Cite as: T. Asano *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abl4348 (2021).

CORONAVIRUS

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

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Autosomal inborn errors of type I IFN immunity and autoantibodies against these cytokines underlie at least 10% of critical COVID-19 pneumonia cases. We report very rare, biochemically deleterious X-linked *TLR7* variants in 16 unrelated male individuals aged 7 to 71 years (mean: 36.7 years) from a cohort of 1,202 male patients aged 0.5 to 99 years (mean: 52.9 years) with unexplained critical COVID-19 pneumonia. None of the 331 asymptomatically or mildly infected male individuals aged 1.3 to 102 years (mean: 38.7 years) tested carry such *TLR7* variants ($p = 3.5 \times 10^{-5}$). The phenotypes of five hemizygous relatives of index cases infected with SARS-CoV-2 include asymptomatic or mild infection (n=2, 5 and 38 years), or moderate (n=1, 5 years), severe (n=1, 27 years), or critical (n=1, 29 years) pneumonia. Two boys (aged 7 and 12 years) from a cohort of 262 male patients with severe COVID-19 pneumonia (mean: 51.0 years) are hemizygous for a deleterious TLR7 variant. The cumulative allele frequency for deleterious *TLR7* variants in the male general population is < 6.5×10^{-4}. We also show that blood B cell lines and myeloid cell subsets from the patients do not respond to TLR7 stimulation, a phenotype rescued by wild-type *TLR7*. The patients' blood plasmacytoid dendritic cells (pDCs) produce low levels of type I IFNs in response to SARS-CoV-2. Overall, X-linked recessive TLR7 deficiency is a highly penetrant genetic etiology of critical COVID-19 pneumonia, in about 1.8% of male patients below the age of 60 years. Human TLR7 and pDCs are essential for protective type I IFN immunity against SARS-CoV-2 in the respiratory tract.

INTRODUCTION

Interindividual clinical variability in the course of SARS-CoV-2 infection is vast, ranging from silent infection to lethal disease (*1*). The greatest risk factor for life-threatening COVID-19 pneumonia is age, with a doubling in risk every five years from the age of five years onward, and a sharp rise after the age of 65 years (*2*, *3*). Other epidemiological risk factors, including common genetic variants, have only modest effects, with odds ratios (ORs) < 2 and typically < 1.5 (*2*). One intriguing observation is the approximately 1.5 times higher risk in men, which seems to be age-independent (*2–4*). The COVID Human Genetic Effort consortium (www.covidhge.com) has enrolled an international cohort of patients, with the aim of investigating genetic and immunological causes of life-threatening COVID-19 pneumonia. We previously tested the hypothesis that critical influenza and critical COVID-19 can be allelic (*5–7*), and showed that life-threatening COVID-19 pneumonia can be caused by rare

inborn errors of autosomal genes controlling TLR3- and IRF7-dependent type I interferon (IFN) immunity (*8*). These disorders were found in 23 men and women aged 17 to 77 years (mean: 48 years). Remarkably, four unrelated patients aged 25 to 50 years had autosomal recessive IFNAR1 (n=2) or IRF7 (n=2) deficiency. These patients had no previous history of severe viral illness, including influenza pneumonia, implying that these genetic disorders unexpectedly show incomplete penetrance for critical influenza. These findings revealed that TLR3- and IRF7-dependent type I IFN immunity is essential for host defense against SARS-CoV-2 infection in the respiratory tract.

We also found pre-existing neutralizing auto-Abs against type I IFN in at least 10% of the patients from this cohort (*9*). These auto-Abs were found in 101 patients, mostly men (95%), and older members of the cohort, which included patients with inborn errors, as they were aged 25 to 87 years (mean: 65 years). These findings have been replicated in five other cohorts (*10–15*). These auto-Abs predated SARS-CoV-2 infection and were highly likely to be causal for critical COVID-19 pneumonia, because (i) they were found in samples drawn before infection in some patients (*9*), (ii) they were found in about 0.3% of the general population before the age of 65 years (*9*), (iii) they were absent from patients with asymptomatic or paucisymptomatic (mild) SARS-CoV-2 infection (*9*), (iv) they were of childhood onset in patients with various disorders — including autoimmune polyendocrinopathy type I (APS-1) — known to be at very high risk of life-threatening COVID-19 (*16*), and (v) they have been shown to underlie a third of adverse reactions to the live attenuated viral vaccine for yellow fever (*17*). Collectively, these studies showed that type I IFNs are essential for protective immunity to SARS-CoV-2 in the respiratory tract, but are otherwise surprisingly redundant. Auto-Abs against type I IFNs also provide a first explanation for both the biased sex ratio and the higher risk of critical COVID-19 in patients over the age of 65 years. Here, we tested the hypothesis that critical and unexplained COVID-19 pneumonia in men may be due to rare variants on the X- chromosome.

RESULTS

Enrichment for very rare TLR7 *non-synonymous variants in male patients*

We tested the hypothesis of genetic homogeneity for X-linked recessive disorders in male individuals with critical COVID-19 pneumonia (hereafter referred to as "patients", see Materials and Methods). We analyzed an international cohort of 1,202 unrelated male patients aged 6 months to 99 years (mean: 52.9 years) that possessed no known inborn errors of TLR3- and IRF7-dependent type I IFN immunity (*8*) and without neutralizing auto-Abs against type I IFNs (*9*) (reported in an accompanying paper (*79*)) (Table S1). We also analyzed 331 asymptomatic or paucisymptomatic infected male subjects aged 1.3 to 102 years (mean: 38.7 years), with positive results for PCR and/or serological screening for SARS-CoV-2 infection (hereafter referred to as "controls") (Table S1). We sequenced the exomes (n=1,035) or genomes (n=498) of these patients and controls. We selected in-frame and out-of-frame non-synonymous variants of protein-coding exons that are very rare, that is, with a minor allele frequency (MAF) below 10^{-4} in the full gnomAD database (v2.1.1) containing sequences from both male and female individuals. We compared the proportions of patients and controls carrying at least one qualifying variant, by Firth bias-corrected logistic regression adjusted for age and ethnicity (*18*) (Fig. S1A). We found non-synonymous variants in at least five patients for 226 of 731 genes on the X chromosome, resulting in a Bonferroni-corrected significance threshold of $2.2\text{x}10^{-4}$ (Data file S1). *TLR7* was the highest ranked of these genes (uncorrected P-value = 3.5×10^{-5}) and the only gene that remained significant after correction for multiple testing (corrected P-value =7.8×10^{-3}), with 21 unrelated patients carrying one very rare (n=4 patients), two very rare (n=1 patient), or one private (n=16 patients) non-synonymous variant (Fig. 1A, Table S2). One variant (L988S) was recurrent, found in three patients, including a patient carrying two very rare variants (M854I;L988S). No such variants were found in the controls. The same analysis performed on very rare (MAF<10^{-4}) synonymous *TLR7* variants showed no enrichment in patients (one carrier) relative to controls (three carriers).

Human TLR7 is an endosomal receptor of ribonucleic acids expressed by B cells and myeloid subsets (*19–23*), the stimulation of which in plasmacytoid dendritic cells (pDCs) results in the production of large amounts of type I IFN (*24–26*). We observed no significant enrichment for coding non-synonymous variants of the X-linked gene *TLR8* (P-value = 0.68, Table S2), the product of which, TLR8, is endosomal and can be stimulated by some synthetic TLR7 agonists, with an expression pattern and signaling pathway overlapping those of TLR7 (*27, 28*). Unlike TLR7, TLR8 is expressed on granulocytes but not on pDCs, possibly accounting for its gain-of-function mutations underlying a phenotype different from type I interferonopathies (*29–31*). Overall, we found an enrichment in very rare or private non-synonymous *TLR7* variants among the male patients with critical COVID-19 pneumonia (n=21, 1.7%) of our cohort (n=1,202), including one man over the age of 60 years.

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

The 21 unrelated patients carried 20 different *TLR7* alleles. We expressed the 20 TLR7 mutant proteins in human embryonic kidney (HEK) 293T cells, which have no endogenous TLR7 and TLR8 expression (*32*), by transient transfection with the corresponding cDNAs. Immunoblotting of

protein extracts with a TLR7-specific mAb showed an absence of TLR7 protein for p.N158Tfs*11 and p.L227fs* and the presence of truncated proteins for K684* and F670Lfs*8 (Fig. 1B). The other mutant TLR7 proteins were produced in normal amounts (Fig. 1B). We tested their function by cotransfection with an NF-κB-specific luciferase reporter. We measured luciferase activity upon stimulation with R848, an agonist of both TLR7 and TLR8 (Fig. 1C). Twelve of the 20 alleles were loss-of-function (LOF) (including L988S in two patients, and M854I;L988S in another), three (p.L372M, p.I657T and p.P715S) were hypomorphic (activity < 25%), and the remaining five were neutral (Fig. 1C, Data file S2). Similar results were obtained with imiquimod and CL264, two TLR7-specific agonists (Fig. S1B, S1C). We also tested eight other private (p.S301P, p.Q710Rfs*18, p.V795F), very rare (MAF $<10^{-4}$; p.A288V) or rare (MAF between 10^{-4} and 10^{-2}; p.V219I, p.A448V, p.R920K, p.A1032T) *TLR7* variants previously reported in patients with critical COVID-19 (*33*, *34*). These variants were expressed as truncated or full-length proteins (Fig. S1D). The proteins encoded by the three private variants were found to be LOF, that encoded by the very rare variant (p.A288V) was hypomorphic, and those encoded by the four rare variants were neutral (Fig. 1C, Fig. S1B). Collectively, these findings suggest that 16 of the 21 patients in our cohort (Table 1), as well as only 6 of the previously reported 12 patients carry deleterious *TLR7* variants.

The cumulative MAF of deleterious TLR7 alleles is < $6.5x10^{-4}$

We also investigated the production and function of all 100 remaining non-synonymous *TLR7* variants identified in the general population (141,456 individuals in gnomAD v2.1) that had been reported in men or had a general MAF > 10^{-5} (Fig. 1D and Fig. S1E, Data file S2). In total, 96 of these variants were missense and three were in-frame small deletions; 10 were weakly expressed, whereas the others had normal levels of expression (Fig. S1F, Data file S2). One variant was a small deletion creating a frameshift found in one man and resulting in an absence of protein production (Fig. S1F, Data file S2). Seven of the 100 variants were LOF and 15 were hypomorphic (< 25% activity) (Data file S2). There were, thus, 24 deleterious *TLR7* variants, including the L988S and A288V variants found in four patients with critical COVID-19 pneumonia. Each of these 24 deleterious variants had an individual MAF < $1.3x10^{-4}$ in men and their cumulative MAF in men was $6.5\ x10^{-4}$ (Data file S2, Table S3). The cumulative MAF of strictly LOF *TLR7* alleles (excluding hypomorphic alleles) in men is about $2.2\ x10^{-4}$ (Data file S2). Overall, we found 12 LOF and three hypomorphic *TLR7* alleles in 16 unrelated men with critical COVID-19 pneumonia, whereas deleterious alleles were not found in men with asymptomatic or paucisymptomatic infection. Moreover, deleterious *TLR7* alleles in the general population had individual and cumulative MAF values in men of < $1.3x10^{-4}$ and < $6.5x10^{-4}$, respectively (Fig. 1E, Data file S2). The rarity of TLR7 deficiency in the general population is consistent with TLR7 deficiency underlying critical COVID-19. Collectively, these findings suggest that X-linked recessive (XR) TLR7 deficiency is a genetic etiology of life-threatening COVID-19 pneumonia in men.

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

The 16 patients were of three major ethnic origins, as confirmed by principal component analysis (PCA) of their exomes or genomes (*35*), and they were resident in seven countries (France *n*=2, Spain *n*=3, Italy *n*=3, Turkey *n*=2, Sweden *n*=1, Iran *n*=4, Colombia *n*=1) (Fig. 2A, Fig. 2C, Fig. S1, Table 1, Data file S3). The patients were hospitalized for critical COVID-19 between March 2020 and June 2021. Blood samples (diluted 1/10) from these 16 patients contained no auto-Abs neutralizing 10 ng/mL IFN-α2 and/or -ω (*9*) (*79*). The patients were aged 7 to 71 years and their mean age was lower than that of the total cohort (mean age of 34.4 years, versus 52.9 years for the total cohort, in which age ranged from 0.5 to 99 years). TLR7-deficient patients accounted for about 1.8% of the patients below the age of 60 years (15 patients) and 1.3% of the entire cohort (16 patients). Two patients died and 14 survived (Fig. 2A, Table 1). Sanger sequencing of the *TLR7* locus in the relatives of these patients identified the deleterious alleles in 16 heterozygous women from eleven families and seven hemizygous men from seven families (Fig. 2A). Based on the ten DNA samples available from the patients' mothers, only one of the *TLR7* variants (L372M) was de novo in the index case. Five of the seven hemizygous relatives of the index cases had antibodies against SARS-CoV-2 (Fig. 2A, Data file S3). One 29-year-old adult (Kindred J, P11) was hospitalized for critical pneumonia, and another 27-year-old adult (L.II.3) was hospitalized for severe pneumonia (with low-flow oxygen (<6L/min)). The remaining three were two five-year-old boys, one of whom had been hospitalized for moderate COVID-19 pneumonia (without oxygen therapy) (D.II.2), the other having no relevant clinical history (M.II.2), and one 38-year-old adult with no relevant clinical history (E.II.4) (Data file S3). The other two male carriers did not report SARS-CoV-2 infection and had negative serological results for antibodies against the SARS-CoV-2 S and N proteins.

Inherited TLR7 deficiency in patients with severe COVID-19 pneumonia

Given these results, we also analyzed 262 other, unrelated male patients with severe (but not critical) COVID-19 pneumonia (mean age: 51.0 years). We identified a new private LOF variant (p.N75H) in two male patients from two Turkish families (P18 and P19), aged 12 and 7 years, respectively, who were subsequently found to be fourth-degree relatives (Fig. 1B, 1C, 1D, Fig. 2B, Fig. S1B, Data file S2, Data file S3). Their

mothers are heterozygous for this variant. The clinical penetrance of critical COVID-19 in men is therefore high, but not complete, and TLR7 deficiency can also underlie severe COVID-19. The absence of biochemically deleterious *TLR8* variants in our cohort of patients with critical COVID-19 (Fig. S2) and its lack of expression on pDCs suggest that *TLR8* is not a modifier of the SARS-CoV-2-related clinical phenotype of TLR7 deficiency, although it is adjacent to *TLR7* on the X chromosome and can be stimulated by overlapping molecules. Perhaps more relevant to the understanding of the incomplete penetrance is the age of the patients. Of the 23 male patients carrying deleterious alleles of *TLR7* infected with SARS-CoV-2, the 20 patients who developed severe (n=3) or critical (n=17) COVID-19 were aged 7-71 years (mean: 32.4 years) whereas the three patients who developed asymptomatic, mild, or moderate infection were younger: 5, 5, and 38 years (mean: 16 years). Blood pDC counts decrease with age (*36–38*), and this may contribute to the apparent increase in penetrance with age. In addition, a VirScan study of the serum samples of five index cases and three TLR7 hemizygous relatives revealed prior infection with diverse viruses (Fig. S3). None had previously been hospitalized for a severe viral illness, including influenza pneumonia. This cohort of patients thus suggests that TLR7 deficiency does not underlie severe disease caused by common viral infections other than SARS-CoV-2, or if so, with lower penetrance.

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

As a first approach to testing the impact of deleterious *TLR7* alleles in the patients' cells, we tested Epstein-Barr virus-transformed B cell lines (EBV-B cells) from healthy controls and patients carrying the hemizygous p.K684* (P12) or p.H781L (P14) variants. The endogenous expression of the p.H781L TLR7 protein was normal, whereas p.K684* generated a truncated protein (Fig. 2D). In response to agonists of TLR7 (imiquimod) or TLR7 plus TLR8 (R848), the EBV-B cell lines carrying these two mutations failed to produce TNF (Fig. 2E, Fig. S4A, S4B). The lentiviral transduction of these TLR7-deficient EBV-B cells (from P12 and P14) with a WT TLR7 cDNA was unsuccessful, despite numerous attempts, and this was also the case for control EBV-B cells, perhaps because the overproduction of TLR7 is toxic in B cells (*39*). Consistent with this view, we were able to express this cDNA in IRAK4- or MyD88-deficient EBV-B cells. We therefore investigated whether the addition of an IRAK4 inhibitor (PF06650833) would permit the expression of WT TLR7 in control and TLR7-mutated EBV-B cells. This approach was successful, and WT TLR7 expression restored responses to TLR7 agonists (after removal of the inhibitor) (Fig. 2F, Fig. S4C). Hemizygosity for LOF *TLR7* alleles thus abolished responses to TLR7 stimulation in EBV-B cells, a phenotype that was rescued by WT TLR7 expression. Collectively, these findings further suggest that XR TLR7 deficiency is a genetic etiology of severe/critical COVID-19 pneumonia.

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

Human TLR7 is known to be expressed and functional only in leukocyte subsets: plasmacytoid and classical dendritic cells (pDCs and mDCs), monocytes (classical, intermediate, and non-classical), and B cells (*27*, *32*, *40*). TLR8 is expressed in mDCs but not pDCs, monocytes but not B cells, and neutrophils (unlike TLR7) (*27*, *32*, *40*). Neither *TLR7* nor *TLR8* mRNAs have been detected in the lung or pulmonary epithelial cells (*41*). Deep immunophenotyping by CyTOF in seven patients with TLR7 deficiency revealed no major abnormalities in 18 peripheral blood leukocyte subsets, including pDCs, mDCs, monocytes, and B cells (Fig. 3A, Fig. S5A). We previously reported inherited IRF7 deficiency in a child with critical influenza pneumonia (*5*) and two unrelated adults with critical COVID-19 pneumonia (*8*). This defect disrupts the amplification of type I IFNs in all cell types, including pDCs, which are normally the main producers of type I IFN upon blood cell stimulation with TLR7 agonists or viruses, due to their constitutive expression of IRF7 (*27*, *42–44*). We hypothesized that TLR7 deficiency in pDCs impairs the production of type I IFN by these cells in response to ssRNA. We confirmed that TLR7 was expressed on pDCs, and that TLR8 was not (Fig. 3B, S5B, S5C). We measured the production of type I IFNs by purified leukocyte subsets (pDCs, mDCs, monocytes, B cells, T cells), in response to TLR7, TLR8 and TLR9 agonists (Fig. 3C, Fig. S5D). We confirmed that pDCs produced 100-1,000 times more type I IFN per cell than other leukocyte subsets upon TLR7 stimulation (Fig. 3C, Fig. S5D). We purified pDCs from P8 and P14 and analyzed their production of type I IFNs in response to CL264 and class C CpG oligonucleotide (CpG-c), relative to that of pDCs from healthy relatives, using a cytometric bead array (CBA) (Fig. 3D). pDCs from P8 and P14 did not produce type I IFNs (or IL-6) upon stimulation with a TLR7 agonist, whereas they responded to a TLR9 agonist (Fig. 3D). Moreover, agonist-induced up-regulation of PD-L1 and CD80 defines the maturation of pDCs into the S1 (PD-L1^{high}/CD80^{low}), S2 (PD-L1^{high}/CD80^{high}), and S3 (PD-L1^{low}/CD80^{high}) subsets (*45*). This maturation was not observed in the pDCs of P8 and P14, but was detected in the pDCs of healthy relatives and controls (Fig. 3E, Fig. S5E). Thus, pDCs from patients with *TLR7* mutations do not respond to TLR7 agonists in terms of maturation into specialized subsets and type I IFN production.

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

A plausible mechanism accounting for the severity of COVID-19 in TLR7-deficient patients is the impairment of type I IFN production by pDCs upon stimulation with SARS-CoV-2, which can enter these cells, but cannot replicate

productively within them (*45*, *46*). Indeed, we previously showed that the activation of human pDCs by SARS-CoV-2 depends on IRAK4 and UNC-93B, but not TLR3 (*45*). We tested the hypothesis that TLR7 is an essential pDC sensor of SARS-CoV-2, upstream from IRAK4 and UNC-93B, by infecting pDCs and pDC-depleted leukocytes from healthy controls and TLR7-deficient patients with SARS-CoV-2 for 24 hours. Control pDC-depleted leukocytes infected with SARS-CoV-2 displayed no significant up- or down-regulation of gene expression (Fig. S6A). By contrast, transcriptomic analysis showed a strong up-regulation of the type I IFN transcriptional module in pDCs from healthy controls, which was greatly reduced in pDCs from TLR7-deficient patients (Fig. 4A). Induction of the 17 type I *IFN* genes in pDCs from TLR7-deficient patients was 10 to 100 times weaker than that in pDCs from healthy individuals (Fig. 4B, S6B). We also analyzed the functional specialization of pDC subsets (S1-, S2-, and S3-pDC subsets) in response to SARS-CoV-2 activation (*45*, *47*). pDCs from P14 cultured with SARS-CoV-2 for 24 hours displayed abnormally low levels of maturation into the S1-subset —the pDC subset principally responsible for IFN-α production upon SARS-CoV-2 infection (Fig. S6C). Finally, we evaluated the amount of type I IFNs secreted by SARS-CoV-2-infected pDCs. All 13 individual IFN-α forms were produced in significantly smaller amounts by TLR7-deficient pDCs than by control pDCs (Fig. 4C, S6D). However, IFN-α production by TLR7-deficient pDCs upon SARS-CoV-2 infection was impaired, but not entirely abolished, as in UNC-93B- or IRF7-deficient pDCs (*8*, *45*), implying that there are also TLR7-independent sensors of SARS-CoV-2 in pDCs and suggesting that TLR9 is involved. The TLR7-deficient pDCs' normal response to TLR9 agonists (Fig. 3D, 4A, 4B, S6D) is consistent with this hypothesis, while also suggesting that genetic or epigenetic variations of TLR9 responses may contribute to the apparently age-dependent penetrance of TLR7 deficiency. Thus, SARS-CoV-2 triggers type I IFN induction in pDCs in a manner that is dependent on TLR7, but not exclusively so. As pDCs are normally the main leukocytes producing type I IFN in such conditions, and type I IFN is essential for protective immunity to SARS-CoV-2 (*8*, *9*), these findings suggest that XR TLR7 deficiency underlies critical or severe COVID-19 pneumonia by disrupting TLR7-and pDC-dependent type I IFN production.

