Association of rare predicted loss-of-function variants of influenza-related type I IFN genes with critical COVID-19 pneumonia

Qian Zhang, … , Laurent Abel, Jean-Laurent Casanova

*J Clin Invest.* 2021. [https://doi.org/10.1172/JCI152474](https://doi.org/10.1172/JCI152474).

**Letter to the Editor**

Infectious disease

To the Editor: Povysil G. et al. report that “rare loss-of-function (LOF) variants in type I interferon (IFN) immunity genes are not associated with severe COVID-19” (1). We disagree with the authors’ interpretation of our data and their own (2), for six reasons: 1) Only predicted LOF (pLOF) variants are relevant for comparison between the two studies, because, unlike us, these authors did not test variants experimentally. The relevant proportion in our data is therefore not 24/659=3.5%, but 9/659=1.36%, whereas theirs is 1/713=0.14%. 2) Our definitions of ‘severe/critical’ patients are different: we defined critical disease as severity grades 6-10 of the WHO scale (3), whereas they restricted their recruitment to grades 7-10 (i.e., excluding patients on high-flow oxygen, considered in our study). Their cohort of ‘mild’ cases may therefore include ‘severe’ COVID-19 cases (grade 6), such as perhaps their ‘mild’ TLR3 pLOF carrier. 3) Their ‘controls’ are subjects from the general population, without depletion of COVID-19 genetic risk factors, whereas we used pauci-/asymptomatic infected subjects (grades 1-3) as ‘controls’. Consequently their power computation in Figure 1 is based on an incorrect hypothesis about the odds ratio, which would be expected to be lower when using general population controls (as they did), than when using pauci- and asymptomatic infected individuals (as we did). 4) The ethnic origin of the patients […]

Find the latest version:

[https://jci.me/152474/pdf](https://jci.me/152474/pdf)
Association of rare predicted loss-of-function variants of influenza-related type I IFN genes with critical COVID-19 pneumonia

To the Editor: Povysil G. et al. report that “rare loss-of-function (LOF) variants in type I interferon (IFN) immunity genes are not associated with severe COVID-19” (1). We disagree with the authors’ interpretation of our data and their own (2), for six reasons:

1) Only predicted LOF (pLOF) variants are relevant for comparison between the two studies, because, unlike us, these authors did not test variants experimentally. The relevant proportion in our data is therefore not 24/659=3.5%, but 9/659= 1.36%, whereas theirs is 1/713=0.14%.

2) Our definitions of ‘severe/critical’ patients are different: we defined critical disease as severity grades 6-10 of the WHO scale (3), whereas they restricted their recruitment to grades 7-10 (i.e., excluding patients on high-flow oxygen, considered in our study). Their cohort of ‘mild’ cases may therefore include ‘severe’ COVID-19 cases (grade 6), such as perhaps their ‘mild’ TLR3 pLOF carrier.

3) Their ‘controls’ are subjects from the general population, without depletion of COVID-19 genetic risk factors, whereas we used pauci-/asymptomatic infected subjects (grades 1-3) as ‘controls’. Consequently their power computation in Figure 1 is based on an incorrect hypothesis about the odds ratio, which would be expected to be lower when using general population controls (as they did), than when using pauci- and asymptomatic infected individuals (as we did).

4) The ethnic origin of the patients differs between the two studies: 58% of our 659 patients (and 8 of our 9 pLOF carriers) were European, versus only 10% of their 713 patients with severe disease (and their pLOF carrier is East Asian).

5) Age is a key factor neglected in their comparison: our sample was much younger (mean age: 51.8 years) than theirs (mean: 65.9 years), and seven of our nine pLOF carriers were < 60 years old. We performed a comparison stratified by age (<60/≥60 years), and no significant difference in pLOF proportion was found between the two studies, even ignoring the only patient carrying a pLOF they found (of
unknown age): 7/458 in our sample vs. 0/192 in their sample ($p=0.11$, Fisher’s exact test) for patients <60 years old, and 2/201 vs. 0/521 ($p=0.07$) for patients ≥60 years old. 6) Finally, and crucially, the authors did not exclude patients with autoantibodies against type I IFN, which account for at least 10% of critical cases and are much more frequent in patients > 60 years of age, particularly men (4).

