ANNUAL REVIEWS

Annual Review of Biomedical Data Science

Human Genomics of COVID-19 Pneumonia: Contributions of Rare and Common Variants

Aurélie Cobat,[1,2,3,*] Qian Zhang,[1,2,3] COVID Human Genetic Effort,[†] Laurent Abel,[1,2,3] Jean-Laurent Casanova,[1,2,3,4,5,*] and Jacques Fellay[6,7,8,*]

[1]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Paris, France; email: aurelie.cobat@inserm.fr

[2]Imagine Institute, Paris, France

[3]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; email: casanova@mail.rockefeller.edu

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

[5]Department of Pediatrics, Necker Hospital for Sick Children, Paris, France

[6]School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; email: jacques.fellay@epfl.ch

[7]Swiss Institute of Bioinformatics, Lausanne, Switzerland

[8]Precision Medicine Unit, Biomedical Data Science Center, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Annu. Rev. Biomed. Data Sci. 2023. 6:465–86

First published as a Review in Advance on May 17, 2023

The *Annual Review of Biomedical Data Science* is online at biodatasci.annualreviews.org

https://doi.org/10.1146/annurev-biodatasci-020222-021705

*These authors contributed equally to this article

†Members of the COVID Human Genetic Effort are listed in the Author Contributions section

Keywords

SARS-CoV-2, COVID-19 pneumonia, GWAS, inborn errors of immunity, type I interferons

Abstract

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection is silent or benign in most infected individuals, but causes hypoxemic COVID-19 pneumonia in about 10% of cases. We review studies of the human genetics of life-threatening COVID-19 pneumonia, focusing on both rare and common variants. Large-scale genome-wide association studies have identified more than 20 common loci robustly associated with COVID-19 pneumonia with modest effect sizes, some implicating genes expressed in the lungs or leukocytes. The most robust association, on chromosome 3, concerns a haplotype inherited from Neanderthals. Sequencing studies focusing on rare variants with a strong effect have been particularly successful,

identifying inborn errors of type I interferon (IFN) immunity in 1–5% of unvaccinated patients with critical pneumonia, and their autoimmune phenocopy, autoantibodies against type I IFN, in another 15–20% of cases. Our growing understanding of the impact of human genetic variation on immunity to SARS-CoV-2 is enabling health systems to improve protection for individuals and populations.

1. INTRODUCTION

More than 600 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and at least 6.5 million deaths from COVID-19 have already been recorded worldwide (1). The clinical manifestations of COVID-19 are highly variable, ranging from silent infection to life-threatening disease, typically beginning with pneumonia. Before effective anti-SARS-CoV-2 vaccines became available, around 3% of infected individuals developed critical COVID-19 pneumonia, requiring supplemental high-flow oxygen (O_2 > 6 L/min), mechanical ventilation (noninvasive or by intubation), or extracorporeal membrane oxygenation (2), with an estimated infection fatality rate of about 0.5–1% (3, 4). Advanced age was, by far, the strongest predictor of COVID-19 severity at the time, with the risk of death doubling with every 5 years of age from childhood onward (3, 4). Unvaccinated men also have a 1.5 times greater risk of death than women (3, 5, 6). Ancestry, social status, and several comorbid conditions have been associated with higher disease severity and death rates, but with modest odds ratios (OR; typically <1.5, rarely >2) (5, 7–9). In the early days of the pandemic, it was already obvious that demographic and clinical factors did not entirely account for the marked interindividual variability of COVID-19's clinical manifestations. The hypothesis of human genetic predisposition was most strongly supported by the rare cases of previously healthy young individuals being admitted to intensive care for respiratory failure. Other clinical presentations have emerged during the pandemic, including multisystem inflammatory syndrome in children (MIS-C) (10) and adults (11), COVID toes (pernio) (12), and long-term neurocognitive, pulmonary, and musculoskeletal sequelae collectively referred to as long COVID or postacute COVID-19 syndrome (13). Here again, clinicians were puzzled by the remarkable differences in clinical manifestations observed at population level and suggestive of a causal or modulating role for human genetic variation (2).

The development of anti-SARS-CoV-2 vaccines rapidly became a global health priority. The massive deployment of several effective vaccines, developed in less than a year, indubitably altered the course of the pandemic, largely decreasing the risks of severe disease, hospitalization, and death in regions of high vaccine coverage (14). However, the success of vaccination has been jeopardized by the limited access to vaccination in lower-income countries, vaccine hesitancy, and the emergence of multiple variants of concern, such as Alpha (B1.1.7), Beta (B.1.351), Delta (B.1.617.2) and Omicron (BA.1, BA.2, BA.4, BA.5 and BQ.1), all of which are more transmissible than the original strain, and some of which increase the risk of severe disease (15–19) or immune escape (20). Moreover, even the most effective RNA vaccines do not prevent infection per se, sometimes resulting in so-called breakthrough pneumonia in vaccinated individuals (21, 22). Hence, the fight against this disease continues, and humanity will benefit greatly from improvements in our understanding of the mechanisms of host defense and immune protection against SARS-CoV-2. Human genetic studies of infectious diseases can point to the primary cause of disease and provide invaluable mechanistic insights (23, 24). In this review, we briefly introduce the field of human genetics of infectious diseases and describe the main genetic findings relating to susceptibility to COVID-19 pneumonia and its severity, with their downstream implications.

2. HUMAN GENETICS OF INFECTIOUS DISEASES

For almost all infectious agents, the clinical manifestations of infection are highly variable, ranging from silent infection to lethal disease (25). The field of human genetics of infectious diseases aims to characterize the genetic variants accounting for this considerable interindividual variability. It was long held as a dominant paradigm that rare infections with weakly virulent microbes or multiple, recurrent infections in a single patient result from rare monogenic inborn errors of immunity (IEIs, also called primary immunodeficiencies), whereas common infections with more virulent pathogens are more influenced by the polygenic inheritance of common alleles (26). IEIs were discovered through individual-based studies focusing on a small number of patients, sometimes even a single patient, initially with sporadic infections. IEIs may be individually rare, but, collectively, they are more common than initially thought, and their study can unravel general mechanisms of diseases that can be triggered by other causes (23, 24).

At the population level, attempts to understand how human genetic variation modulates the individual response to more common pathogens began seven decades ago. One of the first major discoveries was the identification of multiple red blood cell abnormalities associated with a lower risk of severe malaria and subject to strong positive selection in populations living in regions in which malaria was endemic (27). However, host genetic studies with the objective of discovering variants were long hampered by technological limitations: The low throughput of DNA analysis methods at the time obliged researchers to use candidate gene approaches, unless they had access to family samples, which allowed for more solid linkage studies. Most candidate gene studies had relatively small sample sizes and failed to account for population stratification or multiple testing, generating a flurry of false-positive results. Recent progress in large-scale genotyping and sequencing technology, coupled with dramatic improvements in bioinformatics and data science, have finally made it feasible to mine the full human genome for infectious disease–altering variants. Both genome-wide association studies (GWAS) and deep sequencing analyses of individuals with unusually severe clinical presentations have been used successfully, and in a highly complementary fashion, to explore the genetic architecture of human susceptibility to infections. GWAS, mostly based on genome-wide genotyping arrays, have identified many associations between common human genetic variants—generally defined as variants with a minor allele frequency of at least 1%—and complex traits or diseases. They have made it possible to identify chromosomal loci associated with the natural course of disease and responses to treatment in populations infected with HIV-1, hepatitis B and C viruses, *Plasmodium falciparum*, *Mycobacterium tuberculosis*, and *Mycobacterium leprae*, for example (25). However, the risk factors identified were no more than modest at the individual level.

The recent development of next-generation sequencing technologies, making it possible to identify rare coding variants rapidly at genome-wide scale through whole-exome sequencing (WES) or whole-genome sequencing (WGS), has revolutionized the field of human genetics. It has accelerated the discovery of new disease-causing genes and provided molecular insight into the etiology of many IEIs (28, 29). Over the last two decades, we and others have demonstrated that rare monogenic IEIs underlie a growing number of life-threatening viral, bacterial, fungal, and parasitic infections in otherwise healthy individuals with normal resistance to other infectious agents (23, 24, 30, 31). Most of these IEIs are not Mendelian, as they frequently display incomplete penetrance. In addition, they are genetically heterogeneous, with both locus and allelic heterogeneity, with different mutations of several genes underlying the same infectious phenotype, but often united by the same signaling pathway (i.e., physiological homogeneity) (30). For example, Mendelian susceptibility to mycobacterial disease (MSMD) is caused by inborn errors of interferon-gamma (IFN-γ) immunity (32–34), with mutations of 15 genes and 30 allelic

forms already reported. Likewise, forebrain herpes simplex encephalitis can be caused by an IEI of TLR3-dependent type I IFN immunity resulting from mutations of eight genes (35, 36). Since 2001, rare monogenic defects have also been shown to underlie some common infectious diseases in rare patients, as exemplified by the identification of several patients with tuberculosis but no familial history of clinical MSMD carrying causal mutations of MSMD genes (37). These rare IEIs led to the recent discovery of a more common IEI, homozygosity for the P1104A *TYK2* allele, underlying about 1% of cases of tuberculosis in populations of European descent (38–40).

Building on these achievements and long-standing international collaborations in human genomics dating back to the Human Genome Project, the HapMap Project, and The 1000 Genomes Project, the host genetic research community quickly came together in the early weeks of the COVID-19 pandemic to search the human genome for potential clues relating to viral pathogenesis and host immune responses. Several consortia were created, including the COVID-19 Host Genetic Initiative (Covid-19-HGI; **https://www.covid19hg.org**) (41) and the Covid Human Genetic Effort (Covid-HGE; **https://www.covidhge.com**) (42). Existing resources were enhanced and redirected to facilitate the rapid analysis of large numbers of patients and controls. A prime example is provided by the GenOMICC (Genetics of Mortality in Critical Care; **https://genomicc.org**) study, which had been recruiting patients in the United Kingdom since 2015 for the study of emerging infections, sepsis, and other forms of life-threatening illness. This study collected clinical data samples from thousands of critically ill COVID-19 patients and generated full-genome sequence data in record time. The global effort was not restricted to the academic sector either: Several direct-to-consumer companies used their large reservoirs of clients (who agreed to be recontacted for research purposes) to perform genome-wide analyses of susceptibility to infection and symptom severity.

3. HUMAN GENETICS OF COVID-19 PNEUMONIA

Numerous human genetic studies have investigated the genetic determinants of COVID-19 pneumonia. As discussed in the corresponding sections, large-scale GWAS approaches, mostly based on genome-wide SNP (single-nucleotide polymorphism) arrays and single-variant statistics assuming an additive genetic model, led to the identification of multiple common genetic variants associated with a modest increase in the risk of COVID-19 pneumonia. High-throughput DNA sequencing approaches, such as WES or WGS for the identification of rare genetic variants, have also been highly successful, resulting in the discovery of genes and pathways crucial for the control of SARS-CoV-2 infection through rare-variant aggregation tests followed by functional validation.