DISCUSSION

We report XR TLR7 deficiency as a genetic etiology of severe/critical COVID-19 pneumonia in 20 unrelated male patients, aged 7 to 71 years, from seven countries. Only one of these 20 patients (5%) was older than 60 years, consistent with our previous observation that only five of 23 patients (21.7%) with inborn errors of TLR3-dependent type I IFN immunity were older than 60 years (*8*). This suggests that these genetic defects are mostly found in the youngest patients. This contrasts with the situation for auto-Abs against type I IFNs, which are found mostly in patients over the age of 60 years (*8*, *9*) (*79*). Importantly, patients with these auto-Abs do not overlap with those bearing inborn errors of TLR3- or TLR7-dependent type I IFNs. TLR7-deficient patients accounted for about 1.8% of the unrelated male patients with critical COVID-19 pneumonia below the age of 60 years in our cohort and accounted for 1.3% of the total cohort. This proportion remained around the same when severe COVID-19 pneumonia was also taken into account (1.7% males below 60 years; 1.2% of all the male patients in the total cohort). We also found that six of the 12 previously reported patients with a *TLR7* variant had TLR7 deficiency (*33*, *34*). It would be interesting to test experimentally the undisclosed *TLR7* variants reported to be enriched in another study (*48*). Our discovery provides an explanation for the higher risk of severe and critical disease in men than in women under the age of 60 years, complementing our previous observation of a much higher frequency of neutralizing auto-Abs against type I IFNs in men than in women with critical COVID-19 pneumonia for patients over the age of 60 years (*9*).

Previous reports of patients with critical COVID-19 pneumonia due to inborn errors of TLR3-dependent type I IFN immunity (*8*), including autosomal recessive IRF7 or IFNAR1 deficiency (*5*, *6*), or due to auto-Abs neutralizing type I IFNs (*9*, *11–14*, *16*, *17*), strongly suggest that critical disease in TLR7-deficient patients is a consequence of impaired type I IFN production upon SARS-CoV-2 infection. The absence of biochemically deleterious X-linked *TLR8* variants in our cohort of patients suggests that TLR8 is not essential for host defense against SARS-CoV-2. This is consistent with the modest capacity of TLR8 to induce type I IFN and its lack of expression on pDCs (*27*), and with the inflammatory phenotype of TLR8 gain-of-function mutations, which do not underlie a type I interferonopathy (*29–31*). Patients with inherited IRAK4 or MyD88 deficiency, whose cells do not respond to the stimulation of IL-1Rs and TLRs other than TLR3, including TLR7, have not been reported to display any severe viral illness over the almost 20 years since the discovery of IRAK-4 deficiency (*49–52*). Moreover, UNC-93B-deficient pDCs produced normal amounts of type I IFN in response to seasonal influenza virus (*5*). This was intriguing, as strong negative selection operates at the human *TLR7, TLR8,* and *TLR9* loci (*49*, *53*). Our study provides an answer to this riddle, by establishing that TLR7 is essential for protective immunity to SARS-CoV-2. Patients with IRAK4, MyD88, or UNC93B deficiency are now predicted to be vulnerable to SARS-CoV-2 (*54–56*). Critical COVID-19 and seasonal influenza can be caused by inborn errors of TLR3-dependent type I IFN immunity (*5–8*), but susceptibility to these infections is not allelic at the *TLR7* locus. It is, nevertheless, tempting to speculate that TLR7 might also be essential for host defense against more virulent,

pandemic viruses, including both coronaviruses and influenza viruses.

Through the discovery of the essential nature of TLR7 for the induction of type I IFN in response to SARS-CoV-2, our study also reveals the essential function of human pDCs in host defense. The constitutively high levels of IRF7 in these cells make them the most potent producers of type I IFN in the blood, and perhaps in the entire human body, and this has long suggested a possible key role in antiviral immunity (*25*). However, the essential and redundant roles of this leukocyte subset have yet to be determined, in the absence of human pDC-specific deficiencies causally underlying a clinical phenotype. It has long been suspected, but never proved, that pDCs are essential for host defense in natural conditions (*26*, *57–59*). Inherited IRF7 deficiency, which underlies critical influenza or COVID-19 pneumonia, disrupts the production of type I IFNs not only by pDCs (*5*, *8*), but also by all other cell types, including pulmonary epithelial cells (*5*). Likewise, patients with GATA2 deficiency, who are prone to critical influenza (*60*), lack pDCs, but these patients also lack many other blood cell subsets (*61–64*). Inherited IFNAR1 deficiency underlies critical COVID-19 probably due to its broad cellular impact (*5*, *6*, *8*). By contrast, inborn errors of the TLR3 pathway underlie critical influenza or COVID-19 pneumonia by impairing the production of type I IFNs by cells other than pDCs, such as pulmonary epithelial cells (*5–8*, *65*). Our study indicates that pulmonary epithelial cells are not sufficient for host defense against SARS-CoV-2, as these cells do not express TLR7. Inborn errors of TLR7 are pathogenic by impairing the production of type I IFNs by blood pDCs, which are unique in their production of large amounts of both TLR7 and IRF7 (*66*, *67*). pDCs express other viral sensors, including TLR9 (for DNA), MDA5 and RIG-I (for dsRNA) (*68*), but TLR7 deficiency impairs their capacity to produce large enough amounts of type I IFN in response to SARS-CoV-2 in the respiratory tract. Overall, by disrupting pDC-dependent type I IFN production, XR TLR7 deficiency accounts for at least 1% of cases of life-threatening COVID-19 pneumonia in men under 60 years.

MATERIALS AND METHODS

Study design

We searched for X-linked inborn errors of immunity in male patients with critical SARS-CoV-2 pneumonia. We screened our WES database of 1,202 male patients with critical SARS-CoV-2 pneumonia ('patients') and 331 male subjects with asymptomatic or paucisymptomatic infection ('controls'). We tested the association of X-linked genes with critical SARS-CoV-2 pneumonia using a Firth bias-corrected logistic regression model including the first five principal components of the PCA to account for the ethnic heterogeneity of the cohorts and age in years. We then tested the activity of *TLR7* variants in transduced cell lines and of *TLR7* genotypes in hemizygous patients' cell lines. Lastly, we tested the patients' pDCs for their response to both TLR7 agonists and SARS-CoV-2.

Cohort recruitment and consent

This study included 1,202 male patients with life-threatening COVID-19 pneumonia, defined as patients with pneumonia who developed critical disease, whether pulmonary with high-flow oxygen (> 6L/min) or mechanical ventilation (CPAP, BIPAP, intubation), septic shock, or any other type of organ damage requiring ICU admission. This study also included patients with severe COVID-19 pneumonia, defined as hospitalized patients with pneumonia that required low-flow oxygen (<6L/min); moderate COVID-19 pneumonia, defined as patients with pneumonia but did not require oxygen therapy; and mild COVID-19, defined as patients with mild upper respiratory symptoms but without pneumonia. Patients who developed Kawasaki-like syndrome were excluded. The age of the patients ranged from 0.5-99 years, with a mean age of 52.9 years (SD 16.4 years). Asymptomatic or paucisymptomatic individuals (n= 331) were recruited on the basis of positive PCR or serological tests for SARS-CoV-2 in the absence of symptoms. These individuals were close contacts of patients or were recruited after clinical screening. The age of the asymptomatic or paucisymptomatic individuals ranged from 1.3-102 years, with a mean age of 38.7 years (SD: 17.2 years).

All the enrolled subjects provided written informed consent and were collected through protocols conforming to local ethics requirements. For patients enrolled in the French COVID cohort (clinicaltrials.gov NCT04262921), ethics approval was obtained from the CPP IDF VI (ID RCB: 2020-A00256-33) or the Ethics Committee of Erasme Hospital (P2020/203). For subjects enrolled in the COV-Contact study (clinicaltrials.gov NCT04259892), ethics approval was obtained from the CPP IDF VI (ID RCB: 2020-A00280-39). For patients enrolled in the Italian cohort, ethics approval was obtained from the University of Milano-Bicocca School of Medicine, San Gerardo Hospital, Monza – Ethics Committee of the National Institute of Infectious Diseases Lazzaro Spallanzani (84/2020) (Italy), and the Comitato Etico Provinciale (NP 4000 – Studio CORONAlab). STORM-Health care workers were enrolled in the STudio OsseRvazionale sullo screening dei lavoratori ospedalieri per COVID-19 (STORM-HCW) study, with approval from the local IRB obtained on June 18, 2020. Patients and relatives from San Raffaele Hospital (Milan) were enrolled in protocols COVID-BioB/Gene-COVID and, for additional studies, TIGET-06, which were approved by local ethical committee. For patients enrolled in Spain, the study was approved by the Committee for Ethical Research of the Infanta Leonor University Hospital, code 008-20, Committee for Ethical Research of the University Hospital 12 de Octubre, code 16/368 and 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 NIAID through USUHS/TAGC under non-human subject research conditions; no additional IRB consent was required at the NIH. For patients enrolled in the Swedish COVID cohort, ethics approval was obtained from the Swedish Ethical Review Agency (2020-01911 05).

Next-generation sequencing

Genomic DNA was extracted from whole blood. For the 1,533 patients included, the whole exome (n=1035) or whole genome (n=498) was sequenced at several sequencing centers, including the Genomics Core Facility of the Imagine Institute (Paris, France), the Yale Center for Genome Analysis (USA), the New-York Genome Center (NY, USA), and the American Genome Center (TAGC, USUHS, Bethesda, USA), and the Genomics Division-ITER of the Canarian Health System sequencing hub (Canary Islands, Spain).

For WES, libraries were generated with the Twist Bioscience kit (Twist Human Core Exome Kit), the xGen Exome Research Panel from Integrated DNA Technologies (IDT xGen), the Agilent SureSelect V7 kit or the SeqCap EZ MedExome kit from Roche, and the Nextera Flex for Enrichment-Exome kit (Illumina). Massively parallel sequencing was performed on a HiSeq4000 or NovaSeq6000 system (Illumina). For WES analysis performed at CNAG Barcelona, Spain, capture was performed with the SeqCap EZ Human Exome Kit v3.0 (Roche Nimblegen, USA) and 100-bp paired-end read sequences were obtained on a HiSeq 2000-4000 platform (Illumina, Inc. USA). For the OSR Italian cohort, WES was performed with the Agilent SureSelect V7 kit on a NovaSeq6000 system (Illumina).

For WGS on patients of the Italian cohort (TAGC), genomic DNA samples were dispensed into the wells of a Covaris 96 microTUBE plate (1,000 ng per well) and sheared with the Covaris LE220 Focused-ultrasonicator, at settings targeting a peak size of 410 bp (t:78; Duty:18; PIP:450; 200 cycles). Sequencing libraries were generated from fragmented DNA with the Illumina TruSeq DNA PCR-Free HT Library Preparation Kit, with minor modifications for automation (Hamilton STAR Liquid Handling System), with IDT for Illumina TruSeq DNA UD Index (96 indices, 96 samples) adapters. Library size distribution was assessed and the absence of free adapters or adapter dimers was checked by automated capillary gel electrophoresis (Advanced Analytical Fragment Analyzer). Library concentration was determined by qPCR with the KAPA qPCR Quantification Kit (Roche Light Cycler 480 Instrument II). Sequencing libraries were normalized and combined as 24-plex pools and quantified as above, before dilution to 2.9 nM and sequencing on an Illumina NovaSeq 6000 with the S4 Reagent Kit (300 cycles) and 151+8+8+151 cycle run parameters. Primary sequencing data were demultiplexed with the Illumina HAS2.2 pipeline and sample-level quality control was performed for base quality, coverage, duplicates and contamination (FREEMIX < 0.05 by VerifyBamID). For patients enrolled in the Swedish COVID cohort, sequencing was performed at the Clinical Genomics Stockholm unit of the SciLifeLab (Stockholm, Sweden).

We used the Genome Analysis Software Kit (GATK) (version 3.4-46 or 4) best-practice pipeline to analyze our WES data (*69*). We aligned the reads obtained with the human reference genome (hg19), using the maximum exact matches algorithm in the Burrows–Wheeler Aligner (BWA) (*70*). PCR duplicates were removed with Picard tools (picard.sourceforge.net). The GATK base quality score recalibrator was applied to correct sequencing artifacts. Genotyping was performed with GATK GenotypeGVCFs in the interval intersecting all the capture kits ± 50 bp. Sample genotypes with a coverage < 8X, a genotype quality (GQ) < 20, or a ratio of reads for the less covered allele (reference or variant allele) over the total number of reads covering the position (minor read ratio, MRR) < 20% were filtered out. We filtered out variant sites (i) with a call rate <50% in gnomAD genomes and exomes, (ii) a non-PASS filter in the gnomAD database, (iii) falling in low-complexity or decoy regions, (iv) that were multi-allelic with more than four alleles, (v) with more than 20% missing genotypes in our cohort, and (vi) spanning more than 20 nucleotides. Variant effects were predicted with the Ensembl Variant Effect Predictor (VEP) (*71*) and the Ensembl GRCh37.75 reference database, retaining the most deleterious annotation obtained from Ensembl canonical transcripts overlapping with RefSeq transcripts.

Statistical analysis

We performed an enrichment analysis focusing on X chromosome genes on our cohort of 1,202 male patients with life-threatening COVID-19 pneumonia without known inborn errors of TLR3- and IRF7-dependent type I IFN immunity (*8*) and without neutralizing auto-Abs against type I IFNs (*9*), and 331 male individuals with asymptomatic or paucisymptomatic infection (Table S1). We considered variants that were predicted to be loss-of-function or missense, with a MAF below 0.0001 (gnomAD v2.1.1). We compared the proportion of patients and controls carrying at least one non-synonymous using the Firth bias-corrected logistic likelihood ratio test implemented in EPACTS (https://genome.sph.umich.edu/wiki/EPACTS) extended to gene based enrichment analysis. In Firth's regression, a penalty term is placed on the standard maximum likelihood function used to estimate parameters of a logistic regression model (*18*). Firth's can handle genes with no carriers among cases or controls. With no covariates, this corresponds to adding 0.5 in every cell of a 2x2 table of allele counts versus case-control status. We accounted for the ethnic heterogeneity of

the cohorts by including the first five principal components of the PCA in the Firth's logistic regression model. Analyses were also adjusted for age in years. We checked that our adjusted burden test was well-calibrated by also performing an analysis of enrichment in rare (MAF < 0.0001) synonymous variants. PCA was performed with Plink v1.9 software on whole-exome and whole-genome sequencing data, with the 1000 Genomes (1kG) Project phase 3 public database as a reference, using 18,917 exonic variants with a minor allele frequency > 0.01 and a call rate > 0.99.

Cell culture

EBV-B cell lines derived from the patients were grown in complete RPMI 1640 (Life Technologies) supplemented with 10% heat-inactivated fetal bovine serum (FBS). HEK293T cells, derived from the human embryonic kidney 293 cell line, which expresses a mutant version of the SV40 large T antigen, were grown in complete DMEM (Life Technologies) supplemented with 10% FBS. Cells were incubated at 37°C in the presence of 5% CO_2.

Expression vectors and transfection experiments

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

Western blotting

For whole-cell extracts, the cells were lysed by incubation in the following buffer (50 mM Tris-HCl, pH 8.0, 150 mM NaCl, 1% NP40), supplemented with a mixture of protease inhibitors (Sigma-Aldrich), for 30 min at 4°C. The lysates were then centrifuged at 21,000 x *g* for 20 min at 4°C. The supernatants were processed directly for Western blotting. Western blotting was performed on 10 µg of total extract from transfected HEK293T cells, with monoclonal antibodies specific for the leucine-rich repeats to the N terminus within the human TLR7 protein (Cell Signaling Technology; clone, D7), or for amino-acid 1,000 to the C terminus with the human TLR7 protein (Abcam; clone, EPR2088(2)).

Luciferase reporter assay

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

RNA extraction and reverse transcription-quantitative PCR (RT-qPCR)

Total RNA was extracted with the RNeasy Mini Kit (Qiagen), according to the manufacturer's instructions. Reverse transcription was performed on 1 µg of RNA with random primers and the SuperScript® III reverse transcriptase (Invitrogen), according to the manufacturer's protocol. Quantitative PCR was then performed with the TaqMan Fast Universal PCR Master Mix (2X) and the FAM-MGB *Taq*Man *TNF* exons 1-2 (Hs99999-43_m1) probes. The VIC-TAMRA probe for *GUSB* (Applied Biosystems, Cat: 4310888E) was used as an endogenous control. Real-time PCR amplification was monitored with the 7500 Fast Real-Time PCR System (Applied Biosystems). Relative expression levels were determined according to the ΔCt method.

ELISA analysis of TNF production in EBV-B cells

ELISA was performed as previously described (*50*). We suspended $1x10^6$ EBV-B cells per well in RPMI 1640 supplemented with 10% FBS. The cells were activated by incubation with 1 µg/mL R848, and 5 µg/mL imiquimod for 24 hours. The supernatants were harvested after 24 hours of activation. ELISA determinations of TNF in cell culture supernatants were performed with a kit (Thermo Fisher Scientific), according to the manufacturer's instructions.

Stable transduction

The WT coding sequence of *TLR7* was inserted into pTRIP-CMV-puro-2A. For lentivirus production, HEK293T cells were transfected with 1.6 µg pTRIP-CMV-puro-2A-TLR7-WT (or Mutant: K684*), 0.2 µg pCMV-VSV-G (Addgene), 0.2 µg pHXB2 (NIH-AIDS Reagent 22 Program) and 1 µg psPAX2 (Addgene), with X-treme gene 9 (Roche), according to the manufacturer's instructions. Supernatants were harvested after 24 hours and 8 µg/mL protamine sulfate was added. The lentiviral suspension obtained was used to transduce $2x10^5$ EBV-B cells by spinoculation at 1,200 x *g* for 2 hours. The transduced cells were selected by incubation on medium containing 1 µg/mL puromycin for two days. The cells were then selected by incubation for a further two days on medium containing 2 µg/mL puromycin. During viral transduction, the cells were cultured with 5 µM IRAK4 inhibitor (PF06650833) (Bio-techne) to prevent cell death due to the overproduction of TLR7. Selected transduced cells were then stimulated with 1 µg/mL R848 or 5 µg/mL imiquimod for 24 hours without IRAK4 inhibitor. The supernatants were harvested after 24 hours of activation. ELISA determinations of TNF in cell culture supernatants were performed with a kit (Thermo Fisher

Scientific), according to the manufacturer's instructions.

VirScan analysis

Patient serum was analyzed by VirScan in two independent experiments as previously described (*78*). Briefly, an oligonucleotide library encoding 56 amino acid peptides tiling across the genomes of 206 viral species was synthesized on a releasable DNA microarray and cloned into T7 phage. Patient serum containing 2 μg of IgG was added to the phage library, and immunoprecipitation was performed with Protein A and G beads. Enriched peptides were identified by PCR and Illumina sequencing of the peptide cassette from the immunoprecipitated phage.

Deep immunophenotyping by mass cytometry (CyTOF)

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

PBMC enrichment using MACS system

Blood were collected from two healthy individuals and separated by the concentration gradient method with Ficoll® Paque Plus (Cytiva). After isolations of PBMCs, leucocyte subset (T cell, B cell, monocyte, pDC, and mDC) were purified by negative selection using MACS beads system (Milteni Biotec). Cells were plated into a U-bottomed 96-well plate at a density of 2×10^4 cells/well for T cells, B cells, monocytes, pDCs, or mDCs in 200 μL/well RPMI-1640 with GlutaMAX supplemented with 10% FBS or 10×10^4 cells/well for whole blood and PBMCs. Cells were left unstimulated or stimulated with 1μg/mL CL264, 100ng/ml TL8-506 (Invivogen), 1μg/mL R848, 2μM CpG-c (Invivogen), or 12.5ng/ml PMA and 0.125μM ionomycin for 24 hours. The supernatants were harvested after 24 hours of activation. Cytokines production were determined by ELISA (IFN-α - PBL Assay Science, IFN-β- PBL Assay Science, IFN- λ1 (IL-29) - Invivogen, IFN-ω- Invitrogen or IL-8 - R&D SYSTEMS); according to the manufacturer's instructions.

Analysis for TLR7 and TLR8 expression pattern in peripheral blood mononuclear cells (PBMCs) by flow cytometry

Freshly thawed PBMCs from healthy donors were dispensed into a V-bottomed 96-well plate at a density of 1×10^6 cells/well, in 200 μL PBS/well. In brief, cells were stained by incubation with the LIVE/DEAD fixable blue dead-cell staining kit (Thermo Fisher Scientific, 1:800) and FcR blocking reagent (Miltenyi Biotec, 1:25) on ice for 15 min. For surface staining, cells were incubated with anti-γδTCR-BUV611 (BD Biosciences, 1:50), anti-CD183-BV750 (BD Biosciences, 1:20), and anti-CD194-BUV615 (BD Biosciences, 1:20) antibodies on ice for 30 min in 0.1% BSA and 0.01% sodium azide in PBS. They were then incubated with anti-CD141-BB515 (BD Biosciences, 1:40), anti-CD57-FITC (Biolegend, 1:83), anti-TCR Vδ2-PerCP (Biolegend, 1:166), anti-TCR Vα7.2-PerCP/Cyanine5.5 (Biolegend, 1:40), anti-TCR Vδ1-PerCP-Vio 700 (Miltenyi Biotec, 1:100), anti-CD14-Spark Blue 550 (Biolegend, 1:40), anti-CD1c-Alexa Fluor 647 (Biolegend, 1:50), anti-CD38-APC/Fire 810 (Biolegend, 1:30), anti-CD27-APC-H7 (BD Biosciences, 1:50), anti-CD127-APC-R700 (BD Biosciences, 1:50), anti-CD19-Spark NIR 685 (Biolegend, 1:83), anti-CD45RA-BUV395 (BD Biosciences, 1:83), anti-CD16-BUV496 (BD Biosciences, 1:166), anti-CD11b-BUV563 (BD Biosciences, 1:100), anti-CD56-BUV737 (BD Biosciences, 1:83), anti-CD8-BUV805 (BD Biosciences, 1:83), anti-hMR1-BV421 (NIH tetramer facility, 1:100), anti-CD11c-BV480 (BD Biosciences, 1:40), anti-CD45-BV510 (Biolegend, 1:83), anti-CD33-BV570 (Biolegend, 1:83), anti-iNKT-BV605 (Biolegend, 1:25), anti-CD161-BV650 (BD Biosciences, 1:25), anti-CCR6-BV711 (Biolegend, 1:83), anti-CCR7- BV785 (Biolegend, 1:40), anti-CD3-Pacific Blue (Biolegend, 1:83), anti-CD20-Pacific Orange (Life Technologies, 1:50), anti-CD123-Super Bright 436 (Invitrogen, 1:40), anti-CD24-PE-Alexa Fluor 610 (Life Technologies, 1:25), anti-CD25-PE-Alexa Fluor 700 (Life Technologies, 1:25), anti-CD294-Biotin (Invitrogen, 1:50), anti-CD209-PE/Cyanine7 (Biolegend, 1:25), anti-CD117-PE/Dazzle 594 (Biolegend, 1:83), anti-HLA-DR-PE/Fire 810 (Biolegend, 1:50), and anti-CD4-cFluor™ YG584 (Cytek, 1:83) antibodies on ice for at least 30 min. The cells were then washed and stained by incubation with streptavidin-PE/Cy5 (Biolegend, 1:3000) on ice for 30 min. The cells were then fixed and permeabilized for intracellular staining with anti-TLR7-PE (Invitrogen) and anti-TLR8-APC (Biolegend) antibodies, with the eBioscience Foxp3/Transcription Factor Staining Buffer Set (Invitrogen), according to the manufacturer's instructions. The cells were then washed and acquired with a five-laser Cytek Aurora (Cytek) flow cytometer. Antibody clone information is added in a supplemental material (Data file S6).

pDC activation

Freshly purified pDCs were cultured in 96-well plates at a concentration of 5×10^5 cells per mL in the presence of medium alone (RPMI 1640 Medium with GlutaMAX, 10% FBS, 1% MEM NEAA, 1% sodium pyruvate, and 1% penicillin/streptomycin), CL264 (Invivogen, 1 μg/mL), or the SARS-CoV-2 primary strain 220_95 (*45*) at a multiplicity of infection (MOI) of 1. After 24 hours of culture, the pDC supernatant was collected for cytokine quantification, and the PDCs were collected for diversification assessment by flow cytometry. In some experiments, RNA was purified from the pDCs were analyzed by RNA-seq (see below).

