The human genetic determinism of life-threatening infectious diseases: genetic heterogeneity and physiological homogeneity?

Jean-Laurent Casanova1,2,3,4,5, Laurent Abel1,3,4

Published online: 27 May 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

Abstract
Multicellular eukaryotes emerged late in evolution from an ocean of viruses, bacteria, archaea, and unicellular eukaryotes. These macroorganisms are exposed to and infected by a tremendous diversity of microorganisms. Those that are large enough can even be infected by multicellular fungi and parasites. Each interaction is unique, if only because it operates between two unique living organisms, in an infinite diversity of circumstances. This is neatly illustrated by the extraordinarily high level of interindividual clinical variability in human infections, even for a given pathogen, ranging from a total absence of clinical manifestations to death. We discuss here the idea that the determinism of human life-threatening infectious diseases can be governed by single-gene inborn errors of immunity, which are rarely Mendelian and frequently display incomplete penetrance. We briefly review the evidence in support of this notion obtained over the last two decades, referring to a number of focused and thorough reviews published by eminent colleagues in this issue of Human Genetics. It seems that almost any life-threatening infectious disease can be driven by at least one, and, perhaps, a great many diverse monogenic inborn errors, which may nonetheless be immunologically related. While the proportions of monogenic cases remain unknown, a picture in which genetic heterogeneity is combined with physiological homogeneity is emerging from these studies. A preliminary sketch of the human genetic architecture of severe infectious diseases is perhaps in sight.

Introduction
The proportions of infections that are benign and life-threatening in human populations vary enormously from microbe to microbe. This phenomenon of intermicrobial variability is relatively well known and understood, as it seems, at least at first glance, to be determined largely by microbial virulence, almost independently of the human population considered. Admittedly, the notion of virulence is no more than a paraphrase, a term coined to quantify the impact of the microbe in the general population. Its molecular basis remains elusive for the vast majority of microbial isolates. Nevertheless, it has some general value, almost regardless of the microbe and population considered. For example, Ebola virus can be said to be more virulent than herpes simplex virus, because it kills ~60% of those it infects versus less than 0.01% for herpes simplex virus, during primary infections in natural conditions (Garske et al. 2017; Khandaker et al. 2014). However, these proportions undoubtedly vary over time. Ebola, which emerged in 1976 (WHO 1978), will probably gradually lose virulence after hundreds or thousands of years of co-evolution between Ebola viruses and humans. Likewise, the ancestors of herpes simplex virus may have been more virulent and/or ancient humans more susceptible to this virus in the distant past. These proportions also clearly vary over space, as a given microbe may be more harmful in some populations than others, reflecting the influence of specific ecosystems and evolutionary events. This notion will later bring us to the contribution of human genetics, the theme of this issue of the journal. Nevertheless, beyond Ebola and herpes simplex virus, comparisons can be made between all viruses, bacteria, fungi, and parasites, and all microbes can...
be ranked, at least tentatively and provisionally, on a scale of virulence extending from innocuity to lethality.

**Individual microbes and individual humans**

This observation of intermicrobial variability gave rise to the binary notion of virulent vs. opportunistic infectious agents, a naive and questionable dichotomy that attempts to separate microbes into two groups: those that are sufficiently virulent to cause severe disease in “immunocompetent” individuals, and those that cause severe disease only in “immunocompromised” humans. Reality is evidently more complex, because of the almost continuous variation of the proportions of casualties between microbes, making it virtually impossible to separate them into two distinct groups. This concept is also logically inadequate, because any particular human with a life-threatening infectious disease is immunocompromised (i.e., not immunocompetent) with respect to the particular, invading microbe causing the disease concerned. It is inappropriate to restrict “immunodeficiency” to the detection of immunological anomalies, as both the methods of detection and the definition of anomalies evolve continuously. These approximate and simplistic notions have been of some practical medical utility, and have also provided a basis for the scientific field of immunity to infection. However, they do not come close to describing the reality of human infections in an accurate manner, as they do not even attempt to describe the outcomes of populations of humans confronted with populations of microbes. They are inspired by typology and essentialism, as though there really were one generic human “host”, infected by one generic “pathogen”. In the real world, there is no such thing as a host and a pathogen. There are only populations of individual humans and populations of individual microbes.

