A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection

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Abstract

SARS-CoV-2 infection displays immense inter-individual clinical variability, ranging from silent infection to lethal disease. The role of human genetics in determining clinical response to the virus remains unclear. Studies of outliers – individuals remaining uninfected despite viral exposure and healthy young patients with life-hreatening disease – presents a unique opportunity to reveal human genetic determinants of infection and disease.

Text

There are seven known human-tropic coronaviruses (CoV), three of which have caused severe epidemics (Gabutti et al., 2020). These three RNA viruses — SARS-CoV-1 (discovered in 2002), MERS-CoV (2012), and SARS-CoV-2 (2019) — are much more virulent than the other four (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1), which cause common colds and only rare cases of severe disease, including pneumonia. In 2002, SARS-CoV-1 caused an epidemic limited to China. In 2012, MERS-CoV caused an epidemic that began in Saudi Arabia, subsequently spreading primarily in the Middle East before containment. SARS-CoV-2 was first detected in China in 2019, but has since become a devastating ongoing global pandemic. Most SARS-CoV-2 infections are asymptomatic or benign, but SARS-CoV-2 infectious disease 2019 (COVID-19) can cause life-threatening pneumonia. Severe COVID-19 occurs much more frequently in patients over the age of 50 years and/or with comorbid conditions such as pulmonary, cardiovascular, and metabolic disorders (Gabutti et al., 2020) (**Figure 1**). Life-threatening disease probably strikes less than 1 in 1000 infected individuals below the age of 50 without underlying conditions but more than 1 in 10 infected patients over the age of 80 years with multiple comorbidities. The

identification of advanced age and comorbidities as major risk factors is clinically important and suggests that the decline of the body weakens immunity, which may be difficult to translate into molecular, cellular, and immunological terms.

However, there is also a more perplexing, but perhaps less difficult problem. Why are previously healthy children, adolescents, young, or middle-aged adults being admitted to intensive care for respiratory failure due to COVID-19? Why would a 40-year-old man who completed a marathon in October 2019 find himself intubated and ventilated for COVID-19 respiratory failure in April 2020? The COVID Human Genetic Effort (https://www.covidhge.com/) proposes that previously healthy, young patients with severe COVID-19 carry causal genetic variants. This hypothesis is not yet supported by specific genetic epidemiological studies of COVID-19, but it follows a long line of classical genetic studies since 1905, relating to diverse infections in plants and animals, including humans (Casanova and Abel, 2020). Three types of human genetic epidemiological studies merit specific comment. Twin studies have shown that concordance rates for some infectious diseases, such as tuberculosis, are much higher for monozygotic than dizygotic twins. Adoption studies have shown that early death from any type of infection is paradoxically correlated with early death from infection of the biological, but not the foster parents. Finally, susceptibility to various infectious diseases has been shown, particularly by segregation studies, to be heritable and to reflect the impact of a major gene.

Since 1950, genetic and molecular studies have provided an immunological basis for inherited predispositions to infectious diseases. Patient- and family-based studies led to the discovery of autosomal recessive neutropenia and X-linked recessive agammaglobulinemia. These two seminal inborn errors of immunity appeared to be Mendelian, and the pathophysiological mechanism of each was elucidated, providing proof-of-principle for

genetic predisposition to human infectious diseases. These and many other inborn errors of immunity are individually rare and underlie multiple, recurrent, and often unusual infections in individual patients. Since 1985, molecular genetics studies have confirmed these disorders to be Mendelian (monogenic with complete clinical penetrance).

These studies launched a painstaking mission to decipher the genetic basis of susceptibility to infections in humans, from the individual to whole-population levels. This genetic patient-by-patient, family-by family, disorder-by-disorder approach was highly productive in the few patients studied, but seemed unlikely to deliver results of great significance for the general population. First, the phenotype of multiple and familial infections is not observed in most people, who typically display isolated and sporadic infections. Second, populations consist of huge numbers of individuals, so defining the population genetic architecture of infectious diseases through causal analyses and genetics of individual cases is a Herculean task. A more tenable pathway from the population to the individual was proposed, based on associations and biometrics.