Flow cytometry analysis for human pDCs

For assessments of pDC diversification, cells were stained

with Zombie Violet fixable viability dye (Biolegend), BV711 anti-CD123 (Biolegend, clone 6H6), PE anti-CD80 (BD, clone L307.4), and PerCP-efluor 710 anti-PD-L1 (eBioscience, clone MIH1) antibodies. Data were acquired with an LSR Fortessa (BD Biosciences) flow cytometer and analyzed with FlowJo software (Tree Star). Flow cytometry analyses were performed at the flow cytometry core facility of IRSL (Paris, France).

RNA-Sequencing

We collected cells from five individuals in two families: one patient (P8) and two healthy controls (H.II.2, H.II.3) from family H, and one patient (P14) and one healthy control (M.I.1)) from family M. These cells were stimulated with three conditions: non-stimulation, SARS CoV-2, and CpG-c. Total RNA was extracted from pDC cells with RNeasy Micro kits (QIAGEN). RNA-Seq libraries were prepared with the Illumina SMART-Seq® v4 PLUS Kit (TaKaRa) and sequenced on the Illumina NextSeq 4000 platform with single-end 75 bp configuration. The RNA-Seq fastq raw data were inspected with multiQC v1.10 (*72*) to ensure the high quality of data. The sequencing reads were mapped onto the human reference genome GRCh38 with STAR aligner v2.7 (*73*), and the mapped reads were then quantified to determine the gene-level read counts with featureCounts V2.0.2 (*74*) and GENCODE human gene annotation GRCh38.p13 (*75*). The gene-level read counts were normalized and log2-transformed by DESeq2 (*76*), to obtain the gene expression profile of all samples for differential expression analysis. The differential gene expression was analyzed by applying TMM normalization and gene-wise generalized linear model regression with edgeR (*77*). The genes displaying significant differential expression were selected on the basis of |log2-FoldChange| ≥ 2 and FDR ≤ 0.05. The gene-level read counts of IFN genes were transformed to RPKM (Reads Per Kilobase of transcript, per Million mapped reads) by our own scripts, to compare the IFN gene expression of different samples under different stimulations.

Determination of secreted inflammatory cytokines

We measured the production, by pDCs, of IFN-α2, IL-8, IL-6, and IP-10, by determining the levels of these cytokines in culture supernatants with the BD cytometric bead array (CBA), according to the manufacturer's protocol, with a limit of detection of 20 pg/mL. Acquisitions were performed on an LSR Fortessa (BD Biosciences) flow cytometer, and cytokine concentrations were determined with FCAP Array Software (BD Biosciences).

SUPPLEMENTARY MATERIALS

immunology.sciencemag.org/cgi/content/full/6/62/eabl4348/DC1

- Figure S1; Ethnicity information and *TLR7* allele activity
- Figure S2; Allele activity for the *TLR8* variants found in our cohort
- Figure S3; VirScan analysis of specific anti-viral antibodies detected in patient sera
- Figure S4; Levels of TNF induction in EBV-B cells derived from two patients with XR TLR7 deficiency
- Figure S5; Analysis of peripheral blood mononuclear cells from TLR7-deficient men
- Figure S6; Functional analysis in pDCs infected with SARS-CoV-2
- Table S1; Characteristics of the cohort of patients with life-threatening COVID-19 pneumonia and the control cohort of asymptomatic or paucisymptomatic individuals
- Table S2; Statistical analysis of non-synonymous rare variants of *TLR7* and *TLR8* in our cohorts
- Table S3; Summary of *TLR7* variants
- Data file S1; Selection of genes on chromosome X with 5 or more hemizygous carriers (Excel file).
- Data file S2; *TLR7* variant activity reported in this study, in previous studies and in gnomAD (Excel file).
- Data file S3; TLR7-deficient patients with severe/critical COVID-19 in our cohort (clinical information, laboratory findings, and immunological findings) (Excel file).
- Data file S4; Primer sequences for mutagenesis (Excel file).
- Data file S5; Antibody information for CyTOF (Excel file).
- Data file S6; Gating strategy and antibody clone information for 40 color immunophenotyping (Excel file).
- Data file S7; Raw data files (Excel file).

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Acknowledgments: We thank the patients and families; the members the Laboratory of Human Genetics of Infectious Diseases; Y. Nemirovskaya, M. Woollett, D. Liu, S. Boucherit, C. Rivalain, M. Chrabieh and L. Lorenzo for administrative assistance. **Funding:** The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program (UL1TR001866), 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 Fisher Center for Alzheimer's Research Foundation, the Meyer Foundation, the JPB Foundation, 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-IBEID), the French Foundation for Medical Research (FRM) (EQU201903007798), the FRM and ANR GENCOVID project, the ANRS-COV05, ANR GENVIR (ANR-20-CE93-003) and ANR AABIFNCOV (ANR-20-CO11-0001) projects, the European Union's Horizon 2020 research and innovation program under grant agreement no. 824110 (EASI-genomics), the Square Foundation, *Grandir - Fonds de solidarité pour l'enfance*, the SCOR Corporate Foundation for Science, *Fondation du Souffle, Institut National de la Santé et de la Recherche Médicale* (INSERM) and 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). The Cov-Contact Cohort was supported by the REACTing consortium, the French Ministry of Health, and the European Commission (RECOVER WP 6). The Neurometabolic Diseases Laboratory received funding from the European Union's Horizon 2020 research and innovation program (EasiGenomics grant no. 824110 COVID-19/PID12342). A.P. R.P.D., C.R.G. and C.F. were funded by Instituto de Salud Carlos III (COV20_01333 and COV20_01334), the Spanish Ministry of Science and Innovation (RTC-2017-6471-1; AEI/FEDER, UE), Grupo DISA (OA18/017), and Cabildo Insular de Tenerife (CGIEU0000219140 and "Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19"). The laboratories of G.N. and A.N. were supported by a grant awarded to Regione Lazio (PROGETTI DI GRUPPI DI RICERCA 2020) no. A0375-2020-36663, GecoBiomark. A.Am.'s laboratory was supported by 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-IBEID), the FRM (EQU202003010193), ANR (ANR-20-COVI-000 project IDISCOVR and ANR-20-CO11-0004 project FISHBP) and the University of Paris (*Plan de Soutien Covid-19*: RACPL20FIR01-COVID-SOUL). This work was supported in part by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, NIH (grants 1ZIAAI001265 to H.C.S and ZIA AI001270 to L.D.N.). The G.C. laboratory was supported by the Italian Ministry of Health (grant COVID-2020-12371617) and the intramural COVID Host Genetics program. The J.L.F. laboratory was supported in part by the Coopération Scientifique France-Colciencias (ECOS-Nord/COLCIENCIAS/MEN/ICETEX (806-2018) and Colciencias contract 713-2016 (no. 111574455633). The V.S. laboratory was supported by ANR DENDRISEPSIS (ANR-17-CE15-0003) and ANR APCOD (ANR-17-CE15-0003-01), a Fast Grant from the Mercatus Center, FRM, University of Paris PLAN D'URGENCE COVID19. A.-L.N. was supported by the Bettencourt Schueller Foundation and the International PhD program of the Imagine Institute. **Author contributions:** A.K.-K., A.Am., A.C., A.G., A.-L.N., Be.Bo., E.J., F.A.A. F.O., J.R., L.M., M.A., M.M-V., M.M., M.O., MRL.MR., N.M., Pa.Ba., Q.P., Q.Z., S.J.P., Sa.Ko., S.M., T.A., T.K., T.Le V., V.B., V.S., P.Z. and Y.Z. performed or supervised experiments, generated and analyzed data, and contributed to the manuscript by providing figures and tables. A.C., A.B., Au.Pu., Be.Bi., Da.Mat., K.B., L.A., and Y.S. performed computational analyses of data. 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R.P.L. is a non-executive director of Roche and its subsidiary Genentech. The authors declare no other competing interests. **Data and materials availability:** The RNA-seq data for this study have been deposited in the Gene Expression Omnibus database under accession number GSE181787. For patients enrolled in the Italian cohort, patient specimens may be available from Monza, subject to approval by their local IRB, through an MTA. All other data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials.

COVID Human Genetic Effort

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Submitted 13 July 2021
Accepted 12 August 2021
Published First Release 19 August 2021
10.1126/sciimmunol.abl4348

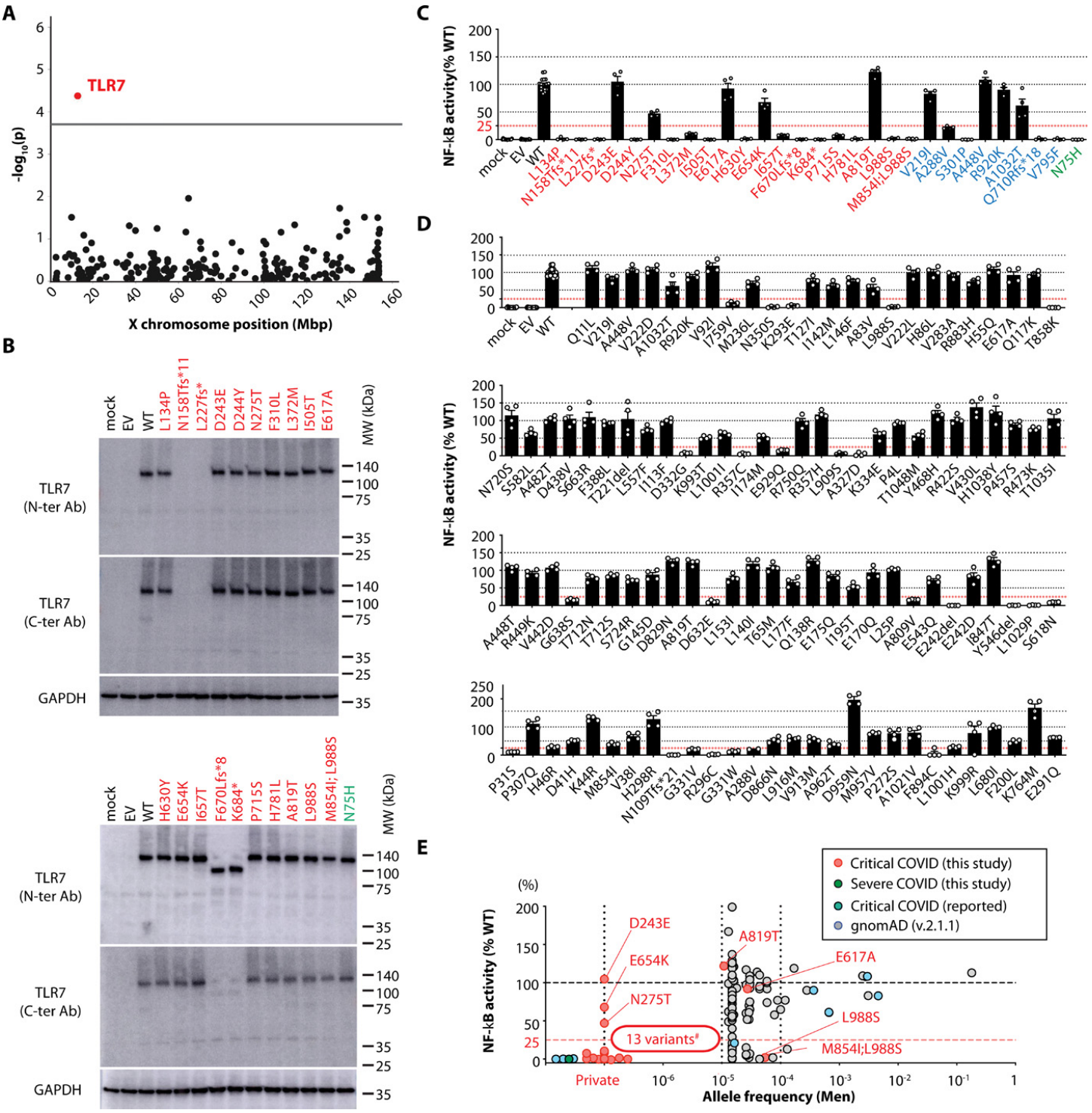
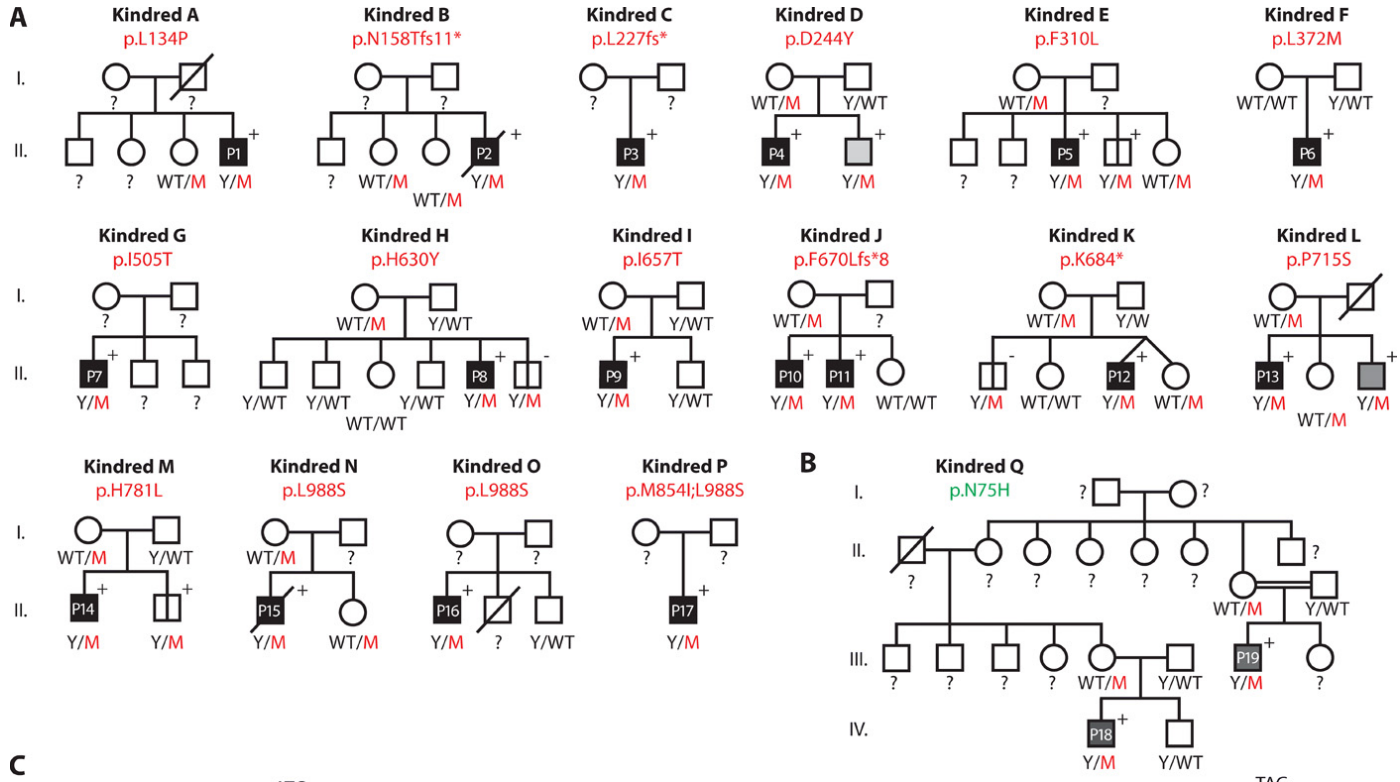
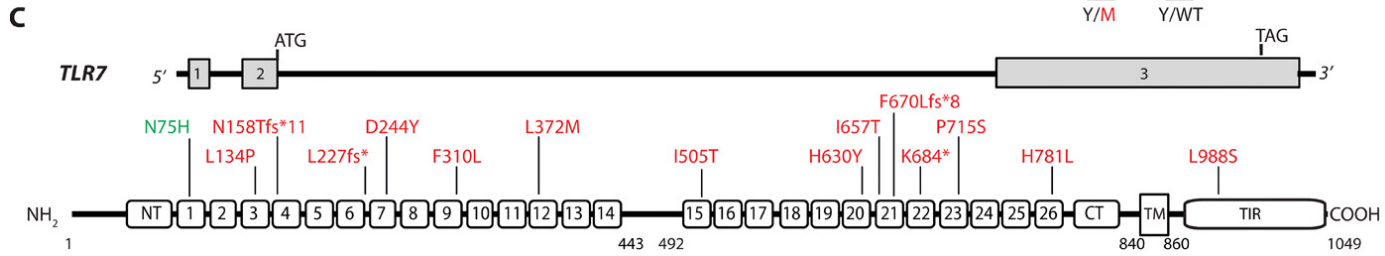
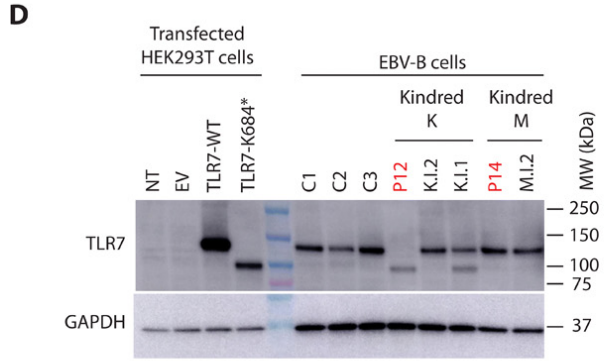
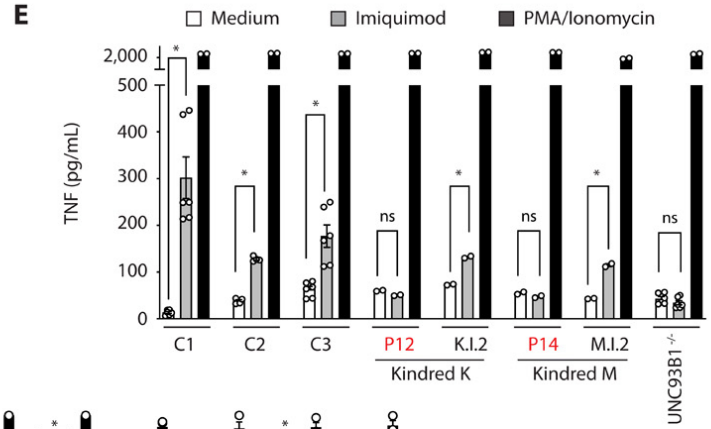


Fig. 1. Enrichment in rare *TLR7* deleterious alleles among men with critical COVID-19 pneumonia. (A) Manhattan plot showing the results of the variant enrichment test for the 190 genes of the X chromosome with at least 5 patients carrying non-synonymous variants. The gray line indicates the corresponding Bonferroni-corrected significance threshold. (**B**) Western blot of extracts from non-transfected HEK293T cells (mock), HEK293T cells transfected with pCMV6 empty vector (EV), the wild-type (WT) *TLR7* allele, or one of the *TLR7* variant alleles of interest. All extracts were probed with monoclonal antibodies specific for the leucine-rich repeats to the N terminus (N-ter) or amino-acid 1,000 to the C terminus (C-ter) within the human TLR7 protein. **(C) (D)** Luciferase assay on HEK293T cells transfected with the pGL4.32 luciferase reporter construct and an expression vector for *Renilla* luciferase together with no vector (mock), EV, WT, or *TLR7* variants: (C) 21 variants found in our cohort and eight previously reported variants, (D) 109 variants found in male individuals from the gnomAD database. After 24 hours, transfected cells were left untreated or were treated by incubation with 1 µg/mL R848 for 24 hours. These data were established from two independent experiments. The *y*-axis represents NF-κB transcriptional activity as a percentage of the WT. The *x*-axis indicates the alleles used for transfection. **(E)** Diagram showing the correlation between allele frequency and NF-κB activity (% of WT). The 20 variants from 21 patients with critical SARS-CoV-2 from our cohort are shown in red, one variant from 2 patients with severe SARS-CoV-2 from our cohort are shown in green, the eight previously reported variants are shown in blue and the 109 variants found in the general population (allele frequency above 10^{-5} in men) are shown in gray. Activity of all LOF/hypomorphic alleles compared to WT allele were statistically significance (one-way ANOVA with Dunnett's post hoc test, $P < 0.01$).









