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Perspective

# From rare disorders of immunity to common determinants of infection: Following the mechanistic thread

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## SUMMARY

The immense interindividual clinical variability during any infection is a long-standing enigma. Inborn errors of IFN- $\gamma$  and IFN- $\alpha/\beta$  immunity underlying rare infections with weakly virulent mycobacteria and seasonal influenza virus have inspired studies of two common infections: tuberculosis and COVID-19. A *TYK2* genotype impairing IFN- $\gamma$  production accounts for about 1% of tuberculosis cases, and autoantibodies neutralizing IFN- $\alpha/\beta$  account for about 15% of critical COVID-19 cases. The discovery of inborn errors and mechanisms underlying rare infections drove the identification of common monogenic or autoimmune determinants of related common infections. This “rare-to-common” genetic and mechanistic approach to infectious diseases may be of heuristic value.

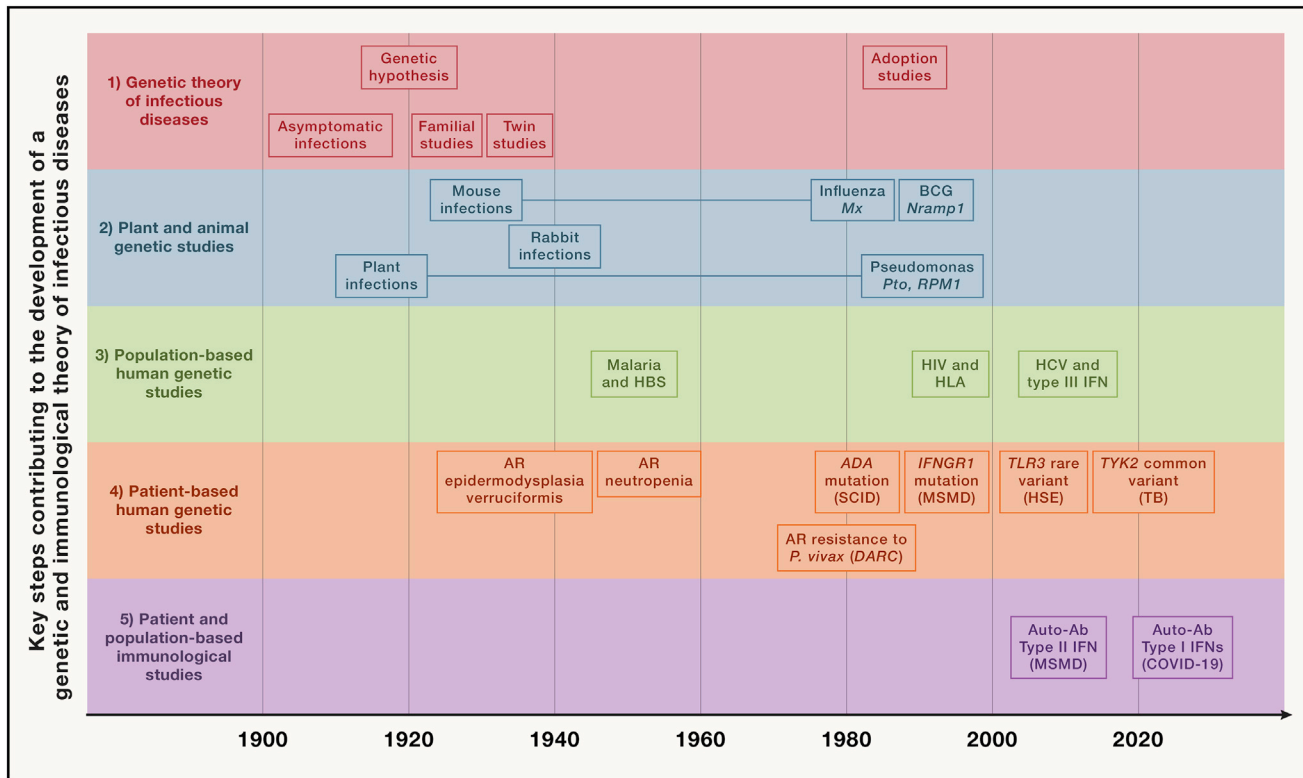
## INTRODUCTION

A key but neglected enigma in the field of microbiology and infectious disease is the immense interindividual clinical variability during any primary infection (Casanova, 2015a; Casanova and Abel, 2021a). We define infection as microbial replication within the host and primary infection as the first infection with a given microorganism. The continuous nature of the microbial world renders this notion more operational than rigorous (e.g., primary infection with SARS-CoV-2 may be different in someone previously infected with SARS-CoV, and the same is true for *Mycobacterium tuberculosis* infection in someone previously infected with *M. bovis*). Throughout evolution, primary infections have been the main threat to humankind, with half of all children dying from fever before the age of 15 years and a life expectancy at birth of about 20–25 years until the end of the 19<sup>th</sup> century (Casanova and Abel, 2005). However, this tragic toll was mostly due to the dazzling diversity of pathogens, rather than their individual virulence. Indeed, life-threatening disease is a rare (<1% of infected individuals) outcome of infection for most (>99%) pathogens, at any given period, and in any given region (Casanova and Abel, 2021b). Plague in the Middle Ages, tuberculosis (TB) between the 17<sup>th</sup> and 19<sup>th</sup> centuries, the 1918 flu pandemic, and the current AIDS and COVID-19 pandemics, along with a few other devastating infections, stand out as global exceptions. High mortality may also be restricted to naive populations, on their first exposure to an infectious disease (e.g., measles in native Americans and in Arctic and Polynesian populations) (Christensen et al., 1953; Shanks et al., 2011; Walker et al., 2015). Nevertheless, most infected subjects remained well or suffered benign disease, even for these examples, and mortality

only rarely exceeded 30% (Casanova and Abel, 2021a). Ironically, the most important unknown in the field of infectious diseases is, thus, the root cause of life-threatening disease, which occurs in only a fraction of infected people. There is no doubt that an infectious agent is necessary to trigger clinical disease, but there is also no doubt that the infectious agent is far from being sufficient to cause severe disease or death.

Historically, microbiologists and infectious disease specialists have tended not to consider this problem because their attention has been focused elsewhere, on the discovery and characterization of pathogens and the prevention and treatment of infectious diseases (Casanova and Abel, 2020). It is probably fair to say that microbiologists have attempted to analyze the impact of microbes in cells and animal models because these approaches could facilitate the development of vaccines or antimicrobial agents, but they have only rarely considered interindividual variability in the course of infection. In parallel, immunologists have been preoccupied with the pursuit of the “antibody enigma” (Kindt, 1984), focusing on its innate and adaptive components, and largely neglecting the field of infectious diseases after Landsteiner’s seminal breakthrough discovery that Ab responses can be mounted against synthetic structures that do not exist naturally (Landsteiner, 1936). Generations of immunologists have studied immunological responses to various non-infectious antigens. The existence of human determinants of severe infectious disease, highlighted at an unprecedented scale by the impact of immunosuppression from the 1960s onward and by human immunodeficiency virus (HIV) infection from the 1980s onward, has not significantly modified their approach. Moreover, the vast majority of life-threatening primary infections cannot be explained by such acquired immunodeficiencies, which more





**Figure 1. Timeline showing some of the key steps that have progressively contributed to the development of a genetic and immunological theory of infectious diseases, grouped into five main parallel fields, from top to bottom**

(1) Germ and genetic theories of infectious diseases (red). Following the establishment of the germ theory of disease between 1865 and 1870 (Louis Pasteur) (Pasteur, 1922–1939) and its radical version with Koch’s postulates in 1882 (Robert Koch) (Koch, 1882), it became widely accepted that life-threatening fevers in animals and humans were infectious. Chief among Koch’s postulates was the notion that a pathogen must be found in all patients with a given disease and not in healthy individuals. Once established, this postulate made it difficult to appreciate and understand the importance of the evidence of both latent (non-replicating, dormant germs in tissues of asymptomatic individuals; Clemens von Pirquet and followers) (von Pirquet, 1909) and unapparent (replicating germs in tissues or bloodstream of asymptomatic individuals; Charles Nicolle) (Nicolle, 1933) silent infections. Human geneticists proposed a genetic solution to the problem of asymptomatic infection. Karl Pearson (Pearson, 1912) and other population geneticists and biometricians, in parallel with Archibald Garrod (Garrod, 1931) and other clinical and biochemical geneticists, proposed that the germline genetic background of the host influences or determines susceptibility or resistance to any given microbe. J.B.S. Haldane proposed that infectious diseases had played a major role in natural selection (Haldane, 1949). Various epidemiological and familial approaches were conducted in the first half of the 20th century, supporting this hypothesis. The most remarkable and convincing investigations were probably twin studies comparing monozygotic and dizygotic twins for concordance for a particular infectious phenotype, in particular for tuberculosis (TB) (Puffer, 1944). Adoption studies, which compare the cause of death of patients with that of their biological and foster parents and are equally powerful, were conducted later (Sorensen et al., 1988).