The ambitious population-based biometrics approach to studying infectious diseases, initiated in the 1950s, highlights the persistent divide between Mendelian geneticists and Galtonian biometricians. The biometric approach began with a spectacular discovery when Anthony Allison found that the sickle cell trait provided 10-fold protection against severe forms of *Plasmodium falciparum* malaria. With hindsight, this discovery told us more about the selective pressure imposed by malaria on the *Homo sapiens* genome than the mechanism by which individual human genomes predispose to malaria. It provided no significant explanation of malaria at the individual level, as it failed to explain why about 1 in 1000 infected children develops severe malaria, or 1 in 10,000 sickle cell trait carriers. Furthermore, despite this initial breakthrough, the biometric approach fell short of its promise. Other

association studies, whether genome-wide or candidate gene-based, have not matched Allison's discovery, in terms of effect size or proportion of the variance explained. However, this approach did yield two important results concerning viruses. Some HLA class I alleles are strongly associated with lower viral loads in the blood and slower disease progression in individuals infected with human immunodeficiency virus (HIV), and homozygotes for a type III IFN (*IFNL3-IFNL4)* haplotype are more likely to clear hepatitis C virus spontaneously during primary infection.

We can hope that genome-wide association studies for COVID-19 will generate results of similar or greater importance. Nevertheless, this approach is intrinsically limited by genetic and phenotypic heterogeneity and by the need for multiple testing corrections. More importantly, statistical association studies do not provide mechanisms. Without determining the chain of cause and consequence, causality between a candidate genotype and a clinical phenotype remains uncertain, no matter how statistically probable. In human medicine, establishing causality between genotype and phenotype requires the rigorous validation of mechanisms at the molecular, cellular, tissue, and whole-organism levels. The genome of the individual must explain the mechanisms underlying severe COVID-19, and this requires in-depth biochemical and immunological studies. Investigators have thus long been faced with the cruel dilemma of deeply understanding a single patient through genetics or attempts at understanding the entire population through biometrics.

After 1996, the horizons of the field of inborn errors of immunity broadened, with discoveries of both Mendelian and non-Mendelian monogenic bases of infectious diseases striking previously healthy, seemingly immune competent patients. This paradigm shift was inspired by two spectacular forward genetics studies in which the genetic bases of susceptibility to influenza virus (*Mx* locus, 1962) or *Mycobacterium bovis* BCG (*Bcg* locus,

1975) were characterized in inbred mice. The protein encoded by *Mx*, a gene cloned by cell complementation, protects mice from influenza virus (Staeheli et al., 1986) and is potentially relevant to COVID-19. Studies of mycobacteria led to the first positional cloning of a mouse gene, with the demonstration that *Nramp1* mutations render animals susceptible to mycobacteria (Vidal et al., 1993).

Unlike specific gene-targeting approaches, these two studies focused on mouse phenotypes suggestive of a narrow pattern of infection susceptibility. These laboratory mice were not challenged with as many microbes as they would encounter in the wild, but elucidation of the underlying genotypes and mechanisms confirmed that the corresponding gene products were probably essential for immunity to only a few infectious agents. Prior to these results, human monogenic inborn errors of immunity were considered to be rare, Mendelian disorders underlying recurrent, multiple, and often unusual infections in individual patients. After, the search for the molecular and cellular basis of human genetic susceptibility to isolated infections, rare or common, began in earnest.

