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

Qian Zhang et al.

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

RATIONALE: We established the COVID Human Genetic Effort (www.covidhge.com) to test the general hypothesis that life-threatening COVID-19 in some or most patients may be caused by monogenic inborn errors of immunity to SARS-CoV-2 with incomplete or complete penetrance. We sequenced the genome of 659 patients of various ancestries infected with SARS-CoV-2 infection. We considered three loci identified in 422 (2020) 23 October 2020

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

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

Corresponding author: Jean-Laurent Casanova (casanova@rockefeller.edu)

This is an open-access article distributed under the terms of the Creative Commons Attribution license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Cite this article as Q. Zhang et al., Science 370, eabd4570 (2020). DOI: 10.1126/science.abd4570

READ THE FULL ARTICLE AT

https://doi.org/10.1126/science.abd4570
Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang1, Paul Bastardo2,3, Zhiyong Liu1,4,5, Jérémie Le Pen6,7, Marcela Moncada-Velez1,8, Jie Chen1,9, Masato Ogishi1,10, Ira K. D. Sabin11,12,13, Stephanie Hodeib14,5, Cecilia Korol15,16, Jérémie Rosain17,18, Kaya Bilgic19, Junqiang Ye1,20, Alexandre Bolze21,22, Benedetta Bigi1,23, Rui Yang1,6, André Augusto Arias1,9,10, Clifton L. Dalgard24,25, Joshua D. Milner26,27,28,29,30, Donald C. Vinh11,12, Trine H. Mogensen6,7,71, Nico Marr22,71, Cédric Laouénan6,3,64,65, COVID-STORM Clinicians1,2,3,79,82,84,86, Anna-Lena Neehus2,3, Aileen Camille Ugurbil1, Aurélien Corneau19, Gaspard Kerner1,2,3, Peng Zhang1,2,3,4,5,6,7,8, Bertrand Boisson1,2,3, Stéphanie Boisson-Dupuis1,2,3, Jacinta Bustamante1,2,3,§, András N. Spaan1,72,3, Jean-Laurent Casanova1,2,3,79,86, Jacques Fellay23,24,25,26, Lucie H. S. Pascal27,28, Fanny Onodi13, Sarantis Korniotis13, Kadriye Kart Yasar56, Sevtap Senoglu56, Aurora Pujol21, Darragh Duffy16, Richard P. Lifton83,84,85,§, and has probably infected at least another 200 million. The clinical manifestations range from silent infection to lethal disease, with an infection fatality rate of 0.1 to 0.9%. Three epidemiological factors increase the risk of severity: (i) increasing age, decade by decade, after the age of 50, (ii) being male, and (iii) having various underlying medical conditions (7). However, even taking these factors into account, there is immense inter-individual clinical variability in each demographic category considered. Following on from our human genetic studies of other severe infectious diseases (2,3), we established the COVID Human Genetic Effort (https://www.covidhge.org) to test the general hypothesis that in some patients, life-threatening coronavirus disease 2019 (COVID-19) may be caused by monogenic inborn errors of immunity to SARS-CoV-2 with incomplete or complete penetrance (4). We enrolled 659 patients (74.5% men and 25.5% women, 13.9% of whom died) of various ancestries between 1 month and 99 years of age (Fig. 1A). These patients were hospitalized for life-threatening pneumonia caused by SARS-CoV-2 (critical COVID-19). We sequenced their whole genome (N = 364) or exome (N = 295), and principal component analysis (PCA) on these data confirmed their ancestries (Fig. 1B).

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

We first tested the specific hypothesis that inborn errors of Toll-like receptor 3 (TLR3)– and interferon regulatory factor 7 (IRF7)–dependent type I interferon (IFN) immunity, which underlie life-threatening influenza pneumonia, may also underlie life-threatening COVID-19 pneumonia (5) (Fig. 2). We considered three loci previously shown to be mutated in patients with critical influenza pneumonia: TLR3 (6), IRF7 (7), and IRF9 (8). We also considered 10 loci mutated in patients with other viral illnesses but directly connected to the three core genes conferring influenza susceptibility: TICAM1/TRIF (9), UNC93B1 (10), TRAF3 (11), TRAF3 (12), IRF3 (13), and NEMO/IKBKG (14) in the TLR3-dependent type I IFN induction pathway, and IFNAR1 (15), IFNAR2 (16), STAT1 (17), and STAT2 (18) in the IRF7- and IRF9-dependent type I IFN amplification pathway. We collected both monoallelic and biallelic nonsynonymous variants with a minor allele frequency (MAF) <0.001 at all 13 loci. Twelve of the 13 candidate loci are autosomal, whereas NEMO is X-linked. For the latter gene, we considered only a recessive model (19). Autosomal-dominant (AD) inheritance has not been proven for six of the 12 autosomal loci (UNC93B1, IRF7, IFNAR1, IFNAR2, STAT2, and IRF9). Nevertheless, we considered heterozygous variants because none of the patients enrolled had been hospitalized for critical viral infections before COVID-19, raising the possibility that any underlying genetic defects that they might have displayed a lower penetrance for influenza and other viral illnesses than for COVID-19, which is triggered by a more virulent virus.

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

We found four unrelated patients with biallelic variants of IRF7 or IFNAR1 (Table 1 and table S1). We also found 113 patients carrying 113 monoallelic variants at 12 loci: TLR3 (N = 7 patients/7 variants), UNC93B1 (N = 10/9), TICAM1 (N = 17/15), TRAF3 (N = 6/6), TRAF3 (N = 12/11), IRF3 (N = 5/5), IRF7 (N = 20/13), IFNAR1 (N = 14/13), IFNAR2 (N = 17/15), STAT1 (N = 4/4), STAT2 (N = 11/11), and IRF9 (N = 4/4). We detected no copy number variation.

