RESEARCH ARTICLE SUMMARY

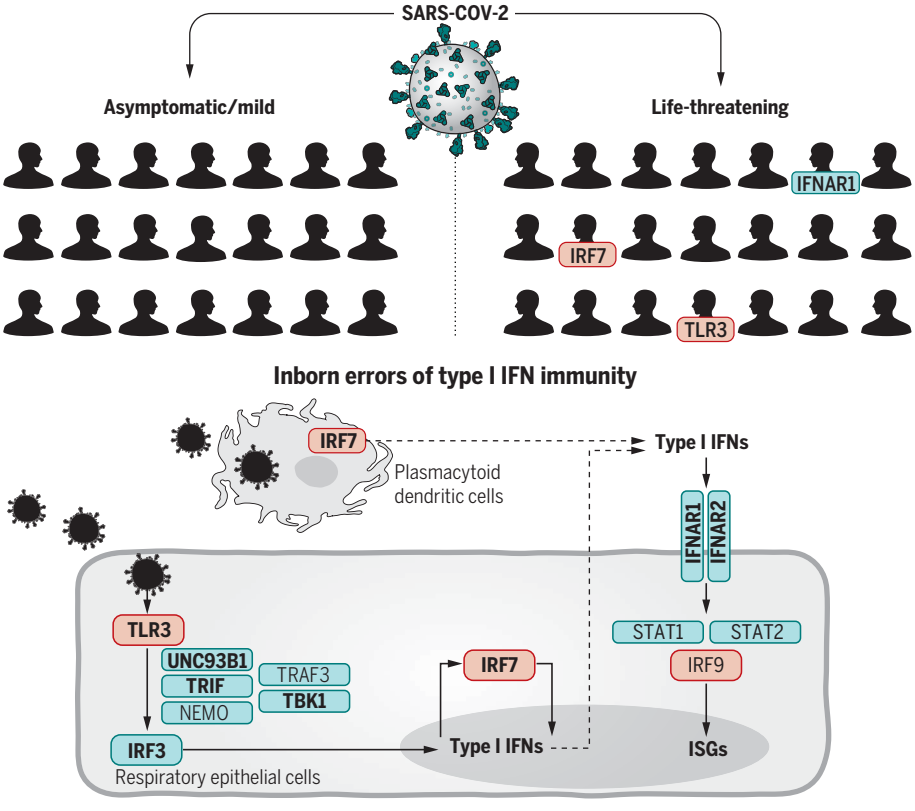
CORONAVIRUS

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 considered 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.



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.

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. ■

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RESEARCH ARTICLE

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

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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: *TICAM1/TRIF* (*9*), *UNC93B1* (*10*), *TRAF3* (*11*), *TBK1* (*12*), *IRF3* (*13*), and *NEMO/IKBKG* (*14*) in the TLR3-dependent type I IFN induction pathway, and *IFNAR1* (*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*, *IFNAR1*, *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 *IFNAR1* (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), *TICAM1* (N = 17/15), *TRAF3* (N = 6/6), *TBK1* (N = 12/11), *IRF3* (N = 5/5), *IRF7* (N = 20/13), *IFNAR1* (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