Rare human "Mendelian infections" had been recognized since the description in 1946 of epidermodysplasia verruciformis, an autosomal recessive predisposition to viral warts and cancer. However, they remained largely neglected until 1996, when the first inborn error of immunity selectively underlying infectious disease segregating in families as a Mendelian trait was molecularly deciphered (**Table 1**). The first and best studied of these conditions is Mendelian susceptibility to mycobacterial disease (MSMD), caused by inborn errors of type II interferon (IFN-γ). Additionally, both Epstein-Barr virus (EBV) and beta-human papillomaviruses (beta-HPV) are usually benign but can cause a lethal disease that is strictly Mendelian. Severe EBV-induced disease can be caused by inborn errors that disrupt the killing of EBV-infected B cells by cytotoxic T and NK cells. These deficiencies affect the collaboration

between two major arms of adaptive immunity. By contrast, epidermodysplasia verruciformis results from disruption of the EVER-CIB1-dependent control of beta-HPV in keratinocytes, a deficiency of non-hematopoietic, cell-intrinsic immunity. Together with MSMD and two other fungal infections, these two disorders define the five known “Mendelian infections”.

These studies paved the way for investigation of other sporadic infectious diseases, testing the hypothesis that they might be monogenic but not Mendelian. This hypothesis has been confirmed by molecular genetic studies, beginning with viral diseases in 2007 (Zhang et al.). The first and best example is that of herpes simplex virus 1 (HSV-1) encephalitis, a sporadic disease caused, in ~5-10% of cases, by mutations affecting the TLR3 or snoRNA31 pathways (forebrain infection) or DBR1 (brainstem infection) (Zhang et al., 2018). These mutations impair neuron-intrinsic immunity to HSV-1 in the central nervous system (CNS). Other examples more closely related to COVID-19 include influenza virus pneumonia, which can be caused by inborn errors impairing antiviral type I and III interferon (IFN) immunity (IFN-α/β and -λ), including IRF7, IRF9, and TLR3 deficiencies, in circulating plasmacytoid dendritic cells and/or pulmonary epithelial cells (Ciancanelli et al., 2015; Hernandez et al., 2018; Lim et al., 2019), and rhinovirus pneumonia, which can be caused by a deficiency of IFN-inducing MDA5 (Asgari et al., 2017; Lamborn et al., 2017). These disorders underlie severe viral disease through the impairment of antiviral type I and/or III IFN immunity.

Similar immunological scenarios, and even some of the same inborn errors, could underlie severe pulmonary COVID-19 in previously healthy young patients with monogenic disorders. In the absence of known human genetic determinants of susceptibility to other coronaviruses, influenza is likely to provide the best comparison. The threshold levels of type I and/or III IFN for protection against SARS-CoV-2 might be similar to those for the 1918 influenza virus, but higher than those for seasonal influenza. IFN-dependent control of the

virus could be profoundly impaired during initial infection in patients with early-onset pneumonia, whereas those whose condition deteriorates later could have milder IFN deficiency, or genetically determined excessive inflammation. For example, *IL18BP* mutations underlie fulminant viral hepatitis because they unleash IL-18-dependent inflammation in the liver, whereas *SH2D1A* mutations underlie hemophagocytosis following B-cell infection with EBV. Inborn errors could impair IFN immunity in leukocytes or pulmonary cells or enhance local or systemic inflammation. It will be interesting to determine whether known inborn errors of inflammation, such as deficiencies of IL-1 or IL-6 immunity, protect against severe forms of COVID-19. Inborn errors of cell-intrinsic immunity in the CNS might be involved in the rarer neurological complications of COVID-19. The anosmia reported by some patients suggests that SARS-CoV-2 may infect the olfactory bulb, from which it may invade the forebrain, as for HSV-1 in patients with *TLR3* mutations.