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

S

evere acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already claimed at least 1 million lives, has been detected in at least 20 million people, and has probably infected at least another 200 million. The clinical manifestations range from silent infection to lethal disease, with an infection fatality rate of 0.1 to 0.9%. Three epidemiological factors increase the risk of severity: (i) increasing age, decade by decade, after the age of 50, (ii) being male, and (iii) having various underlying medical conditions (7). However, even taking these factors into account, there is immense inter-individual clinical variability in each demographic category considered. Following on from our human genetic studies of other severe infectious diseases (2,3), we established the COVID Human Genetic Effort (https://www.covidhge.org) to test the general hypothesis that in some patients, life-threatening coronavirus disease 2019 (COVID-19) may be
without LOF variants in the 13 candidate genes) and control cohorts (patients with mild or asymptomatic disease and individuals from the 1000 Genomes Project).

257 Zhang et al

‡ These authors contributed equally to this work.

1St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. 2Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1613, Necker Hospital for Sick Children, Paris, France. 3University of Paris, Imagine Institute, Paris, France. 4Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, USA. 5Department of Paediatric Infectious Diseases & Virology, Imperial College London, London, UK. 6Yale Center for Genome Analysis and Department of Genetics, Yale School of Medicine, New Haven, CT, USA. 7Zukeran Mind Brain Behavior Institute, Columbia University, New York, NY, USA. 8Helm, San Mateo, CA, USA. 9Primary Immunodeficiencies Group, University of Antwerp UDeM, Medellin, Colombia. 10School of Microbiology, University of Antwerp UDeM, Medellin, Colombia. 11Laboratory of Clinical Immunology and Microbiology, Division of Intraumal Research, NAID, NIH, Bethesda, MD, USA. 12NAID Clinical Genomics Program, NIH, Bethesda, MD, USA. 13Université de Paris, Institut de Recherche Saint-Louis, INSERM U976, Hôpital Saint-Louis, Paris, France. 14Laboratory of Genomics & Cell Biology of Disease, INSERM U944, CNRS UMR 7212, Université de Paris, Institut de Recherche Saint-Louis, Hôpital Saint-Louis, Paris, France. 15Sorbonne Université, Inserm, Centre d’immunologie et des Maladies Infectieuses-Périmétrique, Assistance Publique-Hôpitaux de Paris (AP-HP) Hôpital Pitié-Salpêtrière, Paris, France. 16Translational Immunology Lab, Institut Pasteur, Paris, France. 17Laboratory for Inborn Errors of Immunity, Department of Microbiology, Immunology and Transplantation, Department of Pediatrics, University Hospitals Leuven, KU Leuven, Leuven, Belgium. 18Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 19Sorbonne Université, UMS337, PASS, Plateforme de Cyntométrie de la Pitié-Salpêtrière CoPyS, Paris, France. 20Bioinformatics Platform, Service Frédérale de Recherche Necker, INSERM U9163, Université de Paris, Imagine Institute, Paris, France. 21Neurometabolic Diseases Laboratory, DIBELL-Hospital Duran i Reynals, CIBERER U759, and Catalan Institute of Research and Advanced Studies (ICREA), Barcelona, Spain. 22Department of Immunology, Research Branch, Sidra Medicine, Doha, Qatar. 23School of Life sciences, École Polytechnique Fédérative de Lausanne, Lausanne, Switzerland. 24Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. 25Swiss Institute of Bioinformatics, Lausanne, Switzerland. 26Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, Québec, Canada. 27Specialized Immunology Laboratory of Dr. Shahrrooe’ Sina Medical Complex, Ahvaz, Iran. 28Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. 29Department of Pathology and Laboratory Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia. 30Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shaikh Beheshti University of Medical Sciences, Tehran, Iran. 31The Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shaikh Beheshti, University, Tehran, Iran. 32Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shaikh Beheshti, Iran. 33National Center of Genomics Technology, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia. 34Diabetes Diabetes Institute. Department of Genetics and Bioinformatics, Kuwait. 35Immunology Research Laboratory, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. 36Translational Pathology, Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, Misr, National Guard Health Affairs, Riyadh, Saudi Arabia. 37Cancer & Blood Research, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia. 38Amsterdam UMC, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands. 39Pediatric Department and Centro Tettamanzi-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBMB-Ospedale San Gerardo, Monza, Italy. 40Department of Infectious Diseases, San Gerardo Hospital–University of Milano-Bicocca, Monza, Italy. 41CREA Laboratory, Diagnostic Laboratory, ASST Spedali Civili di Brescia, Brescia, Italy. 42Department of Infectious and Tropical Diseases, Universidade de Brescia and ASST Spedali di Brescia, Brescia, Italy. 43Chief Medical Officer, ASST Spedali Civili di Brescia, Brescia, Italy. 44Bioinformatics and Computational Biosciences Branch, Office of Cyber Infrastructure and Computational Biology, NAID, NIH, Bethesda, MD, USA. 45PRIMEER, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. 46Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. 47Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. 48Inserm U885, Centre National de Recherche de Santé, Université de Paris, Institut de Recherche Saint-Louis, Hôpital Saint-Louis, Paris, France. 49Sorbonne Universités, Université Paris Cité, CNRS, UMR 7285, Ligue pour le Fight contre le Mycoses des Membranes Mucocutanes, Hôpital Saint-Louis, IRLIN, INSERM U1453, AP-HP, Paris, France. 50Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, USA. 51Department of Paediatric Allergy and Immunology, Konya, Turkey. 52Department of Infectious Diseases and Clinical Microbiology, Konya, Turkey. 53Department of Infectious Diseases, University Hospitals Leuven, KU Leuven, Leuven, Belgium. 54Department of Paediatric Allergy and Immunology, Necker Hospital for Sick Children, Paris, France. 55Department of Medical Microbiology, Utrecht UMC, Utrecht, Netherlands. 56Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, Paris, France. 57Translome Biologics, New York, NY, USA. 58Department of Pediatrics, University Hospitals Leuven, KU Leuven, Leuven, Belgium. 59New York Genome Center, New York, NY, USA. 60AP-HP, Hôpital Saint-Louis, Laboratoire d’Immunologie, Paris, France. 61Laboratory of Molecular Immunology, Rockefeller University, New York, NY, USA. 62Howard Hughes Medical Institute, New York, NY, USA. 63Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 64The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 65Inserm, University of Paris, Institut de Recherche en Immunologie et des Maladies Infectieuses (PRIX), Paris, France. 66Department of Microbiology, Immunology and Transplantation, Department of Pediatrics, University Hospitals Leuven, KU Leuven, Leuven, Belgium. 67Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 68Department of Genetics, Yale University School of Medicine, New Haven, CT, USA. 69Yale Center for Genome Analysis, Yale School of Medicine, New Haven, CT, USA. 70Pediatric Hematology and Immunology Unit, Necker Hospital for Sick Children, AP-HP, Paris, France.

