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 1202 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 ($n = 2$) or moderate ($n = 1$), severe ($n = 1$), or critical ($n = 1$) pneumonia. Two patients from a cohort of 262 male patients with severe COVID-19 pneumonia (mean, 51.0 years) are hemizygous for a deleterious TLR7 variant. The cumulative allele frequency for deleterious *TLR7* variants in the male general population is $<6.5 \times 10^{-4}$. We show that blood B cell lines and myeloid cell subsets from the patients do not respond to TLR7 stimulation, a phenotype rescued by wild-type *TLR7*. The patients' blood plasmacytoid dendritic cells (pDCs) produce low levels of type I IFNs in response to SARS-CoV-2. Overall, X-linked recessive TLR7 deficiency is a highly penetrant genetic etiology of critical COVID-19 pneumonia, in about 1.8% of male patients below the age of 60 years. Human TLR7 and pDCs are essential for protective type I IFN immunity against SARS-CoV-2 in the respiratory tract.

INTRODUCTION

Interindividual clinical variability in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is vast, ranging from silent infection to lethal disease (*1*). The greatest risk factor for life-threatening coronavirus disease 2019 (COVID-19) pneumonia is age, with a doubling in risk every 5 years from the age of 5 years onward and a sharp rise after the age of 65 years (*2*, *3*). Other epidemiological risk factors, including common genetic variants, have only modest effects, with odds ratios of <2 and typically <1.5 (*2*). One intriguing observation is the about 1.5 times higher risk in men, which seems to be age independent (*2*–*4*). The COVID Human Genetic Effort consortium (www.covidhge.com) has enrolled

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 Toll-like receptor 3 (TLR3)– and interferon (IFN) regulatory factor 7 (IRF7)–dependent type I IFN immunity (*8*). These disorders were found in 23 men and women aged 17 to 77 years (mean, 48 years). Four unrelated patients aged 25 to 50 years had autosomal recessive IFNAR1 ($n = 2$) or IRF7 ($n = 2$) deficiency. These patients had no previous history of severe viral illness, including influenza pneumonia, implying that these genetic disorders unexpectedly show incomplete penetrance for critical influenza. These findings revealed that TLR3- and IRF7-dependent type I IFN immunity is essential for host defense against SARS-CoV-2 infection in the respiratory tract.

We also found preexisting neutralizing auto-antibodies (auto-Abs) against type I IFN in at least 10% of the patients from this cohort (*9*). These auto-Abs were found in 101 patients, mostly men (95%), and older members of the cohort, which included patients with 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

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

RESULTS

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

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

Human TLR7 is an endosomal receptor of ribonucleic acids expressed by B cells and myeloid subsets (*20*–*24*), the stimulation of which in plasmacytoid dendritic cells (pDCs) results in the production of large amounts of type I IFN (*25*–*27*). We observed no significant enrichment for coding nonsynonymous variants of the X-linked gene *TLR8* (P = 0.68; table S2), the product of which, TLR8, is endosomal and can be stimulated by some synthetic TLR7 agonists, with an expression pattern and signaling pathway overlapping those of TLR7 (*28*, *29*). Unlike TLR7, TLR8 is expressed on granulocytes but not on pDCs, possibly accounting for its gain-of-function mutations underlying a phenotype different from type I interferonopathies (*30*–*32*). Overall, we found an enrichment in very rare or private nonsynonymous *TLR7* variants among the male patients with critical COVID-19 pneumonia (n = 21, 1.7%) of our cohort (n = 1202), including one man over the age of 60 years.