COVID-19 is a completely new disease and the current pandemic dwarfs previous SARS-CoV-1 and MERS-CoV outbreaks. We can, therefore, study newly infected patients on a massive scale, with minimal interference from vaccines, previous related infections, and herd immunity, in sharp distinction to influenza. COVID-19 provides us with a tragic but unparalleled opportunity to define precisely the genetic requirements for the control of an emerging, virulent, viral infection. The body makes use of the pleiotropic functions of many cells to control infection, including subsets of pulmonary cells and leukocytes. Many genes are also pleiotropic. Genome-wide searches for candidate monogenic, or digenic, disorders should therefore be immunologically agnostic, testing diverse genetic hypotheses. Approaches should include searching not only for highly penetrant rare variants, but also for common variants that can be highly penetrant in specific infections, as recently shown for a common monogenic etiology of tuberculosis (Kerner et al., 2019). Moreover, highly penetrant

monogenic disorders should not be considered only in children, as illustrated by the death of a NOS2-deficient patient over the age of 50 years from primary cytomegalovirus infection (Drutman et al., 2020). Amid the uncertainties concerning the genetic architecture of COVID-19 suceptibility, only one thing is almost certain: as for other infectious diseases, there will be considerable genetic heterogeneity, reflecting the multiple layers of host defense that a virus must overcome to lead to mortality.

To understand the genetic requirements for immune control of SARS-CoV-2, in February 2020, we began recruiting COVID-19 patients from as many centers and countries as possible to the COVID Human Genetic Effort (https://www.covidhge.com/). We target young patients (< 50 years) with life-threatening disease and no pre-existing medical conditions. Our initiative has been rapidly expanding, with a growing number of centers that recruit patients, take clinical histories, and send blood samples to sequencing hubs. The exome and genome data are analyzed simultaneously locally at the hubs and centrally by the consortium. Hypotheses of genetic heterogeneity (one causal locus per kindred) and genetic homogeneity (a causal locus in two or more kindreds) are being tested in parallel. The large number of patients may facilitate the detection of promising candidate genotypes in single patients or families, including variants of known viral susceptibility genes.

More importantly, this initiative will also detect genetic homogeneity, if the same gene is mutated in geographically distant patients. The analysis and comparison of genetic variants from a large number of individuals from diverse backgrounds will be crucial, as we cannot solely rely on current databases of data for “healthy” individuals to identify rare variants, which include individuals never before exposed to SARS-CoV-2. A large sample of genomes may also facilitate the detection of a polygenic background for monogenic mutations, or the testing of polygenic signals detected by other studies. Finally, the inclusion

of patients of diverse ancestries will make it possible to detect candidate genotypes specific or common to ancestries, and to consider the evolutionary forces driving variation at these loci (Quintana-Murci, 2019). Once candidate genotypes have been identified, their contribution to the pathogenicity of severe COVID-19 will be investigated with in-depth molecular, cellular, and immunological approaches. Studies of single patients can be illuminating, but more detailed mechanistic studies are required for firm conclusions (Casanova et al., 2014). In these genetic studies, we aim to discover the pathogenesis of unexplained, severe COVID-19 in young, previously healthy patients.

We anticipate that monogenic cases will provide insight into other types of cases, such as severe COVID-19 in elderly patients with several comorbid conditions, suggesting novel therapeutic possibilities for these patients. The pathogenesis may be similar in these patients, with different causes converging on common pathophysiological mechanisms. For example, inborn errors of IFN-γ and IL-17A/F immunity underlie mycobacteriosis and candidiasis, respectively. The same infections occur in patients with autoantibodies against IFN-γ and IL-17A/F, and in patients infected with HIV who have low levels of IFN-γ and IL-17A/F production by $CD4^+$ T cells, providing broader indications for the therapeutic use of IFN-γ. Thus, monogenic cases may clarify pathogenesis more broadly for COVID-19 patients. Such clarification cannot easily be achieved by directly studying patients with acquired immunodeficiencies, due to the many confounding factors and difficulties in determining whether immunological abnormalities in patients are causes or consequences of infection. Genetics provides us with access to the root cause of phenomena.