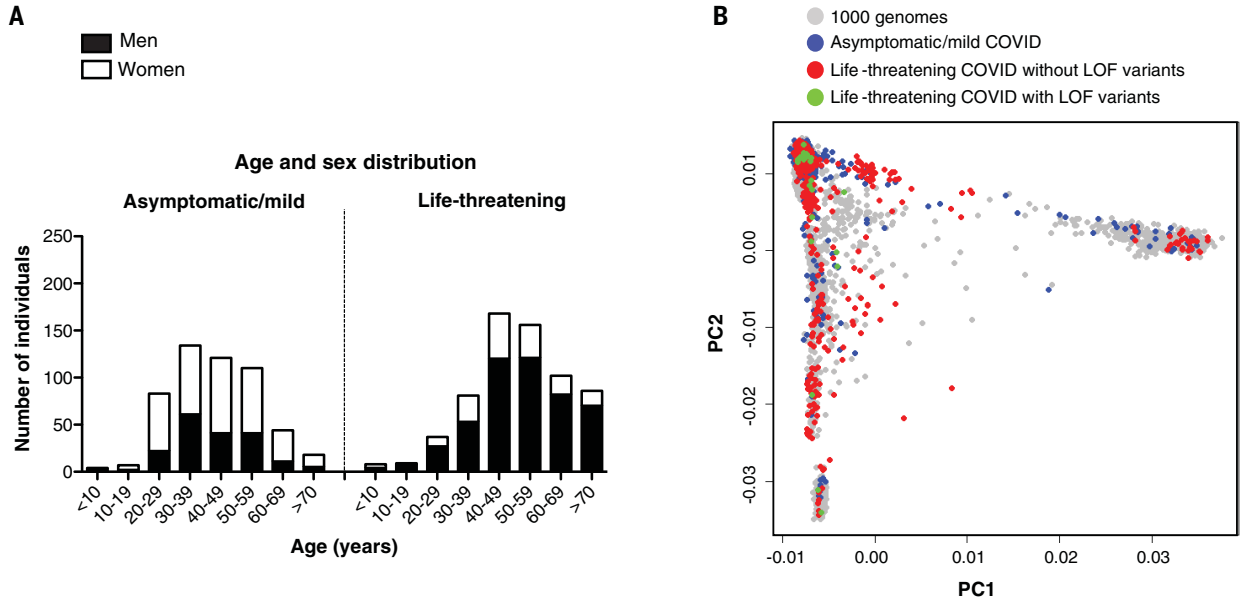

Fig. 1. Demographic and genetic data for the COVID-19 cohort. (**A**) Age and sex distribution of patients with life-threatening COVID-19. (**B**) PCA of patient (with or without LOF variants in the 13 candidate genes) and control cohorts (patients with mild or asymptomatic disease and individuals from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

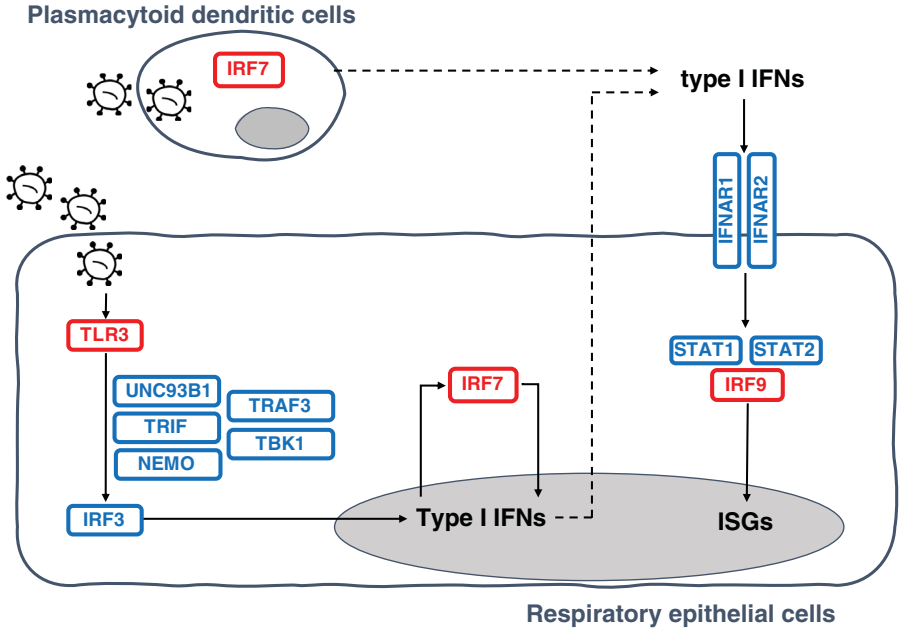

Fig. 2. Illustration of TLR3- and IRF7-dependent type I IFN production and amplification circuit. Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia with incomplete penetrance; deleterious variants of genes encoding biochemically related molecules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

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

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

Gene	Inheritance	Genetic form	Genotype	Gender	Age [years]	Ancestry/residence	Outcome
TLR3	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
TLR3	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
TLR3	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
TLR3	AD	Known	p.Met870Val/WT	M	56	Colombia/Spain	Survived
UNC93B1	AD	New	p.Glu96*/WT	M	48	Venezuela/Spain	Survived
TICAM1	AD	Known	p.Thr4Ile/WT	M	49	Italy	Survived
TICAM1	AD	Known	p.Ser60Cys/WT	F	61	Vietnam/France	Survived
TICAM1	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
TBK1	AD	Known	p.Phe24Ser/WT	F	46	Venezuela/Spain	Survived
TBK1	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
IRF3	AD	Known	p.Glu49del/WT	F	23	Bolivia/Spain	Survived
IRF3	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
IRF7	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italy/Belgium	Survived
IRF7	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
IRF7	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
IRF7	AD	New	p.Gln185*/WT	M	44	France	Survived
IRF7	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
IRF7	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
IRF7	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
IFNAR1	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
IFNAR1	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
IFNAR1	AD	New	p.Pro335del/WT	F	23	China/Italy	Survived
IFNAR2	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