(2) Plant and animal genetic studies (blue). Plant biologists and geneticists also reported early in the 20<sup>th</sup> century that resistance or susceptibility to infection can be genetically determined (Biffen, 1905; Flor, 1942). From the 1920s onward, other researchers approached the question of the host genetics of infectious diseases from the angle of animal models, including mice and rabbits in particular. Their results led to a similar conclusion, as some strains were vulnerable to the infections tested, whereas others were not (Lurie, 1941; Webster, 1939). These were experimental, as opposed to natural, infections. The experiments were powerful. By the late 1930s, the stage was set for major progress and a transition to molecular genetics, building on multiple independent lines of thought and investigation. Molecular discoveries began in mice in 1986, with the identification, by molecular complementation, of the first monogenic infection susceptibility gene, *Mx*, mutations of which underlie influenza virus infections (Staehele et al., 1986), followed by the discoveries, by positional cloning, of the *Bcg* (*Nramp1*) (Skamene et al., 1982; Vidal et al., 1993), *Cmv* (*Ly49h*) (Brown et al., 2001), and *Lps* (*TLR4*) (Poltorak et al., 1998) loci. In parallel, superb studies unraveled the monogenic basis of various infections in various plant species (Dangl and Jones, 2001; Jones et al., 2016), including, in particular, the role of the *Pto* and *RPM1* genes in resistance to *Pseudomonas* in tomato and *Arabidopsis thaliana*, respectively (Grant et al., 1995; Martin et al., 1993).

(3) Population-based human genetic studies (green). At the population level, the field of human genetics of infectious diseases began with the discovery, by Allison in 1954, that the sickle cell trait (HbS) provides significant protection against severe forms of *P. falciparum* malaria (Allison, 1954). Classical genetic epidemiology studies, particularly segregation analyses followed by genome-wide linkage studies, identified major loci for common infectious conditions, such as schistosomiasis and leprosy (Abel and Demeinai, 1988; Alcaïs et al., 2007; Marquet et al., 1996; Mira et al., 2004). Very few candidate gene association studies were successful, and only a handful reported odds ratios (ORs) for developing the disease >2 that were replicated in independent populations; among the most remarkable is the association of some HLA class I alleles with AIDS progression, with hazard ratios for protection of about 0.3 (Kaslow et al., 1996). Finally, genome-wide association studies (GWASs) met with variable success, depending on the infectious disease, with many loci identified in leprosy (Zhang et al., 2009, 2011) with ORs below 2, and, more recently, malaria (Malaria Genomic Epidemiology, 2019), with ORs for protection above 0.5, except for the *HBB* locus. The most remarkable achievement of GWAS in infectious diseases was probably the identification, toward 2010, of *IL28B* variants (*IL28B* encodes the type III IFN- $\lambda$ 3) strongly associated with the clearance of hepatitis C virus (Ge et al., 2009) (OR for clearance ~6). More recently, GWAS in COVID-19 have identified several common variants associated with severe pneumonia, the most significant being located on chromosome 3 with an OR ~2 (COVID-19 Host Genetics Initiative, 2021; Kousathanas et al., 2022; Païro-Castineira et al., 2021).

(4) Patient-based human genetic studies (orange). In the early 1950s, pediatricians and clinical geneticists described the first inborn errors of immunity (IEIs)—then referred to as primary immunodeficiencies (PIDs)—as rare, Mendelian, early-onset conditions underlying both multiple, recurrent, and opportunistic

typically underlie “opportunistic” rather than “idiopathic” infections (Casanova and Abel, 2020, 2021b). These detectable deficits nevertheless suggested that the occurrence of infectious disease in particular patients might have other, hitherto unknown, causes. The search for root causes of severe infectious diseases started some time ago, at the turn of the 20<sup>th</sup> century. It was historically led by human geneticists, in the wake of or in parallel with the work of plant and animal geneticists (Beutler, 2008; Casanova, 2015a, 2015b; Dangl and Jones, 2001; Haller et al., 2018; Vidal et al., 2008).

We covered the history of the field of human genetics of infectious diseases in the 19<sup>th</sup> and 20<sup>th</sup> centuries in a previous review (Casanova and Abel, 2013) (overview in Figure 1). We stressed the importance of classical (from about 1910 onward) and molecular (from about 1950 onward) genetic studies in humans (Casanova, 2015a; Casanova and Abel, 2013, 2021a), together with the considerable influence of pioneering studies in plants and animals (from about 1905 onward) (Dangl and Jones, 2001; Vidal et al., 2008). We reviewed both monogenic and non-monogenic examples of genetic resistance to infection (per se) or disease (in infected individuals) (Casanova and Abel, 2013, 2021a; Quintana-Murci et al., 2007). We also reviewed the three steps, in 1985, 1996, and 2007, by which rare genetic variants underlying monogenic inborn errors of immunity (IEI) in humans were discovered and successively shown to underlie (1) syndromic infectious diseases (i.e., associated with other phenotypes, infectious or otherwise; conditions previously known as “primary immunodeficiencies [PIDs]”), (2) isolated and familial infectious diseases, and (3) isolated and sporadic infectious diseases (Casanova and Abel, 2021a). For these last two categories, IEI underlying the phenotype were found in at least some patients and, sometimes, in single patients, initially with rare infections (from 1996, with disease caused by weakly virulent mycobacteria), or, more recently, with common infections

(from 2001, with TB). It should be stressed that these last two steps were inspired by the discovery of infection susceptibility genes by forward genetics in mice between 1986 (mutations of *Mx* conferring susceptibility to influenza) and 1993 (mutations of *Nramp1* conferring susceptibility to mycobacteria) (Staehele et al., 1986; Vidal et al., 1993) and in plants from 1993 onward (*Pto* and *RPM1* genes involved in resistance to *Pseudomonas* in tomato and *Arabidopsis thaliana*, respectively) (Dangl and Jones, 2001; Grant et al., 1995; Martin et al., 1993). We contrasted these patient- and family-based genetic studies generating experimentally validated information about the causal mechanisms of disease with larger, population-based association studies based principally on statistics and yielding modest risk factors at the individual level (Casanova et al., 2013; Thorball et al., 2021; Zhang et al., 2022a).

Here, we focus on a fourth step forward: the discovery of common determinants of common infectious diseases. Since 2018, studies have shown that homozygosity for the common *TYK2* P1104A variant impairs the IL-23-dependent induction of type II IFN and accounts for about 1% of European cases of TB (Boisson-Dupuis et al., 2018; Kerner et al., 2019, 2021). In 2020–2021, at least 1% of cases of critical COVID-19 pneumonia across major ancestries were found to be due to inborn errors of type I IFN immunity (due to rare variants, especially at the X-linked *TLR7* locus), and at least 15% were due to the occurrence of auto-Abs neutralizing some type I IFNs and already present before infection (Bastard et al., 2021a; Bastard et al., 2020; Casanova and Abel, 2021b; Zhang et al., 2022a). Monogenic disorders and their auto-immune phenocopies can, thus, account for a sizable proportion (>1%) of at least two common infections. Until these reports, the proportion of patients with a common infection understood at the molecular and cellular levels was negligible. This contrasted with rare infections, some of which were understood for a much larger proportion of cases (e.g., disease caused by weakly virulent

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infections, and overt, or at least detectable, immunological abnormalities. The blueprint for conventional IEI is widely agreed to be the description of Bruton's X-linked recessive (XR) agammaglobulinemia in 1952 (Bruton, 1952). Severe congenital neutropenia had, however, been described earlier, in 1950, in children with severe staphylococcal and other bacterial infections and congenital neutropenia, two phenotypes that co-segregated as an autosomal recessive (AR) trait (Kostmann, 1950, 1956). The first IEI conferring predisposition to a single infectious agent was, however, reported even earlier, in 1946, when Wilhelm Lutz described epidermolytic verruciformis (EV) as an AR predisposition to skin-tropic viruses (Lutz, 1946) identified in 1978 by Gérard Orth to be weakly virulent human papillomaviruses (HPVs) (Orth et al., 1978). Immunologists did not consider EV to be an IEI, because of the lack of a detectable leukocyte abnormality, until the discovery of EV-causing genes from 2002 onward led to the gradual recognition that keratinocytes contribute to host defense (de Jong et al., 2018; Ramoz et al., 2002). Defects of the membrane attack complex of complement (underlying infections with *Neisseria*), and X-linked lymphoproliferation (XLP, Epstein-Barr virus) were described later, from different angles, as XLP, like EV, was described as a Mendelian and unexplained (idiopathic) infection (Purtilo et al., 1974, 1977), whereas complement defects were found serendipitously in sporadic cases of *Neisseria* disease (Lim et al., 1976; Petersen et al., 1976). Mendelian resistance to infectious agents was first detected in the 1970s, with the Duffy antigen receptor for chemokines (DARCs) and *P. vivax* malaria (Miller et al., 1976), the genetic basis of which was elucidated in 1995 (Tournamille et al., 1995). It was followed, in the mid-1990s, by the discovery of the link between C-C chemokine receptor 5 (CCR5) variants and resistance to human immunodeficiency virus-1 (HIV-1) (Dean et al., 1996; Liu et al., 1996; Samson et al., 1996). The first mutated gene underlying a conventional IEI, *ADA*, was reported in patients with severe combined immunodeficiency in 1985 (Bonthron et al., 1985). The first mutated gene underlying an isolated infection, *IFNGR1*, was identified in patients with MSMD in 1996 (Jouanguy et al., 1996; Newport et al., 1996). Since 2007, some rare and sporadic infectious diseases (e.g., HSE) have been shown to be caused by rare monogenic defects, with incomplete penetrance (Casanova and Abel, 2021a; Zhang et al., 2007). Since 2001, rare monogenic defects have also been shown to underlie some common infectious diseases in rare patients (e.g., TB in 2001 [Altare et al., 2001] and COVID-19 in 2020 [Zhang et al., 2020]). Since 2018, monogenic causes of infection have been found in a greater proportion of patients with TB (due to homozygosity for a common *TYK2* allele) (Boisson-Dupuis et al., 2018; Kerner et al., 2019, 2021) or COVID-19 (due to hemizyosity for various rare *TLR7* alleles) (Asano et al., 2021; Casanova and Abel, 2021a).