*These authors contributed equally to this work.
†All collaborators and their affiliations appear at the end of this paper.
‡These authors contributed equally to this work.
§Corresponding author. Email: casanova@rockefeller.edu

Fig. 1. Demographic and genetic data for the COVID-19 cohort. (A) Age and sex distribution of patients with life-threatening COVID-19. (B) PCA of patient (with or without LOF variants in the 13 candidate genes) and control cohorts (patients with mild or asymptomatic disease and individuals from the 1000 Genomes Project).
for these 13 genes. Unexpectedly, one of these variants has been reported in patients with life-threatening influenza pneumonia (TLR3 p.Pro554Ser) (6, 20) and another was shown to be both deleterious and dominant-negative (IFNAR1 p.Pro335del) (21). Nine of the 118 biallelic or monoallelic variants were predicted to be LOF (pLOF), whereas the remaining 109 were missense or in-frame indels (table S1). In a sample of 534 controls with asymptomatic or mild SARS-CoV-2 infection, we found only one heterozygous pLOF variation with a MAF <0.001 at the 13 loci (IRF7 p.Leu99fs). A PCA-adjusted burden test on the 12 autosomal loci revealed significant enrichment in pLOF variants in patients relative to controls [P = 0.01; odds ratio (OR) = 8.28; 95% confidence interval (CI) = 1.04 to 65.64] under an AD mode of inheritance. The same analysis performed on synonymous variants with a MAF <0.001 was not significant (P = 0.19), indicating that our ethnicity-adjusted burden test was well calibrated.

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

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

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Genetic form</th>
<th>Genotype</th>
<th>Gender</th>
<th>Age [years]</th>
<th>Ancestry/residence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR3</td>
<td>AD</td>
<td>Known</td>
<td>p.Ser339fs/WT</td>
<td>M</td>
<td>40</td>
<td>Spain</td>
<td>Survived</td>
</tr>
<tr>
<td>TLR3</td>
<td>AD</td>
<td>Known</td>
<td>p.Pro554Ser/WT</td>
<td>M</td>
<td>68</td>
<td>Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>TLR3</td>
<td>AD</td>
<td>Known</td>
<td>p.Trp769*/WT</td>
<td>M</td>
<td>77</td>
<td>Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>TLR3</td>
<td>AD</td>
<td>Known</td>
<td>p.Met870Val/WT</td>
<td>M</td>
<td>56</td>
<td>Colombia/Spain</td>
<td>Survived</td>
</tr>
<tr>
<td>UNC93B1</td>
<td>AD</td>
<td>New</td>
<td>p.Glu69*/WT</td>
<td>M</td>
<td>48</td>
<td>Venezuela/Spain</td>
<td>Survived</td>
</tr>
<tr>
<td>TICAM1</td>
<td>AD</td>
<td>Known</td>
<td>p.Thr41le/WT</td>
<td>M</td>
<td>49</td>
<td>Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>TICAM1</td>
<td>AD</td>
<td>Known</td>
<td>p.Ser60Cys/WT</td>
<td>F</td>
<td>61</td>
<td>Vietnam/France</td>
<td>Survived</td>
</tr>
<tr>
<td>TICAM1</td>
<td>AD</td>
<td>Known</td>
<td>p.Gln392Lys/WT</td>
<td>F</td>
<td>71</td>
<td>Italy</td>
<td>Deceased</td>
</tr>
<tr>
<td>TBK1</td>
<td>AD</td>
<td>Known</td>
<td>p.Phe24Ser/WT</td>
<td>F</td>
<td>46</td>
<td>Venezuela/Spain</td>
<td>Survived</td>
</tr>
<tr>
<td>TBK1</td>
<td>AD</td>
<td>Known</td>
<td>p.Arg308*/WT</td>
<td>M</td>
<td>17</td>
<td>Turkey</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF3</td>
<td>AD</td>
<td>Known</td>
<td>p.Glu49del/WT</td>
<td>F</td>
<td>23</td>
<td>Bolivia/Spain</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF3</td>
<td>AD</td>
<td>Known</td>
<td>p.Asn146Lys/WT</td>
<td>F</td>
<td>60</td>
<td>Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AR</td>
<td>Known</td>
<td>p.Pro364fs/p.Pro364fs</td>
<td>F</td>
<td>49</td>
<td>Italy/Belgium</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AR</td>
<td>Known</td>
<td>p.Met371Val/p.Asp117Asn</td>
<td>M</td>
<td>50</td>
<td>Turkey</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AD</td>
<td>New</td>
<td>p.Arg7fs/WT</td>
<td>M</td>
<td>60</td>
<td>Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AD</td>
<td>New</td>
<td>p.Gln185*/WT</td>
<td>M</td>
<td>44</td>
<td>France</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AD</td>
<td>New</td>
<td>p.Pro246fs/WT</td>
<td>M</td>
<td>41</td>
<td>Spain</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AD</td>
<td>New</td>
<td>p.Arg369Gln/WT</td>
<td>M</td>
<td>69</td>
<td>Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>IRF7</td>
<td>AD</td>
<td>New</td>
<td>p.Phe95Ser/WT</td>
<td>M</td>
<td>37</td>
<td>Turkey</td>
<td>Survived</td>
</tr>
<tr>
<td>IFNAR1</td>
<td>AR</td>
<td>Known</td>
<td>p.Trp73Cys/Trp73Cys</td>
<td>M</td>
<td>38</td>
<td>Turkey</td>
<td>Survived</td>
</tr>
<tr>
<td>IFNAR1</td>
<td>AR</td>
<td>Known</td>
<td>p.Ser422Arg/Ser422Arg</td>
<td>M</td>
<td>26</td>
<td>Pakistan/Saudi Arabia</td>
<td>Deceased</td>
</tr>
<tr>
<td>IFNAR2</td>
<td>AD</td>
<td>New</td>
<td>p.Pro335del/WT</td>
<td>F</td>
<td>23</td>
<td>China/Italy</td>
<td>Survived</td>
</tr>
<tr>
<td>IFNAR2</td>
<td>AD</td>
<td>New</td>
<td>p.Glu140fs/WT</td>
<td>F</td>
<td>54</td>
<td>Belgium</td>
<td>Survived</td>
</tr>
</tbody>
</table>
A  