Reference:


Qian Zhang¹,

Aurélie Cobat¹,²,³,

Paul Bastard²,³,

Luigi D. Notarangelo⁴,⁵,

Helen C. Su⁴,⁵,

Laurent Abel¹,²,³,

Jean-Laurent Casanova¹,²,³,⁶,⁷,@@,

on behalf of COVID Human Genetic Effort (CHGE)*
1. St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA.

2. Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France.


4. Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA.

5. NIAID Clinical Genomics Program, NIH, Bethesda, MD, USA.

6. Howard Hughes Medical Institute, New York, NY, USA.


Correspondence:
Jean-Laurent Casanova
The Rockefeller University
1230 York Avenue, New York, NY 10065, USA
Voice 1 212 327 7331
Fax 1 212 327 7330
casanova@rockefeller.edu

Conflict of interest:
The authors have declared that no conflict of interest exists.

*COVID Human Genetic Effort (CHGE)


1Al Jalila Genomics Center, Al Jalila Children’s Hospital, Dubai, UAE; Genetics Department, Center for Genomic Discovery, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE. 2San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, and Vita Salute San Raffaele University, Milan, Italy. 3Immunology Research Laboratory, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. 4Dasman Diabetes Institute, Department of Genetics and Bioinformatics, Dasman, Kuwait. 5Diabetes Center, University of California San Francisco, San Francisco, CA, USA. 6Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. 7Universidad de Antioquia, Group of Primary Immunodeficiencies, Antioquia, Colombia. 8Pediatric Dermatology, University of Wisconsin School of Medicine, Madison, WI, USA. 9St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. 10The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. 11Pediatric Nephrology, Rheumatology, Dermatology, HFME, Hospices Civils de Lyon, National Referee Centre RAISE, and INSERM U1111, Université de Lyon, Lyon, France. 12St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France; University of Paris, Imagine Institute, Paris, France. 13Department of Pediatrics, British Columbia Children’s Hospital, The University of British Columbia, Vancouver, BC, Canada. 14Icahn School of Medicine at Mount Sinai, New York, NY, USA. 15St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France; University of Paris, Imagine Institute, Paris, France. 16Helix, San Mateo, CA, USA. 17Shupyk National Medical Academy for Postgraduate Education, Kiev, Ukraine. 18Clinical Immunology Unit, Department of Pediatric Infectious Disease, CHU Ibn Rushd and LICA, Laboratoire d'Immunologie Clinique, Inflammation et Allergie, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco. 19SciLifeLab, Department Of Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden. 20Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics and the Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA, USA. 21Medical Genetics, IRCCS Ospedale San Raffaele, Milan, Italy. 22Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Victoria, Australia. 23St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Turnstone Biologics, New York, NY, USA. 24Hospital Universitari Vall d'Hebron (HUVH); Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain 25Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil. 26Dume Institute and Cliniques Universitaires Saint Luc, Université catholique de Louvain, Brussels, Belgium. 27Washington University School of Medicine, St. Louis, MO, USA. 28Department of Anatomy, Physiology & Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. 29School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. 30Instituto Nacional de Pediatría (National
Institute of Pediatrics), Mexico City, Mexico.  
31School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.  
32Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristóbal de La Laguna, Spain; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.  
33Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA.  
34Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPIG), PID Research Laboratory, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Edegem, Belgium.  
35The Genetics Institute Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.  
36Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates.  
37Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden.  
38Institute for Systems Biology, Seattle, WA, USA.  
39Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; Division of Allergy and Immunology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA.  
40Department of Pediatrics, Section of Allergy and Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA; Department of Immunology and Microbiology, University of Colorado School of Medicine, Aurora, CO, USA.  
41Department of Medicine, Haukeland University Hospital, Bergen, Norway.  
42Department of Community Pediatrics, Perinatal and Maternal Medicine, Tokyo Medical and Dental University (TMDU)  
43Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.  
44Laboratory of Neurogenetics of Language and Howard Hughes Medical Institute, The Rockefeller University, New York, NY, USA.  
45St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France; University of Paris, Imagine Institute, Paris, France.  
