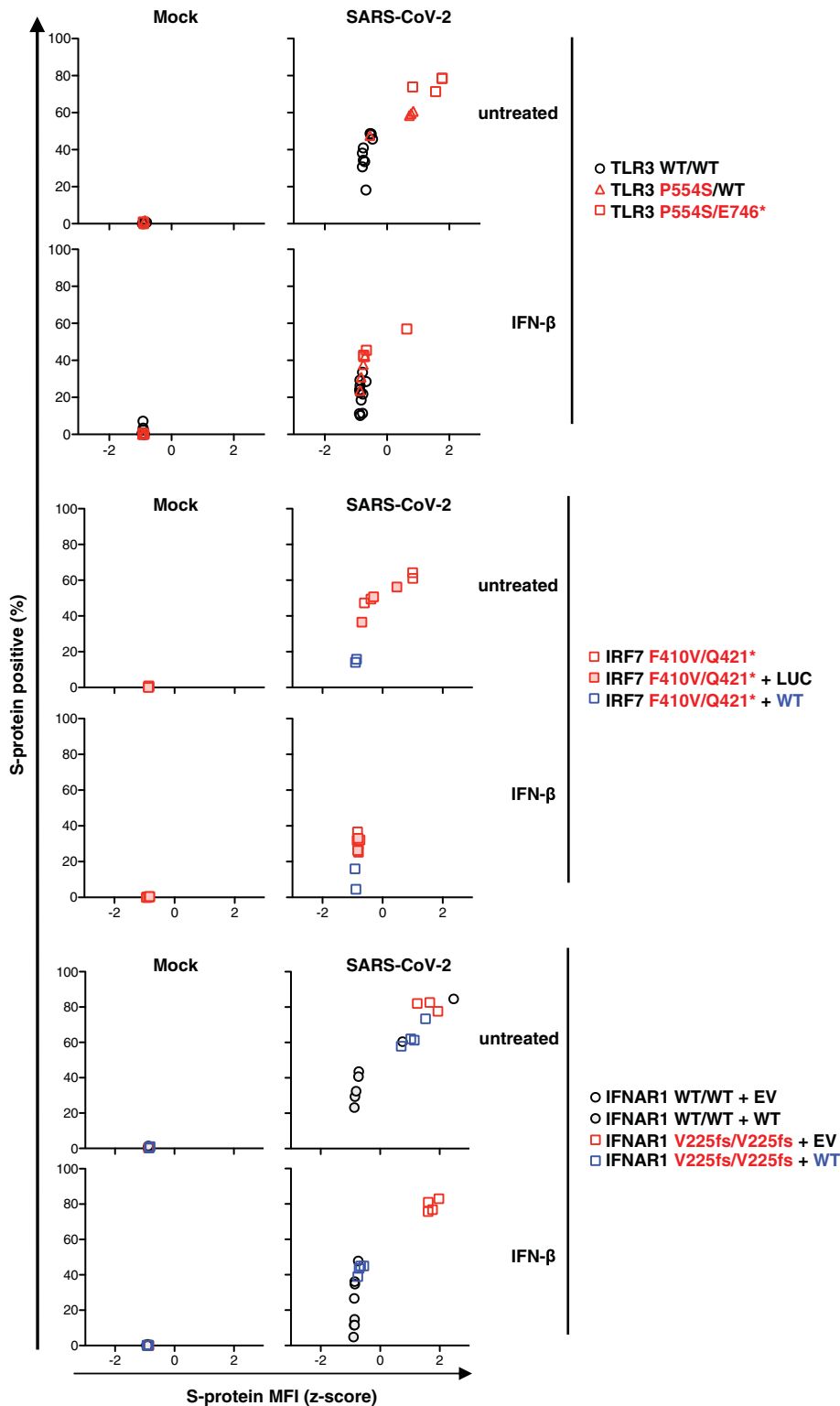


Fig. 6. Cell-intrinsic type I IFN response to SARS-CoV-2. SV40-Fib cells of TLR3^{-/-}, TLR3^{+/-}, IRF7^{-/-}, and IRF7^{-/-} SV40-Fib cells rescued with WT IRF7; IFNAR1^{-/-} SV40-Fib cells, and IFNAR1^{-/-} SV40-Fib cells rescued with WT IFNAR1 were transduced with ACE2 and TMPRSS2 and then either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

IRF7-dependent type I IFN immunity at eight loci were found in as many as 23 patients (3.5%) of various ages (17 to 77 years) and ancestries (various nationalities from Asia, Europe, Latin America, and the Middle East) and in patients of both sexes (Table 1). Our findings suggest that there may be mutations in other type I IFN-related genes in other patients with life-threatening COVID-19 pneumonia. They also suggest that the administration of type I IFN may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection.

