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A global effort to dissect the human genetic basis of resistance to SARS-CoV-2 infection

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SARS-CoV-2 infections display tremendous interindividual variability, ranging from asymptomatic infections to life-threatening disease. Inborn errors of, and autoantibodies directed against, type I interferons (IFNs) account for about 20% of critical COVID-19 cases among SARS-CoV-2-infected individuals. By contrast, the genetic and immunological determinants of resistance to infection per se remain unknown. Following the discovery that autosomal recessive deficiency in the DARC chemokine receptor confers resistance to *Plasmodium vivax*, autosomal recessive deficiencies of chemokine receptor 5 (CCR5) and the enzyme FUT2 were shown to underlie resistance to HIV-1 and noroviruses, respectively. Along the same lines, we propose a strategy for identifying, recruiting, and genetically analyzing individuals who are naturally resistant to SARS-CoV-2 infection.

The COVID-19 pandemic has reminded us that infections are unique among diseases in their potential to rapidly cause massive morbidity and mortality worldwide. Throughout history, infectious diseases have imposed strong selection pressures on humans[1–3]. In particular, viral pandemics, including ones caused by coronaviruses, have occurred repeatedly over the last century, and probably throughout human history[4–7]. Clinical variability in response to infection, viral or otherwise, can be explained, at least in some individuals, by human genetic factors[8]. The introduction of SARS-CoV-2 to a naive population, on a global scale, has provided yet another demonstration of the remarkable clinical variability between individuals in the course of infection, ranging from asymptomatic infections to life-threatening disease[9–11]. Our understanding of the pathophysiology of life-threatening COVID-19 has progressed considerably since the disease was first described in December 2019 (refs. [12,13]), but we still know very little about the human genetic and immunological basis of inborn resistance to SARS-CoV-2. Mean secondary attack rates for SARS-CoV-2 infections can reach up to 70% in specific households[14,15], and a number of families have been reported in which all the members except one of the spouses are infected[16], suggesting that some highly exposed individuals may be resistant to infection with this virus. Here, we review examples of genetically determined susceptibility to severe outcomes of two infectious diseases—tuberculosis (TB) and COVID-19—while covering in greater depth the three known cases of inborn resistance to infections. We then consider candidate genes directly relevant to resistance to SARS-CoV-2 infection. Finally, we propose a strategy for recruiting and genetically analyzing individuals who are naturally resistant to infection with the virus. Above all, we advocate for further studies to develop our understanding of the causal mechanisms of inborn resistance to SARS-CoV-2 infection and provide a framework for the use of this knowledge for therapeutic purposes.

Inborn susceptibility to life-threatening infectious diseases

Human evolution has been marked by microorganisms that are sufficiently pathogenic to exert selective pressure on genes crucial for host defense[2]. One of the deadliest scourges of human health is TB, which has caused an estimated one billion deaths in Europe over the past two millennia[17]. Paradoxically, less than 10% of humans infected with *Mycobacterium tuberculosis* develop TB. Since the turn of the twentieth century, the contribution of human genetics to TB pathogenesis has been deciphered through classic genetics and experimental studies[18,19]. More recently, rare inborn errors of immunity (IEIs), including autosomal recessive interleukin-12 receptor β1 (IL12RB1)[20,21] and tyrosine kinase 2 (TYK2) deficiencies[22], in particular, have been identified in a few people with TB. The broader relevance of this finding was shown when the analysis

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was expanded to more common variants, revealing that homozygosity for the TYK2(P1104A) polymorphism was associated with a high risk of developing TB[17,23]. p.P1104A homozygosity disrupts the capacity of TYK2 to mediate IL-23-dependent IFN-γ immunity to mycobacteria[23]. Its minor allele frequency is highest among Europeans[17]. An analysis of ancient DNA showed that the frequency of TYK2(P1104A) has strongly decreased over the last 2,000 years in Europe owing to strong negative selection, concomitant with the high TB burden in Europe[24].