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

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

The cumulative MAF of deleterious TLR7 alleles is <6.5×10^{-4}

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

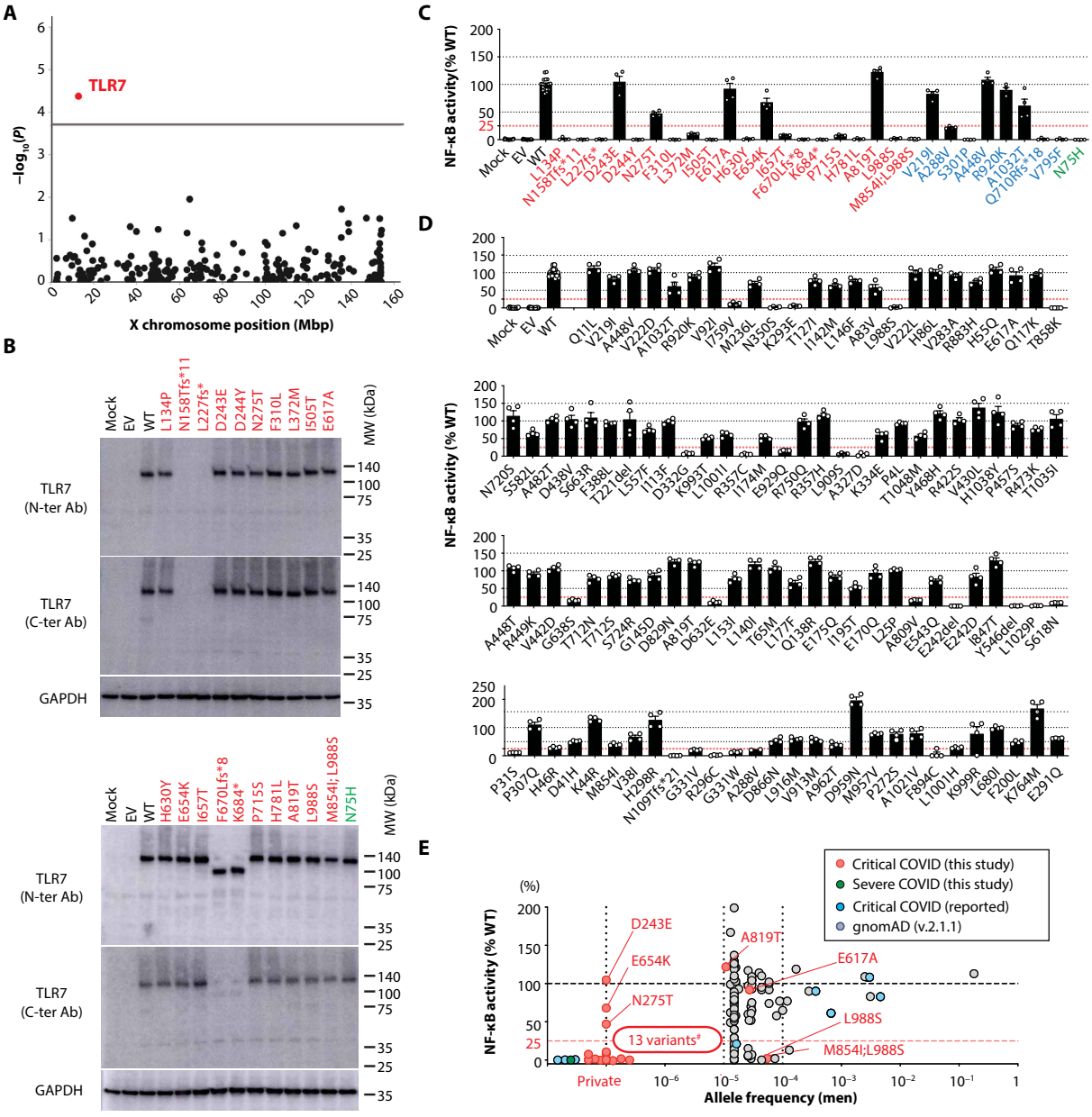

Fig. 1. Enrichment in rare *TLR7* deleterious alleles among men with critical COVID-19 pneumonia. (**A**) Manhattan plot showing the results of the variant enrichment test for the 190 genes of the X chromosome with at least five patients carrying nonsynonymous variants. The gray line indicates the corresponding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

in four patients with critical COVID-19 pneumonia. Each of these 24 deleterious variants had an individual MAF of $<1.3 \times 10^{-4}$ in men, and their cumulative MAF in men was 6.5×10^{-4} (data file S2 and table S3). The cumulative MAF of strictly LOF *TLR7* alleles (excluding hypomorphic alleles) in men is about 2.2×10^{-4} (data file S2). Overall, we found 12 LOF and 3 hypomorphic *TLR7* alleles in 16 unrelated men with critical COVID-19 pneumonia, whereas deleterious alleles were not found in men with asymptomatic or paucisymptomatic

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

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

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

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

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

The 16 patients were of three major ethnic origins, as confirmed by principal components analysis (PCA) of their exomes or genomes (*36*), and they were resident in seven countries (France, $n = 2$; Spain, $n = 3$; Italy, $n = 3$; Turkey, $n = 2$; Sweden, $n = 1$; Iran, $n = 4$; Colombia, $n = 1$) (Fig. 2, A and C; Table 1; fig. S1; and data file S3). The patients were hospitalized for critical COVID-19 between March 2020 and June 2021. Blood samples (diluted 1:10) from these 16 patients contained no auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml) (*9*, *18*). The patients were aged 7 to 71 years, and their mean age was lower than that of the total cohort (mean age of 34.4 years versus 52.9 years for the total cohort, in which age ranged from 0.5 to 99 years). TLR7-deficient patients accounted for about 1.8% of the patients below the age of 60 years (15 patients) and 1.3% of the entire cohort (16 patients). Two patients died and 14 survived (Fig. 2A and Table 1). Sanger sequencing of the *TLR7* locus in the relatives of these patients identified the deleterious alleles in 16 heterozygous women from 11 families and 7 hemizygous men from seven families (Fig. 2A). On the basis of the 10 DNA samples available from the patients' mothers, only one of the *TLR7* variants (L372M) was de novo in the index case. Five of the seven hemizygous relatives of the index cases had Abs against SARS-CoV-2 (Fig. 2A and data file S3). One 29-year-old adult (kindred J, P11) was hospitalized for critical pneumonia, and another 27-year-old adult (L.II.3) was hospitalized for severe pneumonia [with low-flow oxygen (<6 liter/min)]. The remaining three were two 5-year-old boys, one of whom had been hospitalized for moderate COVID-19 pneumonia (without oxygen therapy) (D.II.2) and the other having no relevant clinical history (M.II.2), and one 38-year-old adult with no relevant clinical history (E.II.4) (data file S3). The other two male carriers did not report SARS-CoV-2 infection and had negative serological results for Abs against the SARS-CoV-2 S and N proteins.