3.1. Common Variants

Multiple large-scale GWAS have investigated the genetic factors associated with disease severity by comparing COVID-19 pneumonia patients stratified into various subgroups (hospitalized, requiring ventilation, admitted to the intensive care unit, or deceased) with SARS-CoV-2-infected individuals with asymptomatic or mild clinical presentations, or untested individuals from the general population. More than 15 genomic regions harboring common variants (**Figure 1**) have already been robustly associated with COVID-19 pneumonia (43, 44). The strongest signal—and the very first to be reported, in the spring of 2020—is that for the 3p21.31 locus, where a Neanderthal haplotype was found to be associated with an OR of 1.8 for severe infection (43, 45–48). The association with this locus has been replicated in several independent cohorts. The frequency of the lead SNP ranges from 1% in East Asians to 9% in Europeans and 23% in South Asians, but there is no evidence of between-origin heterogeneity (43). It has proved challenging to identify the causal genes and variants underlying this association due to long-range linkage disequilibrium

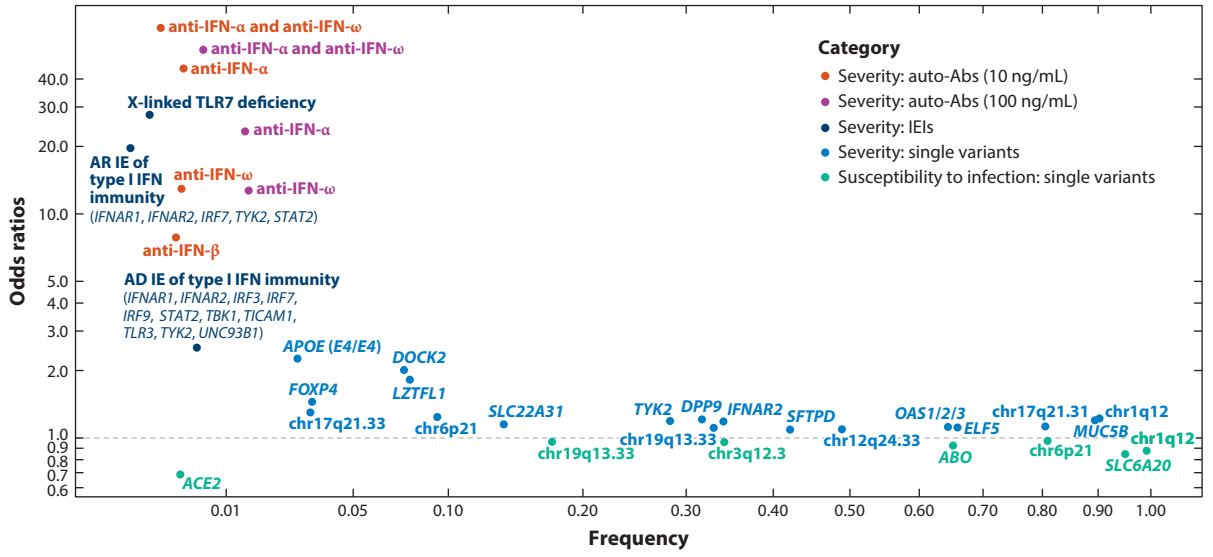

Figure 1

Genetic and immunological determinants of COVID-19 pneumonia. ORs for the associations of auto-Abs against type I IFN, IEIs, and single genetic variants with the severity of COVID-19 pneumonia and resistance to SARS-CoV-2 infection are plotted according to risk factor frequency. For auto-Abs against type I IFN, the ORs and frequency were taken from Reference 114. For X-linked TLR7 deficiency, the OR for the aggregated effect of biochemically proven LOF was taken from Reference 74 and the cumulative frequency of biochemically proven LOF was taken from Reference 76. For other IEIs, the OR for the aggregated effect of homozygous (AR) or heterozygous (AD) predicted LOF was taken from Reference 74 and the corresponding cumulative frequencies were estimated from Gnomad v2.1.1. For single variants, the OR, assuming an additive model, and deleterious allele frequencies were taken from the most recent update of the COVID-19 Host Genetics Initiative GWAS study (43), except for the *DOCK2* and *APOE* loci. The chromosomal region or closest gene is indicated. For the *DOCK2* locus, the OR for the effect of the rs60200309-A variant on the severity of COVID-19 pneumonia under an additive model and the allele frequency for rs60200309-A were taken from Reference 156. For the *APOE* locus, the hazard ratio for the effect of *APOE4* homozygosity as opposed to *APOE3* homozygosity for COVID-19 mortality and the frequency of *APOE4* homozygosity were taken from Reference 157. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; auto-Abs, autoantibodies; IE(I), inborn error (of immunity); IFN, interferon; LOF, loss of function; OR, odds ratio.

in the region and a high local density of genes with a known or putative role in immunity. In silico functional analyses identified *LZTFL1* as the most probable candidate gene (49), but variants of the chemokine receptor genes *CCR9*, *CXCR6*, and *XCR1* may also contribute to the association signal. Some of the additional loci implicated point to a role for known immune-related genes or genes known to be involved in lung function, as detailed below. Surprisingly, given the very high level of polymorphism of both class I and class II HLA (human leukocyte antigen) genes and their demonstrated role in modulating multiple infectious diseases, the few associations identified in the HLA region have proved to be weak. It was not until very large meta-analyses were performed relatively late in the course of the pandemic that genome-wide-significant association signals were confirmed for polymorphisms of both class I and class II HLA genes (43, 47, 48).

The loci pointing to a role for known immune-related genes include the *IFNAR2* gene, encoding the interferon (IFN) alpha/beta receptor 2, for which associations with variants have been replicated in several studies (47, 50). Type I IFNs play a central role in the innate immune response to SARS-CoV-2, as demonstrated by the marked increase in the risk of life-threatening disease associated with rare loss-of-function variants of IFN-related genes and anti-IFN autoantibodies (auto-Abs), as discussed below. It is, therefore, unsurprising that common variants of a subunit of the type I IFN receptor modulate the severity of infection, particularly as the top-ranking

associated variants are expression quantitative trait loci (eQTLs) for *IFNAR2*. An association with a *TYK2* variant has been identified, which is particularly interesting, given the key role of TYK2 in infection and immunity. The common rs34536443 (p.Pro1104Ala) variant, which is protective against some autoimmune diseases (51) but increases the risk of tuberculosis in homozygous individuals (40), has been shown to be associated with a modest increase in the risk of severe COVID-19 (48). Rare loss-of-function *TYK2* variants are discussed below. GWAS have also identified a common haplotype of Neanderthal origin encompassing the *OAS1/2/3* genes on chromosome 12 (12q24.13) that is associated with the risk of hospitalization for COVID-19 (47, 48, 52, 53). The OAS proteins are cytosolic type I IFN–inducible antiviral proteins (54, 55). One of the candidate causal variants in this region is the *OAS1* splice variant rs10774671. The minor and reference G allele at rs10774671, which provides weak protection against severe forms of COVID-19, encodes a longer and more active form of OAS1 (56).

In its most recent meta-analysis including more than 150,000 cases (43), the Covid-19-HGI reported multiple associations between disease severity and genes involved in normal lung function. First, a regulatory variant (rs35705950:G>T) mapping to the promoter region of *MUC5B* was found to be associated with a lower risk of hospitalization. The minor T allele is associated with higher levels of *MUC5B* mRNA and a higher risk of idiopathic pulmonary fibrosis (57). Second, a missense variant of *SFTPD* (rs721917:A>G, p.Met31Thr) was found to be associated with more severe respiratory symptoms. *SFTPD* encodes the surfactant protein D, and the same alternative allele was previously shown to have a negative impact on lung function (58) and to increase the risk of chronic obstructive pulmonary disease (59). Third, a missense variant of *SLC22A31* (rs117169628:G>A, p.Pro256Leu) was also found to be associated with a higher risk of hospitalization. *SLC22A31* encodes a solute carrier protein that is highly expressed in the lung. Finally, a strong association with severe disease was observed with an intronic variant of *DPP9* (rs2109069:G>A) previously reported to increase the risk of idiopathic pulmonary fibrosis (60). These variants have very small effect sizes ($0.8 < OR < 1.2$), but their study may improve our understanding of SARS-CoV-2 pathogenicity by shedding light on the underlying molecular mechanisms.

3.2. Rare Variants

The use of large-scale sequencing approaches has allowed an in-depth exploration of human genetic diversity, including rare and putatively functional genetic variants that are not included in most genotyping arrays and cannot be reliably imputed due to their very low minor allele frequency.

3.2.1. Type I interferon influenza susceptibility loci. Based on our discoveries over the last 20 years, we launched the Covid-HGE, an international consortium with the aim of deciphering the human genetic and immunological basis of the various clinical manifestations of SARS-CoV-2 infection. The first breakthrough emerged from a study testing the hypothesis that candidate inborn errors of TLR3-, IRF7-, and IRF9-dependent type I IFN immunity previously shown to underlie life-threatening influenza pneumonia (2, 23, 24, 30, 31, 61–64) might also underlie critical COVID-19. We considered the three loci (*IRF7*, *IRF9*, and *TLR3*) for which germline mutations are causal for influenza pneumonia (62–64) and 10 other genes (*IFNAR1*, *IFNAR2*, *IRF3*, *IKBKG*, *STAT1*, *STAT2*, *TBK1*, *TICAM1*, *TRAF3*, and *UNC93B1*) encoding products biochemically and immunologically connected to the three core genes, for which deleterious genotypes have been shown to underlie other severe viral diseases (61). We screened a cohort of 659 patients with critical COVID-19 for rare variants predicted to be loss-of-function (pLOF) at these 13 type I IFN influenza susceptibility loci. We found a significant enrichment in these variants in patients with

critical COVID-19 relative to 534 SARS-CoV-2-infected controls who remained asymptomatic or paucisymptomatic, with mild, self-healing, ambulatory disease ($p = 0.01$) (61). We also found that 23 (3.5%) of the patients with critical COVID-19 carried biochemically deleterious germline mutations of 8 of the 13 genes. These patients included four unrelated previously healthy adults aged 25–50 years with autosomal recessive (AR) complete IRF7 or IFNAR1 deficiency. AR IFNAR1, IFNAR2, TBK1, and STAT2 deficiencies were subsequently reported in children with critical COVID-19, and AR TYK2 deficiency was identified in children with COVID-19 pneumonia (65–69).