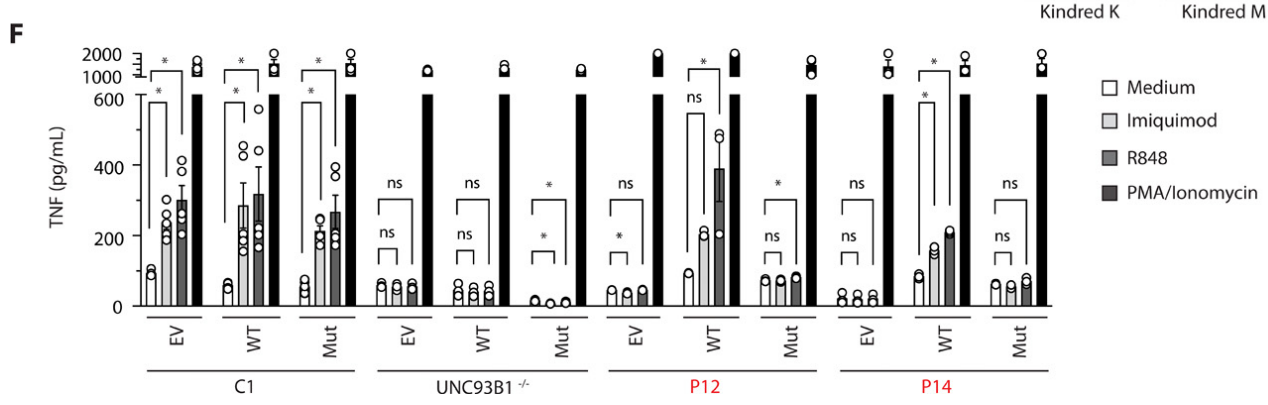
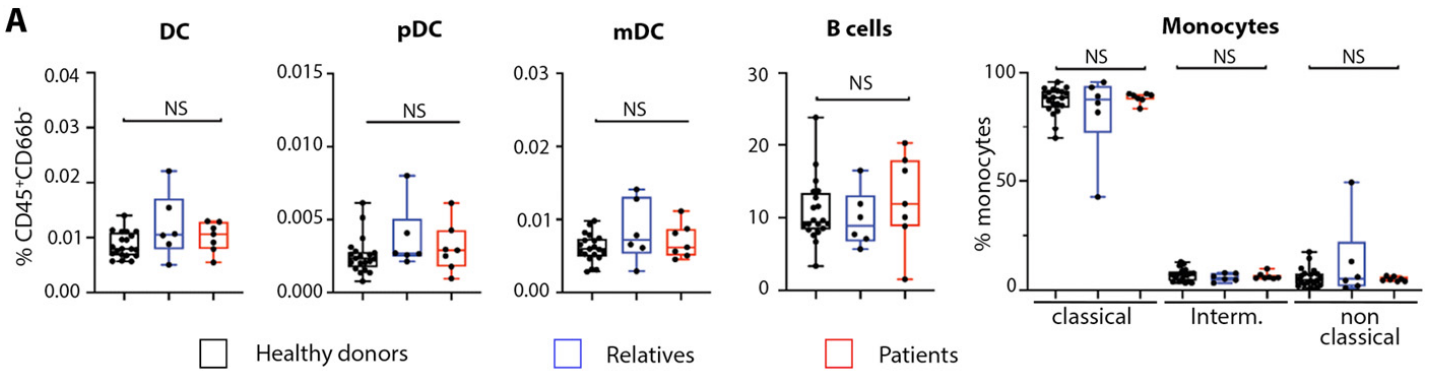
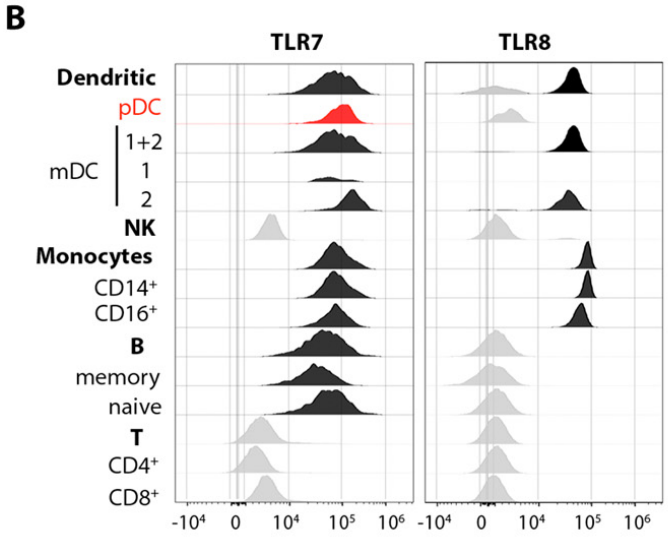
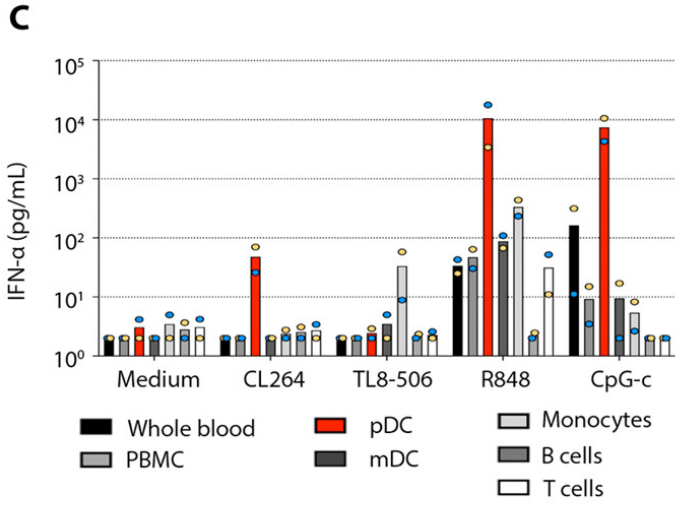
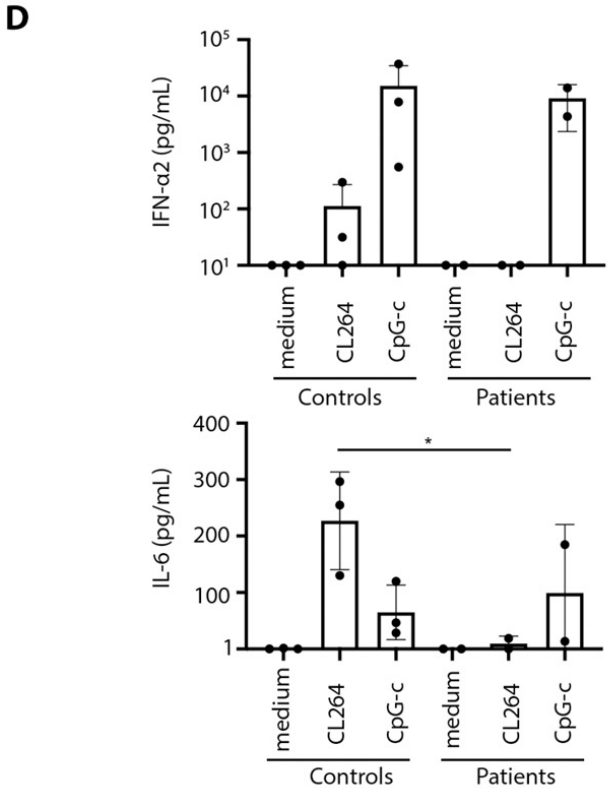


Fig. 2. X-linked recessive TLR7 deficiency in 16 kindreds. (A) Pedigrees of the 16 kindreds containing 17 patients with life-threatening COVID-19 pneumonia (P1-17) bearing deleterious *TLR7* alleles. The mutations are indicated above each pedigree. Solid black symbols indicate patients with critical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









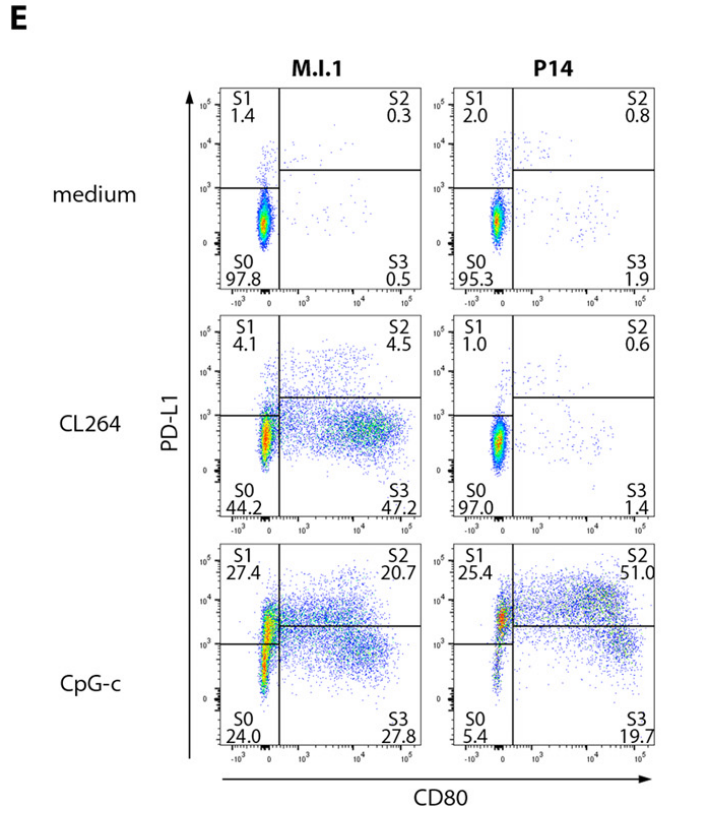


Fig. 3. Type I IFN responses to TLR7 agonist in TLR7-deficient pDCs and leukocytes. (**A**) Frequencies of five leukocyte subsets in whole blood, determined by CyTOF. Healthy donors (black rectangles), relatives not carrying deleterious *TLR7* alleles (blue rectangles) and hemizygous *TLR7* variant carriers (red rectangles) are depicted. (**B**) TLR7 and TLR8 expression in different leukocyte subsets, determined by flow cytometry for the healthy control (C1). The result for another healthy control (C2) is shown in Figure S5C. Gating strategy for the classification in each cell subset is shown in Data file S6. (**C**) IFN-α production in purified leukocyte subsets from two healthy donors (blue or yellow dot) with and without stimulation with various TLR7, 8, or 9 agonists (1 µg/mL CL264, 100 ng/mL TL8-506, 1 µg/mL R848, or 2 µM CpG-c) for 24 hours. The y-axis shows IFN-α production on a logarithmic scale. The red bar corresponds to pDCs. (**D**) pDCs isolated from healthy donors and TLR7-deficient patients (P8, P14) were either left untreated (medium) or were stimulated with CL264 or CpG-c, and the production of IFN-α2 and IL-6 was assessed with CBAs on the supernatant. (**E**) Dotplot showing pDC diversification into subsets S1, S2, and S3 from magnetically sorted blood. pDCs from a TLR7-deficient patient (P14) and a healthy relative (M.I.1) were cultured for 24 hours with medium alone or with 1 µg/mL CL264 or 2 µM CpG-c. Statistical tests were performed using unpaired two-sample *t* test (*: $P < 0.05$).

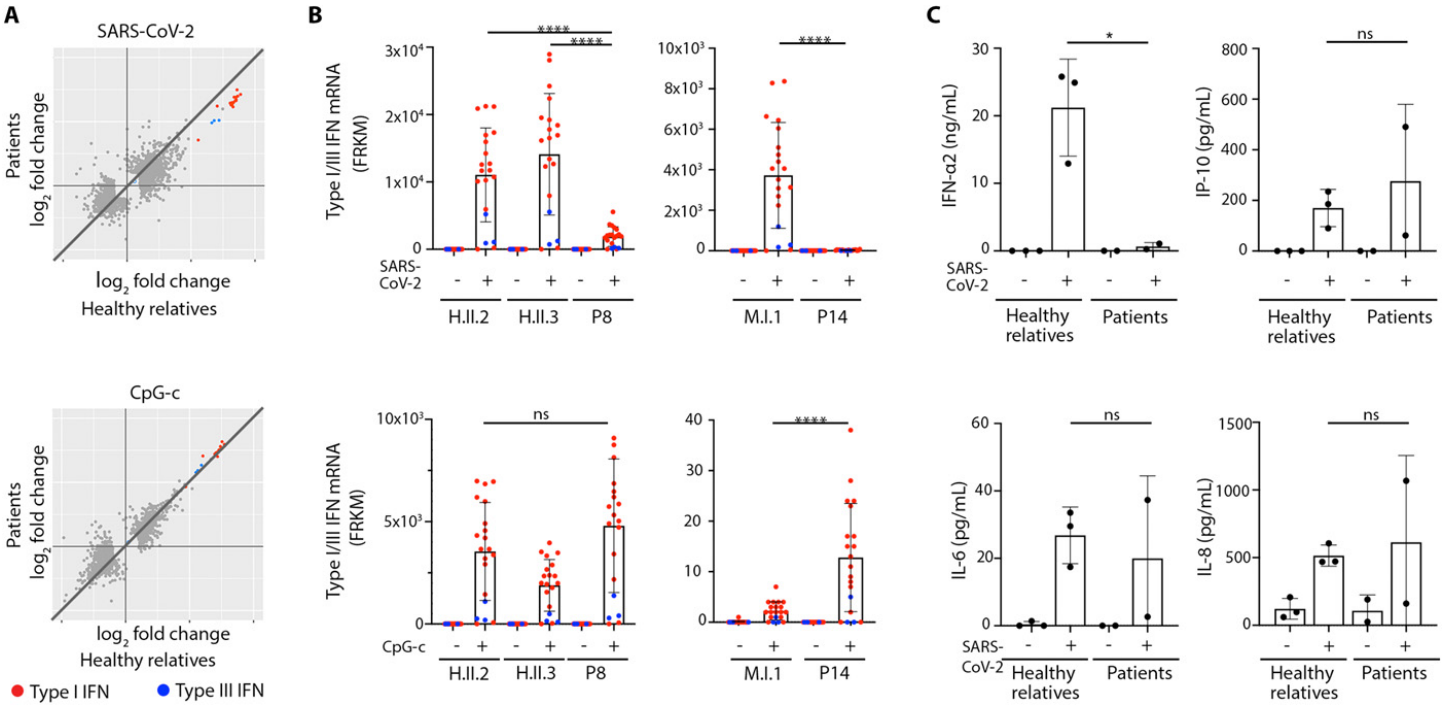


Fig. 4. Type I IFN responses to SARS-CoV-2 infection in TLR7-deficient pDCs. (**A**) pDCs isolated from healthy relatives and TLR7-deficient patients (P8, P14) were either left untreated or were infected with SARS-CoV-2 for 24 hours. RNA profiles were then determined by RNA-seq. Genes with expression >2.0-fold higher or lower in controls after stimulation or infection are plotted as the fold-change in expression. (**B**) Induction of the type I and III IFN genes from (A) infected with SARS-CoV-2 for 24 hours (top) or stimulated with CpG-c (bottom). (**C**) pDCs isolated from healthy relatives and TLR7-deficient patients (P8, P14) were either left untreated or were infected with SARS-CoV-2 for 24 hours and the production of IFN-α2, IP-10, IL-6 and IL-8 was measured with CBAs on the supernatant. Statistical tests were performed using unpaired two-sample *t* test (*: $P < 0.05$, ****: $P < 0.0001$, ns: not significant).

Table 1. X-linked *TLR7* deleterious variants in 16 unrelated male patients with life-threatening COVID-19 pneumonia.

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

* P10's brother (not included in the cohort of 1,202 critical patients with critical COVID-19 pneumonia).
GME Variome, Greater Middle Eastern Variome Project

Science Immunology

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

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Sci. Immunol. **6**, eabl4348.
DOI: 10.1126/sciimmunol.abl4348

Cite as: P. Bastard *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abl4340 (2021).

CORONAVIRUS

Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

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Circulating autoantibodies (auto-Abs) neutralizing high concentrations (10 ng/mL, in plasma diluted 1 to 10) of IFN-α and/or -ω are found in about 10% of patients with critical COVID-19 pneumonia, but not in subjects with asymptomatic infections. We detect auto-Abs neutralizing 100-fold lower, more physiological, concentrations of IFN-α and/or -ω (100 pg/mL, in 1/10 dilutions of plasma) in 13.6% of 3,595 patients with critical COVID-19, including 21% of 374 patients > 80 years, and 6.5% of 522 patients with severe COVID-19. These antibodies are also detected in 18% of the 1,124 deceased patients (aged 20 days-99 years; mean: 70 years). Moreover, another 1.3% of patients with critical COVID-19 and 0.9% of the deceased patients have auto-Abs neutralizing high concentrations of IFN-β. We also show, in a sample of 34,159 uninfected subjects from the general population, that auto-Abs neutralizing high concentrations of IFN-α and/or -ω are present in 0.18% of individuals between 18 and 69 years, 1.1% between 70 and 79 years, and 3.4% >80 years. Moreover, the proportion of subjects carrying auto-Abs neutralizing lower concentrations is greater in a subsample of 10,778 uninfected individuals: 1% of individuals <70 years, 2.3% between 70 and 80 years, and 6.3% >80 years. By contrast, auto-Abs neutralizing IFN-β do not become more frequent with age. Auto-Abs neutralizing type I IFNs predate SARS-CoV-2 infection and sharply increase in prevalence after the age of 70 years. They account for about 20% of both critical COVID-19 cases in the over-80s. and total fatal COVID-19 cases.

INTRODUCTION

Since the start of the COVID-19 pandemic in December 2019, more than 200 million people have been infected with SARS-CoV-2, resulting in at least 4 million deaths, and probably closer to 7 to 9 million deaths worldwide. Interindividual clinical variability in the course of acute infection is vast, extending from silent or mild infection in about 90% of subjects to pneumonia and respiratory failure, both requiring hospitalization, in less than 10% and 2% of cases, respectively. Age is the major epidemiological risk factor for hospitalization or death from pneumonia, the risk doubling with every five years of age (*1*, *2*). The frequencies of critical disease and

death from COVID-19 are higher in men than in women (*3*–*5*). With the COVID Human Genetic Effort (*6*), we previously reported that inborn errors of TLR3- and IRF7-dependent type I IFN induction and amplification can underlie life-threatening COVID-19 pneumonia in a small subset of patients (*7*, *8*). Autosomal dominant disorders were found in 19 patients, but our cohort also included four previously healthy unrelated adults aged 25 to 50 years with autosomal recessive, complete IRF7 (*N*=2) or IFNAR1 (*N*=2) deficiency. These findings indicated that type I IFN immunity is essential for protective immunity to respiratory infection with SARS-CoV-2 but surprisingly redundant otherwise. We also reported that an autoimmune phenocopy of inborn errors of type I IFN-dependent immunity can underlie critical COVID-19 pneumonia (*9*). Indeed, autoantibodies (auto-Abs) neutralizing 10 ng/mL IFN-α2 and/or -ω were found in the blood of at least 10% of an international cohort of patients with life-threatening COVID-19 pneumonia, but in none of the tested individuals with asymptomatic or paucisymptomatic infection (*9*). These auto-Abs were detected in serum or plasma diluted 1/10. The auto-Abs in the patients' undiluted blood can therefore probably neutralize as much as 100 ng/mL IFN-α2 and/or -ω. The 17 subtypes of type I IFNs, including 13 IFN-α subtypes, IFN-ω, IFN-β, IFN-ε, and IFN-κ, bind to the same heterodimeric receptor (IFNAR1 and IFNAR2). (*10*). The 13 IFN-α subtypes and IFN-ω are closely related phylogenetically, while IFN-β, IFN-ε, and IFN-κ are more distant (*9*). The auto-Abs to IFN-α2 and/or -ω were mostly found in men (95%) and in the elderly (half the patients with antibodies being over the age of 65 years) (*9*). These findings were later replicated in independent cohorts from Amsterdam, Lyon, Madrid, New Haven, and San Francisco (*11*–*16*).

These auto-Abs against type I IFNs were found in about 0.3% of a general population sample of 1,227 subjects collected before the pandemic and aged 20 to 69 years, suggesting that they predated SARS-CoV-2 infection and caused critical COVID-19 rather than being triggered by it (*9*). Moreover, production of these antibodies can be genetically driven, and can begin during early childhood, as attested by their presence in almost all patients with autoimmune polyendocrine syndrome type-1 (APS-1) due to germline mutations of *AIRE* (*17*–*19*). APS-1 patients are, indeed, at very high risk of developing severe or critical COVID-19 pneumonia (*20*, *21*). These auto-Abs are also found in patients with combined immunodeficiency and hypomorphic mutations of *RAG1* or *RAG2* (*22*), in men with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome and mutations of *FOXP3* (*23*), and in women with incontinentia pigmenti and heterozygous null mutations of X-linked *NEMO* (*9*). They are also seen in patients treated with IFN-α or IFN-β (*24*, *25*), in patients with systemic lupus erythematosus (*26*, *27*), thymoma (*28*), or with myasthenia gravis (*29*, *30*). Finally, they underlie a third of adverse reactions to the 17D live attenuated vaccine against yellow fever virus (YFV), further suggesting that they were present in these patients, as in patients with critical COVID-19, before viral infection (*31*). Remarkably, for all patients tested, the auto-Abs neutralized the protective effect of ~400 pg/mL IFN-α2 against SARS-CoV-2 or YFV-17D in vitro, even when the plasma was diluted by >1/1,000 (*9*). As blood IFN-α concentrations during acute asymptomatic or paucisymptomatic SARS-CoV-2 infection typically range from 1 to 100 pg/mL (*32*, *33*), and IFN-α levels in the respiratory tract might be even lower yet protective, we hypothesized that auto-Abs neutralizing concentrations of type I IFNs below 10 ng/mL may underlie life-threatening COVID-19 pneumonia in more than 10% of cases. We also hypothesized that the prevalence of auto-Abs against type I IFNs in the general, uninfected, population may increase with age and that these antibodies may be more common in men than in women.