Inherited TLR7 deficiency in patients with severe COVID-19 pneumonia

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

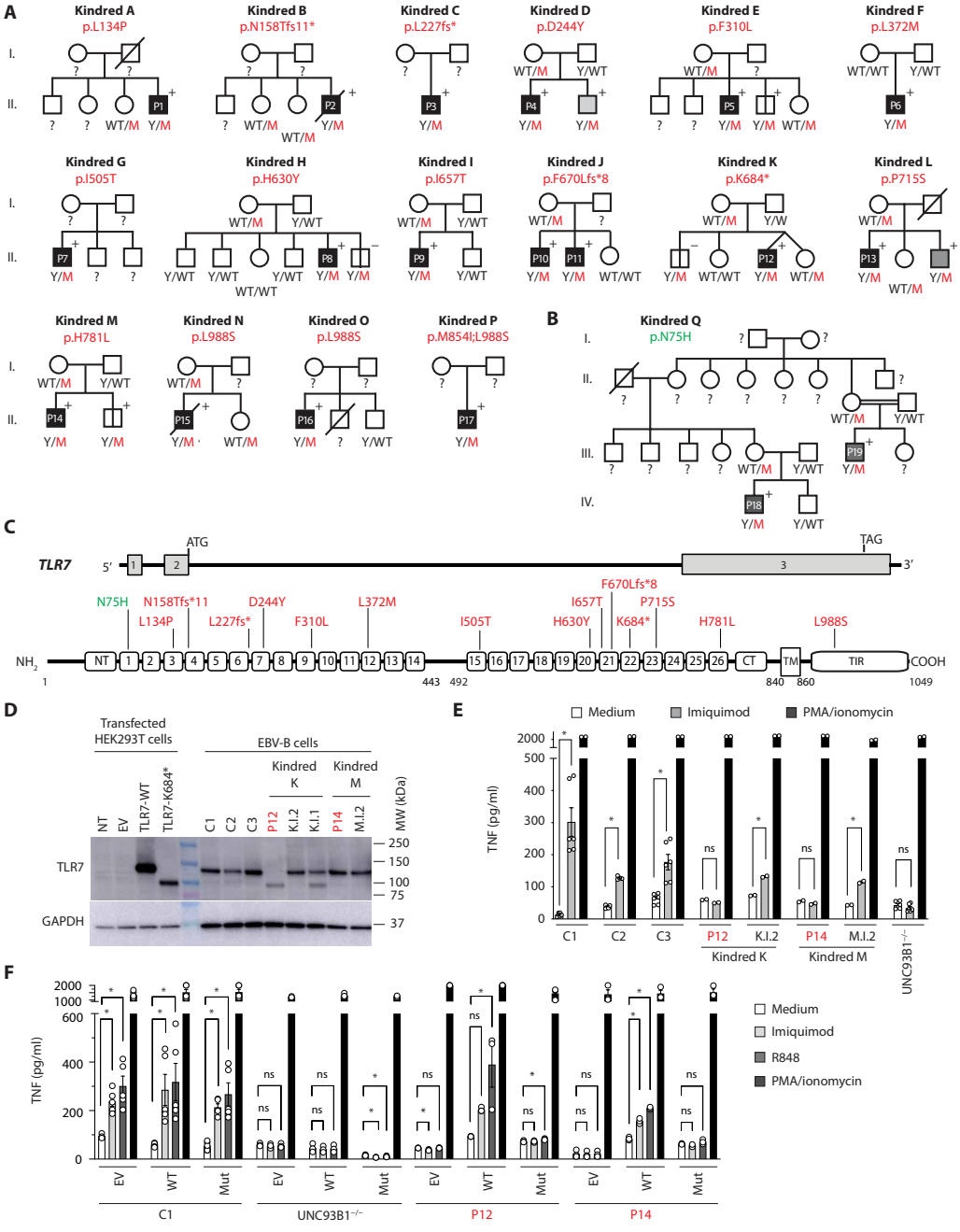

Fig. 2. XR TLR7 deficiency in 16 kindreds. (**A**) Pedigrees of the 16 kindreds containing 17 patients with life-threatening COVID-19 pneumonia (P1 to P17) bearing deleterious *TLR7* alleles. The mutations are indicated above each pedigree. Solid black symbols indicate patients with critical COVID-19,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