Methods

Patients

We included in this study 659 patients with life-threatening COVID-19 pneumonia, defined as patients with pneumonia who developed critical disease, whether pulmonary with mechanical ventilation (CPAP, BIPAP, intubation, hi-flow oxygen), septic shock, or with any other organ damage requiring admission to the intensive care unit. Patients who developed Kawasaki-like syndrome were excluded. The age of the patients ranged from 0.1 to 99 years, with a mean age of 51.8 years (SD 15.9 years), and 25.5% of the patients were female. As controls, we enrolled 534 individuals infected with SARS-CoV-2 based on a positive polymerase chain reaction (PCR) and/or serological test and/or the presence of typical symptoms such as anosmia or ageusia after exposure to a confirmed COVID-19 case, who remained asymptomatic or developed mild, self-healing, ambulatory disease.

Next-generation sequencing

Genomic DNA was extracted from whole blood. For the 1193 patients and controls included, the whole exome ($N = 687$) or whole genome ($N = 506$) was sequenced. We used the Genome Analysis Software Kit (GATK) (version 3.4-46 or 4) best-practice pipeline to analyze our whole-exome-sequencing data (30). We aligned the reads obtained with the human reference genome (hg19) using the maximum exact matches algorithm in Burrows-Wheeler Aligner software (31). PCR duplicates were removed with Picard tools (<http://broadinstitute.github.io/picard/>). The GATK base quality score recalibrator was applied to correct sequencing artifacts.

All of the variants were manually curated using Integrative Genomics Viewer (IGV) and confirmed to affect the main functional protein isoform by checking the protein sequence before inclusion in further analyses. The main functional protein isoforms were TLR3 (NM_003265), UNC93B1 (NM_030930.4), TICAM1 (NM_182919), TRAF3 (NM_145725.2), TBK1 (NM_013254.4), IRF3 (NM_001571), IRF7 (NM_001572.5), IFNAR1 (NM_000629.3), IFNAR2 (NM_001289125.3), STAT1 (NM_007315.4), STAT2

the MFI of mock-infected cells plus 4 SDs. The median SARS-CoV-2 MFI and percentage SARS-CoV-2-positive cells were calculated for each well (independent infection).

Single-molecule array (Simoa) IFN- α digital ELISA

Serum IFN- α concentrations were determined using Simoa technology, with reagents and procedures obtained from Quanterix Corporation (Quanterix SimoaTM IFN α Reagent Kit, Lexington, MA, USA). According to the manufacturer's instructions, the working dilutions were 1:2 for all sera in working volumes of 170 μ l.

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ACKNOWLEDGMENTS

We thank the patients, their families, and healthy donors for placing their trust in us; Y. Nemirovskaya, D. Papandrea, M. Woollet, D. Liu, C. Rivalain, and C. Pattissier for administrative assistance; A. Adeleye, D. Bacikova, E. McGrath Martinez, A. R. Soltis, K. Dobbs, J. Danielson, H. Matthews, and S. Weber for technical and other assistance; M. M. A. Ata and F. Al Ali for their contribution to VirScan experiments; S. Elledge (Brigham and Women's Hospital and Harvard Medical School, Boston, MA) for kindly providing the VirScan phage library used in this study; A. W. Ashbrook, the BSL3 manager of the Rice laboratory assistance; M. Lazzaro, Director of Immigration and Academic Appointments, for assistance; W. Chung, K. Kyrlyuk, S. O'Byrne, D. Pendrick, J. Williamson, C. Andrews, and M. Disco in the J.M. lab for assistance; M. Andreoni (Tor Vergata, Italy) for his clinical contribution; and A. Novelli (Bambino Gesù Hospital, Italy) for his collaboration. We thank the GEN-COVID Multicenter study (<https://sites.google.com/dbm.unisi.it/gen-covid>). This study used the high-performance computational resources of the National Institutes of Health (NIH) HPC Biowulf cluster (<http://hpc.nih.gov>) and the Office of Cyber Infrastructure and Computational Biology (OCIB) High Performance Computing (HPC) cluster at the National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD. The opinions and assertions expressed herein are those of the authors and are not to be construed as reflecting the views of the Uniformed Services University of the Health Sciences (USUHS) or the U.S. Department of Defense (DoD). **Funding:** This work was supported by a generous donation from the Fisher Center for Alzheimer's Research Foundation. The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the NIH (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), the NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercurius Center at George Mason University, the Yale Center for Mendelian Genomics and the GSP Coordinating Center funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956), the French National Research Agency (ANR) under the "Investments for the Future" program (ANR-10-IAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBED), the French Foundation for