With the advent of the COVID-19 pandemic, specific IEIs were shown to have a role in defining susceptibility to severe COVID-19. The COVID Human Genetic Effort (http://www.covidhge.com) reported 23 critically ill people with IEIs at 8 loci governing TLR3- and IRF7-dependent type I IFN induction and amplification[13]. Remarkably, four unrelated and previously healthy adults had autosomal recessive IRF7 or IFNAR1 deficiency. Although rare, the individuals with IEIs demonstrate that type I IFN immunity is indispensable for the control of SARS-CoV-2 infection. This finding led to the subsequent discovery, also by the consortium, of pre-existing neutralizing autoantibodies against type I IFNs as a phenocopy of type I IFN-related IEIs[12]. Subsequent studies in independent cohorts confirmed the presence of neutralizing autoantibodies against type I IFNs in more than 10% of people with severe COVID-19 (refs. [25–30]). More recently, the consortium found that autoantibodies neutralizing lower, more physiological concentrations of type I IFNs account for about 20% of patients older than 70 years with critical pneumonia[31]. Moreover, the consortium also reported that about 1% of male patients younger than 60 years of age with critical pneumonia have X-recessive TLR7 deficiency[32]. Surprisingly, the individuals with IEIs identified and those with autoantibodies had not displayed any particular susceptibility to other severe infectious diseases before exposure to SARS-CoV-2. This finding is consistent with the smaller amounts of type I IFNs induced by SARS-CoV-2 than by seasonal influenza virus, for example[33]. However, type I IFN autoantibodies have been shown to underlie a third of adverse reactions to the live attenuated yellow fever virus vaccine[34]. Collectively, these examples illustrate how the genetic elucidation of an immunological deficit in a few rare individuals can indicate a mechanism that is disrupted by other causes in many more people.

Inborn resistance to infection upon exposure

An individual's genetically determined protection against an infectious disease is the mirror image of genetically determined susceptibility to life-threatening disease. The term 'protective' is applied to a given locus when the allele associated with a lower risk of disease is the least frequent, alternative allele. Far fewer genetic studies on infectious diseases have focused on protective alleles than on susceptibility to infection, whether monogenic or polygenic. In the early 1950s, Anthony Allison showed that the HbS sickle-cell trait is maintained at high frequency in African areas where malaria is endemic, owing to a heterozygous advantage[1] of the allele for providing protection against severe *Plasmodium falciparum* infections[35]. Other examples of protection against poor infection outcomes include the occurrence of specific HLA class I alleles in long-term nonprogressing HIV-1-infected individuals[36], and the role of a type III interferon (*IFNL3-IFNL4*) haplotype in viral clearance following infection with hepatitis C virus (HCV)[37,38]. These alleles confer protection against severe disease in infected people, but not against contraction of the infection itself.

The genetic determinism of resistance to infection has been even less studied than that of protection against poor infection outcomes, and study has always been from a monogenic angle. Only three mechanisms of Mendelian resistance to infection have been identified to date. In the 1970s, Louis Miller discovered that the absence of the Duffy antigen on erythrocytes prevented these cells from becoming infected with *Plasmodium vivax*[39,40]. The molecular genetic basis of this autosomal recessive resistance trait was not determined until the 1990s. The causal variant affects the GATA-1 binding site in the *DARC* promoter, selectively preventing gene transcription in erythroid cells[41]. At about the same time, autosomal recessive CCR5 deficiency was found to confer resistance to infection with HIV-1 (refs. [42–44]). The most common loss-of-function mutation in *CCR5* is a 32-base-pair deletion with a minor allele frequency of 10% in the European population. Finally, autosomal recessive FUT2 deficiency was discovered to confer resistance to gastrointestinal infections with noroviruses[45]. As for *DARC* and the *P. vivax* Duffy binding protein, and *CCR5* and the HIV-1 gp120–gp41 heterodimer, *FUT2* expression is required for binding of the norovirus VPg capsid. It is probably no coincidence that these examples of Mendelian resistance to infection are complete deficiencies of receptors or coreceptors exploited by the pathogen as a means of entering cells. The genetic mechanisms of protection against severe infectious outcomes and those underlying resistance to infection itself are both subject to positive selection, as they provide a survival advantage[46].

