Severe COVID-19 in the young and healthy: monogenic inborn errors of immunity?

Shen-Ying Zhang[1,2,3]✉, *Qian Zhang*[1,2,3]✉, *Jean-Laurent Casanova*[1,2,3,4,5]✉, *Helen C. Su*[6] *and The COVID Team**

Severe COVID-19 is rare in previously healthy individuals who are less than 50 years of age, affecting probably no more than 1 in 1,000 such infected individuals. We suggest that these patients may become critically ill because of monogenic inborn errors that disrupt protective immunity to SARS-CoV-2.

A key scientific issue for researchers studying infectious diseases is the immense clinical variability that occurs among infected individuals[1]. Similar to other human-tropic viral infections, clinical severity following infections with SARS-CoV-2 extends from asymptomatic to life-threatening, and there are various clinical forms of COVID-19. The data emerging from different countries suggest a global case fatality rate of ~6% in virus PCR-confirmed cases of all ages, ranging from <0.01% for children aged 0–9 years to >20% for those aged over 80 years. However, recent serological data suggest that the infection fatality rate may be at least an order of magnitude lower globally. There is compelling evidence for a much higher proportion of casualties in those aged over 50 years and in those with underlying health conditions. However, a small number (~5% of all severe cases) of previously healthy adults under the age of 50 years present with severe COVID-19, including severe pneumonia and, more rarely, encephalitis, cardiovascular disease and other presentations, including the recently reported Kawasaki-like disease (also known as paediatric inflammatory multisystem syndrome or multisystem inflammatory syndrome in children). Why do these younger, healthier patients get severe COVID-19?

Four hypotheses could account for such severe 'idiopathic' cases[1]. First, these patients may be infected with larger amounts of virus or a more virulent SARS-CoV-2 strain. Higher virulence is unlikely, because it would lead to clusters among close contacts, through direct contagion, and there is little evidence for such clusters. A higher initial viral load appears more likely, and this hypothesis is supported by more than a century of experimental inoculations of animals with various viruses. Higher inoculum levels are generally associated with more severe disease. However, it remains unknown whether the most heavily exposed humans (spouses of severe cases or health-care workers treating patients with COVID-19, particularly those with insufficient protection) account for a large proportion of severe idiopathic cases. These people clearly have a much higher risk of infection, and probably of disease, but may not be at higher risk of severe disease if they are young and healthy.

Second, particular environmental conditions, such as the presence or absence of an element in the air inhaled by the patient, may aggravate the infection. The finger has recently been pointed at global pollution, but clinical heterogeneity exists in both polluted and unpolluted areas. Season or climate may also affect the infection process and immunity. Nevertheless, environmental differences may account for epidemic differences between the northern and southern hemispheres, for example, between Ecuador and Iceland, but are less likely to account for differences within single countries or over smaller scales (for example, within the confines of a single city, cruise ship or household).

Third, an inevitable 'somatic transformation' of cells occurs in individual human hosts. Such genetic and epigenetic processes are responsible, for example, for the steady increase in the incidence of shingles after the age of 50 years. Acquired covert illnesses may weaken some individuals prematurely, or the absence of an acquired, protective process may be detrimental. Pulmonary cells and leukocytes may be affected in different ways. An agnostic attitude is therefore essential. Prior infectious history may also be a somatic determinant of disease severity, through the accumulation of immunological memory via the T and B lymphocytes governing adaptive immunity. For example, previous infection with another coronavirus, such as epidemic SARS-CoV or endemic HCoV-229E, might be protective. Alternatively, previous infections with related viruses may be deleterious, as reported for dengue, which is typically silent during the first infection and severe during subsequent infections with different serotypes, owing to antibody-dependent enhancement[2]. Detailed serological studies are required to investigate this aspect of COVID-19.

[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, Necker Hospital for Sick Children, Paris, France.*

[3]*University of Paris, Imagine Institute, Paris, France.*

[4]*Howard Hughes Medical Institute, New York, NY, USA.*

[5]*Pediatric Hematology and Immunology Unit, Necker Hospital for Sick Children, AP-HP, Paris, France.*

[6]*Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.*

**A list of authors and their affiliations appears online.*

✉*e-mail: shzh289@rockefeller.edu; qzhang02@rockefeller.edu; casanova@rockefeller.edu*

https://doi.org/10.1038/s41577-020-0373-7

Finally, severe COVID-19 in previously healthy children and adults may result from monogenic predisposition. This hypothesis is supported by the rarity of severe cases among such individuals during primary infection with SARS-CoV-2. Studies since 1996 have identified a number of monogenic inborn errors of immunity (IEIs) underlying life-threatening infectious diseases, including specific viral diseases, in previously healthy patients[1,3–6]. Two of these IEIs are classic Mendelian disorders (monogenic with complete penetrance) underlying viral illnesses, including familial disease. In autosomal recessive epidermodysplasia verruciformis, mutations in *TMC6*, *TMC8* or *CIB1* result in high susceptibility to skin-tropic beta human papillomaviruses (HPVs). Meanwhile, increased susceptibility to Epstein–Barr virus is seen in patients with X-linked lymphoproliferative syndrome (caused by mutations in the X chromosome genes *SH2D1A* and *XIAP*) and in patients with biallelic mutations in *CD27*, *CD70*, *ITK* or *MAGT1*.