This project will also facilitate the detection of individuals naturally resistant to SARS-CoV-2 infection. Why would the spouse of a patient already ill for days and now in intensive care remain not only healthy but seronegative? How could a health care worker treating

contagious COVID-19 patients with insufficient protection remain healthy and seronegative? If such individuals also test negative for T-cell responses to SARS-CoV-2, it is plausible that some are genetically resistant to the virus. The first example of such a situation was a regulatory DARC variant discovered in the 1970s and deciphered genetically in 1995. In the homozygous state, this variant confers resistance to *Plamodium vivax* by abolishing the expression of a parasite receptor on erythrocytes. Two other known monogenic forms of resistance are more directly relevant to COVID-19. Homozygosity for *CCR5* null mutations protects against CCR5-tropic HIV, and homozygosity for null *FUT2* alleles protects against intestinal norovirus infection. Similarly, we speculate that loss-of-function variants of *ACE2*, encoding a receptor for SARS-CoV-2, might confer resistance, while hypomorphic variants might protect against severe disease in infected individuals. Identifying the genetic basis of resistance to SARS-CoV-2 would provide a pharmacological target for preventing or reducing viral infection in other individuals.

The COVID-19 pandemic has drawn attention to the fact that infections are unique among medical conditions in being able to kill hundreds of thousands of people within a few months. Alas, this fact is well known to developing countries, but the current pandemic provides a tragic but timely reminder to developed countries with short memories. Infections remain the only inevitable, unpredictable, catastrophic medical threat to humankind. The idea that infections were a problem solved once and for all by Pasteur's germ theory and the advances in hygiene, serotherapy, vaccination, aseptic surgery, and anti-infectious drug treatments that followed, is incorrect, complacent, and dangerous.

The COVID-19 pandemic should make us consider an alternative approach to studying infectious diseases. We have all witnessed enormous interindividual clinical variability in response to SARS-CoV-2 exposure, ranging from resistance to death, and everything in

between. Similar variability is observed for all human-tropic microbes, whether viruses, bacteria, fungi, or parasites. The proportion of life-threatening cases varies among microbes, from less than one in a million to greater than one in ten. This clinical variability during primary infection is the fundamental “infection enigma”, which, in 1955, led René Dubos to pen “Second thoughts on the germ theory” (Dubos, 1955). It is now time to test more comprehensively the hypothesis that the clinical manifestations of human infections, including SARS-CoV-2, can be governed by human genetics, at least in outliers resistant to infection or unusually prone to severe disease. This paradigm shift would open up new avenues for studying host-pathogen interactions in the course of evolution, controlling the current COVID-19 threat in the general population, and developing the infrastructure required to thwart future emerging threats.

Figure legend

Figure 1. Monogenic causes of susceptibility or resistance to SARS-CoV-2 infection. In the naïve general population (black), a proportion of people become symptomatic (purple) when infected. Severe cases (red) tend to occur in the elderly or in those patients having co-morbidities. However, rare “idiopathic” severe cases can occur in the young without co-morbidities, and these are hypothesized to represent patients with monogenic causes. A proportion of people remain asymptomatic (blue) when infected. In some instances, these may be people who remain resistant to infection (yellow), who can be identified by their remaining seronegative despite heavy or repeated exposures to the virus. Created with BioRender.

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Monogenic causes of COVID-19