TLR3  

IFN-β mRNA (fold change)  

WT  

E49del  

N146K  

R257H  

G373R  

L401V  

R385Q  

*  

B  

TICAM1  

IFN-β mRNA (fold change)  

WT  

S134P  

N339K  

R263K  

G322S  

G365V  

Q421*  

*  

C  

TBK1  

IFN-β mRNA (fold change)  

WT  

S134P  

N339K  

R263K  

G322S  

G365V  

Q421*  

*  

D  

IRF3  

IFN-β reporter (fold change)  

Untreated  

Sendai virus  

WT  

E49del  

N146K  

R257H  

G373R  

L401V  

R385Q  

*  

E  

IRF7  

IFN-β reporter (fold change)  

Untreated  

Sendai virus  

WT  

R7fs  

S465N  

D557N  

M595L  

Q702R  

*  

F  

IFNAR1  

p-STAT1 (fold change)  

IFN-α  

IFN-γ  

WT  

E49del  

N146K  

R257H  

G373R  

L401V  

R385Q  

*  

G  

IFNAR2  

p-STAT1 (fold change)  

IFN-α  

IFN-γ  

WT  

E49del  

N146K  

R257H  

G373R  

L401V  

R385Q  

*  

Fig. 3. Impact of TLR3, TICAM1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2 variants on type I IFN signaling. (A) TLR3-deficient P2.1 fibrosarcoma cells were stably transfected with plasmids expressing WT or mutant forms of TLR3, and IFNL1 mRNA levels were determined by reverse transcription quantitative PCR. IFNL1 mRNA levels were expressed relative to the housekeeping gene GUS and then normalized. IFNL1 was undetectable in unstimulated cells. The differences between variants and WT were assessed. Asterisks indicate variants with MFI <50% of WT. Variants in red were either left untreated or infected with Sendai virus for 24 hours before the normalized measurement of luciferase activity. The differences between variants and WT were evaluated using two-way ANOVA (*P < 0.05). (B) TICAM1-deficient SV40-Fib cells were transiently transfected with WT or mutant forms of TICAM1, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Normalized luciferase induction was measured 24 hours after transfection. The differences between variants and WT were tested using one-way ANOVA (*P < 0.05). (C) HEK293T cells were transiently transfected with WT and mutant forms of TBK1, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Normalized luciferase activity was measured 24 hours after transfection. The differences between variants and WT were tested using one-way ANOVA (*P < 0.05). (D) IRF3-deficient HEK293T cells were transiently transfected with WT and mutant forms of IRF3, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Cells were either left untreated or infected with Sendai virus for 24 hours before the normalized measurement of luciferase activity. The differences between variants and WT were evaluated using two-way ANOVA (*P < 0.05). (E) HEK293T cells were transiently transfected with WT and mutant forms of IRF7, together with an IFN-β luciferase reporter and a constitutively expressed reporter. Cells were either left untreated or infected with Sendai virus for 24 hours before the normalized measurement of luciferase activity. The differences between variants and WT were tested using two-way ANOVA (*P < 0.05). (F and G) IFNAR1- or IFNAR2-deficient SV40-Fib cells were transiently transfected with WT or mutant forms of IFNAR for 36 hours, and either left untreated or stimulated with IFN-α2 or IFN-γ. Fluorescence-activated cell sorting (FACS) staining with anti-p-STAT1 antibody and the z-score of the MFI were assessed. Asterisks indicate variants with MFI <50% of WT. Variants in red were identified in COVID-19 patients. Variants in blue are known deleterious variants and served as negative controls. EV, empty vector; LT, lipofectamine. Three technical repeats were performed for (A) to (E). Means and SD are shown in the columns and horizontal bars when appropriate.
for IRF7; homozygosity for IFNAR1) and 19 AD deficiencies. These 23 patients did not carry candidate variants at the other 417 loci known to underlie inborn errors of immunity (table S2) (24–26). These findings suggest that at least 23 (3.5%) unrelated patients of the 659 patients tested suffered from a deficiency at one of eight loci among the 13 tested: four patients with a known AR disorder (IRF7 or IFNAR1) (7, 15), 11 with a known AD disorder (TLR3, TICAM1, TBK1, or IRF5) (6, 9, 12, 13, 20), and eight with a previously unknown AD genetic disorder (UNC93B1, IRF7, IFNAR1, or IFNAR2).