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

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

As a first approach to testing the impact of deleterious *TLR7* alleles in the patients' cells, we tested Epstein-Barr virus–transformed B cell lines (EBV-B cells) from healthy controls and patients carrying the hemizygous p.K684* (P12) or p.H781L (P14) variants. The endogenous expression of the p.H781L TLR7 protein was normal, whereas p.K684* generated a truncated protein (Fig. 2D). In response to agonists of TLR7 (imiquimod) or TLR7 and TLR8 (R848), the EBV-B cell lines carrying these two mutations failed to produce tumor necrosis factor (TNF; Fig. 2E and fig. S4, A and B). The lentiviral transduction of these TLR7-deficient EBV-B cells (from P12 and P14) with a wild-type (WT) TLR7 cDNA was unsuccessful, despite numerous attempts, and this was also the case for control EBV-B cells, perhaps because the overproduction of TLR7 is toxic in B cells (*40*). Consistent with this view, we were able to express this cDNA in interleukin-1 (IL-1) receptor–associated kinase 4 (IRAK4)– or myeloid differentiation factor 88 (MyD88)–deficient EBV-B cells. We therefore investigated whether the addition of an IRAK4 inhibitor (PF06650833) would permit the expression of WT TLR7 in control and TLR7-mutated EBV-B cells. This approach was successful, and WT TLR7 expression restored responses to TLR7 agonists (after removal of the inhibitor) (Fig. 2F and fig. S4C). 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 myeloid DCs [pDCs and myeloid (mDCs)], monocytes (classical, intermediate, and nonclassical), and B cells (*28*, *33*, *41*). TLR8 is expressed in mDCs but not pDCs, monocytes but not B cells, and neutrophils (unlike TLR7) (*28*, *33*, *41*). Neither *TLR7* nor *TLR8* mRNAs have been detected in the lung or pulmonary epithelial cells (*42*). Deep immunophenotyping by cytometry by time-of-flight in seven patients with TLR7 deficiency revealed no major abnormalities in 18 peripheral blood leukocyte subsets, including pDCs, mDCs, monocytes, and B cells (Fig. 3A and fig. S5A). We previously reported inherited IRF7 deficiency in a child with critical influenza pneumonia (*5*) and two unrelated adults with critical COVID-19 pneumonia (*8*). This defect disrupts the amplification of type I IFNs in all cell types, including pDCs, which are normally the main producers of type I IFN upon blood cell stimulation with TLR7 agonists or viruses, due to their constitutive expression of IRF7 (*28*, *43*–*45*). We hypothesized that TLR7 deficiency in pDCs impairs the production of type I IFN by these cells in response to single-stranded RNA. We confirmed that TLR7 was expressed on pDCs and that TLR8 was not (Fig. 3B and fig. S5, B and C). We measured the production of type I IFNs by purified leukocyte subsets (pDCs, mDCs, monocytes, B cells, and T cells), in response to TLR7, TLR8, and TLR9 agonists (Fig. 3C and fig. S5D). We confirmed that pDCs produced 100 to 1000 times more type I IFN per cell than other leukocyte subsets upon TLR7 stimulation (Fig. 3C and fig. S5D). We purified pDCs from P8 and P14 and analyzed their production of type I IFNs in response to CL264 and class C CpG oligonucleotide (CpG-c), relative to that of pDCs from healthy relatives, using a cytometric bead array (CBA) (Fig. 3D). pDCs from P8 and P14 did not produce type I IFNs (or IL-6) upon stimulation with a TLR7 agonist, whereas they responded to a TLR9 agonist (Fig. 3D). Moreover, agonist-induced up-regulation of programmed death ligand 1 (PD-L1) and CD80 defines the maturation of pDCs into the S1 (PD-L1^{high}/CD80^{low}), S2 (PD-L1^{high}/CD80^{high}), and S3 (PD-L1^{low}/CD80^{high}) subsets (*46*). This maturation was not observed in the pDCs of P8 and P14 but was detected in the pDCs of healthy relatives and controls (Fig. 3E and fig. S5E). Thus, pDCs from patients with *TLR7* mutations do not respond to TLR7 agonists in terms of maturation into specialized subsets and type I IFN production.