RESULTS

High and intermediate levels of IgG auto-Abs against IFN-α2 and/or IFN-ω in ~20% of patients with critical COVID-19

We recruited a cohort of 3,595 patients hospitalized with critical COVID-19 pneumonia (hereafter referred to as "critical patients", and defined as pneumonia in patients with critical disease, including (i) pulmonary, with high-flow oxygen (> 6 L/min) or mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, intubation), (ii) cardiovascular shock, or (iii) any other organ failure requiring admission to an intensive care unit), including 566 patients of our previously described cohort of 987 patients with critical COVID-19 pneumonia for whom residual samples were available (*9*), 623 individuals with severe COVID-19 pneumonia (with less than 6 L/min of oxygen supplementation, hereafter referred to as "severe patients"), and 1,639 individuals with asymptomatic or paucisymptomatic (mild) upper respiratory tract SARS-CoV-2 infection (the "controls", infected with SARS-CoV-2 (as demonstrated by a positive PCR and/or serological test and/or displaying typical manifestations, such as anosmia/ageusia after exposure to a confirmed COVID-19 case) who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia), including 427 samples from the initial control cohort of 663 individuals (*9*). The patients originated from 38 different countries, across all continents. We did not include patients with moderate pneumonia, who did not receive oxygen therapy (*7*, *9*). We searched for auto-Abs against IFN-α2 and -ω, by establishing novel, sensitive, and robust assays for the detection of circulating IgG auto-Abs. We used Gyros technology (*34*), a high-throughput automated enzyme-linked immunosorbent assay (ELISA)-like assay capable of detecting a large range of auto-Ab levels (Fig. S1A). We

confirmed that the Gyros technique was as sensitive as the techniques previously used (ELISA and Luminex), and that all tested patients with high levels of anti-IFN-α2 and/or anti-IFN-ω auto-Abs on ELISA, as reported in our previous studies (defined as an optical density > 0.5) had high levels of auto-Abs when assessed with Gyros (defined as levels >100) (Fig. S1B). We then screened newly recruited critical or severe patients and controls from our COVID-19 cohort (Fig. 1A). We found high levels of anti-IFN-α2 and/or anti-IFN-ω auto-Abs in 6.9% of critical patients, 3.4% of patients with severe COVID-19, and only 0.6% of the asymptomatic or paucisymptomatic controls (Fig. 1A). We also found that another 12.7% of patients with critical COVID-19 had intermediate levels of anti-IFN-α2 and/or IFN-ω auto-Abs in Gyros assays (defined as levels >30 and <100, based on the distribution observed in healthy controls), whereas this was the case for 8.6% of patients with severe COVID-19 and 11% of the individuals in our control cohort. Collectively, these findings replicate and extend our previous results and those of other groups (*9*, *11–15*, *35*), while suggesting that intermediate levels of auto-Abs against type I IFNs might be neutralizing and underlie critical disease.

Auto-Abs neutralizing 10 ng/mL IFN-α2 and/or -ω in almost 10% of the critical patients

We investigated the ability of these auto-Abs to neutralize high concentrations of type I IFNs, as defined in our previous reports (10 ng/mL IFN-α2 or IFN-ω in medium containing 1/10 plasma or serum, the equivalent of 100 ng/mL IFN-α2 or IFN-ω in undiluted plasma). We tested not only the patients with high levels of auto-Abs, as in our previous study (*9*), but all the available patients with critical COVID-19 (*N*=3,136), or severe COVID-19 (*N*=623), and controls (*N*=1,076) from our expanded cohort. We designed a high-throughput luciferase assay in which we transfected human embryonic kidney (HEK)293T cells with (i) a plasmid containing five IFN-stimulated response element (ISRE) repeats and a firefly luciferase reporter, and (ii) a plasmid encoding the *Renilla* luciferase. We stimulated these cells with an individual recombinant type I IFN (IFN-α2 or IFN-ω), in the presence of plasma diluted 1/10 (plasma 1/10) from patients or controls. We then measured firefly luciferase induction, normalized against *Renilla* luciferase activity (Fig. 1B). We confirmed the robustness of this assay by comparing the results with our previous pSTAT1 flow cytometry data (*9*). Consistent results were obtained for all 50 patients tested with both techniques (Fig. S1C, D). We then tested all patients and controls. Most plasma samples with high auto-Ab levels (>100) against IFN-α2 according to the Gyros assay were neutralizing (Fig. S1E). We found that 9.8% (307 of 3,136) of the critical patients tested and 3.53% (22 of 623) of the severe patients had auto-Abs neutralizing IFN-α2 and/or IFN-ω, versus only 0.37% (4 of 1,076) controls (Fig. 1C) (Table 1 and Table S1). In the patients with neutralizing auto-Abs, these auto-Abs were able to neutralize both IFN-α2 and IFN-ω in 175 of the 307 critical patients (57%), 6 of the severe patients (27%), and none of the controls; IFN-α2 alone in 106 critical patients (34.5%), 11 severe patients (50%), and only one of the controls (25%); IFN-ω alone in 26 of critical patients (8.5%), 5 severe patients (22%), and 3 controls (75%) (Table S1). None of the patients with these auto-Abs had inborn errors of TLR3- or TLR7-dependent type I IFN immunity (*7*, *36*).

Auto-Abs neutralizing 100 pg/mL IFN-α2 and/or -ω in at least 13.6% of critical patients and 6.8% of severe patients

As the amounts of circulating type I IFNs in infected individuals are 100 to 1,000 times lower than the amounts tested previously (*32*, *33*), we investigated the neutralization of more physiological concentrations of type I IFNs, by performing assays with 100 pg/mL type I IFN. We observed a robust response in our luciferase system, in the presence of 1/10 dilutions of control plasma (Fig. S1F). The plasma or serum was diluted 1/10, so the concentration neutralized corresponds to 1 ng/mL IFN in circulating whole blood. With diluted plasma samples from a positive control, we gained at least two orders of magnitude of sensitivity in terms of neutralizing activity, providing proof-of-concept that these auto-Abs can neutralize lower, more physiological, amounts of type I IFNs (Fig. 1D, Fig. S1G), lower than the concentrations previously tested by a factor of 100 (*9*). We then retested all available samples from our extended cohort. Overall, 13.6% of all critical patients tested (*N*=489 of 3,595), 6.5% (*N*=34 of 522) of the severe patients, and 1% of the controls (*N*=17 of 1,639) had circulating auto-Abs that neutralized 100 pg/mL IFN-α2 and/or IFN-ω in plasma 1/10 (Fig. 1E-G) (Table 1 and Table S1). In the patients with neutralizing auto-Abs, these auto-Abs were able to neutralize both IFN-α2 and IFN-ω in 256 of the 489 positive critical patients (52%), 18 of the 34 severe patients (53%), and 1 of the 17 controls (6%); IFN-α2 alone in 104 critical patients (21%), 14 severe patients (41%), and 4 of the controls (23.5%); IFN-ω alone in 129 critical patients (26%), 2 severe patients (6%), and 12 controls (70%) (Table S1). Further dilution of a plasma sample from one patient neutralizing 100 pg/mL of type I IFNs led to a loss of neutralizing activity (Fig. 1D, Fig. S1G). Importantly, for four unrelated patients, all of whom suffered from critical COVID-19, including one who died, samples collected before COVID-19 were available and tested positive for neutralizing auto-Abs against type I IFNs. One neutralized IFN-α2 and IFN-ω at a concentration of 10 ng/mL, two neutralized both cytokines at 100 pg/mL and one IFN-ω only at 100 pg/mL (Fig. S1H). The four patients tested therefore had auto-Abs neutralizing 10 ng/mL or 100 pg/mL IFN-α2 and/or -ω before infection with SARS-CoV-2. These four patients, and another two reported in our previous study (*9*) all, therefore, had auto-Abs

neutralizing type I IFNs before infection with SARS-CoV-2. We then assessed the risk, adjusted for age and sex, of having critical or severe disease for subjects carrying auto-Abs against each individual IFN and the different possible combinations. We found that all auto-Abs, except those neutralizing only IFN-ω at a concentration of 10 ng/mL, were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with controls (Table 1 and Table S2). The strongest association was with auto-Abs against both IFN-α2 and IFN-ω neutralizing concentrations of 10 ng/mL (OR=67, P=8x10^{-13}) and 100 pg/mL (OR=54, P<10^{-13}), followed by those against IFN-α2 +/− IFN-ω neutralizing 10 ng/mL (OR=45, P<10^{-13}) and 100 pg/mL (OR=23, P<10^{-13}) (Table 1). As the serum/plasma samples were diluted 1/10 in these assays, these findings suggest that more than 13.6% of patients with life-threatening COVID-19 have circulating auto-Abs neutralizing 1 ng/mL IFN-α2 and/or IFN-ω in vivo, a greater proportion than the 10% of patients with auto-Abs neutralizing 100 ng/mL reported in previous studies (*9*, *11–15*, *35*).

Auto-Abs neutralize low concentrations of IFN-α2 protective against SARS-CoV-2

We previously reported that plasma diluted 1/100 from patients with auto-Abs against type I IFNs neutralized the ability of IFN-α2 (at a concentration of 20 pM, approximately 400 pg/mL) to block SARS-CoV-2 and YFV-17D replication in Huh-7.5 cells (*9*, *31*). Strikingly, this neutralization was seen in all patients tested, even for a 1,000-fold dilution, and, in most patients, it was more potent than the neutralizing effect of a commercially available neutralizing monoclonal Ab (mAb) against IFN-α2. These auto-Abs against type I IFNs were, therefore, able to neutralize IFN-α2 at concentrations well beyond physiological levels. We therefore hypothesized that patients with lower titers of auto-Abs against type I IFNs, which can neutralize 100 pg/mL but not 10 ng/mL in plasma diluted 1/10, would also neutralize the protective effect of IFN-α2 against SARS-CoV-2. We therefore performed our SARS-CoV-2 assay with 5 pM (~100 pg/mL) or 20 pM (~400 pg/mL) IFN-α2, on five samples from patients with life-threatening COVID-19 and two samples from uninfected elderly individuals with auto-Abs neutralizing 100 pg/mL but not 10 ng/mL IFN-α2. As controls, we tested a commercial mAb against IFN-α2, a sample from a patient with auto-Abs neutralizing 10 ng/mL IFN-α2, and samples from three patients with life-threatening COVID-19 and three healthy controls without detectable auto-Abs against type I IFNs. We found that the 1/100 dilutions of plasma from four of the five critical COVID-19 patients and one of the two elderly individuals with auto-Abs neutralizing 100 pg/mL IFN-α2 were able to neutralize the protective effect of ~400 pg/mL IFN-α2 against SARS-CoV-2, whereas samples from all these individuals fully or partially neutralized ~100 pg/mL IFN-α2 (Fig. 2A). No such neutralizing effect was observed for any of the auto-Ab-negative controls. Overall, our findings indicate that auto-Abs against type I IFNs capable of neutralizing 100 pg/mL IFN in 1% plasma can block the protective effect of ~100 pg/mL or ~400 pg/mL IFN-α2 against SARS-CoV-2. These findings raise the possibility that even 100-fold lower levels of auto-Abs against type I IFNs, capable of neutralizing lower, physiological concentrations of 10 pg/mL IFN-α2, may be present in an even larger proportion of patients. The testing of this hypothesis will require the development of new, more sensitive methods to screen for neutralization.

Neutralization of type I IFNs in the absence of detectable auto-Abs against IFN-α2 or -ω

The neutralization assays performed on all patients and controls revealed that some patients with neutralizing activity against 10 ng/mL IFN-α2 and/or IFN-ω, as shown in luciferase assays, did not have high, or even intermediate levels of IgG auto-Abs in Gyros assays (Fig. S1E). We also observed that some patients with neutralizing auto-Abs had low or undetectable levels of auto-Abs in Luminex assays (Fig. S1I). For these individuals, we assessed the prevalence of IgA and IgM auto-Abs against type I IFNs; we found that none of the patients tested (N=12) had detectable titers of IgA or IgM auto-Abs (Fig. S1J). We then tested the alternative hypothesis that these auto-Abs were directed against the IFNAR1 or IFNAR2 chain of type I IFN receptors, assessing the ability of plasma samples from these patients to neutralize IFN-β. None of the samples from these patients neutralized IFN-β, suggesting that the auto-Abs in these patients were not directed against IFNAR1 or IFNAR2 (Fig. S1K). An alternative plausible hypothesis is that the epitope recognized by the auto-Abs might be concealed by the binding of the cytokine to the plate (ELISA), biotinylation of the cytokine (Gyros), or covalent coupling of the cytokine to magnetic beads at lysine residues (Luminex) (*19*). This observation has important clinical implications, suggesting that a lack of detection of auto-Abs against type I IFNs does not rule out the possibility of such antibodies being present and having neutralization capacity.

Auto-Abs typically neutralize the 13 IFN-α subtypes and/or IFN-ω

In six patients with auto-Abs neutralizing 100 pg/mL but not 10 ng/mL IFN-α2 and/or IFN-ω, we tested the reactivity of the antibodies against the 17 type I IFNs (the 13 IFN-α forms, IFN-ω, IFN-β, IFN-ε, and IFN-κ). Like patients with auto-Abs neutralizing 10 ng/mL type I IFNs (*9*), those capable of neutralizing only 100 pg/mL had detectable auto-Abs against most of the 13 IFN-α forms and/or IFN-ω, albeit at lower levels (Fig. 2B). Of the six patients with auto-Abs against IFN-α and/or IFN-ω tested, only one also had auto-Abs against IFN-β and none had detectable auto-Abs against IFN-ε or IFN-κ. Overall, the patients with auto-Abs against IFN-α2 and/or IFN-ω capable of neutralizing 100 pg/mL IFN displayed patterns of reactivity to the 17 type I IFNs similar

to those reported in previously described patients with auto-Abs neutralizing 10 ng/mL (*9*). We then set up an assay for assessing neutralization of the 13 IFN-α forms, using our luciferase-based assay. We tested two patients with auto-Abs neutralizing IFN-α2 and IFN-ω, two patients with auto-Abs neutralizing only IFN-α2, and two patients with auto-Abs neutralizing only IFN-ω. Interestingly, we found that the APS-1 patient, and the two patients with auto-Abs neutralizing 10 ng/mL IFN-α2 and IFN-ω were able to neutralize all 13 IFN-α subtypes, as were the two patients with neutralizing auto-Abs against IFN-α2. Conversely, in the conditions tested, the two patients with auto-Abs neutralizing IFN-ω only, but not IFN-α2, were not able to neutralize any of the 13 IFN-α subtypes (Fig. 2C). In addition, to confirm that the IgG auto-Abs detected were indeed the cause of the neutralization activity observed, we performed an IgG depletion experiment and found that the removal of the IgG fraction abolished the neutralizing activity, whereas the purified IgG fraction had full neutralizing activity (Fig. S2A). Thus, patients with neutralizing auto-Abs against only IFN-ω do not seem to neutralize any of the 13 IFN-α subtypes, whereas patients with auto-Abs neutralizing IFN-α2 neutralize all these subtypes.

Auto-Abs neutralizing IFN-β in 1.3% of critical patients

We previously reported that auto-Abs neutralizing IFN-β were detected in only two of 101 critical patients with auto-Abs neutralizing 10 ng/mL IFN-α2 and/or IFN-ω (*9*). Given the potential therapeutic use of IFN-β (*37*, *38*), and the absence of IFN-β-neutralization data for COVID-19 patients, we tested a larger number of patients and controls, including patients without auto-Abs against IFN-α or IFN-ω, for auto-Abs against IFN-β, assessing the levels and neutralizing activity of auto-Abs against 10 ng/mL IFN-β. We screened 1,773 patients with critical COVID-19 pneumonia, and found that 1.3% (*N*=23) had neutralizing auto-Abs against IFN-β; by contrast, such antibodies were present in none of the 187 severe patients tested and in only two of the 1,044 controls tested (0.18%) (Fig. 2D, S2B and Table S3). Interestingly, only six of the 23 (21.7%) critical patients also had auto-Abs neutralizing IFN-α2 and/or IFN-ω at 100 pg/mL, and none of the controls had such antibodies. Of note, five of these six patients had auto-Abs neutralizing all three cytokines. All the other critical patients and controls had only neutralizing auto-Abs against IFN-β. The presence of neutralizing auto-Abs against IFN-β was significantly associated with critical, but not severe, disease relative to the controls (Table 1, Tables S2-3). Interestingly, Gyros did not appear to be able to detect auto-Abs against IFN-β, perhaps because of the biotinylation of the cytokine hiding the epitope recognized by the auto-Abs. As most (78.3%) of the patients with neutralizing auto-Abs against IFN-β did not have neutralizing auto-Abs against IFN-α2 or IFN-ω, this suggests that auto-Abs against IFN-β alone may also underlie life-threatening COVID-19 (Table 1).

Neutralizing auto-Abs against type I IFNs in at least 20% of critical patients over 80 years of age

We further assessed the percentage of critical COVID-19 patients positive for neutralizing auto-Abs per decade of life and by sex (Fig. 3A-J, S3A-W) (Tables S1-4). In our previous report, we found that critical COVID-19 patients with auto-Abs neutralizing IFN-α2 or IFN-ω at 10 ng/mL were older (more than half the patients with auto-Abs were over the age of 65 years) and more likely to be male (95% of the antibody carriers were men) (*9*). These results have been confirmed by other groups, albeit with a smaller proportion of men (*11–14*, *35*). In our expanded cohort of patients with critical COVID-19 pneumonia (*N*=3,595), the mean age was 61 years and 73% of the patients were men (Fig. 3A, Table S4). We confirmed that critical patients with auto-Abs neutralizing IFN-α and/or IFN-ω at 10 ng/ml were significantly older than those not carrying auto-Abs (mean age [SD] 65.8 years [14.1] versus 61.6 years [15.5], Firth's multivariable logistic regression, $P=3\text{x}10^{-6}$) and more likely to be male (78.5% versus 71%, Firth's multivariable logistic regression, *P*=0.003). The proportion of critical COVID-19 patients with auto-Abs neutralizing 10 ng/mL IFN-α2 and/or IFN-ω increased continuously, with auto-Abs detected in 5% of patients under the age of 40 years, 6.8% of those between 40 and 49 years of age, 7.1% of those between 50 and 59 years of age, 10.7% of those between 60 and 69 years of age, 12.3% of those between 70 and 79 years, and almost 14% in those over 80 (Fig. 3C-F, S3B-I). In severe patients, the proportion of auto-Abs was much more stable with age (Fig. S3T-W, Firth's multivariable logistic regression *P*=0.16) and sex (Firth's multivariable logistic regression *P*=0.44). Similar results were obtained for critical COVID-19 patients with auto-Abs neutralizing 100 pg/mL IFN-α2 and/or IFN-ω, but with even higher proportions (Fig. 3G-J, S3L-S) (Table S1). Indeed, the proportion of patients with auto-Abs ranged from 9.6% of patients below the age of 40 years, to more than 21% of those over 80 (Fig. 3G-J, S3L-S). In men, the proportion of critical COVID-19 patients carrying auto-Abs neutralizing 100 pg/mL IFN-α2 and/or IFN-ω increased to up to 23% over 80 years of age. A very different pattern was seen for auto-Abs neutralizing 10 ng/mL IFN-β, with a more stable proportion of auto-Abs carriers according to age (Fig. S3J, K, Firth's multivariable logistic regression, *P*=0.68) (Table S3). Overall, the prevalence of auto-Abs neutralizing 10 ng/mL and/or 100 pg/mL IFN-α2 and/or IFN-ω increased sharply with age in critical patients. A striking enrichment in patients with neutralizing auto-Abs against IFN-α2 and/or IFN-ω was observed in the elderly, with more than 20% of patients, and 23% of men, over the age of 80 years with critical COVID-19 having neutralizing auto-Abs against these type I IFNs.

Neutralizing auto-Abs against type I IFNs in at least 18% of deceased patients

The prevalence of auto-Abs against type I IFNs in patients dying from COVID-19 pneumonia is unknown. For the 3,595 patients with critical COVID-19, we analyzed data for the 1,124 who died. These patients were aged 20 days to 99 years (mean age: 71 years), 73% were male, and all had confirmed SARS-CoV-2 infection and critical COVID-19 pneumonia before death (Fig. 4A). In these patients, we analyzed the presence of neutralizing auto-Abs against type I IFNs at concentrations of 10 ng/mL and 100 pg/mL for IFN-α2 and IFN-ω, and at 10 ng/mL for IFN-β (Fig. 4B-J, S4A-K). We found that 13.3% of the deceased patients carried auto-Abs neutralizing 10 ng/mL IFN-α2 and/or IFN-ω (Fig. 4B-F, S4A-E). Strikingly, 18.5% carried auto-Abs neutralizing 100 pg/mL of either or both cytokines (Fig. 4G-J, S4F-I). In addition, 0.9% had auto-Abs neutralizing IFN-β (Fig. S4J-K). An analysis of the prevalence of neutralizing auto-Abs against type I IFNs in these patients who died of COVID-19 by decade of age revealed a moderate increase with age for auto-Abs neutralizing 10 ng/mL (Firth's multivariable logistic regression P=0.03) or 100 pg/mL (Firth's multivariable logistic regression P=0.01) (Table S1-2). For a type I IFN concentration of 100 pg/mL, the prevalence of auto-Abs neutralizing IFN-α2 and/or IFN-ω was 20% below the age of 40 years, 14% for individuals between 40 and 49 years old, 12.5% for those between 50 and 60 years old, 16.3% for those between 60 and 69 years old, 17.9% for those between 70 and 79 years old, and greater than 23% for those over the age of 80 years. Overall, at least 18% of patients dying from COVID-19 pneumonia have auto-Abs capable of neutralizing 100 pg/mL type I IFNs in plasma 1/10.