Medical Research (FRM) (EQU201903007798), the FRM and ANR GENCOV project, ANRS-COV05, the Square Foundation, Grandir-Fonds de Solidarité pour l'Enfance, the SCOR Corporate Foundation for Science, Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Paris. The French COVID Cohort study group was sponsored by Inserm and supported by the REACTing consortium and by a grant from the French Ministry of Health (PHRC 20-0424). Regione Lombardia, Italy (project "Risposta immune in pazienti con COVID-19 e comorbidità"), and the Intramural Research Program of the NIAID, NIH. The laboratory of Genomes & Cell Biology of Disease is supported by "Integrative Biology of Emerging Infectious Diseases" (grant no. ANR-10-LABX-62-IBED), the "Fondation pour la Recherche Médicale" (grant FRM-EQU202003010193), the "Agence Nationale de la Recherche" (ANR FLASH COVID project IDISCOVER cofunded by the "Fondation pour la Recherche Médicale"), University of Paris ("Plan de Soutien Covid-19": RACP20FIR01-COVID-SOUL). I.M. is a senior clinical investigator with the FWO Vlaanderen; I.M. and L.M. are supported by FWO GOC8517N – G0B5120N. The VS team was supported by "Agence Nationale de la Recherche" (ANR-17-CE15-0003, ANR-17-CE15-0003-01) and by Université de Paris "PLAN D'URGENCE COVID19". L.K. was supported by a fellowship from the French Ministry of Research. V.S.-S. is supported by a UKRI Future Leaders Fellowship (MR/S032304/1). S.Z.A.-M. is supported by the Elite Journals Program at King Saud University through grant no. PEJP-16-107. The J.M. laboratory is supported by Columbia University COVID biobank and grant no. UL1TR001873. Work in the Laboratory of Virology and Infectious Disease was supported by NIH grants P01AI138398-S1, 2U19AI118125, and R01AI091707-10S1; a George Mason University Fast Grant; and the G. Harold and Leila Y. Mathers Charitable Foundation. J.L.P. is supported by a European Molecular Biology Organization Long-Term Fellowship (ALTF 380-2018). Work at the Neurometabolic Diseases Laboratory received funding from the European Union's Horizon 2020 research and innovation program under grant no. 824110 (EasiGenomics grant no. COVID-19/PID12342) to A.P., and Roche and Illumina Covid Match Funds to M.G.. C.R.G. and colleagues are supported by Instituto de Salud Carlos III (COV20_01333 and COV20_01334), Spanish Ministry of Science and Innovation, with the funding of European Regional Development Fund-European Social Fund -FEDER-FSE; (RTC-2017-6471-1); AEI/FEDER, UE), and Cabildo Insular de Tenerife (CGIEU0000219140 and "Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19"). D.C.V. is supported by the Fonds de la recherche en santé du Québec clinician-scientist scholar program. H.S. is adjunct faculty at the University of Pennsylvania. A.-L.N. was supported by the Foundation Bettencourt Schueller. The Amsterdam UMC Covid-19 Biobank was funded by the Netherlands Organization for Health Research and Development (ZonMw, NWO-vici 91819627), The Corona Research Fund (Amsterdam UMC), Dr. J. C. Vaillantfonds, and Amsterdam UMC. Work on COVID-19 at the A.G.-S. laboratory is partly supported by NIH supplements to grants U19AI135972, U19AI142733, and R35 HL135834, and to contract HHSN272201800048C, by a DoD supplement to grant W81XWH-20-1-0270, by DARPA project HRO011-19-2-0020, by CRIP (Center for Research on Influenza Pathogenesis), a NIAID funded Center of Excellence for Influenza Research and Surveillance (CEIRS, contract HHSN272201400008C), by a NIAID funded Collaborative Influenza Vaccine Innovation Center (SEM-CIVIC, contract 75N93019C00051) and by the generous support of the JPB Foundation, the Open Philanthropy Project (research grant 2020-215611(5384)) and anonymous donors. The Virscan analysis presented in fig. S11 was performed with financial support from Sidra Medicine. J.R.H. is supported by Biomedical Advanced Research and Development Authority under Contract (HHS010201600031C).