Several other groups were unable to replicate our findings (44, 70–72). There are several possible reasons for this (73), two of which are particularly important. First, the key epidemiological factor driving COVID-19 severity was ignored: Our international cohort was much younger than the other cohorts (mean age of 52 versus 66 years). As discussed below, these inborn errors are much more frequent in patients under the age of 60 years (**Figure 2**). Second, the other groups did not test for auto-Abs against type I IFN, the most common determinant of critical COVID-19, especially in patients over 60 years old (discussed below in Section 5.1). More recently, we confirmed an enrichment in rare pLOF variants at the 13 type I IFN–related influenza susceptibility loci in an extended sample of 3,269 patients with critical COVID-19 relative to 1,373 controls with asymptomatic or mild infection ($p = 2.1 \times 10^{-4}$) (74). The addition of *TYK2* strengthened the association signal, particularly if a recessive model was assumed. We also found that homozygous carriers of rare pLOF variants had a higher risk of life-threatening COVID-19 than heterozygotes,

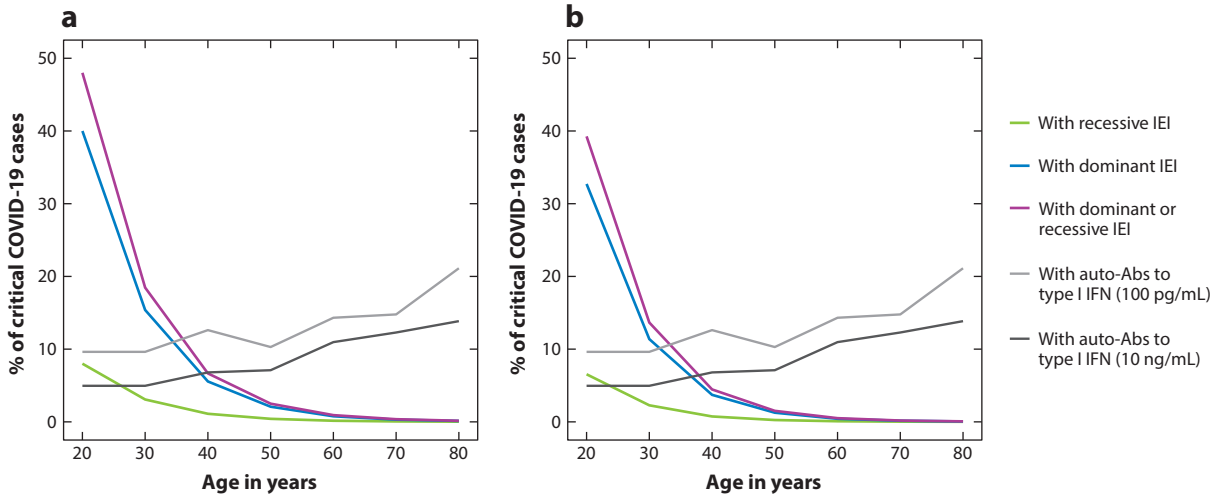

Figure 2

Proportion of critical COVID-19 patients with IEIs and auto-Abs against type I IFN as a function of age. Age-specific proportions of dominant and recessive IEIs among cases of critical COVID-19 pneumonia were estimated with Bayes' theorem as a function of the probability of critical COVID-19 pneumonia for IEI carriers infected with SARS-CoV-2 (i.e., the penetrance). The age-specific frequency of IEIs in the general population and the age-specific critical infection rate were taken from Reference 158. The age-specific frequency of IEIs in the general population was estimated from the frequency of IEIs at birth, assuming a nonspecific mortality rate (i.e., not attributable to COVID-19) of (*a*) 0% or (*b*) 1% per year. Based on our previous findings (67, 159, 160), the frequency of IEIs at birth was set at 10^{-3} for dominant and 5×10^{-4} for recessive IEIs. We assumed a penetrance of 0.2 for dominant IEIs and 0.8 for recessive IEIs, consistent with the estimated effect size for recessive IEIs being larger than that for dominant IEIs. The age-specific proportions of patients with critical COVID-19 producing auto-Abs neutralizing low doses (100 pg/mL; *light gray line*) or high doses (10 ng/mL; *dark gray line*) of IFN-α and/or IFN-ω were taken from Reference 114. Abbreviations: auto-Abs, autoantibodies; IEI, inborn errors of immunity; IFN, interferon.

consistent with the expected higher penetrance of recessive IEIs than of dominant IEIs. In analyses restricted to rare in-frame nonsynonymous variants, we detected no significant enrichment in patients relative to controls. This result was not surprising, as we showed in a previous study (61) that less than 15% of the rare in-frame nonsynonymous variants at the 13 loci were biochemically proven LOF (bLOF) variants, whereas all the pLOF variants were found to be bLOF variants. A similar trend was observed for other immune system genes, even when advanced in silico scoring systems, such as the CADD (Combined Annotation Dependent Depletion) score, were used to stratify the variants (39, 75–77). The study of in-frame nonsynonymous variants will therefore require the experimental characterization of all these variants.

3.2.2. Unbiased screening for chromosome- and genome-wide rare variant burden. We hypothesized that the higher risk of critical COVID-19 in men than in women might be explained by X-linked disorders. We conducted an unbiased X chromosome–wide gene burden test on a cohort of 1,202 unrelated, auto-Ab-negative male patients with critical COVID-19 pneumonia and 331 men with asymptomatic or mild COVID-19. The most strongly associated gene, and the only gene remaining significant after accounting for the number of genes tested, was *TLR7*, with 21 unrelated patients carrying a very rare hemizygous nonsynonymous variant that was completely absent from controls ($p = 3.5 \times 10^{-5}$) (76). Of these 21 patients, 16 carried a *TLR7* allele that was bLOF or hypomorphic. Biochemically proven TLR7 deficiency was identified in four additional male patients with critical COVID-19 (74), as well as in four male patients with severe COVID-19 (67, 76) from the Covid-HGE cohort. Moreover, we confirmed the proposed diagnosis of TLR7 deficiency in 9 of 16 other reported male patients (65, 78–82) with our biochemical assay (76). An enrichment in rare nonsynonymous *TLR7* variants in patients with critical COVID-19 was reported in another two studies, but the variants were not disclosed and the diagnosis of TLR7 deficiency remains to be confirmed, especially in the women (70, 71). Overall, TLR7 deficiency was found to account for about 1% of cases of critical COVID-19 in men (74, 76). The penetrance of TLR7 deficiency for severe or critical COVID-19 among relatives of index cases was high, but incomplete, especially in children. Human TLR7 is an endosomal receptor of ribonucleic acids expressed by B cells and myeloid subsets. Its stimulation in plasmacytoid dendritic cells (pDCs) results in the production of large amounts of type I IFN (76). We showed that blood B cell lines and myeloid cell subsets from patients with TLR7 deficiency did not respond to TLR7 stimulation and that the patients' pDCs produced low levels of type I IFNs in response to SARS-CoV-2, further highlighting the essential role of type I IFN for protection against SARS-CoV-2 (**Figure 3**) (76).

Several large-scale sequencing studies have attempted to identify new genetic causes of severe COVID-19 pneumonia through unbiased genome-wide gene burden analyses (44, 70, 71, 74). None of the genes considered remained statistically significant after stringent correction for the number of genes and phenotypes tested. In addition to *TLR7*, for which association has consistently been reported across studies (70, 71, 74, 76, 78), two genes reached the less conservative exome-wide significance threshold of 2.5×10^{-6} in one study focusing on 5,085 individuals with critical COVID-19 and 571,737 controls, mostly uninfected, from the general population (70): *MARK1* ($p = 1.9 \times 10^{-6}$) and *RILPL1* ($p = 2.4 \times 10^{-6}$), with cases displaying an enrichment in pLOF variants. Nevertheless, these results require further investigation. It should be stressed that stringent correction for multiple testing, while necessary to avoid false positives, is a conservative strategy, and that a lack of formal statistical significance at a genome-wide level does not exclude biological causality and medical significance. The burden of proof can be provided experimentally via biochemical, virological, and immunological experiments, as we previously did for *TLR7* (76). Additional genes may be found by restricting the association analysis to variants proved experimentally to be deleterious.

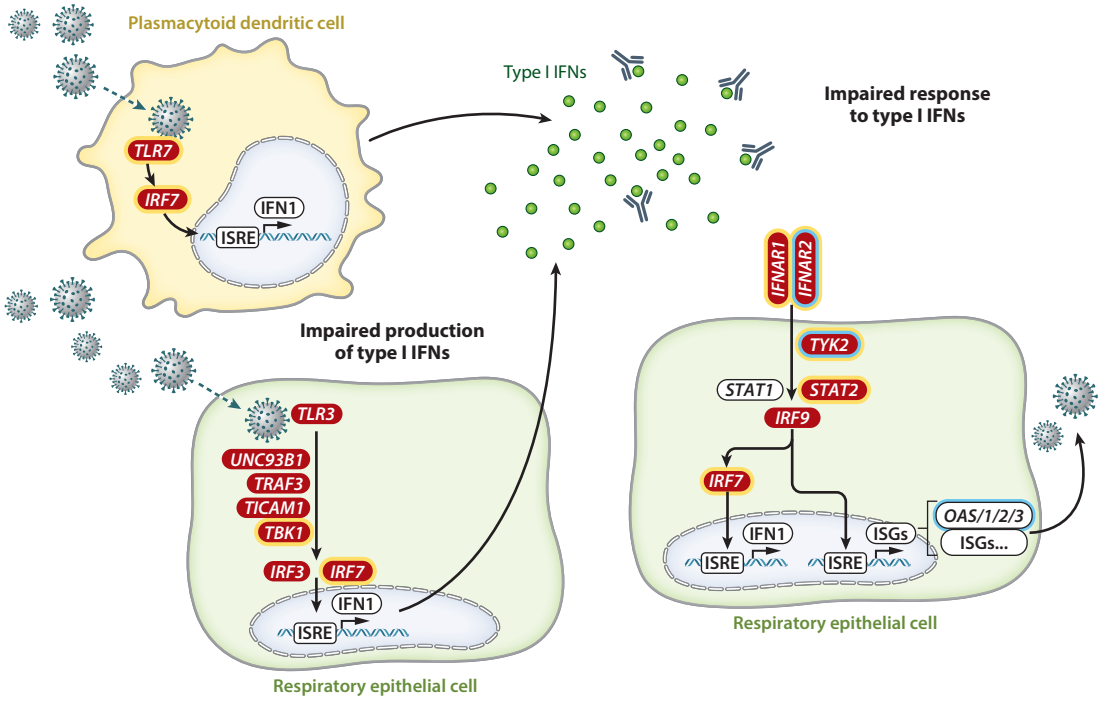

Figure 3

Impaired type I IFN immunity underlies life-threatening COVID-19. Nearly 20% of patients with life-threatening COVID-19 pneumonia have impaired production of or response to type I IFNs due to IEIs (1 to 5%) or to blockade of type I IFN activity by preexisting neutralizing autoantibodies (~15%). IEIs of type I IFN immunity (*red*) have been identified and, in response to SARS-CoV-2 infection, lead to (*left*) an impaired production of type I IFNs in RECs or in blood plasmacytoid dendritic cells or (*right*) an impaired response to type I IFNs in RECs. Genes for which X-linked or autosomal recessive defects have been identified are circled in yellow. Genes for which common variants have been associated by GWAS with severe COVID-19 are circled in blue. Abbreviations: IEIs, inborn errors of immunity; IFN, interferon; ISGs, interferon-stimulated genes; RECs, respiratory epithelial cells.