Candidate SARS-CoV-2 resistance genes

The proportion of humans naturally resistant to SARS-CoV-2 infection is unknown, but a number of candidate genes potentially involved in human inborn resistance to SARS-CoV-2 infection have emerged from several lines of evidence. One is the *ABO* locus, which was identified in genome-wide association studies (GWAS)[47,48]. Although initial data on the impact of blood group on COVID-19 severity were inconsistent, a recent meta-analysis of nearly 50,000 people from 46 studies confirmed an effect of this locus on susceptibility to infection[49]. The protective effect of the O allele, however, is small, with an odds ratio of ~0.90. Although no unified mechanism of resistance has yet been proposed[50], ABO blood groups may play a direct role in infection by serving as coreceptors for SARS-CoV-2 (ref. [47]). Pandemic-associated pernio (chilblain) is a rare manifestation in individuals exposed to SARS-CoV-2 that could provide insight into mechanisms of resistance to infection[51,52]. Pandemic-associated pernio ('COVID toes') mimics the skin lesions of familial chilblain lupus and Aicardi–Goutières syndrome, monogenic disorders caused by mutations leading to an upregulation of type I IFN signaling[53]. Most people with pernio remain seronegative, but the presence of the SARS-CoV-2 spike protein has been demonstrated in skin biopsy specimens, and a robust local type I IFN response has also been observed, suggesting early clearance of the virus[54]. These observations imply the presence of infection, and, thus, the absence of natural resistance to infection. Nevertheless, by understanding the pathophysiology of this phenomenon, we may be able to shed light on host mechanisms restricting viral replication and promoting resilience upon SARS-CoV-2 infection.

In vitro interactome studies have identified additional candidate host genes supporting the viral life cycle. Early in the pandemic, it was discovered that SARS-CoV-2 infection is dependent on the ACE2 receptor for cell entry and the serine protease TMPRSS2 for spike protein priming[55–58]. Indeed, a rare variant located close to *ACE2* was found, by GWAS, to confer protection against SARS-CoV-2 infection, possibly by decreasing *ACE2* expression[59]. Furthermore, although their impact on infection is unknown, some human ACE2 polymorphisms bind the SARS-CoV-2 spike protein with different affinities in vitro[60]. In a genome-wide CRISPR knockout screen for infection with SARS-CoV-2 and other coronaviruses, TMEM41B was identified as a requirement for permissive infection with the virus[61]. TMEM41B is an endoplasmic reticulum transmembrane protein that is also required by flaviviruses[62]. Its impact on SARS-CoV-2 infection remains to be established, but an allele common in East and South Asians has been shown to be associated with a lower capacity to support flavivirus infection in vitro[62]. Like genome-wide CRISPR knockout screens, affinity purification-mass

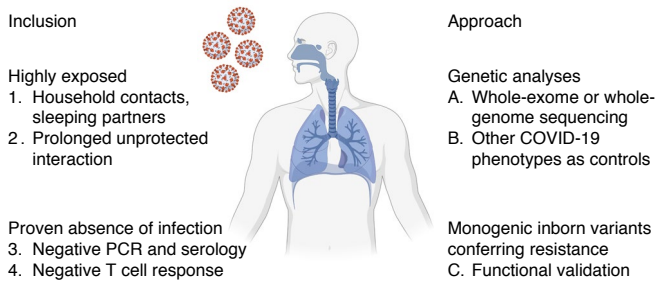

Fig. 1 | A global effort to dissect the human genetic basis of resistance to SARS-CoV-2 infection. Inclusion criteria, and approach for the identification and validation of inborn variants conferring resistance to SARS-CoV-2 infection (http://www.covidhge.com). Created with BioRender.com.

spectrometry on human proteins interacting with SARS-CoV-2 has yielded an extensive protein interaction map[63,64]. Functional assessments of this interactome have resulted in its translation into a catalog of essential host factors required for SARS-CoV-2 infection[65]. Although no human studies linking the SARS-CoV-2 interactome to susceptibility to infection have yet been published, the genes concerned—along with the loci identified by GWAS—can be regarded as candidates for the identification of inborn variants conferring resistance to infection.