**Each human × microbe interaction is unique**

Indeed, infection occurs when real individual human beings, not virtual hosts representative of the human species, encounter real microbial isolates, not virtual microbes representative of their own species. Incidentally, while the definition of the human species is difficult from an evolutionary but not from a physiological standpoint, that of any microbial species is difficult from both evolutionary and physiological standpoints. Moreover, human life and death are notions fundamentally and exclusively attached to individuals, not populations. The same is true for the life and death of microbes and, indeed, any other living organism. Like evolution, physiology and pathology operate at the individual level, and not at the population level. All living organisms are unique in space and time. This revolutionary insight was at the heart of the theories of evolution and physiology put forward by Charles Darwin and Claude Bernard. It is also this notion that makes life sciences so fundamentally different from physical sciences, and sometimes difficult for physicists and mathematicians to understand (Bernard 1865; Darwin 1993). All printed copies of this paper are identical, and will remain so for a long time; whereas, all readers of this paper are different from each other. They will also continue to differ as they age. Ernst Mayr’s “population thinking” and Archibald Garrod’s “chemical individuality” later made reference to this seminal notion of biology, again from the complementary perspectives of evolution and physiology (Bearn 1993; Mayr 1988). Each interaction between a human and a microbe is, therefore, unique in space and time. Moreover, a single human, made of cells that inevitably diverge from each other genetically and epigenetically, is almost never infected by a single microbial organism. Instead, this single, heterogeneous human is infected by many members of the same microbial family, which can evolve, mutating and further diverging within this individual, adding another level of diversity and complexity to the interaction.

**Gigantic inter-individual variability**

In this context, it is not surprising that there is tremendous interindividual variability in the clinical outcomes of almost all primary infections with a given microbe, ranging from a total lack of symptoms and signs to death, as dramatically illustrated with the current pandemics of SARS-CoV-2 infection (Casanova et al. 2020). The most virulent microbes can be innocuous in rare individuals; whereas, the least virulent microbes can kill others, albeit rarely. This is, in a nutshell, what we like to refer to as the “infection enigma” (Casanova 2015a; Casanova and Abel 2013). In principle, the interindividual variability of clinical outcome during infection can be accounted for by the variability of the microbes themselves (inherited or acquired, including after selection by anti-infectious agents), and/or by the variability of the hosts (inherited or acquired, including after infection with other microbes), and/or by factors with no effect on the intrinsic capacities of the host and microbe, such as the numbers of invading microbes and their route of infection. The contribution of these last two factors has been amply documented in both clinical studies and experimental models. The route of infection is critical, as demonstrated by staphylococcal diseases following breaches of the skin (Thomer et al. 2016). Other examples include pneumococcal meningitis after congenital or traumatic cerebrospinal fluid fistulas (Henaff et al. 2017). The microbial inoculum is also critical, as extensively documented in experimental infections in animal models (Vidal et al. 2008). An unfortunate example of an experimental infection in humans is
the Lübeck disaster, when infants were given a live BCG vaccine contaminated with *M. tuberculosis*. It was shown that the inoculated dose of *M. tuberculosis* was strongly correlated with the subsequent risk of tuberculosis (Fox et al. 2016). The size of the microbial inoculum is probably also important in natural infections (Casanova 2015a; Vidal et al. 2008).

**Role of microbial virulence**

Microbial variability within a species (with the caveat that microbial species cannot be defined as rigorously as species of multicellular eukaryotes that reproduce sexually) has occasionally been shown to account for the emergence of more virulent microbial strains (Geoghegan and Holmes 2018; Vouga and Greub 2016). A good example is the difference between seasonal influenza viruses, which arise by genetic drift and strike each year with modest variations of virulence, and pandemic influenza viruses, which arise by genetic shift and strike only a few times per century, with much greater virulence (Ciancanelli et al. 2016; Kash and Taubenberger 2015; Krammer et al. 2018; Taubenberger and Morens 2006). However, these elegant studies of microbial virulence diversity were interpreted under the false premise that the infected human population was homogeneous. For reasons pertaining to both practicality and prejudice, microbes were only rarely, if ever, studied for their particular impact in different individuals. Humans resistant to pandemic influenza, and those vulnerable to seasonal influenza, were ignored, neglected, or, at most, considered to be enigmatic outliers of little interest (Ciancanelli et al. 2016). It remains unclear if such interindividual variability in the course of an endemic or epidemic infection results, at least in part, from intermicrobial variability. Although unlikely, resistance to pandemic influenza might result from infection with a defective virus; whereas, death from seasonal influenza might result from infection with a more virulent virus. This general hypothesis probably deserves more attention from virologists and microbiologists.