3.3. Age-Dependent Genetic Architecture

Inborn errors of type I IFN immunity are more frequent in younger patients (those under 60 years of age) (61, 74, 76), an observation consistent with IEIs being generally more common in children (26, 83). Of the 23 patients first reported to carry biochemically deleterious germline mutations at eight type I IFN–related influenza susceptibility loci, 18 (78%) were under 60 years old (61). TLR7 deficiency was found to account for 1% of cases of critical COVID-19 in men and about 1.8% of cases of critical COVID-19 in men below the age of 60 years (76). In an extended sample of 3,269 patients with critical COVID-19, we identified 57 patients carrying a rare predicted LOF variant at 14 type I IFN–related influenza susceptibility loci (including *TYK2*) or with biochemically proven TLR7 deficiency (74). These patients were significantly younger than the rest of the cohort of patients with critical COVID-19 (43.3 versus 56 years old; $p = 1.7 \times 10^{-5}$) (74). Consistent with these results, we recently reported 12 children (~10%) from an international cohort of 112 pediatric patients hospitalized for COVID-19 pneumonia with biochemically complete recessive inborn errors of type I IFN immunity, including seven children with X-linked recessive TLR7 deficiency and five children with AR IFNAR1, STAT2, or TYK2 deficiency (67). Interestingly, the effect of the major common genetic risk factor for severe COVID-19 pneumonia on chromosome 3 was also found to be more pronounced in individuals under 60 years of age than

in those over 60 years of age (odds of death or severe respiratory failure of 2.7 versus 1.5; *p*-value for the interaction = 0.038) (84). A greater heritability of common SNPs has also been reported in patients under 60 years of age than in those over 60 years of age (85).

Stronger genetic effects in young patients may partly reflect the greater contribution of other risk factors in the elderly, such as comorbid conditions and auto-Abs against type I IFNs (which account for ~15% of critical cases in elderly patients, discussed below in Section 5.1), which become more frequent with increasing age. At the cellular level, aging is also associated with immunosenescence, which may contribute to a defective innate and adaptive response to SARS-CoV-2 infection, thereby conferring a nonspecific predisposition to severe COVID-19 (86). At the molecular level, global type I IFN immunity in the blood (pDCs) and respiratory tract (respiratory epithelial cells) has been shown to decline with age (87–90). The frequency of IEIs may also decline with age in the general population, because IEIs can underlie fatal illness due to influenza or other viruses, resulting in the premature death of affected individuals (2). Cohorts consisting mostly of patients over the age of 60 years would, therefore, have a very low power to identify rare inborn errors, as illustrated in **Figure 2**, which shows the proportion of critical COVID-19 cases expected to be due to IEIs as a function of age. Assuming a frequency of 10^{-3} for dominant IEIs and 5×10^{-4} for recessive IEIs and a penetrance for critical COVID-19 pneumonia of 0.2 and 0.8, respectively, the expected proportion of critical COVID-19 cases due to IEIs would be expected to decrease strongly with age, from more than 15% below the age of 30 to less than 1% after the age of 60.

4. HUMAN GENETICS OF SUSCEPTIBILITY TO SARS-CoV-2 INFECTION

It has been suggested that a fraction of the human population may possess intrinsic resistance to SARS-CoV-2 infection, but this remains unproven (91). Epidemiological observations suggest that some exposed individuals may indeed be resistant; in particular, there have been reports of highly exposed individuals remaining uninfected in the health care setting (92), as well as reports of households in which everyone except one individual became infected (93). Genetic resistance to infection with specific pathogens is rare. The only validated examples in humans are AR resistance to (*a*) *Plasmodium vivax*, linked to a regulatory variant that modifies the GATA-1 binding site in the *DARC* promoter, thereby selectively preventing the expression of the Duffy antigen on red blood cells (94); (*b*) HIV-1, conferred by a 32-bp deletion in *CCR5*, the gene encoding the main HIV-1 coreceptor on $CD4^+$ T cells (95–97); and (*c*) norovirus, due to *FUT2* deficiency (nonsecretor phenotype), which prevents the binding of the norovirus VPg (viral genome–linked protein) capsid to FUT2 (98).

No highly penetrant protective variant against SARS-CoV-2 infection has yet been reported. However, GWAS have identified a few genetic factors as associated with a lower likelihood of infection at the population level (**Figure 1**). One of the first genomic regions to be identified in COVID-19 host genetic studies was the *ABO* locus on chromosome 9 (45). A highly significant association with susceptibility to infection was later observed at the same locus for the SNP rs912805253 (OR ~ 0.9), both in the initial Covid-19-HGI meta-analysis (48) and in a large study by the direct-to-consumer genetics company 23andMe (99). Interestingly, a systematic review confirmed that the ABO association is mostly restricted to susceptibility to infection, with blood group O associated with a significantly lower susceptibility to infection than non-O blood groups (OR = 0.9), whereas most of the other reported genetic regions are associated with disease severity (100). The precise mechanism by which ABO blood status influences SARS-CoV-2 susceptibility remains unclear, but blood antigens are known to alter individual susceptibility to multiple pathogens (101), including other coronaviruses (102).

The angiotensin-converting enzyme 2 (ACE2) protein acts as a functional receptor for the spike glycoprotein of SARS-CoV-2 and other coronaviruses. *ACE2* variants were thus suspected to play a role in modulating infectiousness. However, this gene is under strong negative selection. Putative functional variants are therefore rare, and a very large number of study participants (>50,000 COVID-19 cases and >700,000 controls) were required to identify a relatively rare variant associated with protection against SARS-CoV-2 infection (rs190509934:T>C; frequency of the minor C allele = 0.3%; OR for the additive effect of each copy of the minor C allele = 0.69) (50). This variant, which is located 69 bp upstream from *ACE2*, is an eQTL for the gene: The C allele is associated with lower levels of mRNA, probably accounting for the lower level of susceptibility to infection. This association was replicated in the most recent Covid-19-HGI meta-analysis (43). Five additional loci were identified by GWAS as being more likely to be associated with susceptibility to SARS-CoV-2 infection than with disease severity (43, 103), but the effect sizes were, again, very modest (**Figure 1**) and the mechanisms involved remained mostly undefined. No inborn variant conferring strong resistance to SARS-CoV-2 infection has yet been identified. Human genetic studies of resistance to infection may benefit from large-scale host–viral interactome studies (61) and genome-wide CRISPR knockout (104–112) and activation (104, 112) screens, which can identify candidate genes influencing the viral life cycle. Such studies will require a specific strategy, particularly for the reliable identification of highly exposed subjects potentially resistant to infection (113).

5. DOWNSTREAM IMPLICATIONS OF THE GENETIC FINDINGS

5.1. Biological Insight from Genetic Discoveries: Autoantibodies Neutralizing Type I Interferons

The identification of type I IFN–related IEIs led to the almost simultaneous major discovery that preexisting auto-Abs neutralizing type I IFNs account for about 15% of critical COVID-19 cases (114, 115). While searching for type I IFN–related IEIs in patients with critical COVID-19 pneumonia, we also hypothesized that autoimmune phenocopies of these IEIs might underlie critical COVID-19. Autoimmune phenocopies of IEIs of cytokines have already been described, in which patients with the same or a similar infectious phenotype produce auto-Abs neutralizing the corresponding cytokines. Auto-Abs against cytokines have already been shown to underlie mycobacterial disease (type II IFN), mucocutaneous candidiasis (IL-17A/F), nocardiosis [GM-CSF (granulocyte-macrophage colony-stimulating factor)], and staphylococcal disease (IL-6) (116, 117). Auto-Abs neutralizing type I IFNs were known to occur in some patients receiving IFN therapy, and in patients with systemic lupus erythematosus, myasthenia gravis, thymoma, or autoimmune polyendocrine syndrome type 1 (APS-1) caused by germline mutations of *AIRE*, but they were not thought to confer a predisposition to viral diseases (2, 118). We first reported the presence of auto-Abs neutralizing high, supraphysiological concentrations (10 ng/mL, with plasma diluted 1/10) of IFN-α2 or IFN-ω in about 10% of 987 patients with critical COVID-19 pneumonia, but not in 663 individuals with asymptomatic or mild infection (115). This finding has been largely replicated worldwide in many studies (76, 119–134). We later detected auto-Abs neutralizing lower, more physiological concentrations (100 pg/mL, with plasma diluted 1/10) of IFN-α2 or IFN-ω in 13.6% of 3,595 patients with life-threatening COVID-19 (114). This proportion increased in patients older than 65 years, reaching more than 20% in patients over 80 years old, and was greater in men than in women. Another 1% of patients with critical COVID-19 had auto-Abs neutralizing high concentrations of IFN-β.

Several lines of evidence strongly suggest that autoimmunity to type I IFN plays a causal role in life-threatening COVID-19 (135). For patients for whom plasma sampled before the pandemic

was available, the auto-Abs were found to be present before SARS-CoV-2 infection (115). Patients with APS-1, who produce such auto-Abs from early childhood, were shown to be at very high risk of developing severe or critical COVID-19 pneumonia, especially after 20 years of age (136). These auto-Abs neutralize the antiviral activity of type I IFNs against SARS-CoV-2 in vitro (115) and are found in vivo in the blood and in the respiratory tract of patients (123, 137, 138). Remarkably, these auto-Abs were also found in samples from a fraction of the general population before the pandemic. Their prevalence in the general population remains fairly stable until the age of 70 (at ~1% for auto-Abs neutralizing low doses of IFN-α2 or IFN-ω), but sharply increases thereafter (reaching up to 6.3% after the age of 80 years) (114). Auto-Abs against type I IFNs strongly increase COVID-19 infection fatality rates in unvaccinated populations, especially those neutralizing both IFN-α2 and IFN-ω (135). Screening for auto-Abs against type I IFN in patients infected with SARS-CoV-2, and even in uninfected individuals, is feasible and may be warranted. Individuals carrying such antibodies should be given high priority for vaccination against COVID-19. They may also benefit from specific care, such as the administration of monoclonal antibodies neutralizing the virus or early recombinant IFN-β therapy (139). The exact level of protection against severe COVID-19 pneumonia provided by COVID-19 vaccines in carriers of auto-Abs remains unclear. However, we recently detected auto-Abs against type I IFNs in 24% (10 of 42 tested) of fully vaccinated patients with normal antibody responses who developed critical breakthrough COVID-19 (140), suggesting that at least some of the carriers of these auto-Abs may not be fully protected by the vaccine. The same auto-Abs were subsequently shown to underlie other severe infectious manifestations, such as severe adverse reactions to yellow fever live-attenuated viral vaccine (33) and critical influenza pneumonia (141). In critically ill COVID-19 patients, auto-Abs were also shown to increase the risk of herpesvirus reactivation, which has been associated with a poorer clinical outcome (142, 143).

Auto-Abs against type I IFNs can also be genetically driven, and few IEIs are already known to underlie their production. The most striking example is the production of these auto-Abs from early childhood in nearly all patients with APS-1 due to germline deleterious variants of *AIRE* (4). They have also been reported in patients with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) due to deleterious variants of *FOXP3*, as well as combined immunodeficiency due to biallelic hypomorphic *RAG1* or *RAG2* variants (37–42). A feature common to these IEIs is that they affect T cell tolerance. Interestingly, among the patients with auto-Abs against type I IFN and life-threatening COVID-19, we identified a woman with X-linked incontinentia pigmenti (IP), in which cells activate the same single X chromosome (cells having activated the X chromosome and bearing the null mutation of *NEMO* die during development) (27). A further study of 32 women with IP showed that 25% carried auto-Abs against type I IFNs, suggesting an X-linked germline genetic etiology for type I IFN auto-Abs (115). New IEIs underlying the production of auto-Abs against type I IFN are likely to be discovered in the future, particularly in young patients. It is also tempting to speculate that somatic mutations, which accumulate with age in normal human tissues (144), may be partly responsible for the sharp increase in the prevalence of auto-Abs against type I IFNs after 70 years of age.

