Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Trends in Genetics

CellPress

Forum

Host genetic variability and determinants of severe COVID-19

Patrick Brest [1,*], Baharia Mograbi [1], Jocelyn Gal [2], Paul Hofman [1,3] and Gerard Milano [4,*]

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, convergent studies have provided evidence that host genetic background may contribute to the development of severe coronavirus disease (COVID-19). Here, we summarize how some genetic variations, such as in SARS-CoV-2 receptor angiotensin-converting enzyme 2 or interferon signaling pathway, may help to understand why some individuals can develop severe COVID-19.

Introduction

Despite the widely acknowledged success of the coronavirus disease (COVID-19) mass vaccination campaigns, there are still many areas of concern, such as the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, the presence of long COVID-19 symptoms, and the unpredictable occurrence of severe COVID-19. It is well known that the more or less pronounced variability of reactions between subjects in response to foreign pathological viral infection may be related to germinal genetics [1] or epigenetics (Box 1) [2]. In the context of COVID-19, we previously formulated the hypothesis of a genetic influence on the occurrence of COVID-19, focusing on gene polymorphisms that modulate the expression of **angiotensin-converting enzyme 2** (**ACE2**; see Glossary) proteins, the cellular target of the virus, as well as the expression of the proteases that control its cellular shedding or, conversely, its internalization [3]. Since then, these initial hypotheses suggesting a role of genetics in individual susceptibility to SARS-CoV-2 have been confirmed at the clinical level in patients affected by COVID-19 through correlation studies. In addition, other sources of host genetic variability related to COVID-19 have also been identified. This forum summarizes this update information to more accurately characterize the profile of individuals at risk of developing severe COVID-19. Two approaches are generally used to determine the relationship between gene polymorphisms and their effects in subgroups of subjects. These approaches are genome-wide association studies (**GWASs**) and candidate gene studies.

Main contributions from GWASs

The COVID-19 Host Genetic Initiative (**COVID-19 HGI**)[i] contributes to the collection of data and relevant publications in the context of GWASs applied to COVID-19. Three combined GWASs were reported in this context, including 49 562 patients with COVID-19 from 19 countries [4]. The authors identified a total of 13 significant loci associated with SARS-CoV-2 infections. In particular, an important genetic signal for COVID-19 severity was found at the 3p21.31 locus. Several loci were found to overlap with previously reported links to lung-related phenotypes or autoimmune and inflammatory diseases. Collectively, these observations underscore the importance of lung-related biological pathways in the development of severe COVID-19. Furthermore, another publication from the COVID-19 HGI identified four genetic variants with a possible link to severe SARS-CoV-2 infections [5]. These variants relate to MHC, IFNAR2 (interferon alpha and beta receptor subunit 2), LZTFL1 (leucine zipper transcription factor–like 1, an airway cilia regulator), and DPP9 (dipeptidyl peptidase 9, an enzyme involved in lung disease). This list of genes is noteworthy in the context of severe COVID-19 because it implicates both the specifically implicated organ (respiratory tract) and the key antiviral defense [interferon (IFN) signaling]. D'Antonio and coworkers independently confirmed the results of the COVID-19 HGI study [6]. Interestingly, they found that the severity of COVID-19 was associated with variants affecting gene expression in various tissues, including lung, heart, cerebral cortex, and digestive tract.

In the COVID-19 HGI study, COVID-19 severity was specifically examined in 7491 critically ill patients compared with 48 400 control subjects using whole-genome sequencing [7]. This study identified 16 novel independent associations, including genes involved in IFN signaling, IL10RB (interleukin 10 receptor subunit beta), and PLSCR1 (phospholipid scramblase 1), as well as genes related to BCL11A (BAF chromatin remodeling complex subunit, leukocyte differentiation) and FUT2 (fucosyltransferase 2, blood group antigen secretor factor). The authors

Glossary

Angiotensin-converting enzyme 2 (ACE2): this gene belongs to the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases. This secreted protein catalyzes the cleavage of angiotensin I into angiotensin 1-9 and angiotensin II into the vasodilator angiotensin 1-7. In addition, the encoded protein is a functional receptor for the spike glycoprotein of human coronaviruses such as HCoV-NL63, SARS-CoV, and SARS-CoV-2.