**Role of acquired immunodeficiency**

Paradoxically, while the impact of individual microbes in individual patients has not been systematically studied, predisposition to particular infections has been studied in individual patients in a given population, and even across populations. Acquired immunodeficiency in individual patients has been attributed to previous infections, the best known example being viral infections, and to medicines, such as immunosuppressive drugs in particular. The viruses known to cause immunosuppression include measles virus and human immunodeficiency virus (HIV) (McChesney and Oldstone 1989; Mina et al. 2019; Naniche and Oldstone 2000; Petrova et al. 2019). There are countless immunosuppressive drugs that cause predisposition to severe infections (Koo et al. 2011; Winthrop et al. 2008). There are also probably many currently unknown forms of acquired immunodeficiency, beyond microbes and medicines, including some caused by somatic genetic mutations and epigenetic modifications, which probably contribute to aging-associated immunodeficiency (Brodin et al. 2015; Casanova 2015a; Casanova et al. 2020). However, aging probably preferentially affects immunity to secondary infection or latent microbes (Laemmle et al. 2019), if only because the proportion of primary infections decreases with age; whereas, the proportions of latent and secondary infections increase (Alcais et al. 2010; Feigin and Cherry 1998; Mandell et al. 2004). This is neatly illustrated by zoster, which results from reactivation of varicella zoster virus (VZV). Its incidence rises after 50 years of life and can be prevented by vaccination of VZV-infected individuals in this age group (Lal et al. 2015). Latency is easy to define, but it is more difficult to define secondary infections, because the two (or more) microbes concerned may not differ significantly, despite there being years or decades between the primary and secondary infections. Reactivation from latency can be difficult to differentiate from a new infection (Cardona 2016; Stewart et al. 2003). In addition, each microbe is related to many others, that are nonetheless different from it, making a rigorous definition of primary and secondary infections difficult, if not impossible.

**Major impact of primary infections**

Nevertheless, we will not discuss the human genetic control of secondary or reactivation infections here, for two main reasons. First, the outcome of secondary or latent infections is probably heavily influenced by the adaptive immune system (Brodin et al. 2015; Casanova 2015b; Casanova et al. 2020; Paul 2008), which emerged twice in evolutionary history, through convergent evolution (Cooper 2010; Guo et al. 2009; Hirano et al. 2013; Pancer et al. 2004). Although genetically controlled, this system and the immunity it confers are separated from the germline through the generation of somatically rearranged clonal receptors for antigens. In the course of secondary infection, the adaptive immune system confers enhanced immunity through the memory of past infections, in what is quintessentially a somatic process. Again, we do not mean by this that the process is not under germline genetic control, but we think that it is much more difficult to disentangle the germline and somatic variations influencing outcome for secondary than for primary infections. Second, from both physiological and evolutionary
angles, the fundamental challenge posed to humans and other species by microbial threats results more from primary than from secondary infections. This is well documented in humans, in which life expectancy at birth in natural conditions, with little or no medical care, remained at 20–25 years for at least 10,000 years worldwide, until about the end of the nineteenth century (Cairns 1997; Casanova and Abel 2005). Half of all children died before the age of 15 years, in the vast majority of cases from primary infection rather than from predation, war, or famine. The very recent increase in human life span results mostly from the conquests of hygiene, aseptic surgery, serotherapy, vaccines, and antimicrobial medicines, which followed the germ theory (Casanova and Abel 2005). The tendency of the adaptive immune responses of modern-day humans to become gradually less effective against VZV over time, from the age of 50 years onward, is certainly a major medical problem in 2020, but a minor biological problem, at least from an evolutionary perspective, because of both its very recent occurrence and its negligible impact on reproduction.