5.2. Clinical Implications: Toward Personalized Medicine in Infectious Diseases

Deciphering the genetic architecture of susceptibility to SARS-CoV-2 infection and severe COVID-19 pneumonia is only the first step toward clinical implementation and improved health care. How can we translate the knowledge gained in the genomic screens described above into medically useful strategies? The first and most obvious answer to this question is through the identification of individuals at high risk. The rare deleterious variants of TLR7- and TLR3-dependent

type I IFN immunity genes identified confer a massive increase in the risk of severe disease and account for a significant proportion of cases (e.g., 1% of men with critical disease carry a deleterious *TLR7* variant). One could imagine screening programs, at the population level, in primary care centers, or in emergency rooms (at the time of early COVID-19 diagnosis), providing point-of-care testing for such variants (145). Carriers would then benefit from specific preventive and therapeutic measures. In particular, type I IFN might be useful in patients prone to severe COVID-19 and infected with the virus, provided it is administered at an early stage of infection. Along the same lines, the discovery that auto-Abs against type I IFN account for 20% of COVID-19 deaths has clinical implications. The detection of such auto-Abs before or during early stages of infection is straightforward and warranted. Carriers of these auto-Abs should be vaccinated and given priority for booster injections and may benefit from specific treatments, such as IFN-β, monoclonal antibodies neutralizing SARS-CoV-2, or plasma exchange (146, 147).

A second way forward in the clinical translation of these findings would be the development of polygenic risk scores (PRS), constructed by summing the effects of all genetic variants confirmed to be associated with a phenotype of interest. In recent years, PRS have been shown to have a high predictive value for a range of complex diseases, including cardiovascular, metabolic, and tumoral disorders (148). A few studies have attempted to build PRS for COVID-19, but with little success. Indeed, one of the main factors determining the predictive ability of PRS is the fraction of the phenotypic variance explained by the combination of selected variants, which remains low in COVID-19 host genetic studies of common variants (50, 84, 149). Nevertheless, some private companies already offer polygenic risk prediction for severe COVID-19. However, current tests have low discriminatory power at the individual level and variable accuracy depending on ancestry, making their clinical use questionable (150). Nevertheless, the assessment of patient risk based on a combination of demographic, clinical, and genetic data has the potential to deliver more precise information that could prove useful for personalized health management.

6. CONCLUSION

The SARS-CoV-2 pandemic has highlighted the vast potential of human genomics research when it is performed at a large scale, in real time, and in a highly collaborative manner. One of its greatest successes has been the identification of a molecular explanation for about 20% of cases of critical COVID-19 pneumonia: inborn errors of type I IFN immunity in 1–5% of cases and auto-Abs against type I IFNs in 15–20% of cases. Other IEIs, related or unrelated to type I IFN, may also be involved. Future studies should build upon the observations of the impact of SARS-CoV-2 infection in individuals with previously known IEIs (151). Remarkably, common genetic variants with modest effect sizes were also identified in regions encompassing genes involved in type I IFN immunity. It is tempting to speculate that they may act as modifiers of the clinical expression of IEIs, which display high but incomplete penetrance. Most human genomics studies have focused on COVID-19 pneumonia, with fewer considering resistance to SARS-CoV-2 infection. Interesting results are starting to emerge for MIS-C and already suggest a pathogenesis different from that of COVID-19 pneumonia (152–154). Future research should also encompass other COVID-19-related clinical manifestations, such as long COVID (13) and COVID toes (12), as well as severe adverse effects of vaccination (155) and breakthrough infections (140).

The lessons learned should be used to improve our collective capacity to confront other infectious threats. In particular, COVID-19 has illustrated the central importance of large-scale research infrastructures embedded in health care systems, facilitating the rapid collection and analysis of samples in times of crisis. It has also become clear that it is crucial to define disease outcomes clearly and to gather as many clinical data as possible to minimize patient misclassification,

thereby maximizing statistical power to detect true genetic signals. Ultimately, a better understanding of the impact of human genetic variation on pathogen response will enable health systems to provide appropriate care to protect individuals and populations more efficiently against future infectious threats.

DISCLOSURE STATEMENT

J.-L.C. is an inventor on patent application PCT/US2021/042741, filed July 22, 2021, submitted by The Rockefeller University, which covers diagnosis of susceptibility to, and treatment of, viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. The members of the COVID Human Genetic Effort (CHGE), listed below, also report the following disclosures: Isabelle Meyts has received a research grant from CSL-Behring, paid to KU Leuven, and an honorarium from Boehringer-Ingelheim for a scientific advisory board position, paid to KU Leuven; Vassili Soumelis is an employee of Owkin; Sarah Henrickson is an ad hoc advisory board member for Horizon Therapeutics; and Mikko R.J. Seppänen is a member of the IUIS Inborn Errors of Immunity Expert Committee, the ClinGen Executive Committee of the Immunological Clinical Domain Working Group, and the ESID Genetics Working Party; has received funding from the Sigrid Jusélius Foundation, the Jane and Aatos Erkko Foundation, the Finnish Foundation for Pediatric Research, Helsinki University Hospital Research Funds, and the ERN-RITA Core Center; and is an employee of Helsinki University Hospital, HUS Group Finland, the Joint Authority for Helsinki and Uusimaa, Finland.

AUTHOR CONTRIBUTIONS

A.C., J.F., and J.-L.C. (co-corresponding authors) structured and finalized the manuscript. A.C., J.F., J.-L.C, L.A., and Q.Z. drafted the manuscript and the figures. The COVID Human Genetic Effort (CHGE) comprises Alessandro Aiuti (Vita-Salute San Raffaele University), Saleh Al Muhsen (King Saud University), Fahd Al-Mulla (Dasman Diabetes Institute), Ali Amara (Institut de Recherche Saint-Louis), Mark Anderson (University of California, San Francisco), Evangelos Andreakos (Biomedical Research Foundation of the Academy of Athens), Andrés A. Arias (Universidad de Antioquia), Hagit Baris-Feldman (Tel Aviv University), Paul Bastard (Institut Imagine), Alexandre Belot (Université de Lyon), Bertrand Boisson (Institut Imagine), Alexandre Bolze (Helix), Anastasiia Bondarenko (Shupyk National Medical Academy for Postgraduate Education), Alessandro Borghesi (Fondazione IRCCS Policlinico San Matteo), Ahmed A. Bousfiha (Hassan II University), Petter Brodin (Karolinska Institutet), Manish Butte (University of California, Los Angeles), Giorgio Casari (Vita-Salute San Raffaele University), John Christodoulou (Murdoch Children's Research Institute), Roger Colobran (Hospital Universitari Vall d'Hebron), Antonio Condino-Neto (University of São Paulo), Clifton L. Dalgard (Uniformed Services University of the Health Sciences), Mateus V. de Castro (University of São Paulo), Sara Espinosa-Padilla (Instituto Nacional de Pediatria), Carlos Flores (University Hospital Nuestra Señora de Candelaria), Antoine Froidure (Université Catholique de Louvain), Guy Gorochov (Sorbonne Université), Filomeen Haerynck (Ghent University Hospital), Rabih Halwani (University of Sharjah), Lennart Hammarström (Karolinska Institutet), Sarah Henrickson (University of Pennsylvania), Elena Hsieh (University of Colorado), Yuval Itan (Icahn School of Medicine at Mount Sinai), Chandima Jeewandara (University of Sri Jayewardenepura), Emmanuelle Jouanguy (Institut Imagine), Yu-Lung Lau (University of Hong Kong), Yun Ling (Fudan University), Davood Mansouri (Shahid Beheshti University of Medical Sciences), Isabelle Meyts (KU Leuven), Trine Mogensen (Aarhus University), Lisa F.P. Ng (A*STAR Infectious Disease Labs), Antonio Novelli (Bambino Gesù Children's Hospital), Giuseppe Novelli (University of Rome Tor Vergata), Satoshi Okada

(Hiroshima University), Tayfun Ozcelik (Bilkent University), Qiang Pan-Hammarström (Karolinska Institutet), Rebeca Pérez de Diego (La Paz University Hospital), Jordi Perez-Tur (Instituto de Biomedicina de Valencia-CSIC), David S. Perlin (Center for Discovery and Innovation), Graziano Pesole (University of Bari Aldo Moro), Jonny Peter (University of Cape Town), Anna M. Planas (Institute for Biomedical Research of Barcelona), Carolina Prando (Instituto de Pesquisa Pelé Pequeno Príncipe), Anne Puel (Institut Imagine), Aurora Pujol (Bellvitge Biomedical Research Institute), Lluis Quintana-Murci (Institut Pasteur), Laurent Renia (Lee Kong Chian School of Medicine), Igor Resnick (University Hospital St. Marina), Jose Carlos Rodriguez Gallego (University Hospital of Gran Canaria Dr. Negrín), Jérémie Rosain (Institut Imagine), Lucie Roussel (McGill University Health Centre), Vanessa Sancho Shimizu (Imperial College London), Anna Sediva (Charles University), Mikko R.J. Seppänen (University of Helsinki), Mohammad Shahrooei (KU Leuven), Anna Shcherbina (Dmitry Rogachev National Medical Research Center), Pere Soler Palacín (Hospital Universitari Vall d'Hebron), Vassili Soumelis (Université de Paris), Andras Spaan (The Rockefeller University), Ivan Tancevski (Medical University of Innsbruck), Stuart Tangye (Garvan Institute of Medical Research), Ahmad Abou Tayoun (Al Jalila Children's Specialty Hospital), Şehime Gülsün Temel (Bursa Uludağ University), Christian Thorball (Centre Hospitalier Universitaire Vaudois), Pierre Tiberghien (Etablissement Français du Sang), Stuart E. Turvey (University of British Columbia), Mohammed J. Uddin (Mohammed Bin Rashid University), Furkan Uddin (NeuroGen Healthcare), Diederik van de Beek (University of Amsterdam), Donald C. Vinh (McGill University Health Centre), Joost Wauters (KU Leuven), Mayana Zatz (University of São Paulo), and Shen-Ying Zhang (Institut Imagine). All members of the CHGE contributed ideas and critically edited the manuscript. All authors approved the final version.