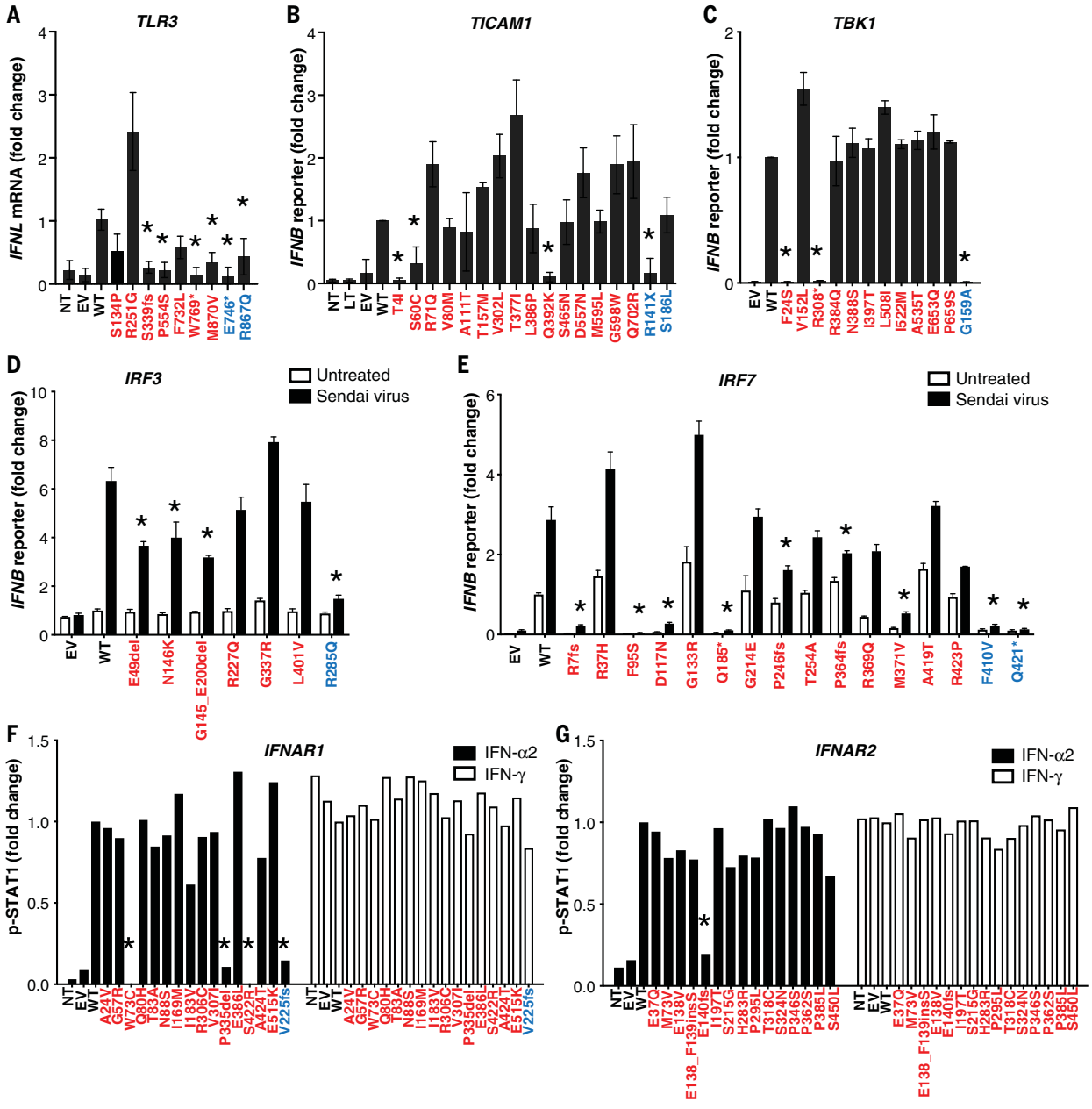

Fig. 3. Impact of *TLR3*, *TICAM1*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, and *IFNAR2* variants on type I IFN signaling. (**A**) TLR3-deficient P2.1 fibrosarcoma cells were stably transfected with plasmids expressing WT or mutant forms of *TLR3*, and *IFNL1* mRNA levels were determined by reverse transcription quantitative PCR. *IFNL1* mRNA levels were expressed relative to the housekeeping gene *GUS* and then normalized. *IFNL1* was undetectable in unstimulated cells. The differences between variants and WT were tested using one-way ANOVA (*$P < 0.05$). (**B**) TICAM1-deficient SV40-Fib cells were transiently transfected with WT or mutant forms of *TICAM1*, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Normalized luciferase induction was measured 24 hours after transfection. The differences between variants and WT were tested using one-way ANOVA (*$P < 0.05$). (**C**) HEK293T cells were transiently transfected with WT and mutant forms of *TBK1*, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Normalized luciferase activity was measured 24 hours after transfection. The differences between variants and WT were tested using one-way ANOVA (*$P < 0.05$). (**D**) IRF3-deficient HEK293T cells were transiently transfected with WT and mutant forms of *IRF3*, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Cells were either left untreated or infected with Sendai virus for 24 hours before the normalized measurement of luciferase activity. The differences between variants and WT were evaluated using two-way ANOVA (*$P < 0.05$). (**E**) HEK293T cells were transiently transfected with WT and mutant forms of *IRF7*, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Cells were either left untreated or infected with Sendai virus for 24 hours before the normalized measurement of luciferase activity. The differences between variants and WT were tested using two-way ANOVA (*$P < 0.05$). (**F** and **G**) IFNAR1- or IFNAR2-deficient SV40-Fib cells were transiently transfected with WT or mutant forms of *IFNAR1* for 36 hours, and either left untreated or stimulated with IFN-α2 or IFN-γ. Fluorescence-activated cell sorting (FACS) staining with anti-p-STAT1 antibody and the *z*-score of the MFI were assessed. Asterisks indicate variants with MFI <50% of WT. Variants in red were identified in COVID-19 patients. Variants in blue are known deleterious variants and served as negative controls. EV, empty vector; LT, lipofectamine. Three technical repeats were performed for (A) to (E). Means and SD are shown in the columns and horizontal bars when appropriate.