COVID-19 HGI: the COVID-19 Host Genetics Initiative is a global initiative to elucidate the role of host genetic factors in the susceptibility and severity of the SARS-CoV-2 virus pandemic.

GWAS: a genome-wide association study (GWA study or GWAS), also known as whole-genome association study (WGA study or WGAS), is an observational study of a genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait or a disease. These studies examine hundreds of thousands of sequenced DNA profiles to detect genetic differences between the presence or not of a particular disease or trait.

SNPs: abbreviation for single-nucleotide polymorphisms.

Box 1. Epigenetic factors and COVID-19 severity

Epigenetics concerns heritable changes in gene function that do not require alteration of the DNA sequence and that are important for the maintenance of tissue homeostasis. Numerous human diseases involve DNA methylation, the most intensively researched epigenetic mark. In particular, these changes in DNA methylation are known to control the activity of DNA and RNA viruses such as human papillomavirus, hepatitis B virus, Epstein-Barr virus, Kaposi sarcoma, and HIV. In addition to the GWASs discussed in this forum, a number of studies have examined the impact of methylation on the severity of COVID-19 and have shown how epigenetic mechanisms also influence COVID-19 outcomes by controlling IFN signaling, ACE2, and immunity-related genes, particularly those that resist inactivation of the X chromosome. These putative biomarkers could be useful in the clinical stratification and management of COVID-19 severe symptoms when combined with other clinical, biological, and genetic factors [2].

suggested that their findings are consistent with a multicomponent model of COVID-19 pathophysiology that includes two major mechanisms predisposing to life-threatening disease: the lack of innate control of viral replication and a higher vulnerability to pulmonary infections and intravascular coagulation.

An update of the COVID-19 HGI based on a meta-analysis of up to 125 584 cases and 2.5 million control subjects (60 studies, 25 countries) identified *MUC5B* (mucin 5B, oligomeric mucus/gel-forming, components of mucus secretions), *SFTPD* (surfactant protein D, contributes to the lung's defense against inhaled microorganisms, organic antigens, and toxins), and *SLC22A31* (solute carrier family 22 member 31, involved in ion transport and transmembrane transport), which are three interesting new loci associated with COVID-19 severity [8]. This observation underlines the link between disease seriousness and lung function and diseases.

Candidate gene studies

Candidate gene studies have their roots at the protein level when the involved genes are known to be critical in the disease or trait development. The goal here was to identify genetic polymorphisms that potentially affect the expression level or functionality of a given protein and to compare the allelic profile between individuals who do or do not exhibit a severe form of COVID-19. As an overall picture, two distinct and complementary areas can be distinguished from studies on candidate genes in the context of COVID-19 severity. They concern ACE2, the cellular receptor of the virus, and the host antiviral IFN-related pathway.

The ACE2 rs2074192 T allele and, in particular, the rs2285666 G allele have recently been associated with more severe forms of COVID-19 in several studies [9,10]. The ACE2 rs2285666 A allele is associated with higher circulating ACE2 levels [11]; thus, conversely, lower ACE2 levels associated with the G allele would result in less protection by the SARS-CoV-2–ACE2 complex at the extracellular level.

Besides, the IFN signaling was found to be severely compromised in patients with severe COVID-19. Individuals carrying the IFN-induced transmembrane protein 3 (IFITM3) rs12252C had a higher risk of developing a severe form of COVID-19. Interestingly, this affected gene is an IFN-induced membrane protein [12]. On a more global level, Zhang and coworkers reported the molecular and cellular determinants of critical COVID-19 pneumonia [13]. The highest risk estimates were associated with the genetic loss of function of TLR3 and TLR7 signaling, two innate immune receptors controlled by IFN type 1 that ensure virus clearance.

Concluding remarks

The notion of various gene variants possibly associated with COVID-19 is now broadly accepted. Using a synthetic approach that combines data from GWASs and candidate gene studies, a common denominator for predisposition to severe COVID-19 is emerging. It appears that gene variants related to the IFN signaling pathway, including membrane proteins such as IFITM3 and enzymes involved in IFN signaling TYK2, play a significant, important role in predisposition to severe COVID-19. In tandem, candidate gene studies increasingly indicate that ACE2 **SNPs** may be related to severe COVID-19, extending previous *in silico*–based predictions [3]. It is now well established that affinity modifications between ACE2 and SARS-CoV-2 variants, such as omicron, play a central role in evasion. This knowledge emphasizes the critical role played by the ACE2 structural entity and underlines the consequences of its gene variations in the host reactivity against the SARS-CoV-2 attack.