SUSCEPTIBILITY or RESISTANCE

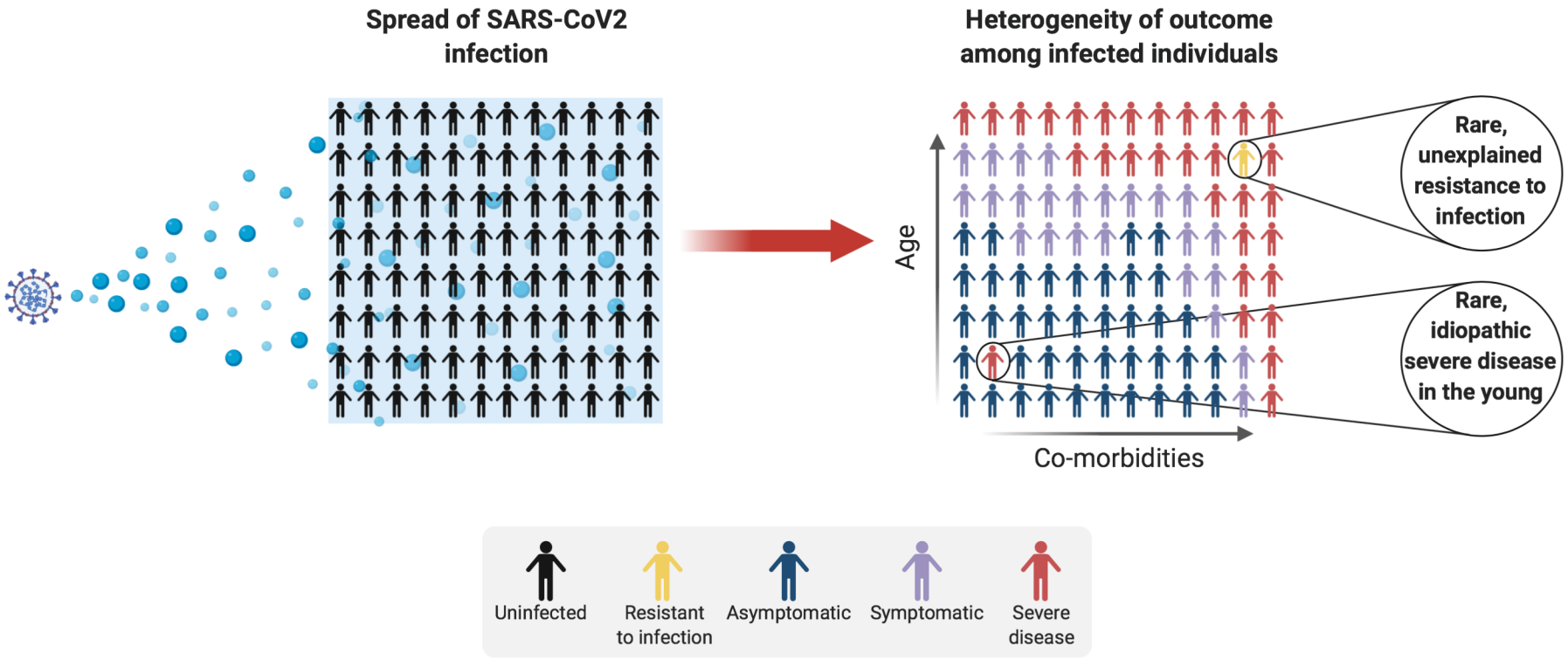

Table 1. Monogenic defects underlying narrow susceptibility to human viral diseases

Outcome	Pathogen (condition)	Gene
Susceptibility	Influenza virus (severe pneumonia)	*IRF7*
		IRF9
		TLR3
	Rhinovirus (severe pneumonia)	*IFIH1*
	Herpes simplex virus 1 (encephalitis)	*UNC93B1*
		TLR3
		TRIF
		TRAF3
		TBK1
		IRF3
		SNORA31
	Herpes simplex virus 1, influenza virus, norovirus (brainstem encephalitis)	*DBR1*
	Beta-papillomavirus (skin warts and cancer)	*TMC6*
		TMC8
		CIB1
	Epstein-Barr virus (hemophagocytosis, lympho-proliferation, lymphoma, hypogammaglobulinemia)	*SH2D1A*
		XIAP
		ITK
		MAGT1
		CD27
		CD70
	Varicella-zoster virus (disseminated disease)	*POLR3A*
		POLR3C
	Human herpes virus-8 (Kaposi sarcoma)	*TNFRSF4*
	Cytomegalovirus (disseminated disease)	*NOS2*
	Hepatitis A virus (fulminant hepatitis)	*IL18BP*
	Live-attenuated measles or yellow fever vaccine (disseminated disease)	*IFNAR1*
		IFNAR2
		STAT2
		IRF9
Resistance	Human immunodeficiency virus	*CCR5*
	Norovirus	*FUT2*