(5) Patient- and population-based immunological studies (magenta). Auto-Abs against four cytokines (type I and II IFNs, IL-6, and IL-17A/F) have been shown to underlie infectious phenocopies of the corresponding inborn errors of cytokines or their response pathways (Ku et al., 2020; Puel et al., 2022). The best characterized are probably auto-Abs neutralizing type II IFN, which underlie a phenocopy of MSMD and, more rarely, TB (Puel et al., 2022; Shih et al., 2021). Auto-Abs neutralizing type I IFNs, first described in the early 1980s, were long thought to be clinically silent, except for a 77-year-old woman with disseminated zoster studied by Ion Gresser (Pozzetto et al., 1984). They were found in almost all patients with autoimmune polyendocrine syndrome type 1 (APS-1) (Husebye et al., 2018; Meager et al., 2006). Since 2020, they have been shown to be strong determinants of at least 15% of cases of life-threatening COVID-19 pneumonia (Bastard et al., 2020, 2021a; Zhang et al., 2022a) and a third of adverse reactions to the live-attenuated yellow fever vaccine (Bastard et al., 2021c). More recently, they have also been shown to account for ~20% of hypoxemic breakthrough COVID-19 cases in fully vaccinated subjects (Bastard et al., 2022b), and ~5% of cases of severe influenza pneumonia in patients younger than 70 years (Zhang et al., 2022).

**Table 1. Monogenic causes of rare Mendelian (typically familial) infectious diseases**

Infectious agent	Clinical phenotype	Immunological mechanism	Disease prevalence	Proportion explained
BCG vaccines and environmental mycobacteria	Mendelian susceptibility to mycobacterial disease (MSMD)	IFN- $\gamma$ deficiency	$10^{-4}$ – $10^{-5}$	~50% <sup>a</sup>
Epstein-Barr virus	B cell lymphoproliferative disease or lymphoma; hemophagocytosis; hypogammaglobulinemia	cytotoxic CD8 <sup>+</sup> T cell deficiency	~ $10^{-5}$	~50%
Human papillomavirus	epidermodysplasia verruciformis tree-man syndrome	EVER-C1B1 deficiency CD28 deficiency	< $10^{-5}$ < $10^{-7}$	~75% ~20%
<i>Candida</i>	chronic mucocutaneous candidiasis	IL-17A/F deficiency	$10^{-4}$ – $10^{-5}$	~50% <sup>a</sup>
Dermatophytes	invasive dermatophytosis	CARD9 deficiency	< $10^{-6}$	>90%

<sup>a</sup>A small proportion of cases are also explained by autoimmune phenocopies of the genetic defects, i.e., autoantibodies neutralizing the corresponding cytokines.

mycobacteria). We, thus, place these findings in a more general context, by reviewing the proportion of cases, for given rare infections, that can be explained by rare monogenic lesions displaying complete (Mendelian) or incomplete (non-Mendelian) penetrance. We also discuss how these concepts, methods, and results were applied to common infections, leading to the discovery of rare, causal IEI in small numbers of patients, drawing us along a mechanistic thread to the discovery of common determinants. Finally, we explain how rare IEI underlying common infections can be used like a compass, pointing researchers in the direction of physiological mechanisms that may be disrupted by common determinants, inherited or otherwise.

### RARE AND MONOGENIC CAUSES OF RARE AND MENDELIAN BACTERIAL AND FUNGAL DISEASES

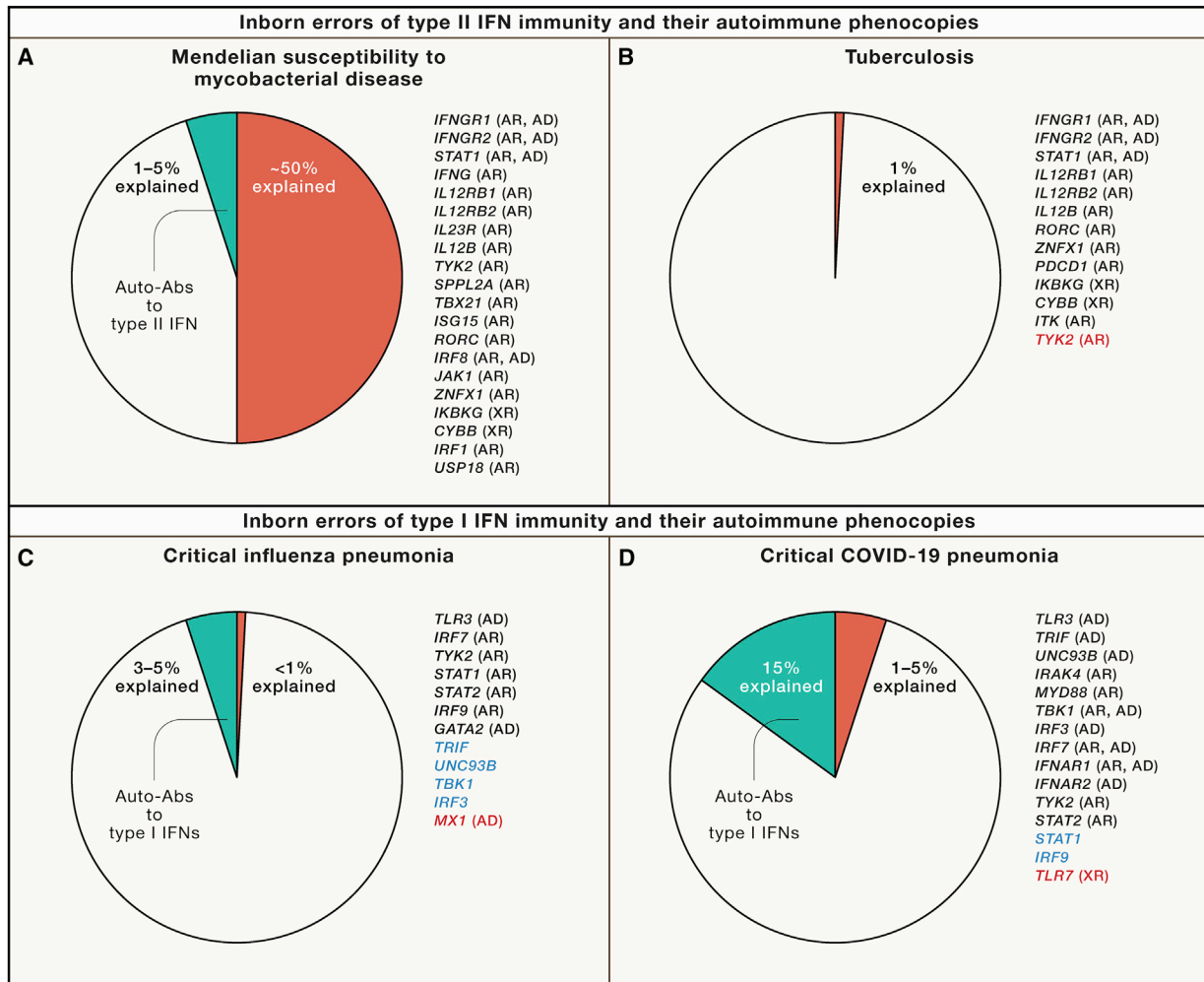
Five infectious diseases known to segregate as Mendelian traits were clarified molecularly from 1996 onward (Table 1; Casanova and Abel, 2021a). Mendelian susceptibility to mycobacterial disease (MSMD) is characterized by clinical disease caused by weakly virulent mycobacteria (i.e., live BCG vaccines and environmental mycobacteria) in otherwise healthy patients (Casanova and Abel, 2002). Its prevalence is probably between  $10^{-4}$  and  $10^{-5}$  in the general population, depending, in part, on ancestry and the associated level of consanguinity. Its 35 known genetic etiologies, due to germline mutations of 20 genes, disrupt the production of, or the response to IFN- $\gamma$ , or both (Bustamante, 2020; Martin-Fernandez et al., 2022; Yang et al., 2020) (J.-L.C. and L.A., unpublished data). These inborn errors of IFN- $\gamma$  immunity account for approximately half the cases of MSMD (Figure 2A). With hindsight, only five of these etiologies—the three that totally abolish IFN- $\gamma$  immunity (biallelic null mutations in *IFNG*, *IFNGR1*, or *IFNGR2*) plus autosomal recessive (AR), complete deficiencies of the STAT1 and IRF1 transcription factors, which therefore impair the induction of key IFN- $\gamma$ -dependent genes (IRF1 itself being STAT1-dependent in this pathway)—are truly Mendelian, as the others appear to have incomplete penetrance, due to residual IFN- $\gamma$  immunity. Furthermore, patients with complete IRF1 deficiency, unlike those with STAT1 deficiency, display no viral disease, suggesting that IRF1 is not essential for the induction of key IFN- $\alpha/\beta$ -dependent genes. Incomplete penetrance for MSMD paved the way for the discovery of IEI of IFN- $\gamma$  immunity

underlying TB, which is caused by mycobacterial species that are at least 1,000 times more virulent.