Genetic and immunological strategies

There are two key challenges in the search for individuals naturally resistant to SARS-CoV-2 infection. First, demonstrating an absence of infection poses a diagnostic hurdle. PCR-based molecular diagnostic approaches using respiratory specimens provide only snapshot information. Serology is useful for assessing the occurrence of prior infections for many viral infections, but some individuals remain seronegative despite infection with SARS-CoV-2 (refs. [66,67]). Pre-existing crossreactive T-cell-mediated immunity as a result of prior infections with other coronaviruses might contribute to a resilient response upon infection with SARS-CoV-2 (refs. [68–71]). At the same time, T cell responses to SARS-CoV-2-specific antigens could provide a sensitive and specific marker for the qualitative assessment of prior infection with SARS-CoV-2 (ref. [68]). A second challenge lies in the probability of virus transmission. The likelihood of infection is influenced by both the duration and intensity of exposure to an infected individual, and the intrinsic transmission characteristics of the pathogen. The basic reproduction number (R_0, the average number of secondary infections produced by a typical case of an infection in a population where everyone is susceptible) of SARS-CoV-2 is between 2.5 and 5.0, on average[72–74]. However, coronaviruses are known to be transmitted during superspreader events with very high secondary attack rates[75]. Identifying these events, other large-scale outbreaks, and households in which one or very few individuals remained uninfected[14–16] would be of particular interest for the study of inborn variants conferring resistance to SARS-CoV-2.

When testing the hypothesis that monogenic inborn variants of immunity confer natural resistance to SARS-CoV-2 infection, we apply a four-step strategy to overcome diagnostic limitations and uncertainties about exposure (Fig. 1). We first focus on uninfected household contacts of people with symptomatic COVID-19 (score of 3 or higher on the World Health Organization's clinical progression scale[76]). We then consider individuals exposed to an index case without personal protection equipment, for at least 1 hour per day, and during the first 3–5 days of symptoms in the index case. Priority is given to the study of serodiscordant spouses and sleeping partners. We subsequently enroll individuals with a negative PCR result when tested plus negative serological results obtained 4 weeks after exposure. Finally, we assess SARS-CoV-2-specific T cell responses in the candidate resistant individuals and compare their responses with those of SARS-CoV-2-infected individuals. We differentiate T cell responses induced by vaccination from those provoked by natural infection. Study participants lacking a SARS-CoV-2-reactive T cell response will be analyzed by whole-exome/genome sequencing. The results will be compared with those for SARS-CoV-2-infected controls, with the aim of identifying rare or common variants with a strong effect on resistance to infection[11–13,77]. Finally, as in studies of IEIs[78], the genetic findings will be validated experimentally, including with cells from the study participants, to dissect the mechanisms of resistance at the molecular, cellular, tissue, immunological, and whole-organism levels (Fig. 1).

Concluding remarks

Historical examples of inborn resistance to infection with other pathogens provide a road map for testing the hypothesis of monogenic inborn resistance to infection with SARS-CoV-2. Some more common inborn variants of resistance in candidate genes may have relatively small effects. However, we also aim to identify candidate genes with potentially rare variants and a large effect size. These variants are of particular interest for two reasons. First, they can provide a deep understanding of the essential biological pathways involved in infection with SARS-CoV-2. Second, they will allow for the development of innovative therapeutic interventions to prevent or treat SARS-CoV-2 infection in others. The proof-of-principle for this second reason of interest has been provided by CCR5 and its antagonist maraviroc, which is used for the treatment of HIV-1 infections in specific settings[79]. In addition, transplantation of CCR5-deficient bone marrow has been successfully applied to cure HIV infection in a few people[80,81]. No specific drug effective against COVID-19 has been discovered since the start of the pandemic. Lessons learned from experiments of nature could potentially guide us toward such specific treatments for COVID-19. We have already enrolled more than 400 individuals meeting the criteria for inclusion in a dedicated resistance study cohort. The collaborative enrollment of study participants is continuing (http://www.covidhge.com), and subjects from all over the world are welcome.

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Competing interests

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Additional information

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COVID Human Genetic Effort

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