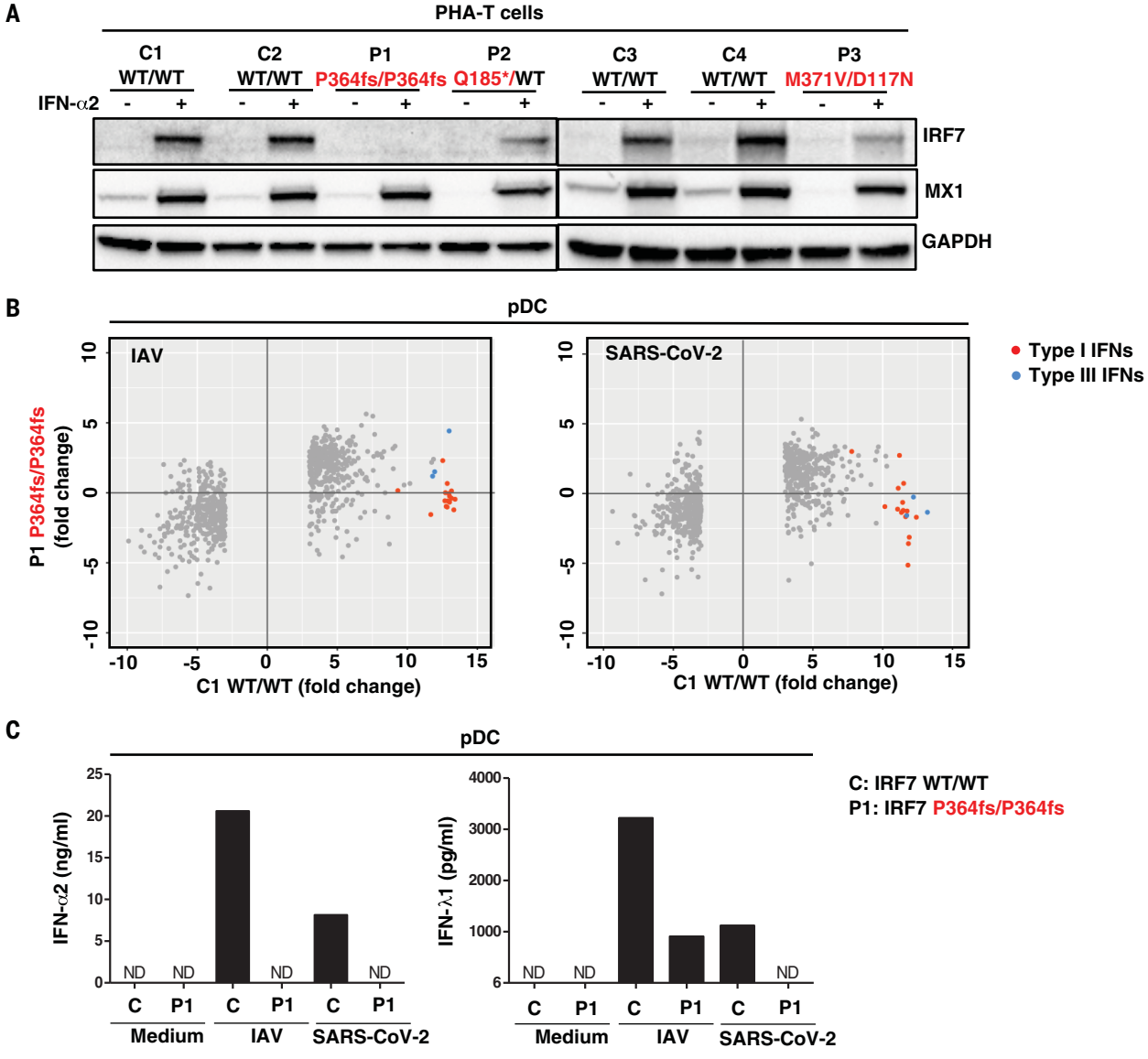

Fig. 4. Type I IFN responses in patient cells defective for IRF7. (**A**) Levels of the IRF7 protein in PHA-T cells from two patients with AR IRF7 deficiency (P1 and P3), one patient with AD IRF7 deficiency (P2), and four healthy donors (C1 to C4). Cells were either left untreated or stimulated with IFN-α2 for 24 hours, and protein levels were measured by Western blotting. MX1 was used as a positive control for IFN-α2 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-α2 and IFN-λ1 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*, *TBK1*, 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-α2 or IFN-β, and that the patient's SV40-transformed fibroblast (SV40-Fib) cells did not respond to IFN-α2 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