Auto-Abs capable of neutralizing IFN-α2 and/or IFN-ω at 10 ng/mL in 0.53%, and at 100 pg/mL in 2.3% of individuals from the general population

We previously tested a sample of 1,227 individuals aged 20 to 65 years from the general population collected in 2015-2017. This sample had an equal sex distribution, and we identified four individuals with auto-Abs against type I IFNs among the 1,227 tested (0.3%), suggesting that the auto-Abs pre-dated COVID-19 (*9*). These findings were replicated at the University of California San Francisco (UCSF) in a sample of 4,041 subjects aged 4 to 90 years (0.32%) (*16*). In the current study, we tested a much larger cohort of 34,159 individuals aged 20 to 100 years from the general population, with an equal distribution between the sexes (Fig. 5A). Samples were collected before 2018 for blood donors at the French blood bank (19,966 individuals), the 3C cohort (801) and in 2019 for participants in the French CONSTANCES cohort (8,850) and Cerba HealthCare (4,542). We performed serological tests for SARS-CoV-2 on the samples collected in 2019, and included only the individuals who had not been infected with SARS-CoV-2 in the sample. We used Gyros to screen this whole cohort for IgG auto-Abs against IFN-α2 and IFN-ω (Fig. 5B, S5A). We did not measure auto-Abs against IFN-β by Gyros. We found that only 0.05% and 4.2% had anti-IFN-α2 and/or anti-IFN-ω auto-Abs above the thresholds of 100 and 30, respectively (Fig. 5B, S5A). We then assessed the ability of these antibodies to neutralize 10 ng/mL IFN-α2 or IFN-ω, for all individuals with a high or intermediate level of IgG auto-Abs against IFN-α2 or IFN-ω. We found 181 individuals with neutralizing auto-Abs, for whom 1/10 dilutions of plasma neutralized 10 ng/mL IFN-α2 and/or IFN-ω, giving an overall prevalence of 0.53% (Fig. 5C-F, S5B-I) (Table S5-6), consistent with our two previous reports (*9*, *16*). We may have slightly underestimated the number of positive individuals, as some may have had neutralizing auto-Abs at too low a titer for detection. Next, we assessed the prevalence of auto-Abs neutralizing 10 ng/mL of IFN-β in 9,583 individuals, and found an overall prevalence of 0.26% (Fig. 5G-H) (Table S5-6). Finally, for a subset of 10,778 samples, we further assessed the ability of plasma/serum samples (diluted 1/10) to neutralize 100 pg/mL IFN-α2 and/or IFN-ω in the luciferase assay (Fig. 5I-J, 6A-H). The prevalence of auto-Abs neutralizing 100 pg/mL IFN-α2 and/or IFN-ω was 2.3% (Table S1).

Sharp increase in the prevalence of auto-Abs against IFN-α2 and/or IFN-ω after the age of 70 years in the general population

We then assessed the percentage of individuals from the general population positive for neutralizing auto-Abs per decade of life and by sex. Strikingly, we noted that the prevalence of auto-Abs neutralizing 10 ng/mL type I IFN was more than 10 times higher in individuals over the age of 70 years than in those below this age (Firth's multivariable logistic regression, $P<10^{-13}$) (Fig. 5C-F, S5B-I) (Table S5-6). The prevalence of auto-Abs capable of neutralizing 10 ng/mL IFN-α2 and/or IFN-ω was 0.17% in individuals below 70 years of age, 0.9% in individuals between 70 and 75 years of age, 1.6% between the ages of 75 and 80 years and more than 4% between the ages of 80 and 85 years. Intriguingly, after 85 years, the prevalence of these antibodies decreased to about 2.6%. These findings were replicated independently in two cohorts of 703 and 376 elderly individuals from Estonia and Japan, tested with Luciferase-based immunoprecipitation assay (LIPS) and ELISA assays, respectively (Fig. S5J, K). A strong increase in the prevalence of auto-Abs neutralizing 100 pg/mL IFN-α2 and/or IFN-ω was observed with age (Fig. 6A-H, S6A-D), with the prevalence almost doubling with every five years from 65 to 85 years of age. Indeed, 0.87% of individuals between the ages of 65 and 70 years, 1.73% of those between 70 and 75 years, and 7.1% of those between 75 and 80 years were positive for auto-Abs. Interestingly, there was an overall decrease in the prevalence of auto-Abs after 85 years of age, especially in men. By contrast, the prevalence of auto-Abs neutralizing

IFN-β did not vary significantly with age (Fig. 5G, H) (Table S4). We then assessed the risk, adjusted for age and sex, of having critical or severe disease, for subjects carrying auto-Abs against each individual IFN and the different possible combinations, relative to the general population. We also found that all auto-Abs were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with the general population (Table 1 and Table S2). The strongest association was again that for auto-Abs neutralizing both IFN-α2 and IFN-ω at 10 ng/mL (OR=30, $P<1 \times 10^{-13}$), followed by those neutralizing IFN-α2 +/− IFN-ω at 10 ng/mL (OR=20, $P<10^{-13}$), and IFN-ω +/− IFN-α2 at 10 ng/mL (OR =15, $P<10^{-13}$) (Table 1). Auto-Abs neutralizing both IFN-α2 and IFN-ω at 100 pg/mL were also highly significant risk factors (OR [95% CI]=12 [9-16], $P<10^{-13}$) (Table 1). Overall, these findings indicate that there is a sharp increase in the prevalence of auto-Abs neutralizing type I IFNs with age in elderly uninfected individuals, with at least 4% of those over the age of 70 years positive for auto-Abs against IFN-α2 and/or IFN-ω, and that these auto-Abs pre-date COVID-19.

DISCUSSION

We report that at least 20% of patients over 80 years of age with life-threatening COVID-19 pneumonia carry circulating auto-Abs neutralizing 100 pg/mL IFN-α2 and/or IFN-ω, and that such antibodies are present in more than 13.6% of patients of all ages with this condition. Some of these auto-Abs are not identified by immunoassays and are only detectable by a neutralization assay. In addition, at least 18% of deceased individuals in most age groups were found to have such auto-Abs. We also report that auto-Abs against IFN-β are found in about 1.3% and 0.9% of critical and deceased patients, most of whom do not have auto-Abs against IFN-α2 and/or IFN- ω. In all four patients tested for whom pre-COVID-19 samples were also available, the auto-Abs against IFN-α2 and/or IFN-ω were clearly present before SARS-CoV-2 infection, as in patients with APS-1 (*9*, *20*), and in two other previously described patients (*9*). Importantly, auto-Abs capable of neutralizing high concentrations of type I IFNs have been found in patients without inborn errors of TLR3- or TLR7-dependent type I IFN immunity (*7*, *36*), suggesting that both inborn errors and auto-Abs are independently causal of critical disease. It is also striking that inborn errors are more common in patients under the age of 60 years, whereas auto-Abs are more common in patients over the age of 70 years. We also report that the prevalence of auto-Abs neutralizing 10 ng/mL (and 100 pg/mL) type I IFNs, except for IFN-β, increases significantly with age in the general population, with 0.17% (1.1%) of individuals positive for these antibodies before the age of 70 years, and more than 1.4% (4.4%) positive after the age of 70 years, with a prevalence of 4.2% (7.1%) between the ages of 80 and 85 years.

These auto-Abs provide an explanation for the major increase in the risk of critical COVID-19 in the elderly. This increase with age is consistent with studies of various auto-Abs since the 1960s (*39–43*). These auto-Abs appear to have remained clinically silent in these individuals until SARS-CoV-2 infection. Our results also suggest that the neutralization of only one type I IFN (IFN-α2, IFN-ω, or IFN-β) can underlie life-threatening COVID-19 (Table 1, Tables S1-S3). Auto-Abs neutralizing 10 ng/mL IFN-β have a frequency only about one tenth that of auto-Abs neutralizing the same concentrations of IFN-α2 and/or IFN-ω (Table 1, Table S3). We have shown that auto-Abs neutralizing 100 pg/mL type I IFN in plasma diluted 1/10, corresponding to the neutralization of 1 ng/mL IFN in vivo, can account for at least 18% of deaths and more than 20% of critical cases in the elderly >80 years of age. It is tempting to speculate that an even greater proportion of life-threatening COVID-19 cases are due to auto-Abs neutralizing lower, physiological concentrations of type I IFNs. In vitro, concentrations of type I IFN as low as 100 pg/mL can impair SARS-CoV-2 replication in epithelial cells (Fig. 2A). Moreover, the levels of type I IFN detected in the blood of patients with acute and benign SARS-CoV-2 infections are in the range of 1 to 100 pg/mL (*32*, *33*).

Our findings have immediate clinical applications. First, it is quick and easy to test for auto-Abs against type I IFNs in patients infected with SARS-CoV-2. Screening for these antibodies is even possible in the general population before infection. The type I IFN-neutralizing activity of these antibodies is a better read-out than their mere detection, which can be falsely negative. Tests should be performed for auto-Abs against at least three individual IFNs: IFN-α2, IFN-ω, and IFN-β. Particular attention should be paid to elderly individuals, and patients with known autoimmune or genetic conditions associated with auto-Abs against type I IFNs (*17–20*, *22*, *23*, *26–29*). Second, patients with auto-Abs against type I IFN should be vaccinated against COVID-19 as a priority. Third, live attenuated vaccines, including YFV-17D and vaccines using the YFV-17D backbone against SARS-CoV-2, should not be given to patients with auto-Abs (*31*, *44*). Fourth, these patients appeared to be healthy before SARS-CoV-2 infection, but they should also be carefully followed for other viral illnesses, as exemplified by adverse reactions to YFV-17D (*31*). Fifth, in cases of SARS-CoV-2 infection in unvaccinated individuals with auto-Abs against type I IFNs, the patients should be hospitalized for prompt management. Early treatment with monoclonal antibodies (*45*, *46*) can be administered in patients without symptoms of severe COVID-19 pneumonia, and IFN-β can be administered in the absence of both pneumonia and auto-Abs against IFN-β (*37*, *38*). Rescue treatment by plasma exchange is another therapeutic option in patients who already have pneumonia (*47*).

Sixth, blood products, especially plasma, should be

screened for anti-IFN auto-Abs and any products containing such antibodies should be excluded from donation (*13*). Plasma from donors convalescing from COVID-19 should be tested for such auto-Abs (*13*). Seventh, given the documented innocuity and potential efficacy of a single injection, early therapy with IFN-β may be considered for the contacts of contagious subjects or during the first week after infection, even in the absence of, or before the documentation of auto-Abs against type I IFNs, in elderly patients, who have a higher risk of critical pneumonia and auto-Abs against IFN-α2 and IFN-ω, but not IFN-β (*48*). Another possibility would be the administration of monoclonal antibodies that can neutralize SARS-CoV-2 (*45*, *46*). Finally, it will be important to decipher the mechanism underlying the development of these auto-Abs, which may differ in patients over and under 65 years of age. Overall, our findings show that auto-Abs neutralizing concentrations of type I IFN lower than previously reported (*9*, *11–16*), but still higher than physiological concentrations, are common in the elderly population. Their prevalence increases with age in the uninfected general population, reaching more than 4% of individuals after the age of 70 years. They underlie about 20% of cases of critical COVID-19 pneumonia in patients over the age of 80 years, and about 20% of total COVID-19 deaths. We previously reported that they can underlie severe adverse reactions to the yellow fever live attenuated virus (*31*). It is tempting to speculate that they may also underlie other severe viral diseases, especially in the elderly.

MATERIALS AND METHODS

Study design

We enrolled, from 38 countries across all continents, 3,595 patients with proven critical COVID-19, 623 patients with severe COVID-19, 1,639 asymptomatic or paucisymptomatic individuals with proven COVID-19, and 34,159 healthy controls in this study. We collected plasma or serum samples for all these individuals to test by immunoassay for the presence of IgG auto-Abs to type I IFNs. All subjects were recruited according to protocols approved by local institutional review boards (IRBs).

COVID-19 classification

The severity of COVID-19 was assessed for each patient as follows (*7*, *9*). "Critical COVID-19 pneumonia" was defined as pneumonia developing in patients with critical disease, whether pulmonary, with high-flow oxygen, mechanical ventilation (Continuous positive airway pressure, bilevel positive airway pressure, intubation), septic shock, or with damage to any other organ requiring admission to the intensive care unit. "Severe COVID-19" was defined as pneumonia developing in patients requiring low-flow oxygen (<6 L/min). The controls were individuals infected with SARS-CoV-2 (as demonstrated by a positive PCR and/or serological test and/or displaying typical symptoms, such as anosmia/ageusia after exposure to a confirmed COVID-19 case) who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia.

Detection of anti-cytokine autoantibodies

Gyros

Cytokines, recombinant human (rh)IFN-α2 (Miltenyi Biotec, ref. number 130-108-984) or rhIFN-ω (Merck, ref. number SRP3061), were first biotinylated with EZ-Link Sulfo-NHS-LC-Biotin (Thermo Fisher Scientific, cat. number A39257), according to the manufacturer's instructions, with a biotin-to-protein molar ratio of 1:12. The detection reagent contained a secondary antibody (Alexa Fluor 647 goat anti-human IgG (Thermo Fisher Scientific, ref. number A21445) diluted in Rexxip F (Gyros Protein Technologies, ref. number P0004825; 1/500 dilution of the 2 mg/mL stock to yield a final concentration of 4 μg/mL). Buffer PBS-T 0.01% and Gyros Wash buffer (Gyros Protein Technologies, ref. number P0020087) were prepared according to the manufacturer's instructions. Plasma or serum samples were then diluted 1/100 in PBS-T 0.01% and tested with the Bioaffy 1000 CD (Gyros Protein Technologies, ref. number P0004253), and the Gyrolab xPand (Gyros Protein Technologies, ref. number P0020520). Cleaning cycles were performed in 20% ethanol.

Multiplex particle-based assay

Serum/plasma samples were screened for autoantibodies (auto-Abs) against IFN-α2 and IFN-ω in a multiplex particle-based assay, in which magnetic beads with differential fluorescence were covalently coupled to recombinant human proteins (2.5 μg/reaction). Beads were combined and incubated with 1/100-diluted serum/plasma samples for 30 min. Each sample was tested once. The beads were then washed and incubated with PE-labeled goat anti-human IgG (1 μg/mL) for an additional 30 min. They were then washed again and used for a multiplex assay on a Bio-Plex X200 instrument.

Enzyme-linked immunosorbent assays (ELISA)

ELISA was performed as previously described. In brief, 96-well ELISA plates (MaxiSorp; Thermo Fisher Scientific) were coated by incubation overnight at 4°C with 2 μg/mL rhIFN-α2 (Miltenyi Biotec, ref. number 130-108-984), and rhIFN-ω (Merck, ref. number SRP3061). Plates were then washed (PBS 0.005% Tween), blocked by incubation with 5% nonfat milk powder in the same buffer, washed, and incubated with 1:50 dilutions of plasma from the patients or controls for 2 hours at room temperature (or with specific mAbs as positive controls). Each sample was tested once. Plates were thoroughly washed. Horseradish peroxidase (HRP)–conjugated Fc-specific IgG fractions from polyclonal goat antiserum against human IgG, IgM or IgA (Nordic Immunological Laboratories) were added to a final concentration of 2 μg/mL. Plates were incubated for 1 hour at room temperature and washed. Substrate was added and the optical density (OD) was measured. A similar protocol was used to test for

antibodies against 12 subtypes of IFN-α, except that the plates were coated with cytokines from PBL Assay Science (catalog #11002-1), or IFN-β (Miltenyi Biotech, ref. number: 130-107-888).

Functional evaluation of anti-cytokine autoantibodies

Luciferase reporter assays

The blocking activity of anti-IFN-α2 and anti-IFN-ω auto-Abs was determined with a reporter luciferase activity. Briefly, HEK293T cells were transfected with a plasmid containing the firefly luciferase gene under the control of the human *ISRE* promoter in the pGL4.45 backbone, and a plasmid constitutively expressing *Renilla* luciferase for normalization (pRL-SV40). Cells were transfected in the presence of the X-tremeGene9 transfection reagent (Sigma-Aldrich, ref. number 6365779001) for 24 hours. Cells in Dulbecco's modified Eagle medium (DMEM, Thermo Fisher Scientific) supplemented with 2% fetal calf serum (FCS) and 10% healthy control or patient serum/plasma (after inactivation at 56°C, for 20 min) were either left unstimulated or were stimulated with IFN-α2 (Miltenyi Biotec, ref. number 130-108-984), IFN-ω (Merck, ref. number SRP3061), at 10 ng/mL or 100 pg/mL, or IFN-β (Miltenyi Biotech, ref. number: 130-107-888) at 10 ng/mL, for 16 hours at 37°C. Each sample was tested once for each cytokine and dose. Finally, cells were lysed for 20 min at room temperature and luciferase levels were measured with the Dual-Luciferase® Reporter 1000 assay system (Promega, ref. number E1980), according to the manufacturer's protocol. Luminescence intensity was measured with a VICTOR-X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). Firefly luciferase activity values were normalized against *Renilla* luciferase activity values. These values were then normalized against the median induction level for non-neutralizing samples, and expressed as a percentage. Samples were considered neutralizing if luciferase induction, normalized against *Renilla* luciferase activity, was below 15% of the median values for controls tested the same day. A similar protocol was used to test for auto-Abs against 12 subtypes of IFN-α, except that we used cytokines from PBL Assay Science (catalog #11002-1) at 1 ng/mL for stimulation.

pSTAT1 induction in PBMC

The blocking activity of anti-IFN-α2 and anti-IFN-ω auto-Abs was determined by assessing STAT1 phosphorylation in healthy control cells following stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum/plasma. Surface-stained healthy control PBMCs (350,000/reaction) were cultured in serum-free RPMI medium with 10% healthy control or patient serum/plasma and were either left unstimulated or were stimulated with IFN-α2 or IFN-ω (10 ng/mL) for 15 min at 37°C. Each sample was tested once. Cells were fixed, permeabilized, and stained for intranuclear phospho-STAT1 (Y701). Cells were acquired on a BD LSRFortessa cytometer with gating on $CD14^+$ monocytes and the data were analyzed with FlowJo software.

Luciferase-based immunoprecipitation assay (LIPS)

Levels of autoantibodies against IFN-α subtypes were measured in luciferase-based immunoprecipitation assay (LIPS), as previously described (9). IFNA1, IFNA2, IFNA8, and IFNA21 sequences were inserted into a modified pPK-CMV-F4 fusion vector (PromoCell GmbH, Germany), in which the firefly luciferase replaced the NanoLuc luciferase (Promega, USA). The resulting constructs were used to transfect HEK293 cells and the IFNA-luciferase fusion proteins were collected in the tissue culture supernatant. For autoantibody screening, we combined $2x10^6$ luminescence units (LU) of IFNA1, IFNA2, IFNA8 and IFNA21 in a single IP reaction mixture (pool 1), and IFNA4, IFNA5, IFNA6 and IFNA7 in another IP reaction mixture (pool 2). Serum samples were incubated with Protein G agarose beads (Exalpha Biologicals, USA) at room temperature for 1 hour in a 96-well microfilter plate (Merck Millipore, Germany), and we then added $2x10^6$ luminescence units (LU) of antigen and incubated for another hour. Each sample was tested once. The plate was washed with a vacuum system and Nano-Glo® Luciferase Assay Reagent (Promega, USA) was added. Luminescence intensity was measured with a VICTOR X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). The results are expressed in arbitrary units (AU), as a fold-difference relative to the mean of the negative control samples.

IgG purification

We demonstrated that the IFN-α2 or IFN-ω neutralizing activity observed was due to auto-Abs and not another plasma factor, by depleting IgG from the plasma with a protein G buffer (Pierce Protein G IgG Binding Buffer, 21011) and column (NAb Protein G Spin Columns, 89953). All buffers were homemade: glycine 0.1 M pH=2.7, Tris 1.5 M pH = 8. Total plasma was loaded onto the column. Each sample was tested once. Purified IgG were then concentrated (Pierce Protein Concentrators PES, 50K MWCO, 88504). Without eluting the IgG, the flow-through fraction (IgG-depleted) was then collected and compared to total plasma in the luciferase neutralization assay.

Statistical analysis

Odds ratios (OR) and P-values for the effect of auto-Abs neutralizing each type I IFN on critical or severe COVID-19, using asymptomatic/mild patients or the general population as controls and adjusted on age in years and sex, were estimated by means of Firth's bias-corrected logistic regression (*49*, *50*) as implemented in the "logistf" R package (https://rdrr.io/cran/logistf/). Effect of age (quantitative in years or binary +/− 65 years) and sex on the presence of neutralizing auto-Abs in each cohort (critical, severe, deceased and general population) was tested by multivariable Firth's bias-corrected logistic regression. The standard error of the

prevalence of neutralizing auto-Abs to each type I IFN per age groups and sex were estimated using the Agresti-Coull approximation (*51*).

Schematic representation

Schematic representations (Fig. 1B) were created with BioRender.com.

SARS-CoV-2 experiment

SARS-CoV-2 strain USA-WA1/2020 was obtained from BEI Resources and amplified in Caco-2 cells at 37°C. Viral titers were measured on Huh-7.5 hepatoma cells in a standard plaque assay. Caco-2 (*H. sapiens,* sex: male, colon epithelial) and Huh-7.5 cells (*H. sapiens,* sex: male, liver epithelial) were cultured in DMEM supplemented with 1% nonessential amino acids (NEAA) and 10% fetal bovine serum (FBS) at 37°C, under an atmosphere containing 5% CO_2. Both cell lines have been tested negative for contamination with mycoplasma. SARS-CoV-2 experiments were performed as follows. Huh-7.5 cells were used to seed 96-well plates at a density of $7.5x10^3$ cells/well. The following day, plasma samples or a commercial anti-IFN-α2 antibody (catalog number 21100-1; R&D Systems) were diluted to 1% and incubated with 5 pM (~100 pg/mL) or 20 pM (~400 pg/mL) recombinant IFN-α2 (catalog number 11101-2; R&D systems) for 1 hour at 37°C (dilutions: plasma samples = 1/100 and anti-IFN-α2 antibody = 1/1,000). Molar ratio was calculated according to the manufacturer's datasheet and with http://molbiol.ru/eng/scripts/01_04.html. Following this incubation period, the cell culture medium was removed from the 96-well plates by aspiration and replaced with the plasma/anti-IFN-α2 antibody and IFN-α2 mixture. Each sample was tested once, in triplicate. The plates were incubated overnight and the plasma/anti-IFN-α2 antibody plus IFN-α2 mixture was removed by aspiration. The cells were washed once with PBS to remove potential anti-SARS-CoV-2-neutralizing antibodies and fresh medium was then added. Cells were then infected with SARS-CoV-2 by directly adding the virus to the wells. Cells infected at a MOI of 0.05 PFU/cell and incubated at 33°C for 48 hours. The cells were fixed with 7% formaldehyde, stained for SARS-CoV-2 with an anti-N antibody (catalog no. GTX135357; GeneTex), imaged and analyzed as previously described (*9*).