ACKNOWLEDGMENTS

The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute; The Rockefeller University; the St. Giles Foundation; the National Institutes of Health (NIH) (grants P01AI061093, R01AI088364, R01AI095983, R01AI127564, R01AI143810, R01AI163029, R01NS072381, R21AI137371, and U19AI162568); the National Center for Advancing Translational Sciences; the NIH Clinical and Translational Science Award program (UL1TR001866); the Fisher Center for Alzheimer's Research Foundation; the Meyer Foundation; the JPB Foundation; the Robertson Therapeutic Development Fund; the Tri-Institutional Stem Cell Initiative Fund; the French National Research Agency (ANR) under the Investments for the Future program (ANR-10-IAHU-01); the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID); the French Foundation for Medical Research (FRM) (EQU201903007798); the French Ministry of Higher Education, Research, and Innovation (MESRI-COVID-19); the FRM and ANR GEN-COVID project (ANR-20-COVI-0003); ANRS (National Agency for AIDS Research) Nord-Sud (ANRS-COV05); ANR grants SEAeHostFactors (ANR-18-CE15-0020-02), LTh-MSMD-CMCD (ANR-18-CE93-0008), CNSVIRGEN (ANR-19-CE15-0009-01), GENVIR (ANR-20-CE93-003), GENMSMD (ANR-16-C17-005), AABIFNCOV (ANR-20-CO11-0001), and GenMIS-C (ANR-21-COVR-0039); the ANR-RHU (Recherche Hospitalo-Universitaire en santé) program (ANR-21-RHUS-08); the European Union's Horizon 2020 research and innovation program under grant agreement 824110 (EASI-genomics); the HORIZON-HLTH-2021-DISEASE-04 program under grant agreement 01057100 (UNDINE); the Square Foundation; Grandir–Fonds de solidarité pour l'enfance; the SCOR Corporate Foundation for Science; Fondation du Souffle; Institut National de la Santé et de la Recherche Médicale (INSERM); REACTing-INSERM; and the Université Paris Cité. J.F.'s work on COVID is supported by

the Ecole Polytechnique Fédérale de Lausanne, the CHUV (Centre Hospitalier Universitaire Vaudois) Foundation, and the Swiss National Science Foundation (310030L_197721).

LITERATURE CITED

1. Dong E, Du H, Gardner L. 2020. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect. Dis.* 20:533–34
2. Zhang Q, Bastard P, COVID Hum. Genet. Effort, Cobat A, Casanova JL. 2022. Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* 603:587–98
3. O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, et al. 2021. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* 590:140–45
4. COVID-19 Forecast. Team. 2022. Variation in the COVID-19 infection-fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis. *Lancet* 399:1469–88
5. Bennett TD, Moffitt RA, Hajagos JG, Amor B, Anand A, et al. 2021. Clinical characterization and prediction of clinical severity of SARS-CoV-2 infection among US adults using data from the US National COVID Cohort Collaborative. *JAMA Netw. Open* 4:e2116901
6. Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, et al. 2020. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 588:315–20
7. Navaratnam AV, Gray WK, Day J, Wendon J, Briggs TWR. 2021. Patient factors and temporal trends associated with COVID-19 in-hospital mortality in England: an observational study using administrative data. *Lancet Respir. Med.* 9:397–406
8. Ricoca Peixoto V, Vieira A, Aguiar P, Sousa P, Carvalho C, et al. 2021. Determinants for hospitalisations, intensive care unit admission and death among 20,293 reported COVID-19 cases in Portugal, March to April 2020. *Eur. Surveill.* 26(33):2001059
9. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, et al. 2020. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 584:430–36
10. Sancho-Shimizu V, Brodin P, Cobat A, Biggs CM, Toubiana J, et al. 2021. SARS-CoV-2-related MIS-C: a key to the viral and genetic causes of Kawasaki disease? *J. Exp. Med.* 218(6):e20210446
11. Ahmad F, Ahmed A, Rajendraprasad SS, Loranger A, Gupta S, et al. 2021. Multisystem inflammatory syndrome in adults: a rare sequela of SARS-CoV-2 infection. *Int. J. Infect. Dis.* 108:209–11
12. Arkin LM, Moon JJ, Tran JM, Asgari S, O'Farrelly C, et al. 2021. From your nose to your toes: a review of severe acute respiratory syndrome coronavirus 2 pandemic–associated pernio. *J. Investig. Dermatol.* 141:2791–96
13. Brodin P, Casari G, Townsend L, O'Farrelly C, Tancevski I, et al. 2022. Studying severe long COVID to understand post-infectious disorders beyond COVID-19. *Nat. Med.* 28:879–82
14. Moghadas SM, Vilches TN, Zhang K, Wells CR, Shoukat A, et al. 2021. The impact of vaccination on coronavirus disease 2019 (COVID-19) outbreaks in the United States. *Clin. Infect. Dis.* 73:2257–64
15. Davies NG, Jarvis CI, Group CC-W, Edmunds WJ, Jewell NP, et al. 2021. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature* 593:270–74
16. Nyberg T, Twohig KA, Harris RJ, Seaman SR, Flannagan J, et al. 2021. Risk of hospital admission for patients with SARS-CoV-2 variant B.1.1.7: cohort analysis. *BMJ* 373:n1412
17. Patone M, Thomas K, Hatch R, Tan PS, Coupland C, et al. 2021. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. *Lancet Infect. Dis.* 21:1518–28
18. Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, et al. 2022. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect. Dis.* 22:35–42
19. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, et al. 2022. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet* 399:437–46
20. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, et al. 2021. SARS-CoV-2 variants, spike mutations and immune escape. *Nat. Rev. Microbiol.* 19:409–24
21. Kuhlmann C, Mayer CK, Claassen M, Maponga T, Burgers WA, et al. 2022. Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *Lancet* 399:625–26

22. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, et al. 2021. Covid-19 breakthrough infections in vaccinated health care workers. *N. Engl. J. Med.* 385:1474–84
23. Casanova JL, Abel L. 2022. From rare disorders of immunity to common determinants of infection: following the mechanistic thread. *Cell* 185:3086–103
24. Casanova JL, Abel L. 2021. Mechanisms of viral inflammation and disease in humans. *Science* 374:1080–86
25. Gibbs KD, Schott BH, Ko DC. 2022. The awesome power of human genetics of infectious disease. *Annu. Rev. Genet.* 56:41–62
26. Alcais A, Quintana-Murci L, Thaler DS, Schurr E, Abel L, Casanova JL. 2010. Life-threatening infectious diseases of childhood: single-gene inborn errors of immunity? *Ann. N. Y. Acad. Sci.* 1214:18–33
27. Kwiatkowski DP. 2005. How malaria has affected the human genome and what human genetics can teach us about malaria. *Am. J. Hum. Genet.* 77:171–92
28. Meyts I, Bosch B, Bolze A, Boisson B, Itan Y, et al. 2016. Exome and genome sequencing for inborn errors of immunity. *J. Allergy Clin. Immunol.* 138:957–69
29. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, et al. 2022. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J. Clin. Immunol.* 42(7):1473–507
30. Casanova JL, Abel L. 2020. The human genetic determinism of life-threatening infectious diseases: genetic heterogeneity and physiological homogeneity? *Hum. Genet.* 139:681–94
31. Casanova JL, Abel L. 2021. Lethal infectious diseases as inborn errors of immunity: toward a synthesis of the germ and genetic theories. *Annu. Rev. Pathol. Mech. Dis.* 16:23–50
32. Martinez-Barricarte R, Markle JG, Ma CS, Deenick EK, Ramirez-Alejo N, et al. 2018. Human IFN-g immunity to mycobacteria is governed by both IL-12 and IL-23. *Sci. Immunol.* 3(30):eaau6759
33. Bustamante J. 2020. Mendelian susceptibility to mycobacterial disease: recent discoveries. *Hum. Genet.* 139:993–1000
34. Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, et al. 2019. Mendelian susceptibility to mycobacterial disease: 2014–2018 update. *Immunol. Cell Biol.* 97:360–67
35. Zhang SY. 2020. Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity. *Hum. Genet.* 139:911–18
36. Bastard P, Manry J, Chen J, Rosain J, Seeleuthner Y, et al. 2021. Herpes simplex encephalitis in a patient with a distinctive form of inherited IFNAR1 deficiency. *J. Clin. Investig.* 131(1):e139980
37. Boisson-Dupuis S. 2020. The monogenic basis of human tuberculosis. *Hum. Genet.* 139:1001–9
38. Boisson-Dupuis S, Ramirez-Alejo N, Li Z, Patin E, Rao G, et al. 2018. Tuberculosis and impaired IL-23-dependent IFN-g immunity in humans homozygous for a common *TYK2* missense variant. *Sci. Immunol.* 3(30):eaau8714
39. Kerner G, Laval G, Patin E, Boisson-Dupuis S, Abel L, et al. 2021. Human ancient DNA analyses reveal the high burden of tuberculosis in Europeans over the last 2,000 years. *Am. J. Hum. Genet.* 108:517–24
40. Kerner G, Ramirez-Alejo N, Seeleuthner Y, Yang R, Ogishi M, et al. 2019. Homozygosity for *TYK2* P1104A underlies tuberculosis in about 1% of patients in a cohort of European ancestry. *PNAS* 116:10430–34
41. COVID-19 Host Genet. Initiat. 2020. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur. J. Hum. Genet.* 28:715–18
42. Casanova JL, Su HC, COVID Hum. Genet. Effort. 2020. A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection. *Cell* 181:1194–99
43. COVID-19 Host Genet. Initiat. 2022. A first update on mapping the human genetic architecture of COVID-19. *Nature* 608:E1–10
44. Kousathanas A, Pairo-Castineira E, Rawlik K, Stuckey A, Odhams CA, et al. 2022. Whole-genome sequencing reveals host factors underlying critical COVID-19. *Nature* 607:97–103
45. Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, et al. 2020. Genomewide association study of severe Covid-19 with respiratory failure. *N. Engl. J. Med.* 383:1522–34
46. Zeberg H, Paabo S. 2020. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature* 587:610–12

47. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, et al. 2021. Genetic mechanisms of critical illness in COVID-19. *Nature* 591:92–98
48. COVID-19 Host Genet. Initiat. 2021. Mapping the human genetic architecture of COVID-19. *Nature* 600:472–77
49. Downes DJ, Cross AR, Hua P, Roberts N, Schwessinger R, et al. 2021. Identification of *LZTFL1* as a candidate effector gene at a COVID-19 risk locus. *Nat. Genet.* 53:1606–15
50. Horowitz JE, Kosmicki JA, Damask A, Sharma D, Roberts GHL, 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.* 54:382–92
51. Dendrou CA, Cortes A, Shipman L, Evans HG, Attfield KE, et al. 2016. Resolving *TYK2* locus genotype-to-phenotype differences in autoimmunity. *Sci. Transl. Med.* 8:363ra149
52. Huffman JE, Butler-Laporte G, Khan A, Pairo-Castineira E, Drivas TG, et al. 2022. Multi-ancestry fine mapping implicates *OAS1* splicing in risk of severe COVID-19. *Nat. Genet.* 54:125–27
53. Zeberg H, Paabo S. 2021. A genomic region associated with protection against severe COVID-19 is inherited from Neandertals. *PNAS* 118(9):e2026309118
54. Dong B, Xu L, Zhou A, Hassel BA, Lee X, et al. 1994. Intrinsic molecular activities of the interferon-induced 2–5A-dependent RNase. *J. Biol. Chem.* 269:14153–58
55. Schwartz SL, Conn GL. 2019. RNA regulation of the antiviral protein 2′-5′-oligoadenylate synthetase. *WIREs RNA* 10:e1534
56. Bonnevie-Nielsen V, Field LL, Lu S, Zheng DJ, Li M, et al. 2005. Variation in antiviral 2′,5′-oligoadenylate synthetase (2′5′AS) enzyme activity is controlled by a single-nucleotide polymorphism at a splice-acceptor site in the *OAS1* gene. *Am. J. Hum. Genet.* 76:623–33
57. Fadista J, Kraven LM, Karjalainen J, Andrews SJ, Geller F, et al. 2021. Shared genetic etiology between idiopathic pulmonary fibrosis and COVID-19 severity. *eBioMedicine* 65:103277
58. Shrine N, Guyatt AL, Erzurumluoglu AM, Jackson VE, Hobbs BD, et al. 2019. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat. Genet.* 51:481–93
59. Hobbs BD, de Jong K, Lamontagne M, Bosse Y, Shrine N, et al. 2017. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis. *Nat. Genet.* 49:426–32
60. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, et al. 2013. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat. Genet.* 45:613–20
61. Gordon DE, Hiatt J, Bouhaddou M, Rezelj VV, Ulferts S, et al. 2020. Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms. *Science* 370(6521):abe9403
62. Ciancanelli MJ, Huang SX, Luthra P, Garner H, Itan Y, et al. 2015. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science* 348:448–53
63. Hernandez N, Melki I, Jing H, Habib T, Huang SSY, et al. 2018. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. *J. Exp. Med.* 215:2567–85
64. Lim HK, Huang SXL, Chen J, Kerner G, Gilliaux O, et al. 2019. Severe influenza pneumonitis in children with inherited TLR3 deficiency. *J. Exp. Med.* 216:2038–56
65. Abolhassani H, Vosughimotlagh A, Asano T, Landegren N, Boisson B, et al. 2022. X-linked TLR7 deficiency underlies critical COVID-19 pneumonia in a male patient with ataxia-telangiectasia. *J. Clin. Immunol.* 42:1–9
66. Schmidt A, Peters S, Knaus A, Sabir H, Hamsen F, et al. 2021. *TBK1* and *TNFRSF13B* mutations and an autoinflammatory disease in a child with lethal COVID-19. *npj Genom. Med.* 6:55
67. Zhang Q, Matuozzo D, Le Pen J, Lee D, Moens L, et al. 2022. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. *J. Exp. Med.* 219(8):e20220131
68. Khanmohammadi S, Rezaei N, Khazaei M, Shirkani A. 2022. A case of autosomal recessive interferon alpha/beta receptor alpha chain (IFNAR1) deficiency with severe COVID-19. *J. Clin. Immunol.* 42:19–24
69. Abolhassani H, Landegren N, Bastard P, Materna M, Modaresi M, et al. 2022. Inherited IFNAR1 deficiency in a child with both critical COVID-19 pneumonia and multisystem inflammatory syndrome. *J. Clin. Immunol.* 42:471–83

70. Butler-Laporte G, Povysil G, Kosmicki JA, Cirulli ET, Drivas T, et al. 2022. Exome-wide association study to identify rare variants influencing COVID-19 outcomes: results from the Host Genetics Initiative. *PLOS Genet.* 18:e1010367
71. Kosmicki JA, Horowitz JE, Banerjee N, Lanche R, Marcketta A, et al. 2021. Pan-ancestry exome-wide association analyses of COVID-19 outcomes in 586,157 individuals. *Am. J. Hum. Genet.* 108:1350–55
72. Povysil G, Butler-Laporte G, Shang N, Wang C, Khan A, et al. 2021. Rare loss-of-function variants in type I IFN immunity genes are not associated with severe COVID-19. *J. Clin. Investig.* 131(14):e147834
73. Zhang Q, Cobat A, Bastard P, Notarangelo LD, Su HC, et al. 2021. Association of rare predicted loss-of-function variants of influenza-related type I IFN genes with critical COVID-19 pneumonia. *J. Clin. Investig.* 131(15):e152474
74. Matuozzo D, Talouarn E, Marchal A, Zhang P, Manry J, et al. 2023. Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19. *Genome Med.* 15:22
75. Li J, Lei WT, Zhang P, Rapaport F, Seeleuthner Y, et al. 2021. Biochemically deleterious human *NFKB1* variants underlie an autosomal dominant form of common variable immunodeficiency. *J. Exp. Med.* 218(11):e20210566
76. Koning R, Bastard P, Casanova JL, Brouwer MC, van de Beek D, Amsterdam U.M.C. COVID-19 Biobank Investig. 2021. Autoantibodies against type I interferons are associated with multi-organ failure in COVID-19 patients. *Intensive Care Med.* 47:704–6
77. Lamborn IT, Jing H, Zhang Y, Drutman SB, Abbott JK, et al. 2017. Recurrent rhinovirus infections in a child with inherited MDA5 deficiency. *J. Exp. Med.* 214:1949–72
78. Fallerini C, Daga S, Mantovani S, Benetti E, Picchiotti N, et al. 2021. Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study. *eLife* 10:e67569
79. Mantovani S, Daga S, Fallerini C, Baldassarri M, Benetti E, et al. 2022. Rare variants in Toll-like receptor 7 results in functional impairment and downregulation of cytokine-mediated signaling in COVID-19 patients. *Genes Immun.* 23:51–56
80. Pessoa NL, Bentes AA, de Carvalho AL, de Souza Silva TB, Alves PA, et al. 2021. Case report: hepatitis in a child infected with SARS-CoV-2 presenting Toll-like receptor 7 Gln11Leu single nucleotide polymorphism. *Virol. J.* 18:180
81. Solanich X, Vargas-Parra G, van der Made CI, Simons A, Schuurs-Hoeijmakers J, et al. 2021. Genetic screening for *TLR7* variants in young and previously healthy men with severe COVID-19. *Front. Immunol.* 12:719115
82. van der Made CI, Simons A, Schuurs-Hoeijmakers J, van den Heuvel G, Mantere T, et al. 2020. Presence of genetic variants among young men with severe COVID-19. *JAMA* 324:663–73
83. Casanova JL, Abel L. 2015. Disentangling inborn and acquired immunity in human twins. *Cell* 160:13–15
84. Nakanishi T, Pigazzini S, Degenhardt F, Cordioli M, Butler-Laporte G, et al. 2021. Age-dependent impact of the major common genetic risk factor for COVID-19 on severity and mortality. *J. Clin. Investig.* 131(23):e152386
85. Cruz R, Almeida SD, Heredia ML, Quintela I, Ceballos FC, et al. 2022. Novel genes and sex differences in COVID-19 severity. *Hum. Mol. Genet.* 31(22):3789–806
86. Bartleson JM, Radenkovic D, Covarrubias AJ, Furman D, Winer DA, Verdin E. 2021. SARS-CoV-2, COVID-19 and the ageing immune system. *Nat. Aging* 1:769–82
87. Splunter MV, Perdijk O, Fick-Brinkhof H, Floris-Vollenbroek EG, Meijer B, et al. 2019. Plasmacytoid dendritic cell and myeloid dendritic cell function in ageing: a comparison between elderly and young adult women. *PLOS ONE* 14:e0225825
88. Schultze JL, Aschenbrenner AC. 2021. COVID-19 and the human innate immune system. *Cell* 184:1671–92
89. Stark GR, Darnell JE Jr. 2012. The JAK-STAT pathway at twenty. *Immunity* 36:503–14
90. Pierce CA, Sy S, Galen B, Goldstein DY, Orner E, et al. 2021. Natural mucosal barriers and COVID-19 in children. *JCI Insight* 6(9):e148694
91. Andreakos E, Abel L, Vinh DC, Kaja E, Drolet BA, et al. 2022. A global effort to dissect the human genetic basis of resistance to SARS-CoV-2 infection. *Nat. Immunol.* 23:159–64

92. Martinez-Sanz J, Jimenez D, Martinez-Campelo L, Cruz R, Vizcarra P, et al. 2021. Role of ACE2 genetic polymorphisms in susceptibility to SARS-CoV-2 among highly exposed but non infected healthcare workers. *Emerg. Microbes Infect.* 10:493–96
93. Reukers DFM, van Boven M, Meijer A, Rots N, Reusken C, et al. 2022. High infection secondary attack rates of severe acute respiratory syndrome coronavirus 2 in Dutch households revealed by dense sampling. *Clin. Infect. Dis.* 74:52–58
94. Tournamille C, Colin Y, Cartron JP, Le Van Kim C. 1995. Disruption of a GATA motif in the *Duffy* gene promoter abolishes erythroid gene expression in Duffy-negative individuals. *Nat. Genet.* 10:224–28
95. Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, et al. 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the *CKR5* structural gene. *Science* 273:1856–62
96. Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, et al. 1996. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* 86:367–77
97. Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, et al. 1996. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 382:722–25
98. Lindesmith L, Moe C, Marionneau S, Ruvoen N, Jiang X, et al. 2003. Human susceptibility and resistance to Norwalk virus infection. *Nat. Med.* 9:548–53
99. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Sonmez T, et al. 2021. Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity. *Nat. Genet.* 53:801–8
100. Gutierrez-Valencia M, Leache L, Librero J, Jerico C, Enguita German M, Garcia-Erce JA. 2022. ABO blood group and risk of COVID-19 infection and complications: a systematic review and meta-analysis. *Transfusion* 62:493–505
101. Cooling L. 2015. Blood groups in infection and host susceptibility. *Clin. Microbiol. Rev.* 28:801–70
102. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PK, et al. 2005. ABO blood group and susceptibility to severe acute respiratory syndrome. *JAMA* 293:1450–51
103. Roberts GHL, Partha R, Rhead B, Knight SC, Park DS, et al. 2022. Expanded COVID-19 phenotype definitions reveal distinct patterns of genetic association and protective effects. *Nat. Genet.* 54:374–81
104. Biering SB, Sarnik SA, Wang E, Zengel JR, Leist SR, et al. 2022. Genome-wide bidirectional CRISPR screens identify mucins as host factors modulating SARS-CoV-2 infection. *Nat. Genet.* 54:1078–89
105. Grodzki M, Bluhm AP, Schaefer M, Tagmount A, Russo M, et al. 2022. Genome-scale CRISPR screens identify host factors that promote human coronavirus infection. *Genome Med.* 14:10
106. Zhu Y, Feng F, Hu G, Wang Y, Yu Y, et al. 2021. A genome-wide CRISPR screen identifies host factors that regulate SARS-CoV-2 entry. *Nat. Commun.* 12:961
107. Wang R, Simoneau CR, Kulsuptrakul J, Bouhaddou M, Travisano KA, et al. 2021. Genetic screens identify host factors for SARS-CoV-2 and common cold coronaviruses. *Cell* 184:106–19.e14
108. Schneider WM, Luna JM, Hoffmann HH, Sanchez-Rivera FJ, Leal AA, et al. 2021. Genome-scale identification of SARS-CoV-2 and pan-coronavirus host factor networks. *Cell* 184:120–32.e14
109. Wei J, Alfajaro MM, DeWeirdt PC, Hanna RE, Lu-Culligan WJ, et al. 2021. Genome-wide CRISPR screens reveal host factors critical for SARS-CoV-2 infection. *Cell* 184:76–91.e13
110. Daniloski Z, Jordan TX, Wessels HH, Hoagland DA, Kasela S, et al. 2021. Identification of required host factors for SARS-CoV-2 infection in human cells. *Cell* 184:92–105.e16
111. Baggen J, Persoons L, Vanstreels E, Jansen S, Van Looveren D, et al. 2021. Genome-wide CRISPR screening identifies TMEM106B as a proviral host factor for SARS-CoV-2. *Nat. Genet.* 53:435–44
112. Rebendenne A, Roy P, Bonaventure B, Chaves Valadao AL, Desmarets L, et al. 2022. Bidirectional genome-wide CRISPR screens reveal host factors regulating SARS-CoV-2, MERS-CoV and seasonal HCoVs. *Nat. Genet.* 54:1090–102
113. Andreakos E, Abel L, Vinh DC, Kaja E, Drolet BA, et al. 2021. A global effort to dissect the human genetic basis of resistance to SARS-CoV-2 infection. *Nat. Immunol.* 23:159–64
114. Bastard P, Gervais A, Le Voyer T, Rosain J, Philippot Q, et al. 2021. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. *Sci. Immunol.* 6(62):eabl4340
115. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, et al. 2020. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 370(6515):abd4585