### The human genetic hypothesis

One of the fundamental evolutionary and physiological problems of mankind is, therefore, that of childhood deaths from infection: what is its root cause, given that most children, including the relatives of those who die, survive infections with the same or related microbes, with no major consequences? The human genetic hypothesis was proposed as a response to this question and documented by means of classical genetics during the first half of the twentieth century. We have reviewed the history of this field elsewhere (Casanova 2015a, b; Casanova and Abel 2013, 2020). Briefly, proof-of-principle that severe infections could have a genetic origin was provided in 1905 for plants, in 1923 for animals, and between 1909 and 1943 for humans, by both biometricians and geneticists (Casanova 2015a, b). Plant biologists provided the first compelling evidence that severe infections can be genetic, and even Mendelian, through their studies of fungal infections of wheat. However, it is interesting to note that Pasteur himself established that one of the two infections of silk worm, flacherie, was also “inherited”, not in the sense that the microbe was transmitted from the parents to the offspring, but that the offspring inherited their parents’ predisposition to infection (Pasteur 1926). Pasteur was not aware of Mendel’s laws of genetics and did not pursue this route of research. The genetic component of plant infections became Flor’s general model, as proposed in 1942 (Flor 1942). Multiple studies documented the importance of the genetic background for the outcome of infection in various animals, including mice, rats, rabbits, and guinea pigs (Casanova 2015a; Lurie 1941; Vidal et al. 2008; Webster 1939). In humans, various epidemiological and clinical genetic approaches were followed from 1909 to the 1940s, the most remarkable and convincing investigations being twin studies comparing monozygotic and dizygotic twins for concordance for a particular phenotype (Casanova and Abel 2013; Casanova et al. 2020; Kallmann and Reisner 1943). Adoptive studies, which are equally powerful, were conducted later (Sorensen et al. 1988).

### The respective contributions of microbiologists, immunologists, and geneticists

Interestingly enough, the problem of interindividual clinical variability in the course of primary infection was not tackled by immunologists and microbiologists. This merits a brief word. Microbiologists fundamentally see the microbe as causal and, therefore, consider interindividual clinical variability to be also due to some form of microbial variability, whether qualitative or quantitative. Even though the vast majority of present-day pathogens kill less than 1% of the individuals they infect, microbiologists generally attribute disease and death to the microbe as a matter of principle, although they generally do not document any particular variation accounting for disease or death in specific patients. Immunologists are the heirs of another historical doctrine. Most are reluctant to admit that their legitimately cherished center of interest, the immune system, even if scaled up or upgraded to the whole organism, can be efficient at the population level, but not at the individual level. The idea that most humans are immunodeficient with respect to at least some microbes is still not admitted by most immunologists, although compelling from a logical point of view. This state of affairs may perhaps be accounted for, at least in part, by the desertion of the field of immunity to infection by many immunologists, in 1917, in response to Landsteiner’s stunning discovery of antibody responses to haptens, i.e., synthetic molecules that do not exist in nature. Immunologists have ever focused on the “antibody enigma” of Kindt and Capra, which differs from the infection enigma described above (Kindt and Capra 1984). The little interest of microbiologists and immunologists in resolving this question may explain why a third group of scholars, plant, animal and human geneticists, decided to tackle the infection enigma.

### Clinical and population genetics

If we fast-forward a little, and narrow our focus down to humans, there was a shift in the field of human genetics of infectious diseases from classic to molecular genetics in the early 1950s. Over the next 60 years, the field remained...
divided into two branches, with clinical and population geneticists tackling the problem from different angles (Casanova and Abel 2013). They addressed the same problem, but formulated different hypotheses and used different methods, both to describe the phenotypes of patients and to analyze their genotypes. Population geneticists conducted population-based studies and paid little attention to detailed clinical phenotypes, family histories, and the underlying mechanisms of disease (Casanova and Abel 2007a). In addition, they genotyped the observed human genetic variation and analyzed it as markers, rather than as candidate genetic lesions. By contrast, clinical geneticists conducted patient- or family-based studies and, given the higher granularity of their approach, undertook detailed clinical studies, with direct searches for candidate disease-causing mutations, and attempted to decipher the mechanisms of disease (Casanova and Abel 2007a). With the benefit of hindsight, there is little doubt that clinical genetics was much more informative than population genetics during the period extending from 1950 to 2010. The greatest achievement in the population genetics of infectious diseases remains the discovery in 1954 of the HbS trait conferring tenfold resistance to severe Plasmodium falciparum malaria, which marked the birth of the field (Allison 1954, 2009). Subsequent population studies did not detect such high levels of genetic protection or predisposition (Casanova and Abel 2013), even those leading to the identification of IL28B variants strongly influencing the clearance of hepatitis C virus infection (Ge et al. 2009; Suppiah et al. 2009; Tanaka et al. 2009; Thomas et al. 2009). In addition, the tenfold resistance to severe malaria told us more about the impact of severe infections on the distribution of human variants (the HbS allele being selected by malaria), than about the causality between human genotypes and severe infections (HbS heterozygotes being incompletely protected from malaria).