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

We tested cells from patients with selected genotypes and showed that PHA-driven T cell blasts (PHA-T cells) from patients with AR or AD IRF7 deficiency had low levels of IRF7 expression (Fig. 4A). We then isolated circulating plasmacytoid dendritic cells (pDCs) from a patient with AR IRF7 deficiency (fig. S9A) (7). These cells were present in normal proportions (fig. S9B), but they did not produce any detectable type I or III IFNs in response to SARS-CoV-2, as analyzed by cytometric bead array (CBA), enzyme-linked immunosorbent assay (ELISA), and RNA sequencing (RNA-seq) (Fig. 4, B and C). We also showed that PHA-T cells from a patient with AR IRF-α/β receptor 1 (IFNAR1) deficiency had impaired IFNAR1 expression and responses to IFN-α2 or IFN-β, and that the patient’s SV40-transformed fibroblast (SV40-Fib) cells did not respond to IFN-α2 or IFN-β (Fig. 5). We then infected TLR3+/−, TLR3−/−, IRF7+/−, SV40-Fib cells, and IRF7−/− SV40-Fib cells rescued with wild-type (WT) IRF7; IFNAR1−/− SV40-Fib cells, and IFNAR1−/− SV40-Fib cells rescued with WT

---

**Fig. 4. Type I IFN responses in patient cells defective for IRF7.** (A) Levels of the IRF7 protein in PHA-T cells from two patients with AR IRF7 deficiency (P1 and P3), one patient with AD IRF7 deficiency (P2), and four healthy donors (C1 to C4). Cells were either left untreated or stimulated with IFN-α2 for 24 hours, and protein levels were measured by Western blotting. MX1 was used as a positive control for IFN-α2 treatment. (B) pDCs isolated from an AR IRF7-deficient patient (P1) and a healthy donor (C1) were either left untreated or infected with influenza A virus (IAV) or SARS-CoV-2, and RNA-seq was performed. Genes with expression >2.5-fold higher or lower in C1 after infection are plotted as the fold change in expression. Red dots are type I IFN genes; blue dots are type III IFN genes. (C) pDCs isolated from healthy donor C and IRF7-deficient patient (P1) were either left untreated (Medium) or infected with IAV or SARS-CoV-2, and the production of IFN-α2 and IFN-λ1 was measured by CBA and ELISA, respectively, on the supernatant. ND, not detected. 
IFNAR1, all of which were previously transduced with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2). SARS-CoV-2 infection levels were higher in mutant cells than in cells from healthy donors, and transduction of WT IRF7 or IFNAR1 rescued their defects (Fig. 6). Collectively, these findings showed that AR IRF7 deficiency impaired the production of type I IFN by pDCs stimulated with SARS-CoV-2, whereas AR and AD deficiencies of TLR3 or AR deficiency of IFNAR1 impaired fibroblast-intrinsic type I IFN immunity to SARS-CoV-2. They also suggest that heterozygosity for LOF variations at the other five mutated loci also underlie life-threatening COVID-19.

Impaired production of type I IFNs in patients in vivo

We tested whether these genotypes impaired the production of type I IFN in vivo during the course of SARS-CoV-2 infection. We measured the levels of the 13 types of IFN-α in the blood of patients during the acute phase of COVID-19. We found that 10 of the 23 patients with mutations for whom samples were available (one with AR IRF7 deficiency, four with AD IRF7 deficiency, one with AD TLR3 deficiency, two with AD TBK1 deficiency, one with AR IFNAR1 deficiency, and one with AD TICAM1 deficiency) had serum IFN-α levels <1 pg/ml (Fig. 7). By contrast, previously published cohorts of patients hospitalized with unexplained, severe COVID-19 had various serum IFN-α levels, significantly higher than our 10 patients [one-way analysis of variance (ANOVA), P = 1.4 × 10^{-7}; Fig. 7] (27, 28). Another 29 patients from our cohort displaying auto-antibodies (auto-Abs) against type I IFNs, reported in an accompanying paper, had undetectable levels of serum IFN-α (29). Moreover, none of the 23 patients with LOF mutations of the eight genes had detectable auto-Abs against type I IFNs (29), strongly suggesting that the two mechanisms of disease are similar but independent. Excluding patients with auto-Abs against type I IFN from the burden test of pLOF variants at the 12 autosomal loci strengthened the association signal (P = 0.007; OR = 8.97; 95% CI = 1.13 to 71.09).

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

Collectively, our data suggest that at least 23 of the 659 patients with life-threatening COVID-19 pneumonia studied had known (six disorders) or new (four disorders) genetic defects at eight loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs. This discovery reveals the essential role of both the double-stranded RNA sensor TLR3 and type I IFN cell-intrinsic immunity in the control of SARS-CoV-2 infection in the lungs, consistent with their previously documented roles in pulmonary immunity to influenza virus (3–8). These genotypes were silent until infection with SARS-CoV-2. The most thought-provoking examples are the AR deficiencies of IRF7 and IFNAR1. AR IRF7 deficiency was diagnosed in two individuals aged 49 and 50 years, and AR IFNAR1 deficiency was diagnosed in two individuals aged 26 and 38 years, and none of the four patients had a prior history of life-threatening infections (Table 1). One patient with IRF7 deficiency was tested and was seropositive for several common viruses, including various influenza A and B viruses (figs. S10 and S11). These genetic defects therefore display incomplete penetrance for influenza respiratory distress and only manifested clinically upon infection with the more virulent SARS-CoV-2.