Chronic mucocutaneous candidiasis (CMC) is caused by the fungus *Candida albicans*. Its prevalence in the general population is between  $10^{-4}$  and  $10^{-5}$ , excluding acquired forms (e.g., AIDS) and CMC occurring in patients with IEI underlying multiple infections but including both “isolated” (i.e., without any other clinical phenotype) and “syndromic” forms (i.e., associated with at least one other clinical phenotype). Its 14 genetic etiologies, due to mutations of 13 genes impairing IL-17A/F immunity, also account for about half the cases (Li et al., 2019; Puel, 2020; Puel and Casanova, 2021; Puel et al., 2011). The proportion of cases that are understood is probably higher for isolated CMC than for syndromic CMC. Inherited RORC deficiency is at the intersection of MSMD and CMC, as patients with this deficiency suffer from both infections, the encoded ROR $\gamma$ C transcription factor being essential for the development of both antifungal Th17 and antimycobacterial Th1\* cells. Interestingly, IFN- $\gamma$  and IL-17 are the lymphokines defining the Th1 and Th17 lineages in mice. Studies of the corresponding IEIs have shown that these lymphokines may be largely redundant in human host defense. However, MSMD patients can suffer from other intramacrophagic infections (IFN- $\gamma$  being more of a macrophage-activating factor than an antiviral IFN) (Nathan et al., 1983), whereas CMC patients occasionally suffer from cutaneous staphylococcal disease.

CMC is a condition of the skin and nails and of the genital and digestive mucosae; *C. albicans* does not cause invasive disease in patients with IEI of IL-17. This situation contrasts with that for inherited CARD9 deficiency, which underlies various invasive infections, typically caused by actinomycete fungi, including *Candida* and dermatophytes (Corvilain et al., 2018; Glocker et al., 2009). All patients with invasive dermatophytic disease (IDD)—a very rare Mendelian infectious disease (prevalence of less than  $10^{-6}$ )—tested suffer from inherited CARD9 deficiency (Lanternier et al., 2013). Intriguingly, CARD9 deficiency typically underlies a single type of infection per patient, an observation that remains unexplained. At least a dozen fungi, mostly actinomycetes, can cause severe disease in CARD9-deficient patients (Corvilain et al., 2018; Glocker et al., 2009; Lanternier et al., 2015; Puel, 2020). These invasive fungal diseases are allelic at the *CARD9* locus. Most, if not all, cases of IDD (>90%) are explained by this unique genotype. By contrast, other invasive fungal





**Figure 2. Proportions of cases of infection explained mechanistically**

(A) MSMD. MSMD strikes about 1/50,000 people. Rare germline variants at 20 loci governing type II IFN immunity account for about 50% of cases. Five deficiencies have complete penetrance: autosomal recessive IFN- $\gamma$ , IFN- $\gamma$ R1, IFN- $\gamma$ R2, STAT1, and IRF1 deficiencies (see text for references). Autoantibodies neutralizing type II IFN (IFN- $\gamma$ ) are found in 1%–5% of cases, with a much greater proportion in individuals of East Asian ancestry, in whom HLA-DRB1 alleles 15:02 and 16:02 are more common.

(B) Tuberculosis. Pulmonary TB strikes about 5%–10% of individuals infected with *Mycobacterium tuberculosis*. Rare germline variants impairing type II IFN immunity account for less than 0.1% of cases, mostly cases of severe tuberculosis in childhood. These disorders are typically genetic etiologies of MSMD with incomplete penetrance for MSMD. *M. tuberculosis* is 1,000–10,000 times more virulent than BCG and environmental mycobacteria, and the penetrance of these disorders is, therefore, much higher for TB than for MSMD. Homozygosity for the P1104A variant of *TYK2* (red) is found in about 1% of TB patients of European descent. This variant is common in these populations and is homozygous in about 1/600 individuals. Autoantibodies against type II IFN have been reported in very few TB patients to date.

(C) Critical influenza pneumonia. Seasonal influenza has a case-fatality ratio between 0.04% and 0.4%. The human genetic basis of critical influenza pneumonia is largely unknown. Germline mutations of seven genes are causal and all impair the TLR3- and IRF7-dependent induction of type I and III IFNs (black). By inference, genes that are biochemically and immunologically connected to the seven core genes and have also been found to underlie other severe viral infections may be considered influenza susceptibility genes with incomplete penetrance, or, at least, as plausible candidate genes (blue). Autoantibodies against type I IFNs were recently found to account for about 5% of cases of critical influenza pneumonia in patients under 70 years old. Severe avian influenza has been studied genetically and variants of the type I IFN-inducible gene *MX1* (red) have been found in ~9% of the patients studied.

(D) Critical COVID-19 pneumonia. Rare germline variants at loci controlling TLR3- or TLR7-dependent type I IFN immunity underlie critical COVID-19 pneumonia in 1%–5% of patients, this proportion being higher in individuals under the age of 60 years than in older individuals. These defects include AR (IFNAR1, TYK2, TBK1, IRAK4, MYD88, STAT2, and IRF7) and XR disorders (TLR7). The most common defect identified in this context is TLR7 deficiency (red), which has a cumulative frequency in the general population of about  $5 \times 10^{-4}$ , but accounts for about 1% of critical cases in males worldwide. By inference, other loci that are biochemically and immunologically related and have been shown to underlie other severe viral infections may also underlie critical COVID-19 (blue). Autoantibodies neutralizing high or low concentrations of type I IFNs have been found in 15%–20% of cases. These antibodies neutralize the 13 forms of IFN- $\alpha$ , or IFN- $\omega$ , or both types of IFN. More rarely, they may neutralize IFN- $\beta$ . These autoantibodies are present before SARS-CoV-2 infection and are also present in uninfected people in the general population. The prevalence of autoantibodies against IFN- $\alpha$  and - $\omega$  is between 0.3 (high concentration neutralized) and 1% (low concentration) until the age of 65 years. It then increases sharply, reaching 4% (high concentration) and 7% (low concentration) in people over 80 years old. By contrast, the prevalence of autoantibodies against IFN- $\beta$  (high concentration) is stable across age groups, at about 0.2%. The risk of critical COVID-19 increases with the number and concentrations of type I IFNs neutralized.

diseases are only rarely explained by CARD9 deficiency. The immunological mechanism of fungal disease in these patients remains unclear but probably involves defective phagocytes, which normally express CARD9 downstream of various cell surface receptors for fungi. Inherited CARD9 deficiency has recently been reviewed (Corvilain et al., 2018; Puel, 2020).

### RARE AND MONOGENIC CAUSES OF RARE AND MENDELIAN VIRAL DISEASES

Epidermodysplasia verruciformis was the first IEI to be described, although it was not recognized as such for over 50 years because of its lack of a hematological or immunological phenotype (Lutz, 1946; Orth, 2008). It is characterized by extremely high levels of susceptibility to defective beta-human papillomaviruses ( $\beta$ -HPVs), which cause flat warts and pityriasis-like lesions in these patients that may progress to non-melanoma skin cancers if they occur on areas exposed to the sun (Orth, 2008). Its prevalence is  $<10^{-5}$ . In its typical form, the patients are normally resistant to other microbes. Biallelic null mutations of one of three genes account for at least 75% of cases (Béziat et al., 2021a). The products of these genes, EVER1, EVER2, and CIB1, form a complex in keratinocytes that probably mediates cell-intrinsic immunity to HPVs by interacting with E5 or E8, the virulence factors found in HPVs other than beta-HPVs (de Jong et al., 2018). Patients with epidermodysplasia verruciformis (EV) are typically not prone to lesions caused by the other four genera of HPVs. A Mendelian form of clinical disease caused by HPVs of the alpha or gamma genus has recently been described, with inherited CD28 deficiency underlying recalcitrant common HPV4 warts and the giant horns defining the HPV2 “tree-man” syndrome (Béziat et al., 2021b). The three affected patients displayed no detectable lesions caused by beta-HPVs. IEI underlying HPV diseases have recently been reviewed (Béziat et al., 2021a).

Another severe viral illness, fulminant Epstein-Barr virus (EBV) disease, may also be familial, with Mendelian inheritance but variable expressivity. Following EBV infection, the underlying inborn errors can manifest in various ways, including hemophagocytosis, B cell proliferative disease, B cell lymphoma, and hypogammaglobulinemia (Purtilo et al., 1974, 1977). Penetrance is incomplete for all these EBV phenotypes in all affected families, regardless of genetic etiology. The global prevalence of fulminant EBV disease is probably  $<10^{-5}$ . The X-linked recessive (XR) form of this disease may be caused by mutations of *SAP*, *XIAP*, or *MAGT1* (Coffey et al., 1998; Nichols et al., 1998; Sayos et al., 1998), whereas its AR forms are due to mutations of *CTPS1*, *TNFRSF9*, *CD27*, *CD70*, or *ITK* (Abolhassani et al., 2017; Alosaimi et al., 2019; Caorsi et al., 2017; Huck et al., 2009; Izawa et al., 2017; Martin et al., 2014; Rodriguez et al., 2019; Somekh et al., 2019; van Montfrans et al., 2012). Together, these mutations probably account for more than half the cases. These genotypes prevent the control of EBV-infected B cells by cytotoxic CD8<sup>+</sup> T cells, as neatly demonstrated for *SAP* deficiency by analyses of both female carriers and revertant male patients (Palendira et al., 2011, 2012). Some deficits preferentially underlie hemophagocytosis (e.g., *SAP* mutations), whereas others preferentially underlie excessive B cell proliferation (e.g., *CD27* and *CD70* mutations). The human genetic and immunological determinants of severe EBV manifes-

tations have recently been reviewed (Tangye, 2020; Tangye and Latour, 2020).