“Mendelian” basis of susceptibility/resistance to infections

By contrast, at least 200 inborn errors of immunity and three Mendelian resistances to infection were reported by 2010 (Casanova 2015b; Casanova and Abel 2007b). This field was actually born in 1946 with the discovery of autosomal recessive epidermodysplasia verruciformis, although its birth was long attributed to the discovery of X-linked agammaglobulinemia in 1952, or of autosomal recessive neutropenia in 1950 (Casanova and Abel 2013, 2020). This field has provided countless examples of inborn errors of immunity underlying one or more infectious diseases (Meyts et al. 2016; Tangye et al. 2020). Key to this discipline is Claude Bernard’s notion of determinism, which differs from that of predisposition commonly adopted by population geneticists. The year of 1996 marked a watershed moment, with the discovery of the first molecular genetic basis of both Mendelian resistance and the first Mendelian predisposition to a specific infectious disease: resistance to HIV infection (Dean et al. 1996; Liu et al. 1996; Samson et al. 1996) and predisposition to weakly virulent mycobacteria (Jouanguy et al. 1996; Newport et al. 1996), respectively. The discovery of the resistance of CCR5-deficient CD4+ T cells to HIV was inspired by elegant studies dating back to 1976 on the lack of Duffy antigens on the erythrocytes of individuals resistant to Plasmodium vivax (Miller et al. 1976). However, the molecular genetic basis of this phenotype was not determined until 1995, with the identification of a subtle mutation in the DARC promoter (Tournamille et al. 1995). The Mendelian basis of a specific, hitherto “idiopathic” mycobacterial infection in otherwise healthy patients was particularly surprising, as it was at odds with findings for other primary immunodeficiencies described from the 1950s onward, these immunodeficiencies being associated with both immunological abnormalities and multiple infections. Mendelian susceptibility to mycobacterial disease (MSMD) was shown to be caused by inborn errors of IFN-γ immunity (Bustamante et al. 2014; Casanova and Abel 2002). The search for the molecular basis of a “Mendelian infection” was inspired by the discoveries of the first monogenic lesions of Mx (Staeheli et al. 1986) and Nramp1 (Skamene et al. 1982; Vidal et al. 1993) in 1986 and 1993, respectively, underlying specific infections in mice (caused by influenza virus and mycobacteria, respectively), and the superb work on monogenic infections in plants (Dangl and Jones 2001; Jones et al. 2016).

Monogenic basis of infectious diseases

Since 1946, only five severe human infectious diseases have been shown to be often familial, and in such cases, to segregate as Mendelian traits (Table 1). They were confirmed to be Mendelian when their molecular genetic basis was discovered, from 1996 onward (Casanova and Abel 2020). Needless to say, the vast majority of infectious diseases are not Mendelian. However, all infections studied to date have turned out to be monogenic, at least in one child. More than 15 human infections fall into this category, including viral, bacterial, fungal, and parasitic diseases (Table 1). Genetic heterogeneity, including both locus and allelic heterogeneity, is a hallmark of the infections most studied genetically. In contrast, these infections also seem to display physiological homogeneity. For example, MSMD is caused by inborn errors of IFN-γ immunity (Casanova and Abel 2002; Martinez-Barricarte et al. 2018; Rosain et al. 2019), with mutations of 15 genes and 30 allelic forms already reported; whereas, chronic mucocutaneous candidiasis (CMC) is
Table 1 Mendelian and monogenic susceptibility/resistance to infection