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

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

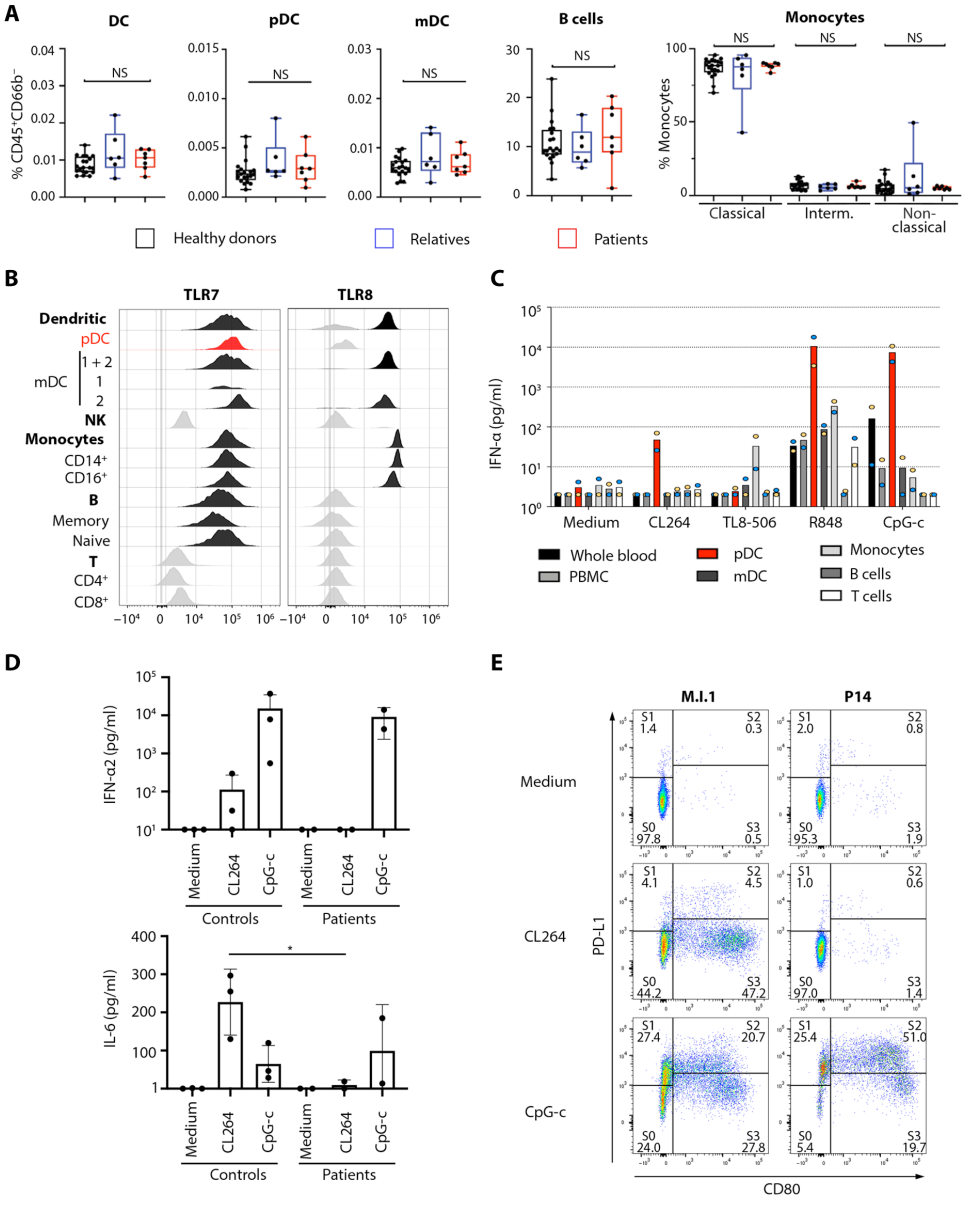

Fig. 3. Type I IFN responses to TLR7 agonist in TLR7-deficient pDCs and leukocytes. (**A**) Frequencies of five leukocyte subsets in whole blood, determined by CyTOF. Healthy donors (black rectangles), relatives not carrying deleterious *TLR7* alleles (blue rectangles) and hemizygous *TLR7* variant carriers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