Moreover, since 2007, other monogenic IEIs have been shown to underlie sporadic (as opposed to familial) viral diseases, with incomplete penetrance (that is, non-Mendelian). The first example is herpes simplex virus 1 (HSV-1) encephalitis, attributable in about 5–10% of cases to mutations affecting the TLR3 or snoRNA31 pathways (forebrain infection) or DBR1 (brainstem infection). Another example is influenza A virus (IAV) pneumonia caused by mutations in *TLR3*, *IRF7* or *IRF9* that impair interferon immunity. Other IEIs underlying severe viral diseases, with incomplete or unknown penetrance, have since been reported[1,7,8]. The discoveries of these IEIs demonstrated that severe disease due to primary infection with a common virus that is benign in the general population can result from a monogenic 'hole' in human immunity.

In patients with these monogenic IEIs, disease immunopathogenesis can involve an impairment of immune mechanisms specific to the virus (for example, *CIB1* mutations affect control of HPV in keratinocytes) or specific to the tissue site (for example, *DBR1* mutations affect immunity to various viruses in the brainstem). Molecularly, these disorders disrupt antiviral immunity through known (for instance, type I and type III interferon pathways[9] in IAV or human rhinovirus pneumonia) or unknown (for example, snoRNA31 deficiency in HSV-1 encephalitis) mechanisms. They may result in an insufficient immune response (for example, patients with IFNAR1 deficiency can develop severe adverse reactions to live attenuated vaccines) or an excessive immune response (for example, patients with IL-18BP deficiency develop excessive inflammation and fulminant viral hepatitis). At the cellular level, IEIs can affect leukocytes or other tissue-resident cells (for example, IEIs in pulmonary epithelial cells affect the control of IAV in the lung). Studies of inborn errors of non-haematopoietic cell-intrinsic immunity have suggested that keratinocytes, pulmonary epithelial cells and cortical neurons are essential for tissue-specific protective immunity to various viruses, scaling immunity to infections up from the immune system to the whole organism[3].

These different immunological scenarios may also underlie severe COVID-19 in patients with monogenic disorders. Pneumonia, encephalitis and Kawasaki-like disease may be caused by different types of disorders. The search for monogenic IEIs conferring predisposition to severe COVID-19 in previously healthy children and young or even middle-aged adults should therefore involve the genome-wide, agnostic testing of genetic hypotheses (see also COVID Human Genetic Effort)[10]. There may be autosomal and X-linked disorders, and recessive, dominant or co-dominant traits. Genetic variants may be loss of function or gain of function. There may be both genetic and physiological homogeneity and heterogeneity. Clinical penetrance may be complete or incomplete, and incomplete penetrance may suggest digenic or even oligogenic disorders. The discovery of monogenic IEIs to SARS-CoV-2 should help unravel the mechanistic basis of the immunopathogenesis of severe COVID-19 in young, previously healthy individuals. Monogenic disorders can provide a basis for genetic diagnosis and counselling, while paving the way for preventive and therapeutic interventions. They also provide mechanistic hypotheses that can be tested in other patients who are critically ill who are older or have comorbidities.

1. Casanova, J.-L. & Abel, L. The human genetic determinism of life-threatening infectious diseases: genetic heterogeneity and physiological homogeneity? *Hum. Genet.* **139**, 681–694 (2020).
2. Wang, T. T. et al. IgG antibodies to dengue enhanced for FcγRIIIA binding determine disease severity. *Science* **355**, 395–398 (2017).
3. Zhang, S.-Y. et al. Human inborn errors of immunity to infection affecting cells other than leukocytes: from the immune system to the whole organism. *Curr. Opin. Immunol.* **59**, 88–100 (2019).
4. Zhang, Y., Su, H. C. & Lenardo, M. J. Genomics is rapidly advancing precision medicine for immunological disorders. *Nat. Immunol.* **16**, 1001–1004 (2015).
5. Bousfiha, A. et al. Human inborn errors of immunity: 2019 update of the IUIS Phenotypical Classification. *J. Clin. Immunol.* **40**, 66–81 (2020).
6. Tangye, S. G. et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. *J. Clin. Immunol.* **40**, 24–64 (2020).
7. Jing, H. & Su, H. C. New immunodeficiency syndromes that help us understand the IFN-mediated antiviral immune response. *Curr. Opin. Pediatr.* **31**, 815–820 (2019).
8. Jouanguy, E. et al. Human inborn errors of immunity to herpes viruses. *Curr. Opin. Immunol.* **62**, 106–122 (2020).
9. Lazear, H. M., Schoggins, J. W. & Diamond, M. S. Shared and distinct functions of type I and type III interferons. *Immunity* **50**, 907–923 (2019).
10. Casanova, J.-L., Su, H. C. & COVID Human Genetic Effort. A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection. *Cell* **181**, 1194–1199 (2020).

Acknowledgements
S.-Y.Z., Q.Z. & J.-L.C. are supported by funding from the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (UL1TR001866 and R01AI088364), the French National Research Agency (ANR; ANR-10-IAHU-01, ANR-10-LABX-62-IBEID and the ANR COVID project), the French Foundation for Medical Research (FRM; EQU201903007798 and the FRM COVID project), the Square Foundation, the Institut National de la Santé et de la Recherche Médicale (INSERM) and the University of Paris. H.C.S is supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases at the NIH.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

RELATED LINKS
COVID Human Genetic Effort: https://www.covidhge.com