| Infectious agent                          | Clinical phenotype | Immunological phenotype | Gene            | Inheritance   |
|------------------------------------------|--------------------|-------------------------|-----------------|---------------|
| BCG vaccines and environmental mycobacteria | MSMD               | IFN-γ deficiency        | IFNGR1, IFNGR2, IL12RB1, IL12B, NEMO, STAT1, CYBB, IRF8, ISG15, TYK2, ROBOC, IL12RB2, IL23R, SPI2LA, JAK1 | Mendelian or monogenic AR, AD, XR
| Mycobacterium tuberculosis              | Tuberculosis (TB)  | IFN-γ deficiency        | IL12RB1, TYK2   | Monogenic AR  |
| Neisseria                                | Invasive disease   | Complement deficiency   | C5, C6, C7, C8A, C8B, C9, CFB, CFD, CFP | Monogenic AR, XR |
| Encapsulated pyogenic bacteria            | Invasive disease   | Complement deficiency   | CIQA, CIQB, CIQC, CI5, C2, C3, C4A, C4B, CFH, CF1 | Monogenic AR |
| Streptococcus pneumoniae                 | Invasive disease   | TIR response deficiency | IRAK4, MYD88, NEMO, HOIL1, HOIP, RPSA | Monogenic AR, AD |
| Staphylococcus aureus                    | Recurrent disease  | TLR2 response deficiency | TIRAP, IL6RA, ZNF341, STAT3, IL6ST | Mendelian or monogenic AR, AD |
| Tropheryma whipplei                      | Whipple’s disease  | IRF4 deficiency         | IRF4            | Monogenic AD  |
| Epstein–Barr virus                       | X-linked lymphoproliferative disease; severe infection; B-cell lymphoma | SH2D1A, XIAP, CD27, CD70, ITK, TNFRSF9, MAGT1 | SH2D1A, XIAP, CD27, CD70, ITK, TNFRSF9, MAGT1 | Mendelian or monogenic AR, XR |
| Human papillomavirus                     | Epidermodysplasia verruciformis | EVER-CIB1 deficiency | EVER1, EVER2, CIB1 | Monogenic AR |
|                                        | Recurrent respiratory papillomatosis | NLRP1 gain of function (GOF) | NLRP1 | Monogenic AR |
| Herpes simplex virus (HSV)               | Forebrain encephalitis | TLR3-IFN-α/β deficiency | UNCS3B, TLR3, TRAF3, TRIF, TBK1, IRF3 | Monogenic AR, AD |
|                                        | snoRNA31 deficiency | SNORA31               |                 | Monogenic AD  |
| HSV, influenza, etc.                     | Brainstem encephalitis | DBR1 deficiency       | DBR1            | Mendelian AR  |
| Influenza                                | Severe influenza   | Type I and III IFN deficiency | IRF7, IRF9, TLR3 | Monogenic AR, AD |
| Cyto/megalovirus (CMV)                   | Lethal infection   | NOS2 deficiency        | NOS2            | Monogenic AR  |
| Rhinovirus, Respiratory syncitial virus  | Recurrent/severe infections | MDA5 deficiency       | IFIHI1          | Monogenic AR  |
| Rhinovirus                               |                      |                        |                 | Monogenic AR  |
| Human herpes virus 8                     | Kaposis sarcoma    | OX40 deficiency        | OX40            | Monogenic AR  |
| Hepatitis A virus                        | Fulminant hepatitis | IL18BP deficiency      | IL18BP          | Monogenic AR  |
| Live measles and yellow fever vaccines   | Severe infections  | IFN-α/β response deficiency | IFNAR1, IFNAR2, STAT1, STAT2 | Monogenic AR |
| Candida                                  | CMC                | IL-17 deficiency       | IL17F, IL17RA, IL17RC, TRAF3, TRAF2, STAT1, JNK1 | Mendelian AR, AD |
| Dermatophytes                            | Invasive dermatophytosis | CARD9 deficiency | CARD9 | Mendelian AR |
| Trypanosoma evansi                       | Trypanosomiasis    | APOL1 deficiency       | APOL1           | Monogenic AR  |
| Plasmodium vivax                         | Resistance to infection | Lack of receptor for pathogen in erythrocytes | DARC | Mendelian AR |
| Human immunodeficiency virus-1           | Resistance to infection | Lack of receptor for pathogen in CD4+ T cells | CCR5 | Mendelian AR |
| Norovirus                                | Resistance to infection | Lack of receptor for pathogen in intestinal epithelium | FUT2 | Mendelian AR |