Conclusion

The AR form of IFNAR1 deficiency highlights the importance of type I IFN production relative to type III IFN production, which is also impaired by defects of TLR3, IRF7, and IRF9 (5). This conclusion is also supported by our accompanying report of neutralizing auto-Abs against type I IFNs, but not type III IFNs, in other patients with life-threatening COVID-19 pneumonia (29). Inborn errors of TLR3- and
SV40-Fib cells rescued with WT IRF7; IFNAR1 V225fs/V225fs + EV

TLR3 WT/WT
TLR3 P554S/WT
TLR3 P554S/E746*

IRF7 F410V/Q421* + WT
IRF7 F410V/Q421* + LUC

IFN-α

S-protein MFI (z-score)

Fig. 6. Cell-intrinsic type I IFN response to SARS-CoV-2. SV40-Fib cells of TLR3
and IRF7 cells were previously transduced with either WT IFNAR1 or empty vector (EV).
SV40-Fib cells were previously transduced with either WT IRF7 or negative control (Luc).
IFNAR1-deficient S-protein levels were measured by high-content microscopy with gating on ACE2+ cells. IRF7-deficient IFNAR1 WT/WT + EV
IFNAR1 WT/WT + WT
IFNAR1 V225fs/V225fs + EV
IFNAR1 V225fs/V225fs + WT

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

Methods

Patients

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

Next-generation sequencing

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

All of the variants were manually curated using Integrative Genomics Viewer (IGV) and confirmed to affect the main functional protein isoform by checking the protein sequence before inclusion in further analyzes. The main functional protein isoforms were TLR3 (NM_001289125.3), STAT1 (NM_007315.4), STAT2 (NM_001572.5), IFNAR1 (NM_000629.3), IFNAR2 (NM_013254.4), IRF3 (NM_001571), IRF7 (NM_182919), TRAF3 (NM_145725.2), TBK1 (NM_013254.4), IRF3 (NM_001571), IRF7 (NM_001572.5), IFNAR1 (NM_000629.3), IFNAR2 (NM_001289125.3), STAT1 (NM_007315.4), STAT2
both the HMZDelFinder and CANOES for deletions in the 13 genes of interest using regression with the likelihood ratio test. We ascribed the duplicated region in IKBKG using a specific pipeline previously described (32). The analysis of IKBKG was customized to unmask the duplicated region in IKBKG using a specific pipeline previously described (32). We searched the next-generation–sequencing data for deletions in the 13 genes of interest using both the HMZDelFinder (33) and CANOES (34) algorithms.

Statistical analysis
We performed an enrichment analysis on our cohort of 659 patients with life-threatening COVID-19 pneumonia and 534 SARS-CoV-2–infected controls, focusing on 12 autosomal IFN-α-related genes. We considered variants that were pLOF with a MAF <0.001 (gnomAD version 2.1.1) after experimentally demonstrating that all of the pLOF variants seen in the cases were actually LOF. We compared the proportion of individuals carrying at least one pLOF variant of the 12 autosomal genes in cases and controls by means of logistic regression with the likelihood ratio test. We accounted for the ethnic heterogeneity of the cohorts by including the first three principal components of the PCA in the logistic regression model. PC adjustment is a common and efficient strategy for accounting for different ancestries of patients and controls in the study of rare variants (35–38). We checked that our adjusted burden test was well calibrated by also performing an analysis of enrichment in rare (MAF <0.001) synonymous variants of the 12 genes. PCA was performed with Plink version 19 software on whole-exome sequencing data and the 1000 Genomes (1kG) Project phase 3 public database as a reference, using 27,480 exonic variants with a MAF >0.01 and a call rate >0.99. The OR was also estimated by logistic regression and adjusted for ethnic heterogeneity.

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

SARS-CoV-2 infection in patient SV40-Fib
To make patient-derived fibroblasts permissive to SARS-CoV-2 infection, we delivered human ACE2 and TMPRSS2 cDNA to cells by lentivirus transduction using a modified SCRPSY vector (GenBank ID: KT368137.1). SARS-CoV-2 strain USA-WAI/2020 was obtained from BEI Resources. ACE2/TMPRSS2-transduced cells were either left untreated or treated with 500 U/ml IFN-β (1H45-1, PBL Assay Science) 4 hours before infection. Cells were infected with SARS-CoV-2 (MOI = 0.5) for 1 hour at 37°C. After 24 hours of infection, cells were fixed and taken out of the BSL3 for staining.

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

SARS-CoV-2 infection in patient SV40-Fib
To make patient-derived fibroblasts permissive to SARS-CoV-2 infection, we delivered human ACE2 and TMPRSS2 cDNA to cells by lentivirus transduction using a modified SCRPSY vector (GenBank ID: KT368137.1). SARS-CoV-2 strain USA-WAI/2020 was obtained from BEI Resources. ACE2/TMPRSS2-transduced cells were either left untreated or treated with 500 U/ml IFN-β (1H45-1, PBL Assay Science) 4 hours before infection. Cells were infected with SARS-CoV-2 (MOI = 0.5) for 1 hour at 37°C. After 24 hours of infection, cells were fixed and taken out of the BSL3 for staining.

After fixation, cells were stained with SARS-CoV-2 and ACE2 primary antibodies (0.5 and 1 μg/ml, respectively). Primary antibodies were as follows: for SARS-CoV-2, human monoclonal anti-spike-SARS-CoV-2 CI21 antibody (40), and for ACE2, mouse monoclonal Alexa Fluor 488–conjugated antibody (RAB0323G-100UG, R&D Systems). Images were acquired with an ImageXpress Micro XLS microscope (Molecular Devices) using the 4× objective. MetaXpress software (Molecular Devices) was used to obtain single-cell mean fluorescence intensity (MFI) values.

Data analysis on single-cell MFI values was done in the R environment (version 4.0.2). ACE2/TMPRSS2-transduced cells were classified as ACE2 positive when the ACE2 log MFI was superior to the log mean MFI of mock-transduced cells plus 2.5 SDs. We excluded all wells with <150 ACE2-positive cells before SARS-CoV-2 scoring. ACE2-expressing cells were classified SARS-CoV-2 positive when the fluorescence intensity value was superior to
the MFI of mock-infected cells plus 4 SDs. The median SARS-CoV-2 MFI and percentage SARS-CoV-2-positive cells were calculated for each well (independent infection).