These two known Mendelian viral infectious diseases (caused by HPVs and EBV), like the two Mendelian fungal infectious diseases (*Candida*, dermatophytes), and the only known Mendelian bacterial infectious disease (mycobacteria), are rare conditions, each of which can be genetically explained in most patients, especially in multiplex kindreds (i.e., families with two or more relatives displaying the phenotype considered). As discussed above, not all known genetic etiologies underlie the corresponding infectious diseases with complete penetrance, and the proportion of explained sporadic cases is probably lower, especially in patients suffering from a syndromic form of infection. The discovery of new genetic etiologies in the future is therefore anticipated. We also expect to see the discovery of new Mendelian infectious diseases, particularly in rare multiplex kindreds, together with their genetic etiologies, as illustrated by CD28 deficiency for alpha- and gamma-HPVs considered collectively, and, previously, by the discovery of DBR1 deficiency underlying viral infection of the brainstem with apparently complete penetrance in individual patients for at least one of the three known causal viruses (HSV-1, influenza virus, and norovirus) (Zhang et al., 2018). Indeed, rare multiplex kindreds with other rare and unexplained infections have been reported in the medical literature.

### RARE AND MONOGENIC CAUSES OF RARE AND NON-MENDELIAN INFECTIOUS DISEASES

Since 2007, some rare infectious diseases have been shown to be monogenic but never, or at least exceedingly rarely, Mendelian; their underlying IEI display incomplete penetrance (Table 2). Admittedly, there is a continuum between Mendelian (fully penetrant) and non-Mendelian monogenic (incompletely penetrant) IEI, if only because monogenic lesions may be Mendelian in some, but not other populations, making this dichotomy more operational and didactic than rigorous and scientific. The first and best studied of these infections is probably childhood herpes simplex virus 1 (HSV-1) herpes simplex encephalitis (HSE). This disease is typically sporadic, with a prevalence of about  $10^{-4}$  in children (Zhang, 2020b). It is generally lethal if left untreated, but sequelae are observed in most acyclovir-treated survivors. Forebrain HSE can be caused by IEI of TLR3-dependent type I IFN immunity resulting from mutations of eight genes (Andersen et al., 2015; Audry et al., 2011; Bastard et al., 2021b; Casrouge et al., 2006; Herman et al., 2012; Pérez de Diego et al., 2010; Sancho-Shimizu et al., 2011; Zhang et al., 2007). Other patients carry mutations of *SNORA31*, defining another pathway (Lafaille et al., 2019). Overall, these genetic etiologies account for  $<10\%$  of cases in children. Similar forebrain infections in adults remain unexplained; they may be due to the reactivation of HSV-1 from latency, but they may also have a different pathogenesis.

Brainstem HSE is rarer in children and the only genetic explanation identified to date is an AR deficiency of DBR1, the only known RNA lariat-debranching enzyme, with complete penetrance for at least one of the three viruses detected in the three known families (Zhang et al., 2018). The mechanism by which the excessive accumulation of RNA lariats underlies HSE is unknown but probably involves cell-intrinsic immunity to these viruses in the brainstem.

**Table 2. Monogenic causes of rare non-Mendelian (typically sporadic) infectious diseases**

Infectious agent	Clinical phenotype	Immunological mechanism	Prevalence	Proportion explained
<i>Neisseria</i>	invasive disease	complement deficiency	$10^{-3}$ – $10^{-4}$	1%–5%
<i>Streptococcus pneumoniae</i>	invasive disease	TLR and IL-1R response deficiency	$\sim 10^{-4}$	<5%
<i>Staphylococcus aureus</i>	invasive disease	TLR2 response deficiency IL-6 response deficiency	$< 10^{-5}$	<1%
<i>Tropheryma whipplei</i>	Whipple's disease	IRF4 deficiency	$< 10^{-6}$	<1%
Herpes simplex virus 1	encephalitis	TLR3-IFN- $\alpha/\beta$ deficiency snoRNA31 deficiency DBR1 deficiency <sup>a</sup>	$\sim 10^{-4}$	5%–10%
Human herpes virus 8	endemic Kaposi sarcoma	OX40 deficiency	$< 10^{-5}$	<1%
Cytomegalovirus	disseminated disease	NOS2 deficiency	$< 10^{-5}$	<1%
Enterovirus	rhombencephalitis	TLR3/MDA5-IFN- $\alpha/\beta$ deficiency	$< 10^{-5}$	<1%
Varicella zoster virus	encephalitis and pneumonia	POL3RA and POL3RC deficiency	$< 10^{-5}$	<5%
Influenza	severe pneumonia	type I and III IFN deficiency	$\sim 10^{-5}$	<1%
Rhinovirus	recurrent/severe infections	MDA5 deficiency	$10^{-4}$ – $10^{-5}$	<5%
Human papillomavirus	recurrent respiratory papillomatosis	NLRP1 gain of function	$\sim 10^{-5}$	<1%
Hepatitis A virus	fulminant hepatitis	IL-18BP deficiency	$< 10^{-5}$	<1%
Live measles and yellow fever vaccines	severe infections	type I IFN response deficiency	$< 10^{-6}$	<25%

<sup>a</sup>Inherited DBR1 deficiency underlies brainstem infection with HSV-1, influenza virus, or norovirus.

Indeed, monogenic forebrain HSE is due to a deficiency of cell-intrinsic immunity to HSV-1 in cells resident in the central, but not in the peripheral nervous system. This was established by modeling HSE with iPSC-derived cortical and trigeminal neurons (Lafaille et al., 2012; Zimmer et al., 2018). Cortical neurons lacking TLR3 are much more susceptible to HSV-1 than control cortical neurons, but trigeminal neurons with and without TLR3 are equally susceptible to this virus (and more so than control cortical neurons, accounting for the virus infecting trigeminal but not cortical neurons in most infected individuals). The genetic study of HSE revealed that non-leukocytic, cell-intrinsic immunity to viruses in a specific organ, and even a specific territory, can be life-saving (Casanova and Abel, 2021b; Nathan, 2021; Paludan et al., 2021; Zhang et al., 2019). It also revealed the first inborn error of type I IFN immunity, inherited STAT1 deficiency, in a child with a syndromic form of HSE, whose MSMD was due to the abolition of responses to type II IFN (Dupuis et al., 2003).

No other rare, sporadic, severe infectious disease is better understood than HSE, in terms of the proportion of cases explained molecularly (about 5%–10%). Many other rare, severe, sporadic infections are understood in only a single patient (e.g., CMV disease in a patient lacking NOS2; Drutman et al., 2020), a single multiplex kindred (e.g., Whipple's disease and IRF4 haploinsufficiency; Guérin et al., 2018), or in unrelated patients with mutations of the same single gene (e.g., isolated congenital asplenia and RPSA haploinsufficiency underlying invasive pneumococcal disease; Bolze et al., 2013). A few are explained by mutations of a few genes that, individually, never account for more than 1% of cases (e.g., invasive pneumococcal or staphylococcal disease in patients with IRAK4 or MyD88 deficiency; Picard et al., 2010). Other examples include HHV8-driven Kaposi sarcoma (Jackson et al., 2016), severe respiratory viral infections other than influ-

enza and COVID-19 (Asgari et al., 2017; Lamborn et al., 2017), and varicella zoster virus encephalitis (Ogunjimi et al., 2017). The study of two other viral illnesses—adverse reactions to live attenuated measles and yellow fever vaccines, which are rarely familial (Casanova and Abel, 2021b; Casanova et al., 2022; Duncan et al., 2021), and critical influenza pneumonia, which is typically sporadic (Ciancanelli et al., 2015; Hernandez et al., 2018; Lim et al., 2019)—converged, together with studies of HSE, on type I IFNs, and these discoveries played an important role in the study of COVID-19, as described below.

### RARE MONOGENIC CAUSES OF COMMON INFECTIOUS DISEASES

Two common infectious diseases deserve a special mention because they were found to have rare monogenic causes: TB and COVID-19. The study of their genetic basis has benefited from that of the related rare infectious diseases, MSMD for TB and severe influenza pneumonia for COVID-19 pneumonia. Rare inborn errors identified as causal for MSMD have been found in patients without MSMD, with TB as their sole phenotype (Figure 2B; Boisson-Dupuis, 2020). This finding attested to the incomplete penetrance of these disorders for MSMD, with higher and probably complete penetrance for TB, given that *M. tuberculosis* is about 1,000–10,000 times more virulent than BCG and environmental mycobacteria (as TB strikes 1/10 infected subjects whereas MSMD strikes between 1/10,000 and 1/100,000 infected individuals). Two equally rare disorders stand out as having been diagnosed in more than one patient with TB: AR complete IL-12R $\beta$ 1 and TYK2 deficiencies. Interestingly, both these disorders impair both IL-12- and IL-23-dependent IFN- $\gamma$  immunity. The penetrance of MSMD by the age of 30 years



is probably about 50% for IL-12R $\beta$ 1 deficiency (de Beaucoudrey et al., 2010). As both these disorders are rare, with a frequency of less than  $10^{-5}$  in the general population, and about half the cases are detected on the basis of the MSMD phenotype of the patient, they probably account for only a very small proportion of cases of TB (even though their penetrance for TB is probably very high, if not complete, upon exposure to *M. tuberculosis*). However, they have provided proof-of-principle that IFN- $\gamma$  deficiency can underlie isolated TB in humans without MSMD (Altare et al., 2001; Kreins et al., 2015; Ogishi et al., 2022).