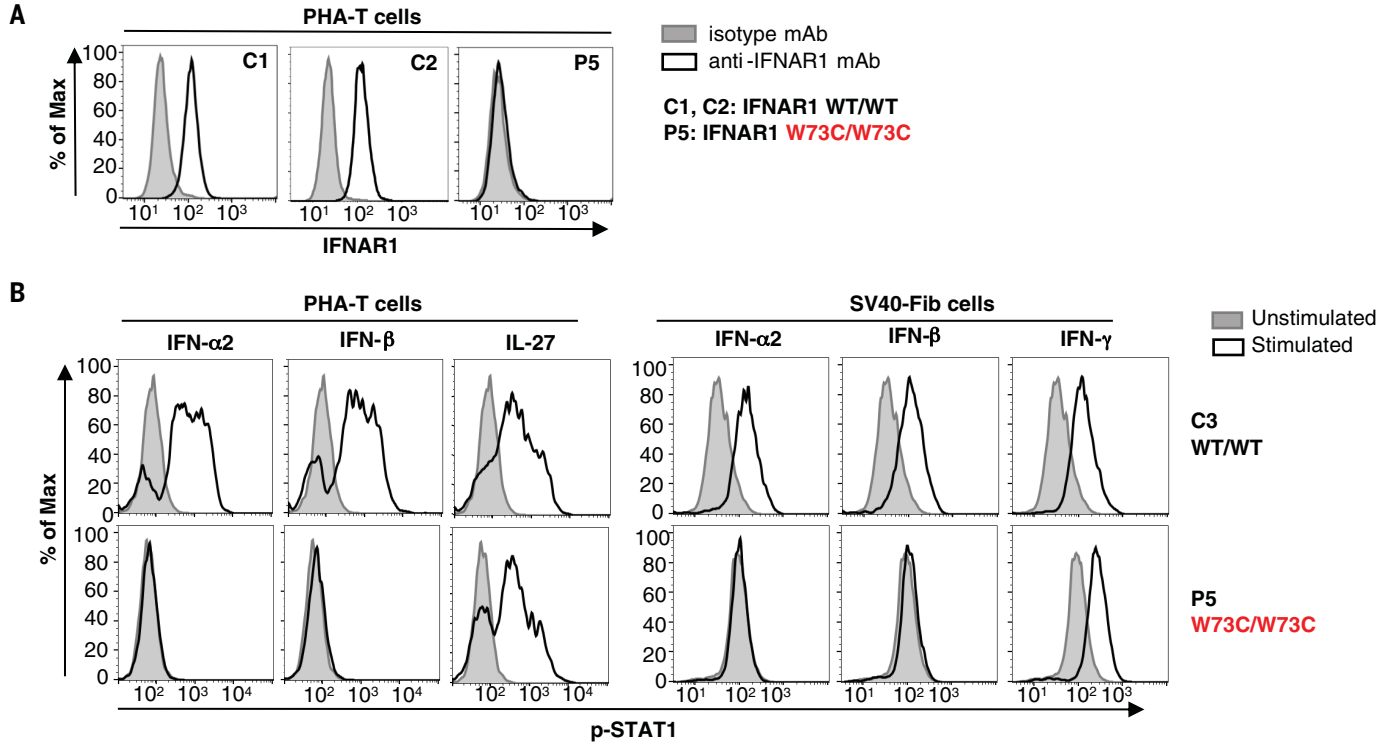

Fig. 5. Type I IFN responses in patient cells defective for IFNAR1. (**A**) FACS staining of IFNAR1 on the surface of PHA-T cells from a patient with AR IFNAR1 deficiency (P5) and healthy donors (C1 and C2). (**B**) PHA-T cells and SV40-Fib from a patient with AR IFNAR1 deficiency (P5) and a healthy donor (C3) were stimulated with IFN-α2 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