The multitude of SNPs related to the severity of COVID-19 opens new promising perspectives for developing models incorporating clinical factors, as recently proposed by Dite and coworkers [14]. It is advisable that such models be validated prospectively in independent cohorts. The cumulative evidence of genetic predisposition to severe COVID-19 also points to an urgent need to elucidate the functional impact of gene polymorphisms through the use of genome editing in appropriate models (Figure 1) [15].

It should be kept in mind that COVID-19 severity may change along with virus evolution. This implicates that genetic findings from the early pandemic might not be strictly applicable to the new variants. It remains true that increased knowledge of genetic predisposition to severe COVID-19 will contribute to a better definition of at-risk populations.

Acknowledgments

Funding is acknowledged from the French government (Agence Nationale de Recherche, ANR) through the 'Investments for the Future' LABEX SIGNALIFE (ANR-11-

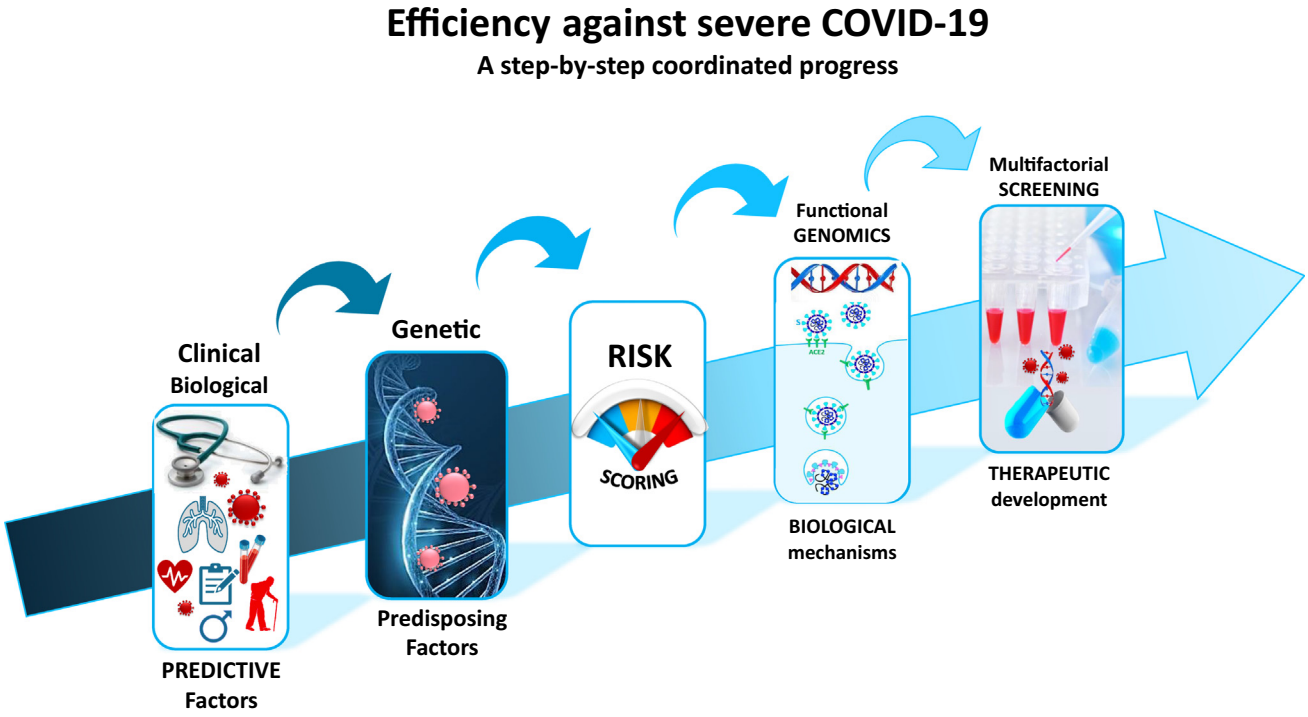

Figure 1. Severe coronavirus disease (COVID-19): Step-by-step coordinated progress. Several steps may contribute to improved detection and tackling of severe COVID-19. Since the pandemic outbreak, several complementary studies have contributed to a better understanding of the disease and, more recently, the possibility to characterize at-risk populations, with the likely emergence of personalized therapies.