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

Sera from patients with COVID-19 were tested for IFN-α expression using a digital ELISA platform. The test measures the concentration of IFN-α specific to a particular strain of SARS-CoV-2, allowing for a more sensitive detection compared to traditional ELISAs.

**REFERENCES AND NOTES**

9. 21487888
13. A. Novelli (Bambino Gesù Hospital, Italy) for his collaboration. We thank the following individuals and institutions for technical and other assistance: M. M. A. Ata and F. Al Ali for their contribution to VirScan experiments; S. Elledge (Brigham and Women’s Hospital and Harvard Medical School, Boston, MA) for performing the experiments described in this study; and are not to be construed as reflecting the views of the physician. Funding: The National Human Genome Research Institute (NHGRI) Bambino Gesù Biobank (http://nhgri.nih.gov) and the Office of Cyber Infrastructure and Computational Biology (OCICB) High Performance Computing (HPC) cluster at the National Institute of Advancing Translational Sciences (NCATS), the 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) (UM1HG006505 and U24HG008956), the French National Research Agency (ANR) under the “Investments for the Future” program (ANR-10-IAIH-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IEBID), and the French Foundation for
The authors declare no competing financial interests. J.-L.C. is listed as an inventor on an application US20210155155 filed by The Rockefeller University that encompasses aspects of this publication. R.L. is a non-executive director of Roche and its subsidiary Genentech. Data and materials availability: Plasma, cells, and genomic DNA are available from J.-L.C. or D.V.D. under a material transfer agreement with The Rockefeller University. The whole-genome sequencing datasets described in this manuscript are available at Dryad (44). The whole-genome sequencing datasets used for the analyses, including critical patients and symptomatic controls described in this manuscript, were deposited in dbGaP under accession number phs002245.v1. All other data are available in the manuscript or the supplementary material. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