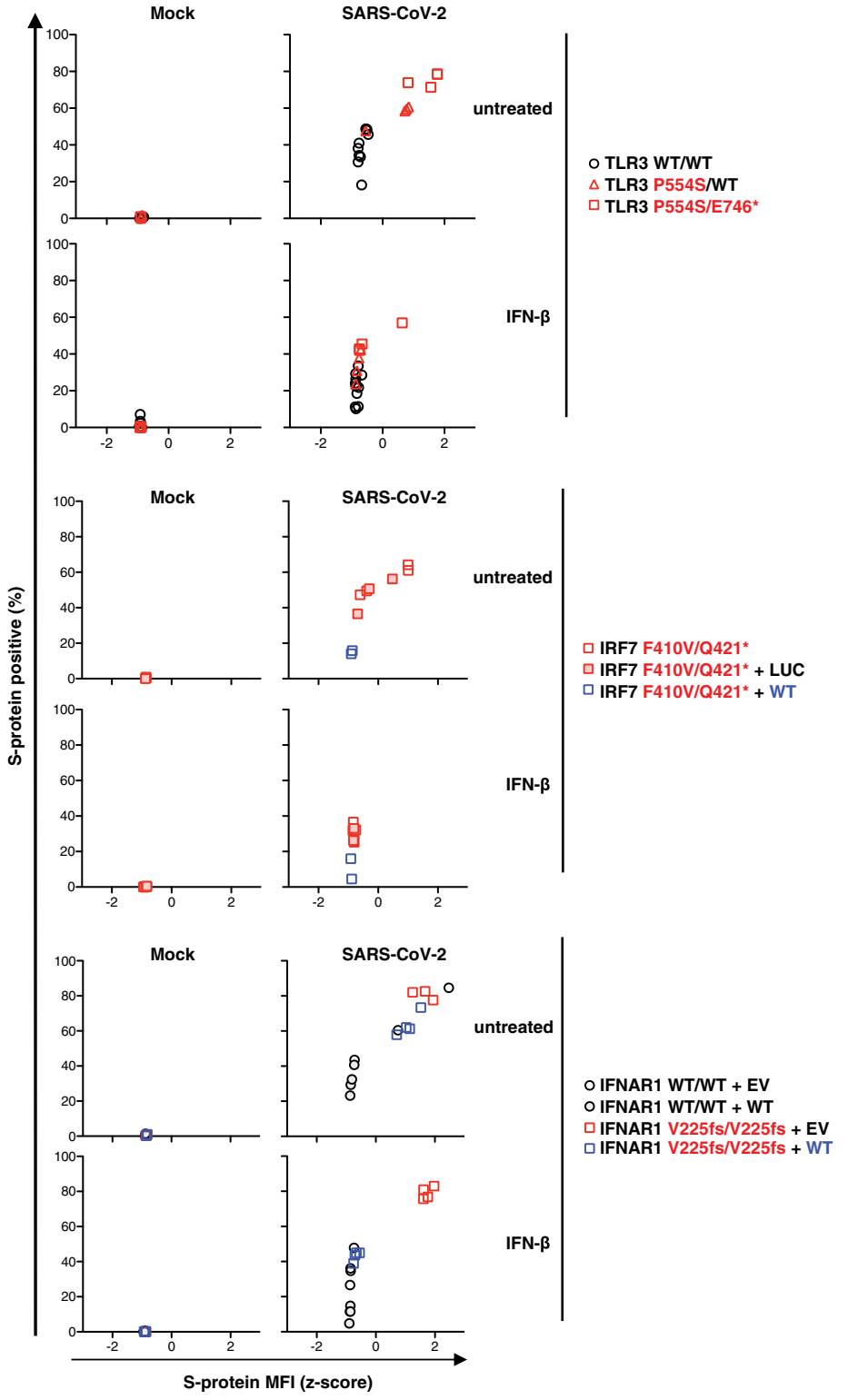

Fig. 6. Cell-intrinsic type I IFN response to SARS-CoV-2. SV40-Fib cells of TLR3$^{-/-}$, TLR3$^{+/-}$, IRF7$^{-/-}$, and IRF7$^{-/-}$ SV40-Fib cells rescued with WT IRF7; IFNAR1$^{-/-}$ SV40-Fib cells, and IFNAR1$^{-/-}$ SV40-Fib cells rescued with WT IFNAR1 were transduced with ACE2 and TMPRSS2 and 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 analyzes. 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

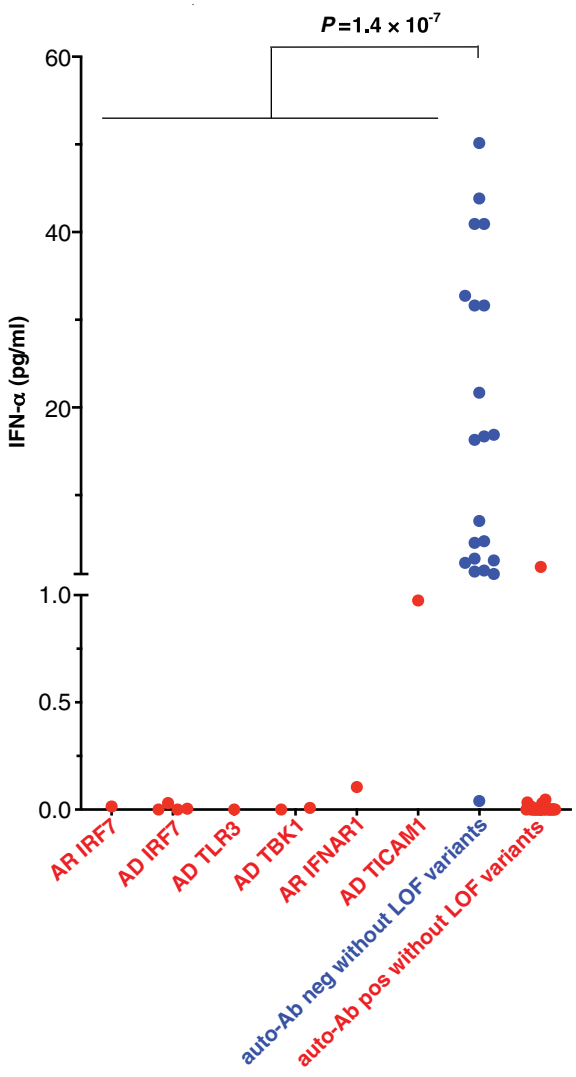

Fig. 7. In vivo type I IFN responses to SARS-CoV-2 infections. Plasma levels of 13 IFN-α were measured by Simoa. Auto-Ab(+) without LOF variants indicates COVID-19 patients with neutralizing anti-IFN-α auto-Abs in our accompanying report (*29*). *P* values indicated were evaluated using one-way ANOVA.

(NM_005419.4), and IRF9 (NM_006084.5). The analysis of IKBKG was customized to unmask the duplicated region in IKBKG using a specific pipeline previously described (*32*). We searched the next-generation–sequencing data for deletions in the 13 genes of interest using both the HMZDelFinder (*33*) and CANOES (*34*) algorithms.