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

DISCUSSION

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

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

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

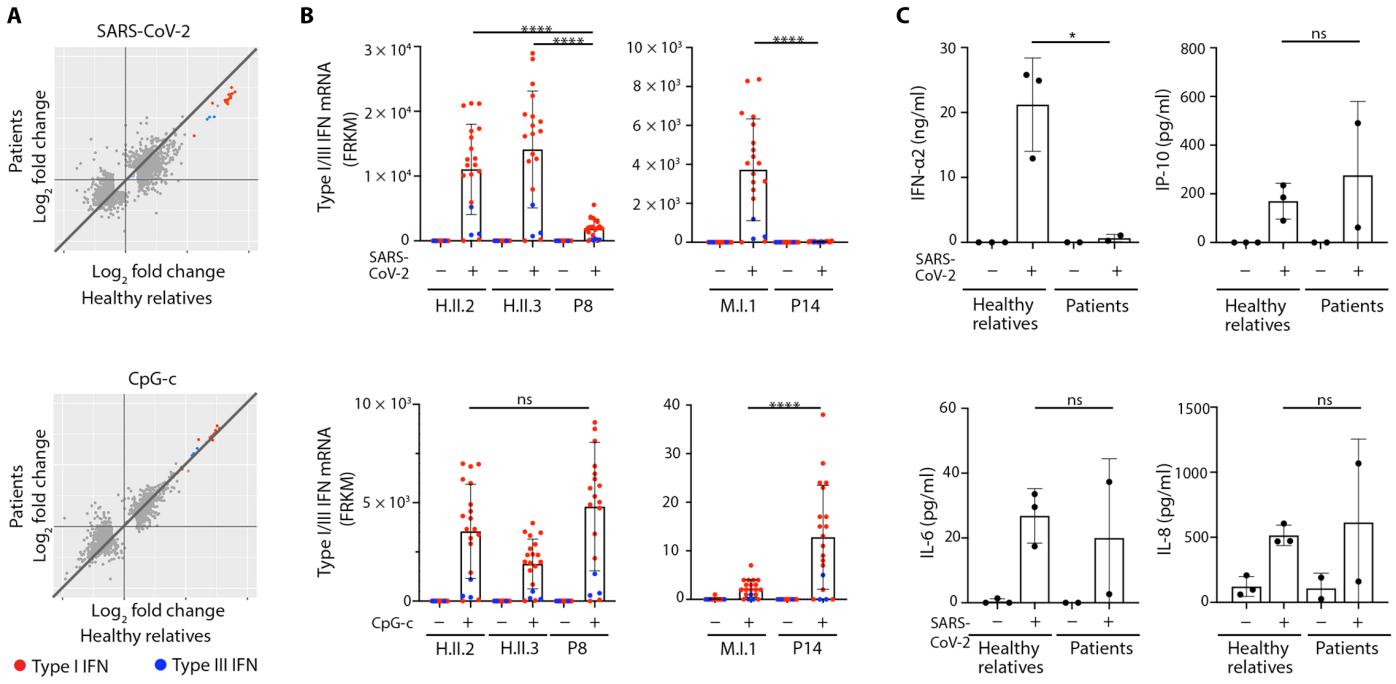

Fig. 4. Type I IFN responses to SARS-CoV-2 infection in TLR7-deficient pDCs. (**A**) pDCs isolated from healthy relatives and TLR7-deficient patients (P8 and P14) were either left untreated or were infected with SARS-CoV-2 for 24 hours. RNA profiles were then determined by RNA-seq. Genes with an expression of >2.0-fold higher or lower in controls after stimulation or infection are plotted as the fold change in expression. (**B**) Induction of the type I and III IFN genes from (A) infected with SARS-CoV-2 for 24 hours (top) or stimulated with CpG-c (bottom). (**C**) pDCs isolated from healthy relatives and TLR7-deficient patients (P8 and P14) were either left untreated or were infected with SARS-CoV-2 for 24 hours, and the production of IFN-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 and *****P* < 0.0001).

including autosomal recessive IRF7 or IFNAR1 deficiency (*5*, *6*), or due to auto-Abs neutralizing type I IFNs (*9*, *11*–*14*, *16*, *17*), strongly suggest that critical disease in TLR7-deficient patients is a consequence of impaired type I IFN production upon SARS-CoV-2 infection. The absence of biochemically deleterious X-linked *TLR8* variants in our cohort of patients suggests that TLR8 is not essential for host defense against SARS-CoV-2. This is consistent with the modest capacity of TLR8 to induce type I IFN and its lack of expression on pDCs (*28*) and with the inflammatory phenotype of TLR8 gain-of-function mutations, which do not underlie a type I interferonopathy (*30*–*32*). Patients with inherited IRAK4 or MyD88 deficiency, whose cells do not respond to the stimulation of IL-1Rs and TLRs other than TLR3, including TLR7, have not been reported to display any severe viral illness over the almost 20 years since the discovery of IRAK-4 deficiency (*50*–*53*). Moreover, UNC-93B–deficient pDCs produced normal amounts of type I IFN in response to seasonal influenza virus (*5*). This was intriguing, as strong negative selection operates at the human *TLR7*, *TLR8*, and *TLR9* loci (*50*, *54*). Our study provides an answer to this riddle, by establishing that TLR7 is essential for protective immunity to SARS-CoV-2. Patients with IRAK4, MyD88, or UNC-93B deficiency are now predicted to be vulnerable to SARS-CoV-2 (*55*–*57*). Critical COVID-19 and seasonal influenza can be caused by inborn errors of TLR3-dependent type I IFN immunity (*5*–*8*), but susceptibility to these infections is not allelic at the *TLR7* locus. It is, nevertheless, tempting to speculate that TLR7 might also be essential for host defense against more virulent, pandemic viruses, including both 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 (*26*). However, the essential and redundant roles of this leukocyte subset have yet to be determined, in the absence of human pDC-specific deficiencies causally underlying a clinical phenotype. It has long been suspected, but never proved, that pDCs are essential for host defense under natural conditions (*27*, *58*–*60*). Inherited IRF7 deficiency, which underlies critical influenza or COVID-19 pneumonia, disrupts the production of type I IFNs not only by pDCs (*5*, *8*) but also by all other cell types, including pulmonary epithelial cells (*5*). Likewise, patients with GATA2 deficiency, who are prone to critical influenza (*61*), lack pDCs, but these patients also lack many other blood cell subsets (*62*–*65*). Inherited IFNAR1 deficiency underlies critical COVID-19 probably due to its broad cellular impact (*5*, *6*, *8*). By contrast, inborn errors of the TLR3 pathway underlie critical influenza or COVID-19 pneumonia by impairing the production of type I IFNs by cells other than pDCs, such as pulmonary epithelial cells (*5*–*8*, *66*). Our study indicates that pulmonary epithelial cells are not sufficient for host defense against SARS-CoV-2, as these cells do not express TLR7. Inborn errors of TLR7 are pathogenic by impairing the production of type I IFNs by blood pDCs, which are unique in their production of large amounts of both TLR7 and IRF7 (*67*, *68*). pDCs express other viral sensors, including TLR9 (for DNA), melanoma differentiation-associated protein 5 (MDA5), and retinoic