The other example is critical COVID-19 pneumonia. The study of this disease built on previous studies of influenza pneumonia that had led to the identification of AR IRF7 (Ciancanelli et al., 2015), IRF9 (Hernandez et al., 2018), STAT1 (Le Voyer et al., 2021), or STAT2 deficiency (Freij et al., 2020), or autosomal dominant TLR3 deficiency (Lim et al., 2019), in children with unexplained, severe seasonal influenza pneumonia (Figure 2C). TLR3 is an endosomal sensor of dsRNA that can be activated by viral intermediates or by-products to induce type I and III IFNs. It can also control baseline, tonic type I IFN levels by hitherto unknown mechanisms in at least some non-leukocytic cell types, including fibroblasts and cortical neurons, and perhaps pulmonary epithelial cells (Gao et al., 2021). STAT1, STAT2, and IRF9 form the ISGF-3 complex, which is activated by type I or III IFNs (STAT1 homodimers also governing cellular responses to type II IFN) (Stark and Darnell, 2012; Stark et al., 1998). IRF7 is the key transcription factor driving the amplification of type I and III IFNs, with only IFN- $\beta$  being somewhat IRF7-independent. The high levels of constitutive *IRF7* expression in plasmacytoid dendritic cells (pDCs) make these cells the most potent known producers of antiviral IFNs among the >400 discernable cell types in the human body. These findings suggested that the disruption of TLR3-dependent type I and/or III IFN immunity might account for life-threatening influenza pneumonia. The penetrance of AD TLR3 deficiency for severe influenza is incomplete, as patients with HSE carrying the same genotype are normally resistant to influenza virus. It was not initially possible to estimate the penetrance of IRF7 and IRF9 deficiencies, as both disorders were described in single patients. A recent study showed that the penetrance of IRF7 deficiency is incomplete (Campbell et al., 2022). STAT1 and STAT2 deficiencies have incomplete penetrance too, suggesting that the penetrance of IRF9 deficiency is also probably incomplete. Severe influenza has, in rare instances, been reported in patients with autosomal dominant GATA2 deficiency (Sologuren et al., 2018), possibly due to the lack of pDCs in these patients (Zhang, 2020a). Finally, deleterious heterozygous variants of the type I IFN-inducible gene *MX1* have also been found in 9.7% of patients with severe avian influenza (Chen et al., 2021).

Rare genetic disorders underlying critical influenza pneumonia were also found in a small number of patients with the more common critical COVID-19 pneumonia and no history of critical influenza (Figure 2D; Zhang et al., 2020). These two viral infectious diseases of the respiratory system are, thus, allelic at loci governing TLR3- and IRF7-dependent type I IFN immunity. Penetrance is incomplete for critical influenza and, perhaps, also for critical COVID-19. IEI of type I IFN immunity previously identified in patients with severe viral infections other than influenza have also

been found in some patients with life-threatening COVID-19 (Zhang et al., 2020). The penetrance of the dominant IEI, which were found in <3% of critical cases, is unknown. Two rare etiologies of critical COVID-19 pneumonia stand out because of their recessive mode of inheritance and associated higher penetrance: IRF7 and IFNAR1 deficiencies. These deficiencies were found in four unrelated previously healthy adults aged 25–50 years hospitalized for COVID-19. Remarkably, up to seven IRF7-deficient patients have recently been diagnosed; all suffered from severe viral respiratory diseases, including influenza and COVID-19, but not from viral illnesses of other tissues (Campbell et al., 2022). Two other unrelated IFNAR1-deficient patients and one TBK1-deficient patient with critical COVID-19 have also been independently reported (Abolhassani et al., 2022; Khanmohammadi et al., 2022; Schmidt et al., 2021). Critical COVID-19 pneumonia strikes about 2%–4% of infected individuals (Zhang et al., 2022a); these recessive genetic disorders are individually rare and account collectively for well below 1% of critical cases (i.e., less than 0.03% of infected subjects), mostly patients under 60 years old. However, they have provided proof-of-principle that type I IFN deficiency can underlie life-threatening COVID-19 pneumonia. Recent genetic studies of multisystem inflammatory syndrome in children (MIS-C) have also successfully identified AR deficiencies of multiple genes in the type I IFN-inducible OAS-RNase L pathway (J.-L.C. and L.A., unpublished data). The study of MSMD led to the discovery of rare AR IEI of type II IFN immunity in rare patients with TB, whereas that of severe influenza led to the discovery of rare AR IEI of type I IFN immunity in rare patients with critical COVID-19. These rare patients may be negligible in terms of public health, but they have provided mechanistic insights that have proved invaluable.

### COMMON MONOGENIC DETERMINANTS OF TUBERCULOSIS

TB has killed more humans than any other single infectious disease, accounting for at least one billion deaths in human history (Paulson, 2013). European populations were decimated by TB between the 15<sup>th</sup> and 20<sup>th</sup> centuries. This condition was favored worldwide by the aggregation of humans into ever-expanding communities during the Neolithic period. However, less than 10% of individuals infected with *M. tuberculosis* develop TB, which, if left untreated, probably kills at least half of those affected. *M. tuberculosis* is a bacterium that can reside and persist in macrophages. The discovery that rare inborn errors of IFN- $\gamma$  immunity could underlie TB in a few patients without MSMD taught us that IFN- $\gamma$  was essential for protective immunity to *M. tuberculosis*. This led to the discovery that homozygosity for the common P1104A variant of *TYK2* is found almost exclusively in TB patients of various ancestries (Table 3; Boisson-Dupuis et al., 2018). Homozygosity for P1104A also underlies MSMD, with a much lower penetrance than for TB, because of the higher virulence of *M. tuberculosis* than of BCG and environmental mycobacteria. This variant was further shown to impair (but not abolish) the IL-23 response pathway, as profoundly as a complete deficiency of *TYK2* but selectively, thereby impairing IFN- $\gamma$  production by specific lymphocyte subsets without damaging the IL-12 response pathway (or the IL-10 and type I IFN pathways) (Martinez-Barricarte et al., 2018; Ogishi et al., 2022).

**Table 3. Common monogenic and autoimmune determinants of two common infectious diseases**

Infectious agent	Clinical phenotype	Immunological mechanism	Disease prevalence <sup>a</sup>	Proportion explained
<i>Mycobacterium tuberculosis</i>	tuberculosis	IL-23-dependent IFN- $\gamma$ deficiency (homozygosity for <i>TYK2</i> P1104A)	5%–10%	1% <sup>b</sup>
SARS-CoV-2	life-threatening COVID-19 pneumonia	type I IFN deficiency (inborn errors) type I IFN deficiency (autoimmune)	2%–4%	1%–5% <sup>c</sup> 15%–20%

<sup>a</sup>Prevalence is provided for individuals infected with the corresponding microbe.

<sup>b</sup>In individuals of European origin.

<sup>c</sup>In individuals under the age of 60 years.

The frequency of this variant is highest in Europeans, about 4% of whom carry it, leading to a prevalence for homozygosity of about 1/600. It is absent in sub-Saharan Africa and very rare in East Asia and has a prevalence of about 1% in other regions of the world. Consistent with these findings, the patients with TB due to P1104A homozygosity in the original study were from Latin America, Europe, and the Greater Middle East. They accounted for about 1% of the total number of cases in this highly diverse cohort of patients. In a subsequent study focusing on a European population, homozygosity for P1104A was found to account for about 1% of cases of TB in British individuals after World War II (Kerner et al., 2019). This unbiased, population-based study was made possible by the data of the UK Biobank (Bycroft et al., 2018). Lifetime penetrance for the development of TB upon infection was estimated at about 80% for P1104A homozygotes.

Finally, the P1104A allele was shown to originate from a founder effect about 30,000 years ago in Western Eurasians (Kerner et al., 2021). The haplotype carrying this variant is small (6 kb) and limited to three single-nucleotide variants upstream of P1104A and another three downstream. The study of ancient DNA has revealed that the frequency of P1104A increased to about 10% around 3,000 years ago, possibly by genetic drift. Its decrease in frequency over the last 2,000 years has been one of the most rapid in this prevalence category, strongly suggesting that negative selection was involved. The cause of this negative selection is unknown and open to speculation, but these results are consistent with a decline in P1104A prevalence due to purging driven by the historically very high burden of TB in Europe (Kerner et al., 2021). About one billion Europeans are estimated to have died from TB in the last 2,000 years (Kerner et al., 2019; Paulson, 2013). Overall, the study of MSMD, including the discovery of IEI through analyses of single patients, has led to the discovery of a common monogenic etiology accounting for about 1% of past and present cases of TB in humans of European descent. The P1104A variant of *TYK2* is common in Europeans (>1%), and although European homozygotes for this variant are rare (<1%, 1/600), they account for about 1% of cases of TB.