Statistical analysis

We performed an enrichment analysis on our cohort of 659 patients with life-threatening COVID-19 pneumonia and 534 SARS-CoV2–infected controls, focusing on 12 autosomal IFN-related genes. We considered variants that were pLOF with a MAF <0.001 (gnomAD version 2.1.1) after experimentally demonstrating that all of the pLOF variants seen in the cases were actually LOF. We compared the proportion of individuals carrying at least one pLOF variant of the 12 autosomal genes in cases and controls by means of logistic regression with the likelihood ratio test. We accounted for the ethnic heterogeneity of the cohorts by including the first three principal components of the PCA in the logistic regression model. PC adjustment is a common and efficient strategy for accounting for different ancestries of patients and controls in the study of rare variants (*35*–*38*). We checked that our adjusted burden test was well calibrated by also performing an analysis of enrichment in rare (MAF <0.001) synonymous variants of the 12 genes. PCA was performed with Plink version 1.9 software on whole-exome– and whole-genome–sequencing data and the 1000 Genomes (1kG) Project phase 3 public database as a reference, using 27,480 exonic variants with a MAF >0.01 and a call rate >0.99. The OR was also estimated by logistic regression and adjusted for ethnic heterogeneity.

Reporter assays

Cell lines or SV40-Fib cells with known defects were transiently or stably transfected with WT, mutant variants, IFN-β- or ISRE-*firefly* luciferase reporter, and pRL-TK-*Renilla* luciferase reporter. Reporter activity was measured with the Dual-Luciferase Reporter Assay System (Promega) according to the manufacturer's instructions. *Firefly* luciferase activity was normalized against *Renilla* luciferase activity and expressed as a fold change. TRAF3-deficient human embryonic kidney (HEK) 293T cells were kindly provided by M. Romanelli (*39*).

pDC activation by SARS-CoV-2 and cytokine production

pDCs from an IRF7$^{-/-}$ patient and a healthy donor matched for age and sex were cultured in the presence of medium alone, influenza virus (A/PR/8/34, 2 μg/ml; Charles River Laboratories), or the SARS-CoV-2 primary strain 220_95 (GISAID accession ID: EPI_ISL_469284) at a multiplicity of infection (MOI) of 2. After 12 hours of culture, pDC supernatant was collected for cytokine quantification. IFN-α2 levels were measured using CBA analyzis (BD Biosciences) in accordance with the manufacturer's protocol using a 20 pg/ml detection limit. IFN-λ1 secretion was measured in an ELISA (R&D Systems, DuoSet DY7246), in accordance with the manufacturer's instructions.

SARS-CoV-2 infection in patient SV40-Fib

To make patient-derived fibroblasts permissive to SARS-CoV-2 infection, we delivered human ACE2 and TMPRSS2 cDNA to cells by lentivirus transduction using a modified SCRPSY vector (GenBank ID: KT368137.1). SARS-CoV-2 strain USA-WA1/2020 was obtained from BEI Resources. ACE2/TMPRSS2-transduced cells were either left untreated or treated with 500 U/ml IFN-β (11415-1, PBL Assay Science) 4 hours before infection. Cells were infected with SARS-CoV-2 (MOI = 0.5) for 1 hour at 37°C. After 24 hours of infection, cells were fixed and taken out of the BSL3 for staining.

After fixation, cells were stained with SARS-CoV-2 and ACE2 primary antibodies (0.5 and 1 μg/ml, respectively). Primary antibodies were as follows: for SARS-CoV-2, human monoclonal anti-spike-SARS-CoV-2 C121 antibody (*40*), and for ACE2, mouse monoclonal Alexa Fluor 488–conjugated antibody (FAB9332G-100UG, R&D Systems). Images were acquired with an ImageXpress Micro XLS microscope (Molecular Devices) using the 4× objective. MetaXpress software (Molecular Devices) was used to obtain single-cell mean fluorescence intensity (MFI) values.

Data analysis on single-cell MFI values was done in the R environment (version 4.0.2). ACE2/TMPRSS2-transduced cells were classified as ACE2 positive when the ACE2 log MFI was superior to the log mean MFI of mock-transduced cells plus 2.5 SDs. We excluded all wells with <150 ACE2-positive cells before SARS-CoV-2 scoring. ACE2-expressing cells were classified SARS-CoV-2 positive when the fluorescence intensity value was superior to

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 IFNα 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 µl.

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SUPPLEMENTARY MATERIALS

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MDAR Reproducibility Checklist

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