116. Puel A, Bastard P, Bustamante J, Casanova JL. 2022. Human autoantibodies underlying infectious diseases. *J. Exp. Med.* 219(4):e20211387
117. Ku CL, Chi CY, von Bernuth H, Doffinger R. 2020. Autoantibodies against cytokines: phenocopies of primary immunodeficiencies? *Hum. Genet.* 139:783–94
118. Pozzetto B, Mogensen KE, Tovey MG, Gresser I. 1984. Characteristics of autoantibodies to human interferon in a patient with varicella-zoster disease. *J. Infect. Dis.* 150:707–13
119. Goncalves D, Mezidi M, Bastard P, Perret M, Saker K, et al. 2021. Antibodies against type I interferon: detection and association with severe clinical outcome in COVID-19 patients. *Clin. Transl. Immunol.* 10:e1327
120. Shaw ER, Rosen LB, Cheng A, Dobbs K, Delmonte OM, et al. 2021. Temporal dynamics of anti-type I interferon autoantibodies in COVID-19 patients. *Clin. Infect. Dis.* 75(1):e1192–94
121. Savvateeva E, Filippova M, Valuev-Elliston V, Nuralieva N, Yukina M, et al. 2021. Microarray-based detection of antibodies against SARS-CoV-2 proteins, common respiratory viruses and type I interferons. *Viruses* 13(12):2553
122. Troya J, Bastard P, Planas-Serra L, Ryan P, Ruiz M, et al. 2021. Neutralizing autoantibodies to type I IFNs in >10% of patients with severe COVID-19 pneumonia hospitalized in Madrid, Spain. *J. Clin. Immunol.* 41:914–22
123. van der Wijst MGP, Vazquez SE, Hartoularos GC, Bastard P, Grant T, et al. 2021. Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. *Sci. Transl. Med.* 13:eabh2624
124. Vazquez SE, Bastard P, Kelly K, Gervais A, Norris PJ, et al. 2021. Neutralizing autoantibodies to type I interferons in COVID-19 convalescent donor plasma. *J. Clin. Immunol.* 41:1169–71
125. Wang EY, Mao T, Klein J, Dai Y, Huck JD, et al. 2021. Diverse functional autoantibodies in patients with COVID-19. *Nature* 595:283–88
126. Abers MS, Rosen LB, Delmonte OM, Shaw E, Bastard P, et al. 2021. Neutralizing type-I interferon autoantibodies are associated with delayed viral clearance and intensive care unit admission in patients with COVID-19. *Immunol. Cell Biol.* 99:917–21
127. Chauvineau-Grenier A, Bastard P, Servajean A, Gervais A, Rosain J, et al. 2021. Autoantibodies neutralizing type I interferons in 20% of COVID-19 deaths in a French hospital. Res. Sq. rs.3.rs-915062/v1. **https://doi.org/10.21203/rs.3.rs-915062/v1**
128. Solanich X, Rigo-Bonnin R, Gumucio VD, Bastard P, Rosain J, et al. 2021. Pre-existing autoantibodies neutralizing high concentrations of type I interferons in almost 10% of COVID-19 patients admitted to intensive care in Barcelona. *J. Clin. Immunol.* 41(8):1733–44
129. Raadsen MP, Gharbharan A, Jordans CCE, Mykytyn AZ, Lamers MM, et al. 2022. Interferon-α2 autoantibodies in convalescent plasma therapy for COVID-19. *J. Clin. Immunol.* 42:232–39
130. Chang SE, Feng A, Meng W, Apostolidis SA, Mack E, et al. 2021. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat. Commun.* 12:5417
131. Ziegler CGK, Miao VN, Owings AH, Navia AW, Tang Y, et al. 2021. Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19. *Cell* 184:4713–33.e22
132. Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodriguez Y, Gallo JE, et al. 2021. COVID-19 convalescent plasma composition and immunological effects in severe patients. *J. Autoimmun.* 118:102598
133. Carapito R, Li R, Helms J, Carapito C, Gujja S, et al. 2022. Identification of driver genes for critical forms of COVID-19 in a deeply phenotyped young patient cohort. *Sci. Transl. Med.* 14:eabj7521
134. Eto S, Nukui Y, Tsumura M, Nakagama Y, Kashimada K, et al. 2022. Neutralizing type I interferon autoantibodies in Japanese patients with severe COVID-19. *J. Clin. Immunol.* 42:1360–70
135. Manry J, Bastard P, Gervais A, Le Voyer T, Rosain J, et al. 2022. The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies. *PNAS* 119:e2200413119
136. Bastard P, Orlova E, Sozaeva L, Levy R, James A, et al. 2021. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J. Exp. Med.* 218(7):e20210554
137. Lopez J, Mommert M, Mouton W, Pizzorno A, Brengel-Pesce K, et al. 2021. Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. *J. Exp. Med.* 218(10):e20211211

138. Sposito B, Broggi A, Pandolfi L, Crotta S, Clementi N, et al. 2021. The interferon landscape along the respiratory tract impacts the severity of COVID-19. *Cell* 184:4953–68.e16
139. Bastard P, Zhang Q, Zhang SY, Jouanguy E, Casanova JL. 2022. Type I interferons and SARS-CoV-2: from cells to organisms. *Curr. Opin. Immunol.* 74:172–82
140. Bastard P, Vazquez S, Liu J, Laurie MT, Wang CY, et al. 2022. Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs. *Sci. Immunol.* In press
141. Zhang Q, Pizzorno A, Miorin L, Bastard P, Gervais A, et al. 2022. Autoantibodies against type I IFNs in patients with critical influenza pneumonia. *J. Exp. Med.* 219(11):e20220514
142. Busnadiego I, Abela IA, Frey PM, Hofmaenner DA, Scheier TC, et al. 2022. Critically ill COVID-19 patients with neutralizing autoantibodies against type I interferons have increased risk of herpesvirus disease. *PLOS Biol.* 20:e3001709
143. Mathian A, Breillat P, Dorgham K, Bastard P, Charre C, et al. 2022. Lower disease activity but higher risk of severe COVID-19 and herpes zoster in patients with systemic lupus erythematosus with pre-existing autoantibodies neutralising IFN-α. *Ann. Rheum. Dis.* 81:1695–703
144. Sun S, Wang Y, Maslov AY, Dong X, Vijg J. 2022. SomaMutDB: a database of somatic mutations in normal human tissues. *Nucleic Acids Res.* 50:D1100–8
145. Levy R, Zhang P, Bastard P, Dorgham K, Melki I, et al. 2021. Monoclonal antibody–mediated neutralization of SARS-CoV-2 in an IRF9-deficient child. *PNAS* 118(45):e2114390118
146. de Prost N, Bastard P, Arrestier R, Fourati S, Mahevas M, et al. 2021. Plasma exchange to rescue patients with autoantibodies against type I interferons and life-threatening COVID-19 pneumonia. *J. Clin. Immunol.* 41:536–44
147. Vinh DC, Abel L, Bastard P, Cheng MP, Condino-Neto A, et al. 2021. Harnessing type I IFN immunity against SARS-CoV-2 with early administration of IFN-β. *J. Clin. Immunol.* 41(7):1425–42
148. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, et al. 2018. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* 50:1219–24
149. Huang QM, Zhang PD, Li ZH, Zhou JM, Liu D, et al. 2022. Genetic risk and chronic obstructive pulmonary disease independently predict the risk of incident severe COVID-19. *Ann. Am. Thorac. Soc.* 19:58–65
150. Kaiser J. 2021. DNA test to predict odds of severe COVID-19 draws scrutiny. *Science* 372:1139
151. Tangye SG, COVID Hum. Genet. Effort Consort. 2023. Impact of SARS-CoV-2 infection and COVID-19 on patients with inborn errors of immunity. *J. Allergy Clin. Immunol.* 151:818–31
152. Lee D, Le Pen J, Yatim A, Dong B, Aquino Y, et al. 2022. Inborn errors of OAS–RNase L in SARS-CoV-2–related multisystem inflammatory syndrome in children. *Science* 379(6632):abo3627
153. Chou J, Platt CD, Habiballah S, Nguyen AA, Elkins M, et al. 2021. Mechanisms underlying genetic susceptibility to multisystem inflammatory syndrome in children (MIS-C). *J. Allergy Clin. Immunol.* 148:732–38.e1
154. Lee PY, Platt CD, Weeks S, Grace RF, Maher G, et al. 2020. Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of *SOCS1*. *J. Allergy Clin. Immunol.* 146:1194–200.e1
155. Bolze A, Mogensen TH, Zhang SY, Abel L, Andreakos E, et al. 2022. Decoding the human genetic and immunological basis of COVID-19 mRNA vaccine–induced myocarditis. *J. Clin. Immunol.* 42:1354–59
156. Namkoong H, Edahiro R, Takano T, Nishihara H, Shirai Y, et al. 2022. *DOCK2* is involved in the host genetics and biology of severe COVID-19. *Nature* 609:754–60
157. Ostendorf BN, Patel MA, Bilanovic J, Hoffmann HH, Carrasco SE, et al. 2022. Common human genetic variants of *APOE* impact murine COVID-19 mortality. *Nature* 611:346–51
158. Herrera-Esposito D, de Los Campos G. 2022. Age-specific rate of severe and critical SARS-CoV-2 infections estimated with multi-country seroprevalence studies. *BMC Infect. Dis.* 22:311
159. Asano T, Boisson B, Onodi F, Matuozzo D, Moncada-Velez M, et al. 2021. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. *Sci. Immunol.* 6:eabl4348
160. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, et al. 2020. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 370(6515):eabd4570

Annual Review of Biomedical Data Science

Volume 6, 2023

Contents

Errata

An online log of corrections to *Annual Review of Biomedical Data Science* articles may be found at http://www.annualreviews.org/errata/biodatasci