aWe refer to monogenic disorders with complete clinical penetrance as Mendelian, and those with incomplete penetrance as monogenic
bAR autosomal recessive, AD autosomal dominant, XR X-linked recessive
cWe list only genes found mutated in two or more patients with TB. Most MSMD-causing genes are also rare genetic etiologies of TB. We do not indicate any difference between allelic forms. This is particularly relevant for TYK2, as homozygosity for loss of function (LOF) variants is a rare etiology of TB, whereas homozygosity for the P1104A allele is common in the general population and may account for about 1% of TB cases in humans of European descent (Boisson-Dupuis et al. 2018; Kerner et al. 2019)
dVariants of RPSA underlie isolated congenital asplenia
eVariants of STAT3, ZNF341 and IL6ST underlie staphylococcal disease and a few other infections
caused by inborn errors of IL-17A/F immunity (Li et al. 2017, 2019, Puel et al. 2012), with mutations of 10 genes and 11 allelic forms. The notions of genetic heterogeneity and physiological homogeneity have gained momentum from next-generation sequencing (NGS) studies. In this respect, 2010 marked another watershed moment, as NGS provided both clinical and population geneticists with the same genetic data. It is probably fair to say that NGS has brought clinical and population genetics closer than ever, with both fields now analyzing the same types of data. Thanks to this joint, synergistic approach, the search for monogenic lesions underlying severe infectious diseases has blossomed, as exemplified by the population-based discovery of homozygosity for the P1104A TYK2 allele as a factor conferring predisposition to tuberculosis (Boisson-Dupuis et al. 2018; Kerner et al. 2019). We do not mean to imply that all new genetic etiologies can easily and immediately be connected physiologically with known etiologies. For example, SNORA31 mutations have been found to underlie herpes simplex encephalitis, but appear to be unconnected to mutations in the TLR3 pathway (Lafaille et al. 2019). This work may take time, as it is much like a giant jigsaw puzzle. However, we are willing to predict that this hypothesis often applies and that there will probably be a single, final, assembled molecular puzzle corresponding to each severe infectious disease.

**Human genetics of infectious diseases: quod vadis?**

Three key questions, at the crossroads of clinical and population genetics, have emerged from these studies. First, does this model of monogenic lesions, typically with incomplete penetrance (complete penetrance observed more rarely), and with genetic heterogeneity and physiological homogeneity, apply to all severe infections? All infections studied to date have been found to be monogenic, in at least one patient, but does this apply to all infections, rare or common? Second, are there only rare genetic etiologies, accounting for only a small proportion of any common infection (and arguably a higher proportion of rare infections)? The recent identification of homozygosity for TYK2 P1104A as a common recessive etiology of tuberculosis, suggests that monogenic (but not Mendelian) infections may be more common than previously thought (Boisson-Dupuis et al. 2018; Kerner et al. 2019). What is the proportion of monogenic forms, for any given infection, including common infections? Third, what are the determinants of incomplete penetrance? This is of importance, especially as different infections have been shown to be allelic, and even driven by the same allele in different patients, as illustrated by herpes simplex encephalitis and influenza pneumonitis, which seem to strike different patients with TLR3 mutations (Lim et al. 2019; Zhang et al. 2007). Genetic modifiers may be involved, although other factors mentioned above, such as microbe numbers and the route of infection, probably also play a key role. There are probably also digenic and oligogenic forms of predisposition to infection. Large population-based studies should help us to tackle these three problems. For example, the pandemics of SARS-CoV-2 infection led to the COVID Human Genetic Effort (https://www.covidhge.com/), which is an international consortium that aims to analyze the human genetic basis of life-threatening COVID-19 in previously healthy and relatively young (< 50 years) patients. In this context, it is worth mentioning that monogenic resistance to infections has not grown, as a field, as quickly and broadly as studies of monogenic forms of predisposition. The three compelling cases of resistance were discovered in 1976, 1996, and 2003 for infections with Plasmodium vivax (Miller et al. 1976), HIV (Dean et al. 1996; Liu et al. 1996; Samson et al. 1996), and norovirus (Lindesmith et al. 2003), respectively, and the genetic lesion underlying resistance to P. vivax was not described until 1995 (Tournamille et al. 1995). It is surprising that this field has not taken off yet, particularly in light of the small but distinct proportion of humans completely resistant to infection with some very common pathogens, as attested by negative serological tests.