### COMMON MONOGENIC DETERMINANTS OF COVID-19

The other infectious disease for which the cause of a sizable proportion of cases has been clarified through earlier studies of rare IEI is COVID-19 critical pneumonia. About 0.5%–1% of people infected with COVID-19 die, with considerable between-country variation (COVID-19 National Preparedness Collaborators, 2022), with life-threatening disease occurring in about 2%–4% of infected individuals, and a doubling of the risk for every 5 years

of age, from childhood onward (O’Driscoll et al., 2021). The causal virus, SARS-CoV-2, is an RNA virus that infects the respiratory tract, whence it can spread to other tissues via the bloodstream. Based on previous discoveries of rare inherited TLR3, IRF7, STAT1, STAT2, and IRF9 deficiencies in children with life-threatening influenza pneumonia (Campbell et al., 2022; Le Voyer et al., 2021; Zhang, 2020a), rare autosomal IEI affecting TLR3-dependent type I IFN immunity were discovered in patients with life-threatening COVID-19 (Zhang et al., 2020). Remarkably, AR and complete defects of IFNAR1, IRF7, and TBK1 were found in previously healthy patients (Abolhassani et al., 2022; Khanmohammadi et al., 2022; Schmidt et al., 2021; Zhang et al., 2020, 2022b). All these disorders, including the recessive defects, were rare, with genotype frequencies <10<sup>-5</sup> in the general population and probably <10<sup>-3</sup> in patients with critical disease (Zhang et al., 2020). Most of these patients were less than 60 years old. TLR3, which is not expressed by blood pDCs, is expressed by respiratory epithelial cells (RECs), in which it is essential for type I IFN immunity to influenza virus (Lim et al., 2019) and, by inference from experiments on fibroblasts, for immunity to SARS-CoV-2 (Zhang et al., 2020).

In a subsequent, unbiased approach, XR TLR7 deficiency was found to underlie critical COVID-19 in as many as 1% of men under the age of 60 years (Asano et al., 2021). The cumulative frequency of TLR7 deficiency in the general population is about 5 × 10<sup>-4</sup>. TLR7 is expressed by pDCs, but not RECs. Type I IFN immunity, which may be TLR3- and REC-dependent, or TLR7- and pDC-dependent, is therefore essential for host defense against SARS-CoV-2 in the respiratory tract. The candidate gene approach-based discovery of AR IFNAR1 and IRF7 deficiencies in four unrelated adults with critical COVID-19 aged 25–50 years who had previously been healthy provided the fundamental information that type I IFN is essential for host defense against SARS-CoV-2, but potentially otherwise redundant in host defense, even over several decades. This redundancy was confirmed not only by reports of other patients with IFNAR1 or IRF7 deficiency (Campbell et al., 2022) but also by the surprising observation of common loss-of-function (LOF) alleles of *IFNAR1* and *IFNAR2* in the Pacific and Arctic regions, respectively (Bastard et al., 2022a; Duncan et al., 2022). Recessive inborn errors of type I IFNs, including XR TLR7 and AR IFNAR1, STAT2, and *TYK2* deficiencies, were even found in about 10% of international children hospitalized for COVID-19 pneumonia (Zhang et al., 2022b). Who would have predicted such a level of redundancy of type I IFNs and, in the case of IRF7 deficiency, of combined type I and III IFNs? The discovery, by genome-wide analysis, of TLR7 deficiency alone did not necessarily incriminate type I IFNs, but its concomitant association with

IFNAR1 and IRF7 deficiency did. Moreover, no enrichment in TLR8 variants was found in patients with critical COVID-19, although both genes are X-linked and share largely overlapping agonists and signaling pathways. The key difference is that TLR7, unlike TLR8, is expressed in type I IFN-producing pDCs.

The identification of various AR inborn errors (IFNAR1, IRF7, TBK1), with a frequency probably  $<10^{-5}$  in the general population and  $<10^{-3}$  in patients with critical disease preceded the discovery, in an unbiased approach, of a single etiology, XR TLR7 deficiency, with frequencies of about  $5 \times 10^{-4}$  and  $10^{-2}$ , respectively, in the two corresponding groups of male subjects. Overall, TLR7 deficiency accounts for the same proportion (1%) of critical COVID-19 cases in men across major ancestries as P1104A TYK2 homozygosity accounts for cases of TB in Europeans. The deleterious TLR7 variants are, however, rare individually ( $<0.02\%$ ) and collectively (cumulative frequency  $<0.07\%$ ), contrasting with the common P1104A TYK2 allele ( $>1\%$ ). Hemizyosity for TLR7 LOF variants (1/1,500) is also collectively rarer than homozygosity for the P1104A variant (1/600). In different ways, these two recessive defects are common etiologies accounting for the same proportion (1%) of different forms of the corresponding common infectious diseases: critical COVID-19 pneumonia for TLR7 in men worldwide and pulmonary TB for TYK2 in Europeans. The negative selection operating on the TLR7 locus globally (Barreiro et al., 2009) and P1104A TYK2 specifically (Kerner et al., 2021) attests to the fitness cost of the corresponding deleterious genotypes.

### COMMON AUTOIMMUNE DETERMINANTS OF COVID-19

The discovery of AR IRF7 deficiency in a child with critical influenza pneumonia thus led to that of AR IRF7, IFNAR1, and XR TLR7 deficiencies, and AD TLR3 pathway deficiencies, in adults with critical COVID-19 pneumonia. These disorders implicated the disruption of TLR3- and TLR7-dependent type I IFN immunity as a core mechanism of disease. This key causal and mechanistic insight led to the discovery that circulating auto-Abs capable of neutralizing the 13 IFN- $\alpha$  and/or IFN- $\omega$  at a concentration of 10 ng/mL *in vitro* (using plasma diluted 1/10) account for at least 10% of cases of critical COVID-19 pneumonia (Bastard et al., 2020). Half the affected patients were found to be over 65 years of age, and most were men. As a control, such auto-Abs were not found in SARS-CoV-2-infected subjects with silent or mild upper respiratory tract infections. In a subsequent study, the neutralization of lower, more physiological concentrations of IFN- $\alpha$  and/or IFN- $\omega$  (100 pg/mL, again with plasma diluted 1/10), and of IFN- $\beta$ , was found to underlie 15% of critical cases, and 20% of cases in patients over the age of 80 years (Bastard et al., 2021a). These studies have been replicated in at least 26 other cohorts in the Americas, Europe, and Asia (Abers et al., 2021; Acosta-Ampudia et al., 2021; Akbil et al., 2022; Bastard et al., 2021; Busnadiego et al., 2022; Carapito et al., 2021; Chang et al., 2021; Chauvineau-Grenier et al., 2022; Eto et al., 2022; Frasca et al., 2022; Goncalves et al., 2021; Koning et al., 2021; Lamacchia et al., 2022; Lemarquis et al., 2021; Mathian et al., 2022; Meisel et al., 2021; Raadsen et al., 2022; Savvateeva et al., 2021; Simula et al., 2022; Solanich et al., 2021; Soltani-Zangbar et al., 2022; Troya et al., 2021; van der Wijst et al., 2021; Vazquez et al., 2021; Wang et al., 2021; Ziegler et al., 2021).

These auto-Abs had been known for 40 years, in patients treated with recombinant IFN- $\alpha$  or - $\beta$  (Zhang et al., 2022a), or with autoimmune conditions, such as systemic lupus erythematosus (SLE), myasthenia gravis, thymoma, autoimmune polyendocrinopathy syndrome type 1 (APS-1), immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), or RAG1/RAG2 hypomorphic mutations (Bastard et al., 2020, 2021d). They were generally thought to be clinically silent, with the exception of one case reported by Ion Gresser (Pozzetto et al., 1984) (an otherwise healthy patient with unexplained auto-Abs) and a small series reported by Luigi Notarangelo (patients whose RAG mutations and combined T and B cell immunodeficiency may also have directly underlain viral illnesses) (Walter et al., 2015). However, auto-Abs against four other cytokines had previously been shown to underlie infectious phenocopies of the corresponding inborn errors of cytokines or their response pathways (Ku et al., 2020; Puel et al., 2022). Perhaps the best characterized and, arguably, the most closely related example is mycobacterial disease, which can be caused by inborn errors of type II IFN or auto-Abs neutralizing type II IFN (Ku et al., 2020; Puel et al., 2022; Figure 2A). These auto-Abs underlie severe disease caused by weakly virulent mycobacteria and, more rarely, TB (Puel et al., 2022; Shih et al., 2021), especially in East Asian populations, in which HLA-DRB1 alleles 15:02 and 16:02 are common (Ku et al., 2016; Shih et al., 2021).

Several other lines of evidence indicate that auto-Abs against type I IFNs are causal for critical COVID-19 (Figure 2D; Manry et al., 2022). First, they were found in samples taken before infection, in the cases for which such samples were available and tested (Bastard et al., 2020). Second, they appear early in childhood in patients with APS-1, in whom the course of COVID-19 is very severe (Bastard et al., 2021d). Third, they can underlie adverse reactions to the live attenuated yellow fever vaccine in patients not infected with SARS-CoV-2 (Bastard et al., 2021c); they were also recently found in about 20% of hypoxemic breakthrough COVID-19 cases in fully vaccinated subjects (Bastard et al., 2022b), and in 5% of patients with critical influenza pneumonia under 70 years old (Zhang et al., 2022). Fourth, they are found in the nasal mucosae of patients during the first few days of infection with SARS-CoV-2, during which they actually impair type I IFN responses (Lopez et al., 2021). Fifth, these auto-Abs are found in the general population, their frequency increasing with age and reaching 4% after the age of 70 years and 7% between the ages of 80 and 85 years (Bastard et al., 2021a). Overall, they account for 20% of COVID-19 deaths across all age groups. The discovery of exceedingly rare IEL of type I IFN immunity, first in patients with critical influenza and then in patients with critical COVID-19, led to the discovery of a common genetic etiology of critical COVID-19 pneumonia (XR TLR7 deficiency, underlying 1% of cases in male patients), and then to the detection of auto-Abs against type I IFNs, which underlie about 20% of COVID-19 deaths.