46Bioinformatics and Applied Genomics Unit, Department of Microbiology, Hellenic Pasteur Institute, Athens, Greece.  
47Molecular Pathology, Department of Biomedicine, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu Estonia.  
48Chang Gung University, Taoyuan County, Taiwan.  
49Department of Paediatrics & Adolescent Medicine, The University of Hong Kong, Hong Kong, China.  
50Shanghai Public Health Clinical Center, Fudan University, Shanghai, China.  
51Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA.  
52Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, The Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshviri Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.  
53Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium; Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium.  
54University Clinic for Children's Diseases, Department of Pediatric Immunology, Medical Faculty, University “St.Cyril and Methodij” Skopje, North Macedonia.  
55Department of Biomedicine and Department of Infectious Diseases, Aarhus University, Aarhus, Denmark.  
56Tokyo Medical & Dental University Hospital, Tokyo, Japan.  
57A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore; Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore.  
58Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy.  
59Laboratory of Medical Genetics, IRCCS Bambino Gesù Children’s Hospital, Rome, Italy.  
60Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.  
61Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan.  
62Department of Molecular Biology and Genetics, Bilkent University, Bilkent - Ankara, Turkey.  
63Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden.  
64Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain.  
65Institut de Biomedicina de València-CSIC, CIBERNED, Unitat Mixta
de Neurologia i Genètica, IIS La Fe, Vallencia, Spain. 66 IIBB-CSIC, IDIBAPS, Barcelona, Spain.
67 Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. 68 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France; University of Paris, Imagine Institute, Paris, France. 69 Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospital de Llobregat, Barcelona, Spain; Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain; Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Barcelona, Spain. 70 Human Evolutionary Genetics Unit, CNRS U2000, Institut Pasteur, Paris, France; Human Genomics and Evolution, Collège de France, Paris, France. 71 A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore; Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore. 72 University Hospital St. Marina, Varna, Bulgaria.
73 Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canary Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. 74 Department of Paediatric Infectious Diseases and Virology, Imperial College London, London, UK; Centre for Paediatrics and Child Health, Faculty of Medicine, Imperial College London, London, UK. 75 Department of Immunology, Second Faculty of Medicine Charles University, V Úvalu, University Hospital in Motol, Prague, Czech Republic. 76 Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Rare Diseases Center and Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. 77 Saeed Pathobiology and Genetics Lab, Tehran, Iran; Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. 78 Department of Immunology, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia. 79 Central European Institute of Technology & Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czech Republic. 80 Department of Pharmacology & Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. 81 Pediatric Infectious Diseases and Immunodeficiencies Unit, Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain. 82 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; University Medical Center Utrecht, Utrecht, The Netherlands. 83 Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria. 84 Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; St Vincent’s Clinical School, Faculty of Medicine, UNSW Sydney, NSW, Australia. 85 Department of Pediatrics, British Columbia Children’s Hospital, The University of British Columbia, Vancouver, BC, Canada. 86 Centre for Precision Therapeutics, Genetic and Genomic Medicine Centre, NeurIGen Children Healthcare, Dhaka, Bangladesh. 87 Mohammed Bin Rashid University of Medicine and Health Sciences, College of Medicine, Dubai, United Arab Emirates; The Centre for Applied Genomics, Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada. 88 Department of Neurology, Amsterdam Neuroscience, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands. 89 Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, Québec, Canada; Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, Québec, Canada. 90 Department of Pediatric Pneumology, Immunology and Intensive Care, Charité Universitätsmedizin, Berlin University Hospital Center, Berlin, Germany; Labor Berlin GmbH, Department of Immunology, Berlin, Germany; Berlin Institutes of Health (BIH), Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany. 91 Biosciences Institute, University of São Paulo, São Paulo, Brazil. 92 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France; University of Paris, Imagine Institute, Paris, France.