Author contributions: A.G., A.A., A.A.A., A.L.S., A.-L.N., A.C., A.C., A.P., B.B., B.S.R., C.A., C.M., C.K., C.L., C.M.S., C.L.D., D.D., E.M., E.J., F.A., F.A.-M., F.O., F.A., F.K., G.N., G.S., G.G., H.-H.H., H.K.A.S., H.S., I.K.D.S., I.M., J.L.P., J.R., J.E.H., J.C., J.M., J.Y., K.D., K.B., L.A., L.L.-D., L.K., L.M., L.B.-M., L.B., L.D.N., M.M.-V., M.C., M.O., M.C., M.N., M.F.T., M.S., M.F.A., N.M., N.S., P.B., P.M., Q.Z., Q.Z., Q.P., R.L., R.Y., S.A.T., S.Z.A.-M., S.H., S.K., S.H., S.B.-D., T.K., T.M., T.H.M., V.S.-S., V.S., V.B., W.S., X.D., Y.S., and Z.D. either performed or supervised experiments, generated and analyzed data, and contributed to the manuscript. A.S., A.C.U., A.B., A.O., A.P., B.B., D.V., D.B., F.R., G.K., J.M., P.Z., S.-Y.Z., T.L.-V., Y.S., and Y.Z. performed computational analysis. A.S., A.N.S., A.M.-N., A.B., C.R., D.M., D.C.V., E.Q.-R., F.H., I.M., I.V., J.B., J.-C.G., L.R.B., L.R., L.I., M.D., P.B., P.S.-P., P.-E.M., R.H., R.C., S.K., S.P., T.O., Y.T.-L., K.K., S.S., J.F., and S.N.K. evaluated and recruited patients to COVID and/or control cohorts. Q.Z. and J.-L.C. wrote the manuscript. All authors edited the manuscript. J.-L.C. supervised the project. **Competing interests:**

The authors declare no competing financial interests. J.-L.C. is listed as an inventor on patent application US63/055,155 filed by The Rockefeller University that encompasses aspects of this publication. R.L. is a non-executive director of Roche and its subsidiary Genentech. **Data and materials availability:** Plasma, cells, and genomic DNA are available from J.-L.C. or D.V. under a material transfer agreement with Rockefeller University/Research Institute-McGill University Health Centre. pSCRPSY_TMPRSS2-2A-Neor_ACE2 and Huh-7.5 cells are available upon request from C.R. under a material transfer agreement with The Rockefeller University, or The Rockefeller University and Apath, LLC, respectively. Clinical data, DNA, and other patient samples are available from the Amsterdam UMC Covid-19 Biobank (D.v.d.B.) under a material transfer agreement with Amsterdam UMC. Material and reagents used are almost exclusively commercially available and nonproprietary. Requests for materials derived from human samples may be made available, subject to any underlying restrictions on such samples. J.-L.C. can make material transfer agreements available through The Rockefeller University. Detailed genotype counts for all coding variants in the genes investigated in this manuscript are available at Dryad (41). The whole-genome sequencing datasets used for the analyses, including critical patients and asymptomatic controls described in this manuscript, were deposited in dbGaP under accession number phs002245.v1.p1. All other data are available in the manuscript or the supplementary material. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

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References (42 and 43)

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22 June 2020; accepted 16 September 2020

Published online 24 September 2020

10.1126/science.abd4570

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

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Science **370** (6515), eabd4570.

DOI: 10.1126/science.abd4570originally published online September 24, 2020

The genetics underlying severe COVID-19

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

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