SUPPLEMENTARY MATERIALS

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Supplementary Materials and Methods

Figures S1 to S6

Tables S1 to S6; these tables are found on the tabs of a single Excel spreadsheet that contains the raw data

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Acknowledgments: We thank the patients and their families for placing their trust in us. We warmly thank the members of both branches of the Laboratory of Human Genetics of Infectious Diseases. We warmly thank Y. Nemirovskaya, M. Woollett, D. Liu, S. Boucherit, C. Rivalain, M. Chrabieh and L. Lorenzo for administrative assistance. We also thank the staff of the Imagine facilities: C. Bureau, L. Colonna, S. Paillet, N. Ghouas, M. Sy. We are also grateful to the legal team and technology transfer staff of the Imagine Institute: M. Pilorges, R. Marlanges, E. Rubino, W. Loewen, D. Beudin, N. Wuylens. We thank all the staff of the Imagine Institute, Necker Hospital and Necker sorting center for their help. We warmly thank S. Nagashima (Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan). **Funding:** The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercatus Center at George Mason University, the Yale Center for Mendelian Genomics and the GSP Coordinating Center funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956), the Yale High Performance Computing Center (S10OD018521), the Fisher Center for Alzheimer's Research Foundation, the Meyer Foundation, the JPB Foundation, 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-IBEID), the French Foundation for Medical Research (FRM) (EQU201903007798), the FRM and ANR GENCOVID project (ANR-20-COVI-0003), ANRS Nord-Sud (ANRS-COV05), ANR GENVIR (ANR-20-CE93-003) and ANR AABIFNCOV (ANR-20-CO11-0001) projects, the European Union's Horizon 2020 research and innovation program under grant agreement No 824110 (EASI-genomics), the Square Foundation, *Grandir - Fonds de solidarité pour l'enfance*, the *Fondation du Souffle*, the SCOR Corporate Foundation for Science, *Institut National de la Santé et de la Recherche Médicale* (INSERM) and the University of Paris. P.B. was supported by the French Foundation for Medical Research (FRM, EA20170638020). P.B., J.R. and T.L.V. were supported by the MD-PhD program of the Imagine Institute (with the support of the Fondation Bettencourt Schueller). Work in the Laboratory of Virology and Infectious Disease was supported by the NIH (P01AI138398-S1, 2U19AI111825, and R01AI091707-10S1), a George Mason University Fast Grant, and the G. Harold and Leila Y. Mathers Charitable Foundation. The French COVID Cohort study group was sponsored by INSERM and supported by the REACTing consortium and by a grant from the French Ministry of Health (PHRC 20-0424). The Cov-Contact Cohort was supported by the REACTing consortium, the French Ministry of Health, and the European Commission (RECOVER WP 6). This work was also partly supported by the Intramural Research Program of the NIAID and NIDCR, NIH (grants ZIA AI001270 to LDN and 1ZIAAI001265 to HCS). This program is supported by the *Agence Nationale de la Recherche*, reference ANR-10-LABX-69-01. K. Kisand's group was supported by the Estonian Research Council grant PRG117 and PRG377. R. Halwani was supported by an Al Jalila Foundation Seed Grant (AJF202019), Dubai, UAE, and a COVID-19 research grant (CoV19-0307) from University of Sharjah, UAE. L. Imberti reported funding from Regione Lombardia, Italy (project "Risposta immune in pazienti con COVID-

19 e co-morbidità"). L. Imberti and G.L. Marseglia reported funding from Regione Lombardia, Italy (project "Risposta immune in pazienti con COVID-19 e co-morbidità"). This research was partially supported by the Instituto de Salud Carlos III (COV20/0968). J. R. Heath reported funding from Biomedical Advanced Research and Development Authority HHSO10201600031C. S. Okada reports funding Research Program on Emerging and Re-emerging Infectious Diseases from Japan Agency for Medical Research and development, AMED (Grant Number: JP20fk0108531). G. Gorochov was supported by ANR Flash COVID-19 program and SARS-CoV-2 Program of the Faculty of Medicine from Sorbonne University iCOVID programs. The Three-City (3C) Study was conducted under a partnership agreement among the INSERM, the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study was also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques". S. Debette was supported by the University of Bordeaux Initiative of Excellence. P. K. Gregersen reports funding from the National Cancer Institute, NIH, under Contract No. 75N91019D00024, Task Order No. 75N91021F00001. J.W. is supported by an FWO Fundamental Clinical Mandate (1833317N). Sample processing at IrsiCaixa was possible thanks to the crowdfunding initiative YoMeCorono. Work at Vall d'Hebron was also partly supported by research funding from Instituto de Salud Carlos III grant PI17/00660 cofinanced by the European Regional Development Fund (ERDF). C.R.G. and colleagues of the Canarian Health System Sequencing Hub were supported by the Instituto de Salud Carlos III (COV20_01333 and COV20_01334, Spanish Ministry of Science and Innovation RTC-2017-6471-1; AEI/FEDER, UE); from Grupo DISA (OA18/017 and OA20/024); and Cabildo Insular de Tenerife (CGIEU0000219140 and "Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19"). C.M.B. is supported by a MSFHR Health Professional-Investigator Award. P.Q.H. and L.H. were funded by the European Union's Horizon 2020 research and innovation program (ATAC, 101003650). Work at Y.-L. Lau's laboratory in the University of Hong Kong (HKU) was supported by the Society for the Relief of Disabled Children. MBBS/PhD study of D.L. Leung in HKU was supported by the Croucher Foundation. J.L.F. was supported in part by the Cooperation Scientifique France-Colciencias (ECOS-Nord/COLCIENCIAS/MEN/ICETEX (806-2018) and Colciencias contract 713-2016 (code 111574455633). A.K. was in part supported by grants NU20-05-00282 and NV18-05-00162 issued by the Czech Health Research Council and Ministry of Health, Czech Republic. L.P. was funded by Program Project COVID-19 OSR-UniSR and Ministero della Salute (COVID-2020-12371617). I.M. 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 Model Foundation. I.M. has received funding under the European Union's Horizon 2020 research and innovation program (grant agreement No. 948959). E.A. received funding from the Hellenic Foundation for Research and Innovation (INTERFLU, no. 1574). M.V. received funding from the Sao Paulo Research Foundation (FAPESP) [grant number 2020/09702-1] and JBS S.A [grant number 69004]. The NH-COVAIR study group consortium was supported by a grant from the Meath Foundation.
Author contributions: P.B., A.G., T.L.V., J.R., Q.P., E.M., H.-H.H., S.E., L.H., M.G.P., L.B., A.P.M., R.Y., M.M., P.P., K.S., J.M., S.T.-A., A.B., K.S., E.S., L.B.R., M.M., A.A., B.C. A.F., S.M.H., O.M.D., Y.Z., B.B., V.B., S.-Y.Z., L.D.N., H.C.S., K.K., S.O., A.P., E.J., C.M.R. and Q.Z. performed or supervised experiments, generated and analyzed data, and contributed to the manuscript by providing figures and tables. J.M., A.C., and L.A. performed computational analyses of data. P.B., N.D.-P., Y.T.L., C.-E.L., B.A.-B., A.G., J.P., P.M., P.R., F.C., J.T., J.R., L.L., J.-C.L., S.G., S.T.-A., A.B., K.S., P.G., D.D., P.-L.T., D.S., A.S., B.M., V.T., J.R.H., J.C.F., J.-M.A., A.C.-N., L.I., A.B., R.C., P.Bo., A.B., A.L.S., A.M.P., F.H., S.D., R.L.N., T.M., A.A.B., T.O., S.K., C.R., S.P., P.Q.H., L.H., A.D., A.K., C.N.M., A.A., G.C., V.L.L, F.C., L.A.B., E.D.-G. L.V., D.V.D.B., S.G.T., S.B., D.D., L.Q.-M., M.C.N., R.A., D.A., I.,B., H.B.-F., J.W., I.M. D.H., N.S.S.-A., R.H., K.D., J.S., S.M.S., L.G., A.K., F.M., Y.N., J.S.-V., A.H.D., S.P.K, N.M.B., S.A.A.A.-K, Y.S., J.T., O.B., N.Y.K., Y.-L.-L, D.L., M.C., J.M., R.K., L.F.R., C.B., M.S.A., R.R.-B., R.M., M.V., M.Z., A.C.G., F.V., G.M., D.C.V., L.R., S.R.O., A.S., E.A., S.S., I.T., J.F., S.L., K.B., R.P.L., S.M., S.B., V.V., O.H., A.P.O., T.H.M., L.R., J.M., S.D., X.D.L., X.D., F.M., M.Z., P.S.-P., R.C., G.G., X.S.M., S.S., J.M.-P., D.R., M.V., P.K.G., L.P., C.R.-G., L.D.N., H.C.S., P.T., Q.Z., and J.-L.C. evaluated and recruited patients to COVID and/or control cohorts of patients, and/or cohorts of individuals from the general population. P.B. and J.-L.C. wrote the manuscript. J.-L.C. supervised the project. All the authors edited the manuscript. **Competing interests:** Jean-Laurent Casanova is an inventor on patent application PCT/US2021/042741, filed July 22, 2021, submitted by The Rockefeller University, that covers diagnosis of, susceptibility to, and treatment of, viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. M. C. Nussenzweig is an inventor on patent application PCT/US2021/070472 submitted by The Rockefeller University that covers neutralizing anti-SARS-CoV-2 antibodies and methods of use thereof. M. C. Nussenzweig reports being on the Scientific Advisory Board of Celldex and Frontier Biotechnologies. Richard P. Lifton reports being a non-executive director of Roche. France Mentré receives fees for consulting from IPSEN and Da Volterra. Her research group receives research grants from Roche, Sanofi and Da Volterra. **Data and materials availability:** All the data are available in the manuscript or in the supplementary materials. Plasma, cells, and genomic DNA are available from J.-L.C. under a material transfer agreement with The Rockefeller University or the Imagine Institute. Huh-7.5 cells are available on request from C.M.R. under a material transfer agreement with The Rockefeller University and Apath, LLC. The materials and reagents used are almost exclusively commercially available and nonproprietary. Materials derived from human samples may be made available on request, subject to any underlying restrictions concerning such samples. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, permitting 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; authorization from the rights holder before using such material. For patients enrolled in the Italian cohort, patient specimens may be available from Monza, subject to approval by their local IRB, through an MTA.

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CoV-Contact Cohort

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Submitted 13 July 2021
Accepted 16 August 2021
Published First Release 19 August 2021
10.1126/sciimmunol.abl4340

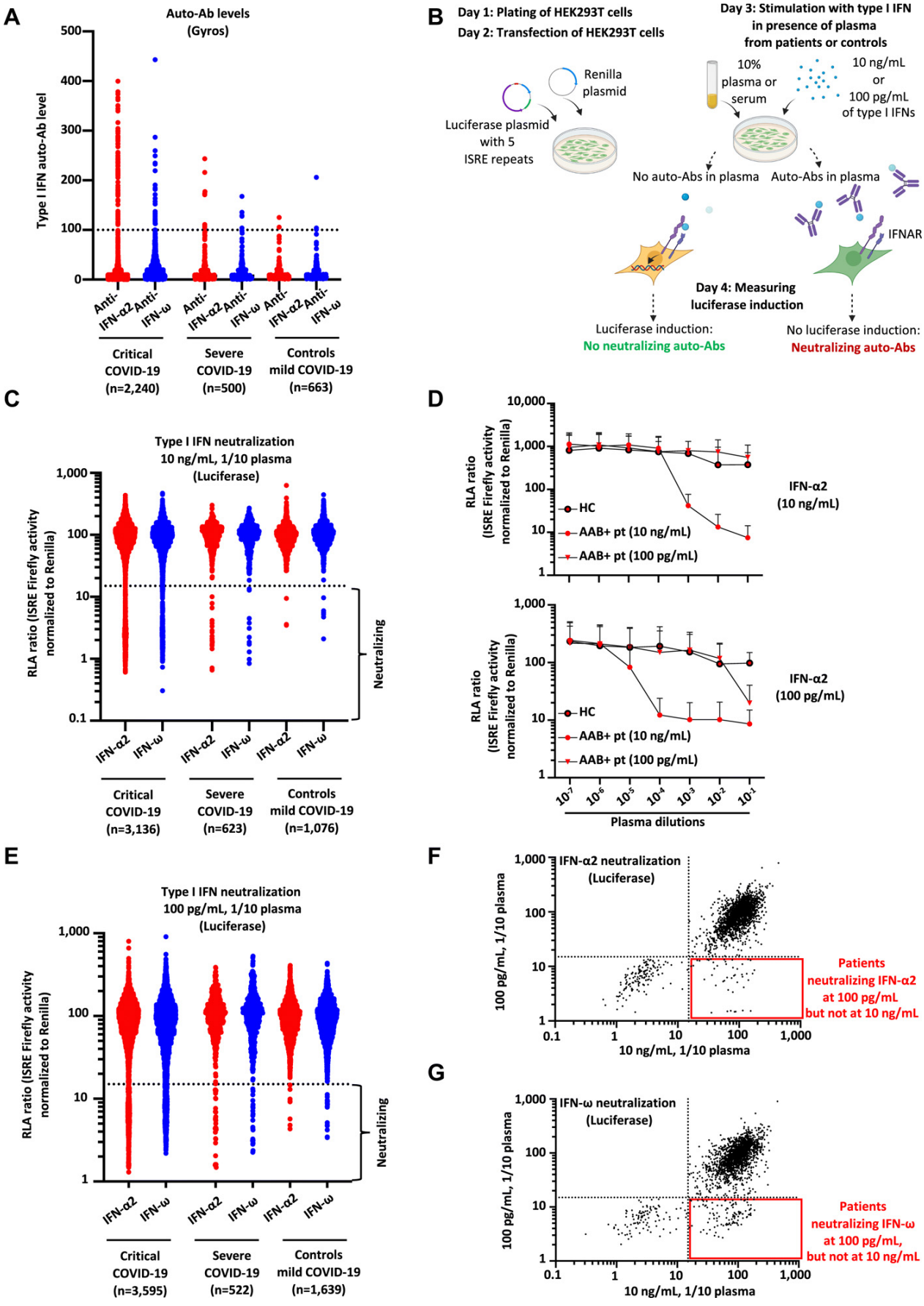

Fig. 1. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19. (A) Gyros (high-throughput automated ELISA) results for auto-Abs against IFN-α2 and/or IFN-ω in patients with critical COVID-19 (*N*=2,240), severe COVID-19 (*N*=500), or asymptomatic/mild SARS-CoV-2 infection (*N*=663). **(B)** Schematic representation of the neutralization assay developed in HEK293T cells, using a luciferase system. ISRE: interferon-sensitive response elements. **(C)** Results for the neutralization of 10 ng/mL IFN-α2 or IFN-ω in the presence of plasma 1/10 from patients with critical COVID-19 (*N*=3,136), severe COVID-19 (*N*=623), or controls with mild/asymptomatic infection (*N*=1,076). Relative luciferase activity is shown (ISRE dual luciferase activity, with normalization against *Renilla* luciferase activity) after stimulation with 10 ng/mL IFN-α2 or IFN-ω in the presence of plasma 1/10. RLA: relative luciferase activity. **(D)** RLA after stimulation with IFN-α2 at a concentration of 10 ng/mL or 100 pg/mL, with various dilutions of plasma from a positive control (from 1/10 to $1/10^7$) neutralizing 10 ng/mL of type I IFNs (AAB+ pt, 10 ng/mL), a patient neutralizing 100 pg/mL of type I IFNs but not 10 ng/mL (AAB+ pt, 100 pg/mL), and a healthy control (HC). AAB: auto-Ab. Pt: patient. **(E)** Neutralization of 100 pg/mL IFN-α2 or IFN-ω in the presence of plasma 1/10 from patients with critical COVID-19 (*N*=3,595), severe COVID-19 (*N*=522), or controls with asymptomatic/mild infection (*N*=1,639). **(F)** Plot showing luciferase induction after stimulation with 10 ng/mL or 100 pg/mL IFN-α2, in the presence of plasma from patients with critical COVID-19. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Patients with antibodies neutralizing both 10 ng/mL and 100 pg/mL IFN-α2 are shown in the bottom left corner, whereas the patients in the bottom right corner had antibodies capable of neutralizing only 100 pg/mL IFN-α2. **(G)** Plot showing luciferase induction after stimulation with 10 ng/mL or 100 pg/mL IFN-ω, for patients with critical COVID-19.

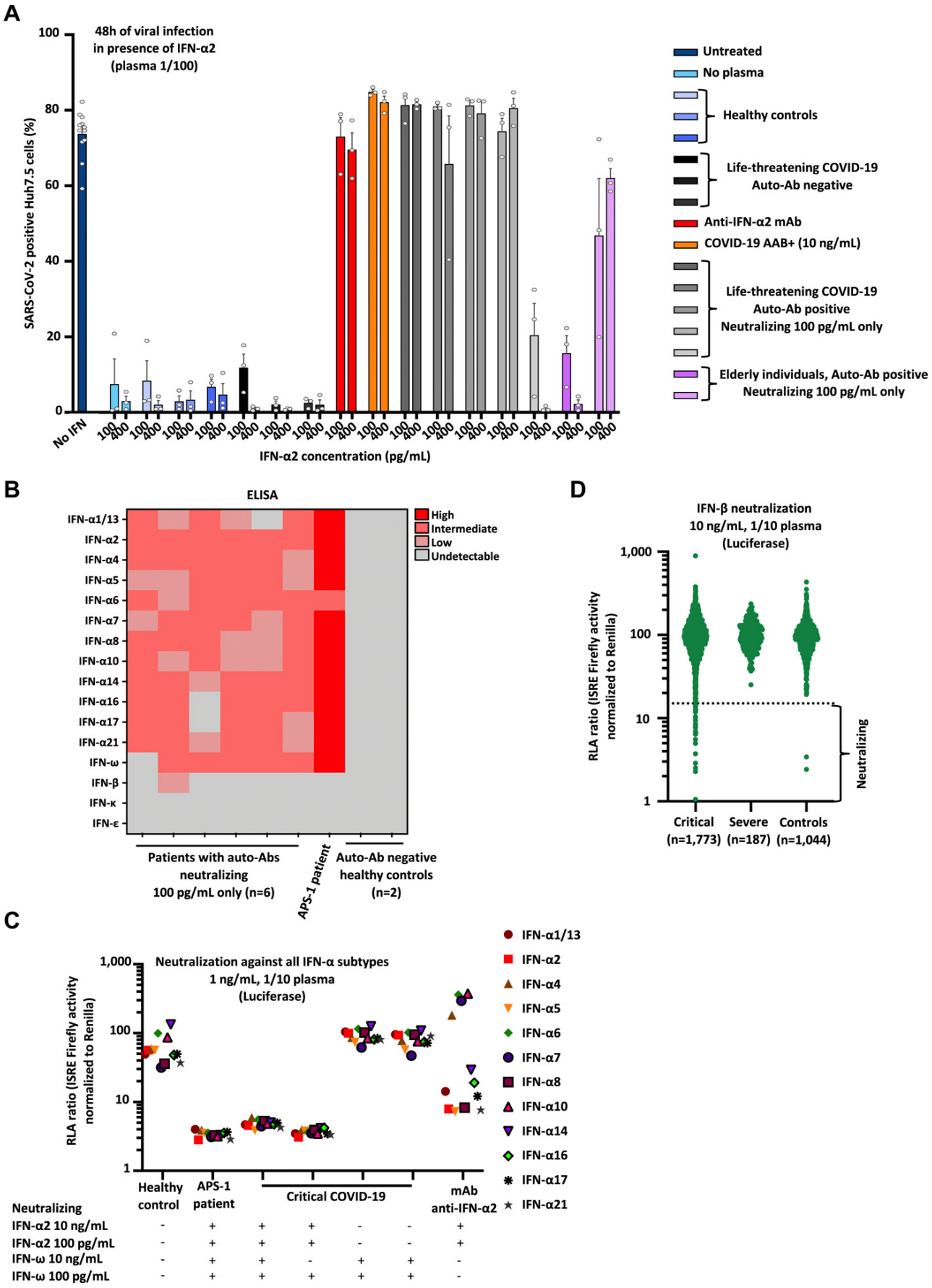

Fig. 2. Enhanced SARS-CoV-2 replication, despite the presence of IFN-α2, in the presence of plasma from patients with auto-Abs neutralizing 100 pg/mL IFN-α2. (A) SARS-CoV-2 replication in Huh-7.5 cells untreated (in dark blue), or treated with ~100 pg/mL or ~400 pg/mL IFN-α2 in the presence of 1/100 plasma from healthy controls without auto-Abs (*N*=3, in blue), from patients with life-threatening COVID-19 but without auto-Abs against IFN-α2 (*N*=3, in black), a commercial anti–IFN-α2 antibody (mAb, in red); from a patient with life-threatening COVID-19 and auto-Abs neutralizing 10 ng/mL IFN-α2 in plasma 1/100 (COVID-19 AAB+, *N*=1, in orange), from patients with life-threatening COVID-19 and auto-Abs neutralizing 100 pg/mL IFN-α2 in plasma 1/100 (*N*=5, in grey); elderly individuals with auto-Abs neutralizing 100 pg/mL IFN-α2 in plasma 1/100 (*N*=2, in purple). Each dot represents a technical replicate. All experiments were done in triplicate. **(B)** ELISA (enzyme-linked immunosorbent assay) for auto-Abs against the 13 IFN-α forms, IFN-ω, IFN-β, IFN-ε, and IFN-κ in patients with life-threatening COVID-19 and auto-Abs neutralizing 100 pg/mL IFN-α2 (*N*=6), APS-1 patient with life-threatening COVID-19 and auto-Abs neutralizing 10 ng/mL IFN-α2 and IFN-ω (*N*=1), and healthy controls (*N*=2). **(C)** RLA after stimulation with the all individual IFN-α at a concentration of 1ng/mL, with 1/10 plasma from a healthy control (negative control), an APS-1 patient (positive control), patients with life-threatening COVID-19 and neutralizing IFN-α2 and/or IFN-ω, or a monoclonal antibody anti-IFN-α2. **(D)** Neutralization of 10 ng/mL IFN-β in the presence of plasma 1/10 from patients with critical COVID-19 (*N*=1,773), severe COVID-19 (*N*=187), or asymptomatic/mild controls (*N*=1,044).