COVID-19 Clinicians

Children’s Research Institute, Victoria, Australia. 26University of São Paulo, São Paulo, Brazil. 27Washington University School of Medicine, St. Louis, MO, USA. 28The Americas Genome Center: Uniformed Services University of the Health Sciences, Bethesda, MD, USA. 29Centre for Bioinformatics and System Biology, Department of Life Sciences, Imperial College London, South Kensington Campus, London, UK. 30University of California, San Francisco, CA, USA; Chan Zuckerberg Biohub, San Francisco, CA, USA. 31Bai Jeral Wada Hospital for Children, Mumbai, India. 32School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. 33Instituto Nacional de Pediatría (National Institute of Pediatrics), Mexico City, Mexico. 34Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland. 35Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Canarian Health System, Santa Cruz de Tenerife, Spain. 36University of Antioquia, Medellin, Colombia. 37Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA. 38Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPIG), Pid Research Lab, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Edegem, Belgium. 39The Genetics Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. 40Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, UAE. 41Institute for Systems Biology, Seattle, WA, USA. 42Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 43Anschutz Medical Campus, Aurora, CO, USA. 44Kaken, Tokyo, Japan. 45Hellenic Pasteur Institute, Athens, Greece. 46University of Tartu, Tartu, Estonia. 47Chang Gung University, Taoyuan County, Taiwan. 48The University of Hong Kong, Hong Kong, China. 49Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. 50Yale School of Medicine, New Haven, CT, USA. 51New York University, New York, NY, USA. 52Shahid Beheshti University of Medical Sciences, Tehran, Iran. 53Semmelweis University Budapest, Budapest, Hungary. 54#KU Leuven, Department of Immunology, Microbiology and Transplantation, Leuven, Belgium. 55Columbia University Medical Center, New York, NY, USA. 56University Clinic for Children’s Diseases, Skopje, North Macedonia. 57Aarhus University, Aarhus, Denmark. 58Tokyo Medical & Dental University Hospital, Tokyo, Japan. 59Singapore Immunology Network, Singapore. 60National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. 61Bambino Gesù Children’s Hospital, Rome, Italy. 62Department of Biomedicine and Prevention, University of Rome “Tor Vergata,” Rome, Italy. 63Trinity College, Dublin, Ireland. 64Hiroshima University, Hiroshima, Japan. 65Bilkent University, Ankara, Turkey. 66Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. 67IBB-CSIIC, IIBAPS, Barcelona, Spain. 68Facultades Pequeño Príncipe e Instituto de Pesquisa Pé Figueiro Príncipe, Curitiba, Brazil. 69Neurometabolic Diseases Laboratory, IDIBELL–Hospital Duran I Reynals; Catalan Institution for Research and Advanced Studies (ICREA); CIBERER U595, ISCIII Madrid Spain, Barcelona, Spain. 70Institut Pasteur (CNRS UMR2000) and Collège de France, Paris, France. 71Infectious Diseases Horizontal Technology Center and Singapore Immunology Network, Agency for Science Technology and Research (A*STAR), Singapore. 72#Medical Genetics, University of Siena, Siena, Italy; Genetics Medica, Azienda Ospedaliero-Universitaria Senese, Italy; GEN-COVID Multicenter Study. 73Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Canary Islands, Spain. 74Imperial College London, London, UK. 75Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA. 76#Seeded Pathobiology and Genetic Lab, Tehran, Iran. 77Uniformed Services University of the Health Sciences, Bethesda, MD, USA. 78Hospital Universitari Vall d’Hebron, Barcelona, Spain. 79Medical City Center Utrecht, Amsterdam, The Netherlands. 80#Garvan Institute of Medical Research, Sydney, Australia. 81The University of British Columbia, Vancouver, Canada. 82Holy Family Red Crescent Medical College, Centre for Precision Therapeutics, NeuroGen Children’s Healthcare, Genetics and Genomic Medicine Centre, NeuroGen Children’s Healthcare, Dhaka, Bangladesh. 83Mohammed Bin Rashid University of Medicine and Health Sciences, College of Medicine, Dubai, UAE; The Centre for Applied Genomics, Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada. 84#Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, The Netherlands. 85University of California, San Francisco, CA, USA. 86McGill University Health Centre, Montreal, Canada. 87Charité–Berlin University Hospital Center, Berlin, Germany. 88Molecular Biophysics Division, Faculty of Physics, A. Mickiewicz University, Uniwersytetu Poznanskiego 2, Poznań, Poland. 89Rockefeller University, Howard Hughes Medical Institute, Rockefeller Hospital, New York, NY, USA. 90*Leaders of the COVID Human Genetic Effort. NIAID-USUHS/TAGC COVID Immunity Group Huie Jing1,2, Wesley Tung1,2, Christopher R. Luthers1, Brady M. Bauman1, Samantha Shaffer2,4, Liuin Zheng3,4, Zinan Zhang4, Satoshi Kubo4,5, Samuel D. Chauvin4,6, Kazuyuki Meguro1,2, Elana Shaw1,4, Michael Lenardo7,4, Justin Lacks7, Eric Karlins8,9, Daniel M. Hupalo7,8, John Rosenberger7,9, Gauthaman Sukumar7,10, Matthew D. Wilkerson7,11, Xijun Zhang7,8,†Kerstin Gagel1,2, Mikael Fält9,12, Didier Domergues1,2, Jean-Jacques Guillet1,2, Christian Hasselblad1,2, Kevin Jernigan3,4, Colin Jackson4,3, Career Johnston1,2, Caroline Klareskog4,3, Tim Konigsrainer1,2, Michael Koralnik1,2, Douglas Kormann1,2, Henrik Kroger1,2, Marka Kupphoff1,2, Yannick Langrez1,2, Hannah Laurenson1,2, Mathias Levsen1,2, Franziska Litz1,2, Tarek Liu1,2, Zacharias Lindell-Eriksson1,2, Patricia Lindquist1,2, Trishout Liu1,2, Catherine Lord1,2, Michaela Löwitz1,2, Christian McDevitt4,3, Christopher McEwan6,1, Richard M. McFarland1,2,4, Yumi Meng2,4, Virginia Milling1,2, Karla Mistry1,2, Andrea Moebel1,2, Karsten Moosmann1,2, Thomas M. Myklebust1,2, Jurgen Nadel1,2, Sven Neumann1,2, John Newell1,2, Robert Neuhaus1,2, Flavia Noguera1,2, David Opriessnig4,3,1, Che-Kang Ou1,2, Mariko Oyamada1,2, Mark Ozturk1,2, Mathias Palm1,2, Michele Parente1,2, Robbert Ploeg1,2, Adam Pollack1,2, Daniel Posch1,2, Patricia Preiss1,2, Peter Przykucki1,2, Charles Quinn1,2,5,7,5,7, Rachel Ring1,2, Jennifer Rock1,2, Koichi Sakai1,2, Andrew Sambrook1,2, Jennifer Sambrook1,2, Christian Schuster1,2, Virgil Schuchardt1,2, Craig Schumacher1,2, Paul Seeburger1,2, Justin Seitz1,2, Jan Senkbeil1,2, Michael Shlomchik1,2, Bernhard Spaninger1,2, Vivian Sparwasser1,2, Claudia Steiner1,2, Karl Stiehm1,2, Emanuele Sturla1,2, Reinhard Stohr1,2, Andrew Stone1,2, Lisa Sunnarborg1,2, Jan Svendsen1,2, Joonho Chul Yoo1,2, Christopher Yoo1,2, Andreas Ziegler1,2, Tanja Zsigmond1,2, Dan Zschocke1,2, 1Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. 2NIAID Clinical Genomics Program, National Institutes of Health, Bethesda, MD, USA. 3Department of Pharmacology & Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. 4Laboratory of Immune System Biology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. 5NIAD Collaborative Bioinformatics Resource, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD, USA. 6Bioinformatics and Computational Biosciences Branch, Office of Cyber Infrastructure and Computational Biology, NIAID, NIH, Bethesda, MD, USA. 7The American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. SUPPLEMENTARY MATERIALS science.sciencemag.org/content/370/6515/eabd4570/suppl/DC1 Materials and Methods Figs. S1 to S31 Tables S1 and S2 References (42 and 43) MDAR Reproducibility Checklist View/request a protocol for this paper from Bio-protocol. 22 June 2020; accepted 16 September 2020 Published online 24 September 2020 10.1126/science.abd4570
Inborn errors of type I IFN immunity in patients with life-threatening COVID-19


Science 370 (6515), eabd4570.
DOI: 10.1126/science.abd4570originally published online September 24, 2020

The genetics underlying severe COVID-19

The immune system is complex and involves many genes, including those that encode cytokines known as interferons (IFNs). Individuals that lack specific IFNs can be more susceptible to infectious diseases. Furthermore, the autoantibody system dampens IFN response to prevent damage from pathogen-induced inflammation. Two studies now examine the likelihood that genetics affects the risk of severe coronavirus disease 2019 (COVID-19) through components of this system (see the Perspective by Beck and Aksentijevich). Q. Zhang et al. used a candidate gene approach and identified patients with severe COVID-19 who have mutations in genes involved in the regulation of type I and III IFN immunity. They found enrichment of these genes in patients and conclude that genetics may determine the clinical course of the infection. Bastard et al. identified individuals with high titers of neutralizing autoantibodies against type I IFN-α2 and IFN-α in about 10% of patients with severe COVID-19 pneumonia. These autoantibodies were not found in infected people who were asymptomatic or had milder phenotype or in healthy individuals. Together, these studies identify a means by which individuals at highest risk of life-threatening COVID-19 can be identified.

Science; this issue p. eabd4570, p. eabd4585; see also p. 404

Use of this article is subject to the Terms of Service

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title Science is a registered trademark of AAAS.

Copyright © 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works