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

MATERIALS AND METHODS

Study design

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

Cohort recruitment and consent

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

All the enrolled participants provided written informed consent and were collected through protocols conforming to local ethics requirements. For patients enrolled in the French COVID cohort (ClinicalTrials.gov NCT04262921), ethics approval was obtained from the Comité de Protection des Personnes Ile De France VI (ID RCB, 2020-A00256-33) or the Ethics Committee of Erasme Hospital (P2020/203). For participants enrolled in the COV-Contact study (ClinicalTrials.gov NCT04259892), ethics approval was obtained from the CPP IDF VI (ID RCB, 2020-A00280-39). For patients enrolled in the Italian cohort, ethics approval was obtained from the University of Milano-Bicocca School of Medicine, San Gerardo Hospital, Monza–Ethics Committee of the National Institute of Infectious Diseases Lazzaro Spallanzani (84/2020) (Italy), and the Comitato Etico Provinciale (NP 4000–Studio CORONAlab). STORM-Health care workers were enrolled in the STudio OsseRvazionale sullo screening dei lavoratori ospedalieri per COVID-19 (STORM-HCW) study, with approval from the local institutional review board (IRB) obtained on 18 June 2020. Patients and relatives from San Raffaele Hospital (Milan) were enrolled in protocols COVID-BioB/Gene-COVID and, for additional studies, TIGET-06, which were approved by local ethical committee. For patients enrolled in Spain, the study was approved by the Committee for Ethical Research of the Infanta Leonor University Hospital, code 008-20; Committee for Ethical Research of the University Hospital 12 de Octubre, code 16/368; the Bellvitge University Hospital, code PR127/20; the University Hospital of Gran Canaria Dr. Negrín, code 2020-200-1 COVID-19; and the Vall d'Hebron University Hospital, code PR(AMI)388/2016. Anonymized samples were sequenced at the National Institute of Allergy and Infectious Diseases (NIAID) through Uniformed Services University of the Health Sciences (USUHS)/the American Genome Center (TAGC) under nonhuman subject research conditions; no additional IRB consent was required at the National Institutes of Health (NIH). For patients enrolled in the Swedish COVID cohort, ethics approval was obtained from the Swedish Ethical Review Agency (2020-01911 05).

Next-generation sequencing

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

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

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

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

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

Statistical analysis

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

Cell culture

EBV-B cell lines derived from the patients were grown in complete RPMI 1640 (Life Technologies) supplemented with 10% heat-inactivated fetal bovine serum (FBS). HEK293T cells, derived from the HEK293 cell line, which expresses a mutant version of the SV40 large T antigen, were grown in complete Dulbecco's modified Eagle's medium (Life Technologies) supplemented with 10% FBS. Cells were incubated at 37°C in the presence of 5% CO_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 reintroduced into a Myc-DDK-pCMV6 vector (OriGene). HEK293T cells, which have no endogenous TLR7 or TLR8 expression, were transfected with the Myc-DDK-pCMV6 vector, empty or containing the WT, or a variant allele, in the presence of the X-tremeGENE 9 DNA Transfection Reagent (Sigma-Aldrich), according to the manufacturer's instructions.

Western blotting

For whole-cell extracts, the cells were lysed by incubation in the following buffer [50 mM tris-HCl (pH 8.0), 150 mM NaCl, and 1% NP-40), supplemented with a mixture of protease inhibitors (Sigma-Aldrich), for 30 min at 4°C. The lysates were then centrifuged at 21,000*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 mAbs specific for the leucine-rich repeats to the N terminus within the human TLR7 protein (Cell Signaling Technology, clone, D7) or for amino acid 1000 to the C terminus with the human TLR7 protein [Abcam, clone, EPR2088(2)].