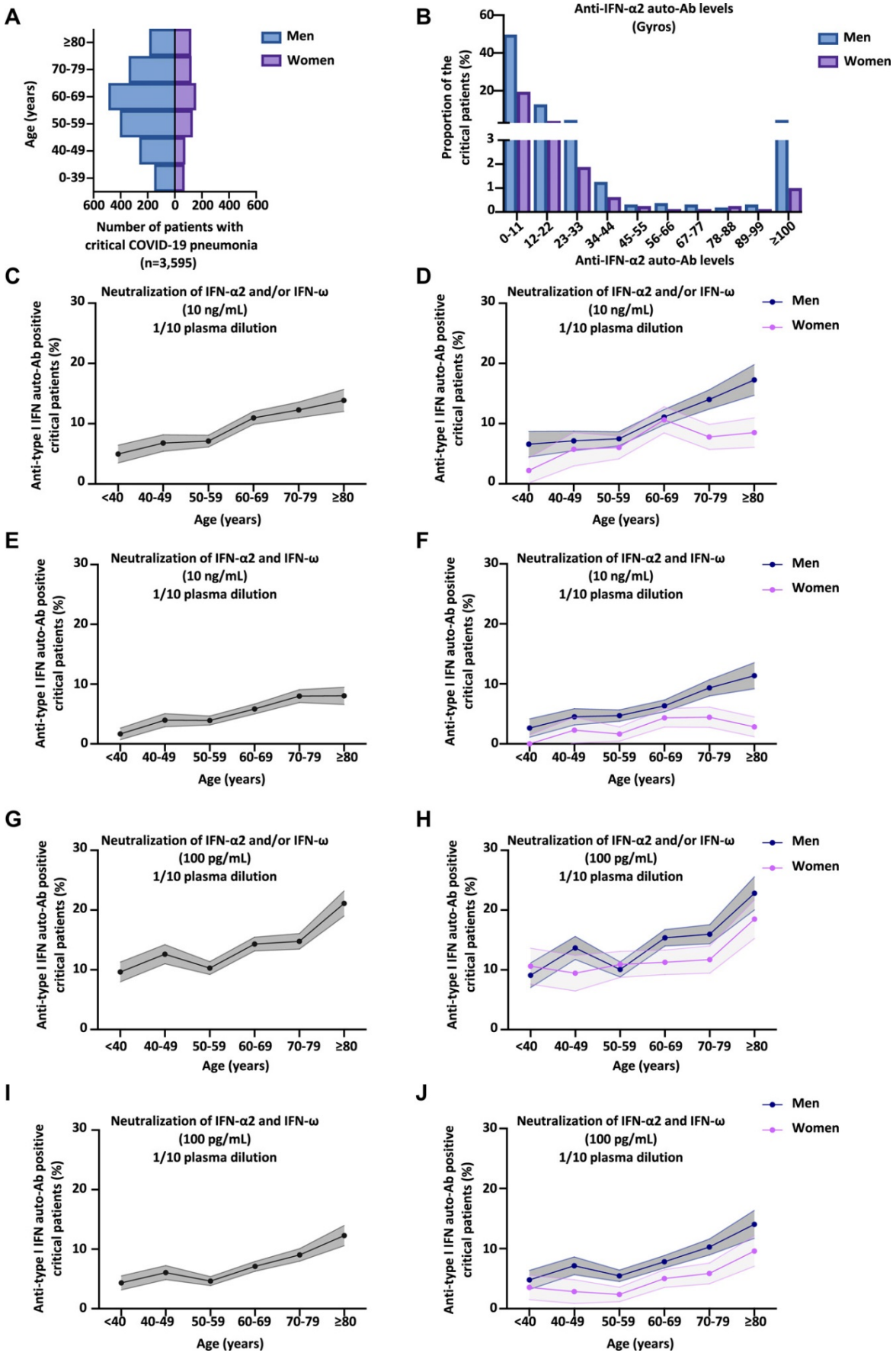

Fig. 3. Higher prevalence of neutralizing auto-Abs against type I IFNs in elderly patients with critical COVID-19. **(A)** Bar plot of the age and sex distribution of the patients with life-threatening COVID-19 included in our expanded cohort (*N*=3,595). **(B)** Graph showing the anti-IFN-α2 auto-Ab levels, assessed by Gyros, in patients with life-threatening COVID-19. Men and women are shown separately. The upper section of the Y-axis starts at 3%. **(C-J)** Proportion by decade of patients with critical COVID-19, and positive for neutralizing auto-Abs (in plasma 1/10) against **(C)** IFN-α2 and/or IFN-ω, at 10 ng/mL, for both sexes. **(D)** IFN-α2 and/or IFN-ω, at 10 ng/mL, for men or women. **(E)** IFN-α2 and IFN-ω, at 10 ng/mL, for both sexes. **(F)** IFN-α2 and IFN-ω, at 10 ng/mL, for men or women. **(G)** IFN-α2 and/or IFN-ω, at 100 pg/mL, for both sexes. **(H)** IFN-α2 and/or IFN-ω, at 100 pg/mL, for men or women. **(I)** IFN-α2 and IFN-ω, at 100 pg/mL, for both sexes. **(J)** IFN-α2 and IFN-ω, at 100 pg/mL, for men or women.

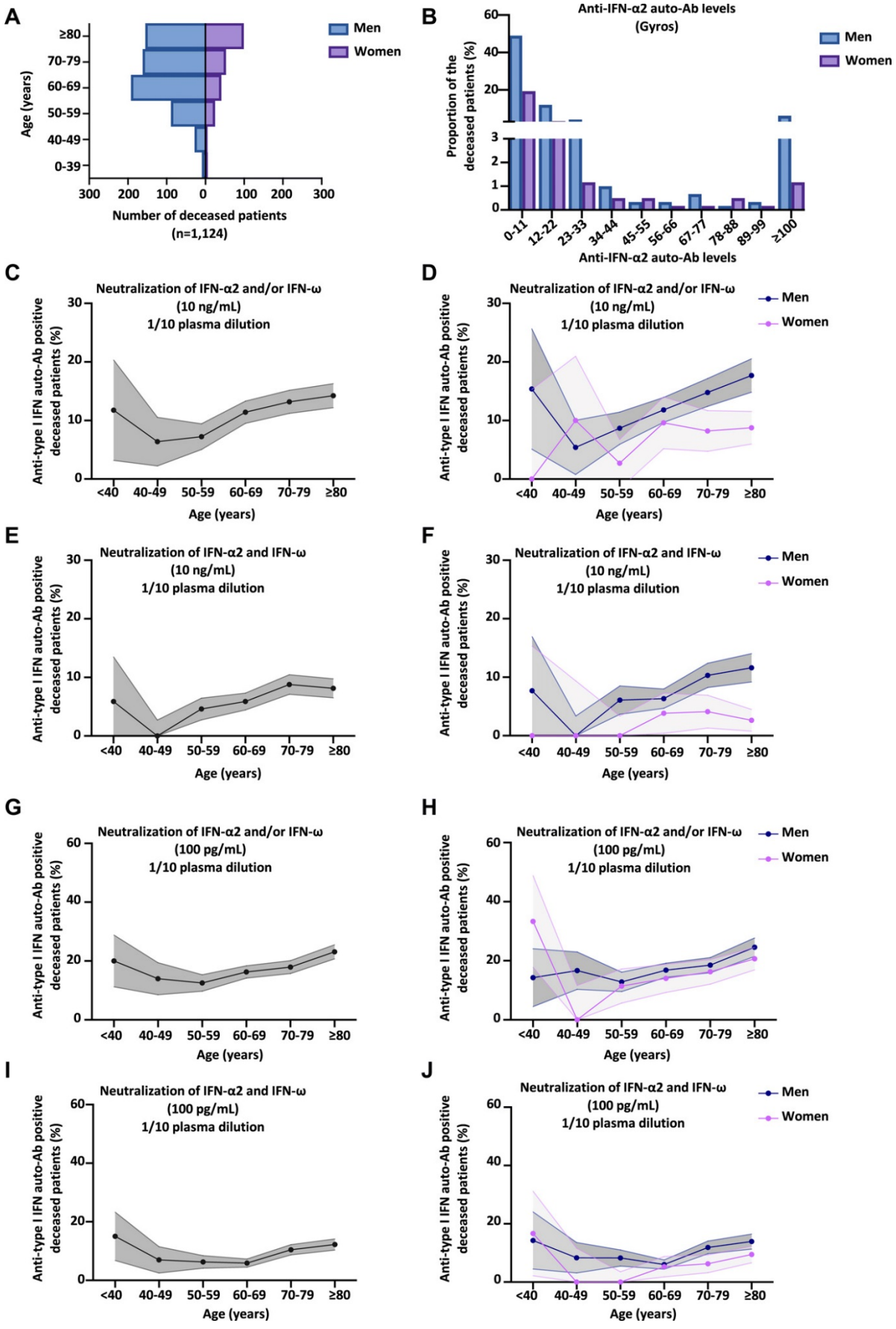

Fig. 4. Higher prevalence of neutralizing auto-Abs against type I IFNs in patients who died of COVID-19. (A) Bar plot of the age and sex distribution of the patients who died of COVID-19 included in our cohort (*N*=1,124). **(B)** Graph showing the anti-IFN-α2 auto-Ab levels, assessed by Gyros, in patients who died of COVID-19. Men or women are shown separately. The upper section of the Y-axis starts at 3%. **(C-J)** Proportion by decade of patients who died of COVID-19, and positive for neutralizing auto-Abs (in plasma 1/10) against **(C)** IFN-α2 and/or IFN-ω, at 10 ng/mL, for both sexes. **(D)** IFN-α2 and/or IFN-ω, at 10 ng/mL, for men or women. **(E)** IFN-α2 and IFN-ω, at 10 ng/mL, for both sexes. **(F)** IFN-α2 and IFN-ω, at 10 ng/mL, for men or women. **(G)** IFN-α2 and/or IFN-ω, at 100 pg/mL, for both sexes. **(H)** IFN-α2 and/or IFN-ω, at 100 pg/mL, for men or women. **(I)** IFN-α2 and IFN-ω, at 100 pg/mL, for both sexes. **(J)** IFN-α2 and IFN-ω, at 100 pg/mL, for men or women.

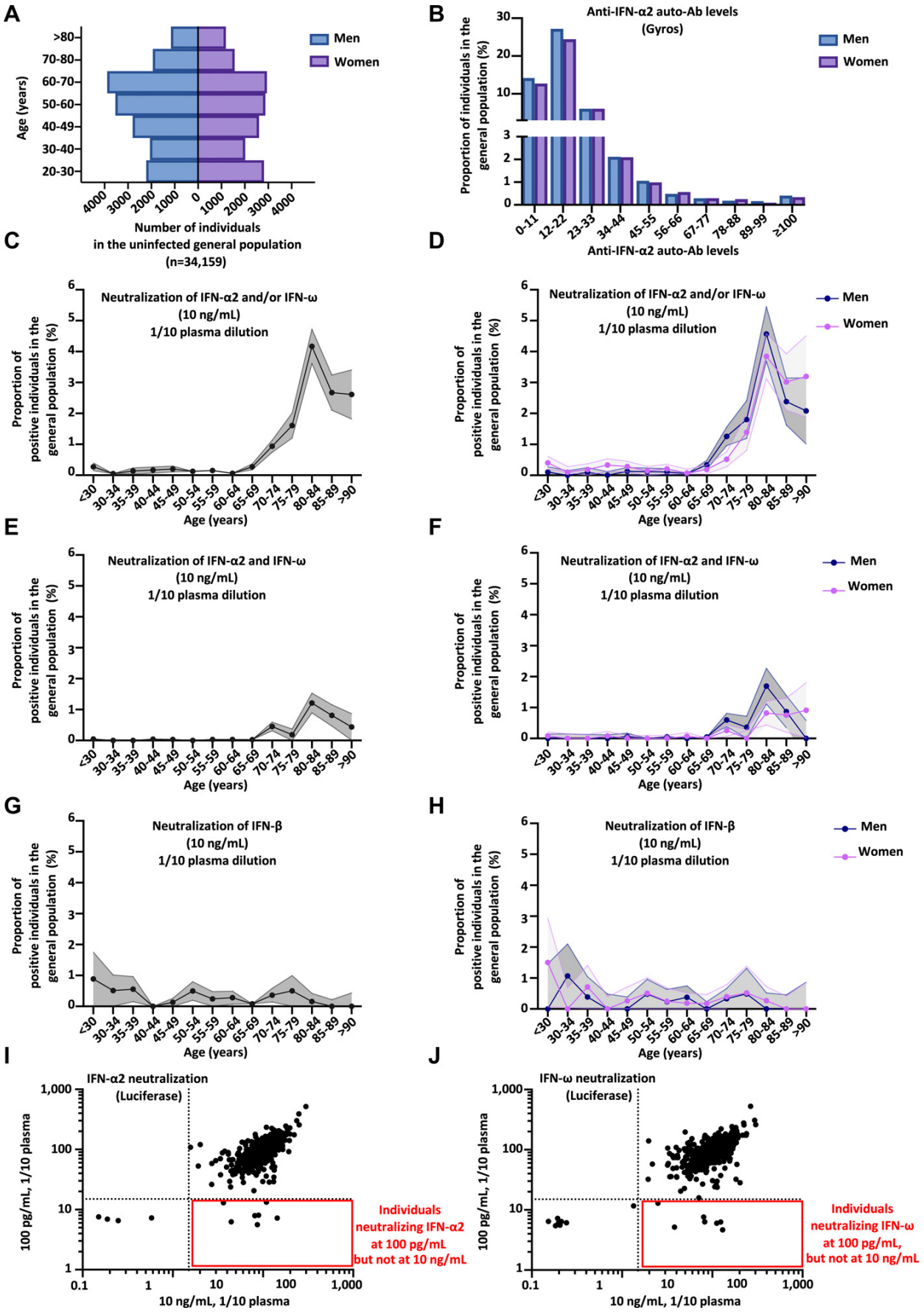

Fig. 5. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω at 10 ng/mL are more prevalent in the elderly, in the general population. **(A)** Bar plot of the age and sex distribution of individuals from the general population (*N*=34,159). **(B)** Graph showing the IFN-α2 auto-Ab levels, assessed by Gyros, in individuals from the general population. Men or women are shown separately. The upper section of the Y-axis starts at 3%. **(C-H)** Proportion by 5 years of individuals from the general population, and positive for neutralizing auto-Abs (in plasma 1/10) against **(C)** IFN-α2 and/or IFN-ω, at 10 ng/mL, for both sexes. **(D)** IFN-α2 and/or IFN-ω, at 10 ng/mL, for men or women. **(E)** IFN-α2 and IFN-ω, at 10 ng/mL, for both sexes. **(F)** IFN-α2 and IFN-ω, at 10 ng/mL, for men or women. **(G)** IFN-β, at 10 ng/mL, for both sexes. **(H)** IFN-β, at 10 ng/mL, for men or women. **(I)** Plot showing luciferase induction after stimulation with 10 ng/mL or 100 pg/mL IFN-α2, in the presence of plasma from individuals from the general population. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Individuals with antibodies neutralizing both 10 ng/mL and 100 pg/mL IFN-α2 are shown in the bottom left corner, whereas the individuals in the bottom right corner had antibodies capable of neutralizing only 100 pg/mL IFN-α2. **(J)** Plot showing luciferase induction after stimulation with 10 ng/mL or 100 pg/mL IFN-ω, for individuals from the general population.

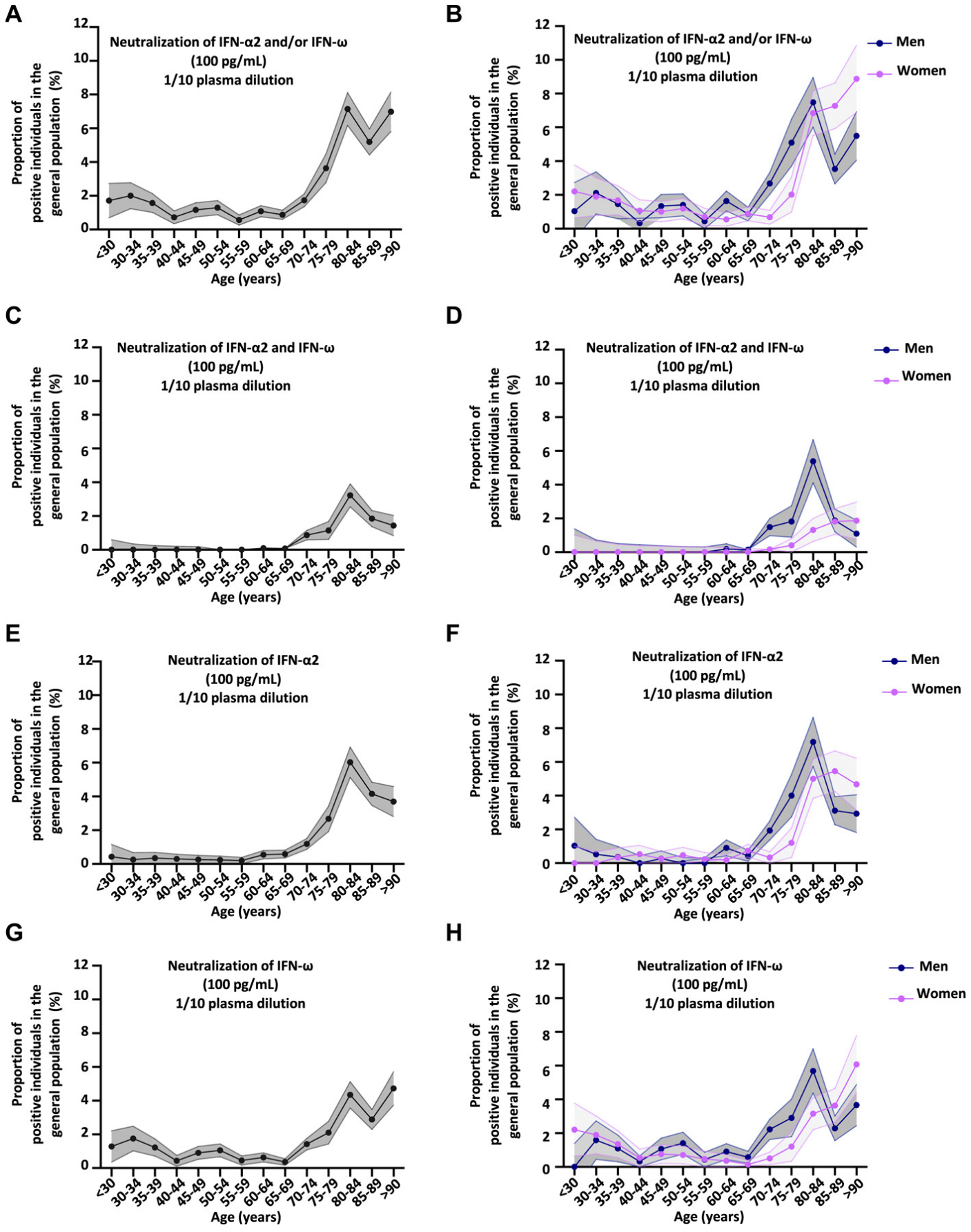

Fig. 6. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω at 100 pg/mL are more prevalent in the elderly, in the general population. (A-H) Proportion, binned every 5 years, of individuals from the general population, and positive for neutralizing auto-Abs (in plasma 1/10) against **(A)** IFN-α2 and/or IFN-ω, at 100 pg/mL, for both sexes. **(B)** IFN-α2 and/or IFN-ω, at 100 pg/mL, for men or women. **(C)** IFN-α2 and IFN-ω, at 100 pg/mL, for both sexes. **(D)** IFN-α2 and IFN-ω, at 100 pg/mL, for men or women. **(E)** IFN-α2, at 100 pg/mL, for both sexes. **(F)** IFN-α2, at 100 pg/mL, for men or women. **(G)** IFN-ω, at 100 pg/mL, for both sexes. **(H)** IFN-ω, at 100 pg/mL, for men or women.

Table 1. Risk of critical COVID-19 pneumonia for subjects carrying auto-Abs to specific sets of type I IFNs, when compared with that of asymptomatic/mild infection, adjusted on age and sex. Odds ratios (OR) and *P*-values were estimated by means of Firth's bias-corrected logistic regression. The numbers and proportions of subjects with critical COVID-19 pneumonia (patients) and asymptomatic or mild infection (controls) are shown in Figs. 1 to 3. Two combinations are not shown due to insufficient number of individuals: anti-IFN-β (10 ng/mL) and anti-IFN-α2 (100 pg/mL) auto-Abs only; anti-IFN-β (10 ng/mL) and anti-IFN-ω (100 pg/mL) auto-Abs only.

Anti-type I IFN auto-Ab positive (amount of type I IFN neutralized, in plasma diluted 1/10)	**Proportion of critical patients with neutralizing auto-Abs**	**OR [95% CI]**	***P*-value**
anti-IFN-α2 and anti-IFN-ω auto-Abs (10 ng/mL)	5.6%	67 [4-1109]	$7.8x10^{-13}$
anti-IFN-α2 and/or anti-IFN-ω auto-Abs (10 ng/mL)	9.8%	17 [7-45]	$< 10^{-13}$
anti-IFN-α2 auto-Abs (10 ng/mL)	9%	45 [9-225]	$< 10^{-13}$
anti-IFN-α2 auto-Abs only (10 ng/mL)	3.4%	21 [4-107]	$1.8x10^{-09}$
anti-IFN-ω auto-Abs (10 ng/mL)	6.4%	13 [4-38]	$1.4x10^{-12}$
anti-IFN-ω auto-Abs only (10 ng/mL)	0.8%	3 [0.9-10]	0.057
anti-IFN-α2 and anti-IFN-ω auto-Abs (100 pg/mL)	7.1%	54 [11-275]	$< 10^{-13}$
anti-IFN-α2 and/or anti-IFN-ω auto-Abs (100 pg/mL)	13.6%	13 [8-21]	$< 10^{-13}$
anti-IFN-α2 auto-Abs (100 pg/mL)	10%	23 [10-55]	$< 10^{-13}$
anti-IFN-α2 auto-Abs only (100 pg/mL)	2.9%	10 [3-26]	$2.8x10^{-09}$
anti-IFN-ω auto-Abs (100 pg/mL)	10.7%	13 [7-23]	$< 10^{-13}$
anti-IFN-ω auto-Abs only (100 pg/mL)	3.6%	6 [3-12]	$3.9x10^{-10}$
anti-IFN-β auto-Abs (10 ng/mL)	1.3%	8 [2-36]	$1.7x10^{-3}$
anti-IFN-β auto-Abs only (10 ng/mL)	0.96%	5 [1-25]	0.043
anti-IFN-β auto-Abs (10 ng/mL) and, anti-IFN-α2 and/or anti-IFN-ω auto-Abs (100 pg/mL)	0.34%	16 [0.5-497]	0.018
anti-IFN-β (10 ng/mL) and, anti-IFN-α2 and anti-IFN-ω auto-Abs (100 pg/mL)	0.28%	16 [0.5-502]	0.019

Science Immunology

Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

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Sci. Immunol. **6**, eabl4340.
DOI: 10.1126/sciimmunol.abl4340