LABX-0028-01 and IDEX UCAJedi ANR-15-IDEX-01) and [AD-ME project R19162DD]; CANC'AIR Genexposomic project, Cancéropole PACA; DREAL PACA, ARS PACA, Région Sud, INSERM cancer; INCA Plan Cancer; Children Medical Safety Research Institute (CMSRI, Vaccinophagy project R17033DJA).

Declaration of interests

The authors declare no competing interests.

Resources

[i]www.covid19hg.org

[1]Université Côte d'Azur, Institute of Research on Cancer and Aging in Nice (IRCAN), Centre Antoine Lacassagne, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Fédération Hospitalo-Universitaire (FHU) OncoAge, F-06189 Nice, France
[2]University Côte d'Azur, Centre Antoine Lacassagne, Epidemiology and Biostatistics Department, 33 avenue de Valombrose, F-06189 Nice, France
[3]Université Côte d'Azur, Centre Hospitalier Universitaire (CHU) de Nice, Laboratory of Clinical and Experimental Pathology, FHUOncoAge, Hospital-Integrated Biobank (BB-0033-00025), F-06001 Nice, France
[4]Centre Antoine Lacassagne, Service de Valorisation Scientifique, F-06100 Nice, France

*Correspondence:
patrick.brest@univ-cotedazur.fr (P. Brest) and
gerard.milano@nice.unicancer.fr (G. Milano).

https://doi.org/10.1016/j.tig.2022.10.003

References

1. Ferris, M.T. and Heise, M.T. (2014) Quantitative genetics in the study of virus-induced disease. *Adv. Virus Res.* 88, 193–225
2. Kgatle, M.M. *et al.* (2021) COVID-19 Is a multi-organ aggressor: Epigenetic and clinical marks. *Front. Immunol.* 12, 752380
3. Brest, P. *et al.* (2020) Host polymorphisms may impact SARS-CoV-2 infectivity. *Trends Genet.* 36, 813–815
4. COVID-19 Host Genetics Initiative (2021) Mapping the human genetic architecture of COVID-19. *Nature* 600, 472–477
5. Horowitz, J.E. *et al.* (2022) Genome-wide analysis provides genetic evidence that ACE2 influences COVID-19 risk and yields risk scores associated with severe disease. *Nat. Genet.* 54, 382–392
6. D'Antonio, M. *et al.* (2021) SARS-CoV-2 susceptibility and COVID-19 disease severity are associated with genetic variants affecting gene expression in a variety of tissues. *Cell Rep.* 37, 110020
7. Kousathanas, A. *et al.* (2022) Whole-genome sequencing reveals host factors underlying critical COVID-19. *Nature* 607, 97–103
8. COVID-19 Host Genetics Initiative (2022) A first update on mapping the human genetic architecture of COVID-19. *Nature* 608, E1–E10
9. Chen, F. *et al.* (2021) The impact of ACE2 polymorphisms on COVID-19 disease: Susceptibility, severity, and therapy. *Front. Cell. Infect. Microbiol.* 11, 753721
10. Sabater Molina, M. *et al.* (2022) Polymorphisms in ACE, ACE2, AGTR1 genes and severity of COVID-19 disease. *PLoS One* 17, e0263140
11. Wu, Y.H. *et al.* (2017) The ACE2 G8790A polymorphism: involvement in type 2 diabetes mellitus combined with cerebral stroke. *J. Clin. Lab. Anal.* 31, e22033
12. Zhang, Y. *et al.* (2020) Interferon-induced transmembrane protein 3 genetic variant rs12252-C associated with disease severity in coronavirus disease 2019. *J. Infect. Dis.* 222, 34–37
13. Zhang, Q. *et al.* (2022) Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* 603, 587–598
14. Dite, G.S. *et al.* (2021) An integrated clinical and genetic model for predicting risk of severe COVID-19: A population-based case-control study. *PLoS One* 16, e0247205
15. Brest, P. *et al.* (2021) Using genetics to dissect SARS-CoV-2 infection. *Trends Genet.* 37, 203–204