Luciferase reporter assay

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

RNA extraction and reverse transcription qPCR

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

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

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

Stable transduction

The WT coding sequence of *TLR7* was inserted into pTRIP-CMV-puro-2A. For lentivirus production, HEK293T cells were transfected with 1.6 μg of pTRIP-CMV-puro-2A-TLR7-WT (or mutant, K684*), 0.2 μg of pCMV-VSV-G (Addgene), 0.2 μg of pHXB2 (NIH-AIDS Reagent 22 Program), and 1 μg of psPAX2 (Addgene), with X-treme gene 9 (Roche), according to the manufacturer's instructions. Supernatants were harvested after 24 hours, and protamine sulfate (8 μg/ml) was added. The lentiviral suspension obtained was used to transduce 2×10^5 EBV-B cells by spinoculation at 1200*g* for 2 hours. The transduced cells were selected by incubation on medium containing puromycin (1 μg/ml) for 2 days. The cells were then selected by incubation for a further 2 days on medium containing puromycin (2 μg/ml). 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 R848 (1 μg/ml) or imiquimod (5 μg/ml) for 24 hours without IRAK4 inhibitor. The supernatants were harvested after 24 hours of activation. ELISA determinations of TNF in cell culture supernatants were performed with a kit (Thermo Fisher Scientific), according to the manufacturer's instructions.

VirScan analysis

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

Deep immunophenotyping by mass cytometry (CyTOF)

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

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

Blood were collected from two healthy individuals and separated by the concentration gradient method with Ficoll Paque Plus (Cytiva). After isolations of peripheral blood mononuclear cells (PBMCs), leucocyte subset (T cell, B cell, monocyte, pDC, and mDC) was purified by negative selection using MACS beads system (Miltenyi Biotec). Cells were plated into a U-bottomed 96-well plate at a density of 2×10^4 cells per well for T cells, B cells, monocytes, pDCs, or mDCs in RPMI 1640 (200 μl per well) with GlutaMAX supplemented with 10% FBS or 10×10^4 cells per well for whole blood and PBMCs. Cells were left unstimulated or stimulated with CL264 (1 μg/ml), TL8-506 (100 ng/ml; Invivogen), R848 (1 μg/ml), 2 μM CpG-c (Invivogen), or phorbol 12-myristate 13-acetate (PMA; 12.5 ng/ml) and 0.125 μM 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 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 per well, in 200 μl of phosphate-buffered saline (PBS) per well. Briefly, cells were stained by incubation with the LIVE/DEAD fixable blue dead-cell staining kit (Thermo Fisher Scientific; 1:800) and Fc receptor blocking reagent (Miltenyi Biotec; 1:25) on ice for 15 min. For surface staining, cells were incubated with anti-TCRγδ-BUV611 (BD Biosciences; 1:50), anti–CD183-BV750 (BD Biosciences; 1:20), and anti–CD194-BUV615 (BD Biosciences; 1:20) Abs on ice for 30 min in 0.1% bovine serum albumin and 0.01% sodium azide in PBS. They were then incubated with anti–CD141-BB515 (BD Biosciences; 1:40), anti–CD57-FITC (BioLegend; 1:83), anti-TCR 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) Abs on ice for at least 30 min. The cells were then washed and stained by incubation with streptavidin-PE/Cy5 (BioLegend; 1:3000) on ice for 30 min. The cells were then fixed and permeabilized for intracellular staining with anti–TLR7-PE (Invitrogen) and anti–TLR8-APC (BioLegend) Abs, with the eBioscience Foxp3/Transcription Factor Staining Buffer Set (Invitrogen), according to the manufacturer's instructions. The cells were then washed and acquired with a five-laser Cytek Aurora (Cytek) flow cytometer. Ab clone information is added in the Supplementary Materials (data file S6).

pDC activation

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

Flow cytometry analysis for human pDCs

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

RNA sequencing

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

Determination of secreted inflammatory cytokines

We measured the production, by pDCs, of IFN-α2, IL-8, IL-6, and interferon gamma-induced protein 10 (IP-10), by determining the levels of these cytokines in culture supernatants with the BD CBA, according to the manufacturer's protocol, with a limit of detection of 20 pg/ml. Acquisitions were performed on an LSRFortessa (BD Biosciences) flow cytometer, and cytokine concentrations were determined with FCAP Array software (BD Biosciences).

SUPPLEMENTARY MATERIALS

www.science.org/doi/10.1126/sciimmunol.abl4348
Figs. S1 to S6
Tables S1 to S3
Data files S1 to S7

View/request a protocol for this paper from *Bio-protocol*.

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X-linked COVID-19 risk factor

Age and male sex are two prominent risk factors for developing life-threatening COVID-19 after SARS-CoV-2 infection. Asano *et al*. analyzed 1202 critical male COVID-19 patients to examine whether non-synonymous variants in genes on the X chromosome are a risk factor for developing COVID-19 pneumonia. Toll-like receptor 7 (TLR7) variants resulting in TLR7 deficiency occurred in 16 unrelated males, most of which were under age 60. Plasmacytoid dendritic cells (pDCs), primary producers of type I interferon (IFN-I), from TLR7-deficient patients were unresponsive to TLR7 stimulation and displayed impaired production of IFN-I in response to SARS-CoV-2. These results identify X-linked

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recessive TLR7 deficiency as a genetic risk factor for COVID-19 pneumonia in males and demonstrate a key role for intact pDC IFN-I in protective immunity against SARS-CoV-2.