### CONCLUDING REMARKS

With a molecular explanation for about 1% of cases of pulmonary TB in European adults and 20% of cases of critical COVID-19 pneumonia across patients of most ages and ancestries (1%–5% due to inborn errors of type I IFN immunity and

15%–20% due to auto-Abs against type I IFNs), we are beginning to unravel the root causes of at least two common infectious diseases at individual level, and in a sizable proportion of individuals at population level. The proportion of cases of TB explained by HIV infection in developing countries may be as high as 15% (Kwan and Ernst, 2011), which, incidentally, also indicates that the development of TB is conditional on a human immunodeficiency, whether inherited or acquired. By analogy with COVID-19, it is tempting to speculate that auto-Abs against type II IFN might underlie a proportion of TB cases. This recent progress was made possible by the study of small numbers, and even, sometimes, single patients with either of these common infections (Casanova et al., 2014), and this approach was dependent on earlier studies of even fewer patients with rarer, related infections. The study of TB built on studies of MSMD, whereas that of COVID-19 built on studies of influenza. Why did this approach succeed? Probably because it led to the discovery of mechanisms of disease in individual patients, at the molecular, cellular, and immunological levels, with disease actually occurring in individual patients—“whole organisms”—rather than being considered in populations of patients, who do not form a “meta-organism.” Incidentally, the success of the patient-based, mechanistic approach, focusing on causes and consequences from atomic to whole-organism levels, may, to some extent, explain the difficulties encountered by the population-based, statistical approach, which is a topic to be discussed elsewhere. Hopefully, a confluence of the two approaches may be in sight, for the greater good of science and medicine.

Does it matter that we now understand these two life-threatening infectious diseases in a significant proportion of patients? The question can be posed, as the fields of microbiology and infectious diseases have historically focused on three other goals: (1) the discovery of microbes, their life cycle (cellular microbiology *in vitro* and animal models *in vivo*), and pharmacological approaches to interrupting this life cycle (drugs); (2) the development of vaccines: live attenuated microbes, then heat-killed microbes, recombinant proteins, and, more recently, mRNAs; and (3) the analysis of T and B cell adaptive responses to microbes, as a way of using antibodies or T cells to prevent or treat infection. The human genetic study of infectious diseases, a fourth approach that remains dwarfed by the others in terms of the volume of scientific publications, has always been seen as a third wheel. After all, why do we need to understand the root cause—the host determinant of infectious diseases—if we can prevent or treat these diseases without needing to resort to this knowledge? Investigators in this field have therefore sometimes been perceived as “conquerors of the useless” (Terray, 1961, 2008). COVID-19 provides a good example. We have witnessed over the last 2 years how research on COVID-19 has been extraordinarily focused on ways to prevent or treat this disease—as for all infections. Now that vaccines against SARS-CoV-2 seem to work relatively well, apparently even in type I IFN-deficient individuals, why does it matter that critical disease can be caused by deficiencies of type I IFNs? Would somatic oncogenes or germline tumor suppressor genes (e.g., *BRCA1*) have been discovered or their discovery found to be of interest if some herb tea could prevent cancer? We can think of two responses to this legitimate interrogation.

The first answer is medical. Fully understanding infectious diseases, from the angle of human determinants, has diagnostic and therapeutic implications. Microbes are becoming increasingly resistant to anti-infectious agents, as illustrated by the rapid spread of multidrug-resistant TB. Microbes can also resist vaccines, as illustrated by cases of “breakthrough” COVID-19 hypoxemic pneumonia (Bastard et al., 2021a; Bergwerk et al., 2021), or may escape vaccines altogether, as illustrated by the spread of pneumococcal serotypes not covered by current vaccines. Efficient vaccines can also be very difficult to develop in the first place, as illustrated for TB, malaria, and HIV. In the long term, it is not certain that we can win the arms race with microbes using only drugs and vaccines. Vaccines, in particular, disrupt both the current biodiversity and the natural evolution of the microbes they target. Viewed from this angle, it is interesting that the two infections for which we have developed a molecular understanding are caused by defects of immunity mediated by type I IFNs—antiviral molecules—and type II IFN, an antimycobacterial molecule, both of which are commercially available. The use of type II IFN in patients with TB or, as a preventive measure, in P1104A homozygotes living in areas of endemic TB would appear to be a reasonable approach worth testing. Likewise, 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. The specific type I IFN to be used may be determined by the nature of the predisposition. IFN- $\alpha$ 2 and IFN- $\beta$  are good options in patients with a functional response pathway and without neutralizing auto-Abs against the IFN concerned, whereas mAbs neutralizing the virus would be a better option in patients with a defective type I IFN responsive pathway (Lévy et al., 2021).

The other response to the question is biological. The discovery of the molecular and cellular basis of interindividual clinical variability in the course of primary infection allows us to revisit immunology from the angle of host defense against pathogens at individual, whole-organism level, and in the conditions of a natural ecosystem (Casanova and Abel, 2004; Nathan, 2021; Pulendran and Davis, 2020; White and Caskey, 1988). This contrasts with the history of immunology, which, since 1881, has been constructed largely from the angle of vaccination and therefore from the perspective of antigen-specific responses but also on the basis of experiments conducted *in vitro* or in animal models *in vivo*, and, implicitly, at the level of a population considered to be uniform. Indeed, immunology has been built from the perspective of typology, with the idea that general principles apply not only to all individuals of a species but also to most, if not all animal species, and if not to all vertebrates, then at least all mammals. This assumption has proved to be largely correct for the general architecture of immunity and was spectacularly useful as a first step to combating infections medically. However, this paradigm obviously does not explain interindividual variability in the course of infection, whether in humans or in other species, and this is, or at least should be the quintessential immunological enigma. If anything, this paradigm prevents us from understanding this enigma because of its typologist nature. The host genetic approach is based on nominalism, which is itself rooted in the idea that each living organism is unique in space and time, as is each natural interaction between a microbe and a host, accounting for their infinite potential outcomes. The



human genetic approach—a pathogen-centered, natural, nominalist approach—is already revealing increasing numbers of findings at odds with major immunological notions established in the antigen-centered, experimental, typologist tradition (Béziat et al., 2021b; Israel et al., 2017; Notarangelo et al., 2020; Yang et al., 2020; Zhang et al., 2018), potentially heralding a shift in the immunological paradigm (Kuhn, 1962; Polanyi, 1958; Timmins, 2013).

Using Stokes' classification of science (Stokes, 1997), one can probably consider the search for human genetic and immunological determinants of infectious diseases as driven more by a “quest for fundamental understanding” than “considerations of use.” Indeed, the principles governing the prevention and cure of infectious diseases were established in 1881 by Louis Pasteur with the discovery of vaccination (Pasteur, 1922–1939) and in 1932 by Gehrard Domagk with the discovery of anti-infectious agents (Domagk, 1935). This contrasts with other fields of medical research, in which progress in medicine lags behind that in science. The field of infectious diseases is specific in that regard, and one might even wonder if its early medical success has not hampered its subsequent scientific development. This singularity is due to another specific feature of infectious diseases: their environmental component, the pathogen, is both known and necessary. There is little doubt that their infectious nature has also facilitated the discovery of underlying IEI, by permitting the study of patients sharing at least the same environmental cause of disease. Despite these two related and notable differences between infectious and non-infectious diseases, this “rare-to-common” genetic and mechanistic approach has been inspired by the study of other diseases. Indeed, the general mechanism of at least three other common conditions—hypertension (Lifton, 2004–2005), hypercholesterolemia (Goldstein and Brown, 2015; Horton et al., 2007), and diabetes (Yang and Chan, 2016)—was elegantly cracked by a similar “rare-to-common” approach. Collectively, these findings are of heuristic value. The documentation of causality between an inborn error and a clinical phenotype, together with clarification of the molecular and cellular mechanism of disease, in a few patients or even a single patient, can pave the way for the discovery of other causes, genetic, or otherwise, including autoimmune phenocopies, triggering the same mechanism of disease in many more patients. In other words, developing a deep understanding of disease in a single patient appears to be a better starting point than developing a superficial understanding of thousands of patients (Casanova et al., 2014). Decoding the molecular and cellular mechanisms of disease in a single patient seems to be more insightful and fruitful than estimating associations between genomic regions and disease in large populations. For physiological studies, the legacy of Mendel and Garrod has surpassed that of Galton and Pearson, whose legacy evidently turned out to be greater for evolutionary studies (Pickrell and Reich, 2014; Quintana-Murci, 2019).

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J.-L.C. and L.A. co-wrote the manuscript and secured the funding support.

#### DECLARATION OF INTERESTS

J.-L.C. served on the scientific advisory boards of ADMA Biologics, Kymera Therapeutics, and Elixiron Immunotherapeutics. J.-L.C. is an inventor on patent application PCT/US2021/042741, filed July 22, 2021, submitted by The Rockefeller University that covers diagnosis of susceptibility to, and treatment of, viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases.

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