**Clinical implications**

The discovery that many severe infections can have a monogenic basis, with incomplete penetrance and genetic heterogeneity but physiological homogeneity, at least in some patients, has important clinical and biological implications. At the clinical level, these findings provide patients with a molecular diagnosis and open up possibilities for the genetic counseling of their families. An understanding of the pathogenesis of a disease is always useful clinically, in the long term, if not more rapidly. This, in turn, paves the way for preventive or therapeutic approaches aiming to restore immunity. For example, an infection caused by an inherited deficiency of a cytokine can best be prevented or treated with the corresponding recombinant cytokine, or a key product controlled by that cytokine. The best example of this to date is provided by recombinant IFN-γ treatment in patients with genetic defects impairing the production of IFN-γ (Alangari et al. 2011; Holland 2001). It is also worth mentioning that the elucidation of the pathogenesis of an infectious disease in rare monogenic cases can shed light onto the mechanisms at work in other, more common patients, such as those infected with HIV (Zhang et al. 2017). Finally, vaccine development will also benefit from this approach, as its aim is to protect genetically predisposed individuals; whereas, the vaccination of naturally resistant
individuals is not necessary and may be a major confounding factor in any trial (Glass et al. 2012). The biological implications of these studies are also important. An inherited deficiency defines the redundant and non-redundant roles of the corresponding gene, and its ecologically relevant and evolutionarily selected functions (Barreiro and Quintana-Murci 2010; Quintana-Murci 2019; Quintana-Murci and Clark 2013). These studies define immunity to infection in natura (Quintana-Murci et al. 2007). This contrasts with and complements the study of experimental infections in experimental conditions in animal models of disease (Casanova and Abel 2004; Fortin et al. 2007; Quintana-Murci et al. 2007). Such studies also define the levels of redundancy of human genes: genes with low levels of redundancy underlie multiple infections when mutated; whereas, highly redundant genes underlie one or a few infections; completely redundant genes underlie no infectious phenotype; and beneficially redundant genes underlie resistance to one or more infections when mutated (Casanova and Abel 2018).

**Biological implications**

The biological implications of the field are already apparent, perhaps more so than the clinical implications. Indeed, the human genetic approach that launched this description of immunity to infection in natural conditions has already overturned many immunological dogmas (Casanova et al. 2013). For example, TLRs other than TLR3 and IL-1Rs were thought to be crucial for host defense against various infectious agents. The discovery of IRAK4 and MyD88 deficiencies showed that they were, instead, collectively essential for host defense against pneumococcus and staphylococcus, but otherwise largely redundant (Casanova et al. 2011; Ku et al. 2007; Picard et al. 2003; von Bernuth et al. 2008, 2012). This approach has also revealed the role of cells other than leukocytes in immunity (Zhang et al. 2019). For example, mutations of TLR3 were shown to underlie herpes simplex virus encephalitis and influenza pneumonia, not by disrupting leukocytic immunity, but by impairing cortical neuron and pulmonary epithelial cell intrinsic immunity to viruses (Casanova et al. 2011; Casrouge et al. 2006; Lafaille et al. 2012; Lim et al. 2019; Zhang et al. 2007; Zimmer et al. 2018). The reasons why these and other studies are at odds with immunological studies and predictions is a topic of interest extending well beyond the scope of this chapter. Suffice it to say that immunity to infection in natural conditions, which can be best studied by human genetics, has been found to have a much higher level of redundancy than previously anticipated (Casanova and Abel 2018). The specificity of an inborn error of immunity for a particular infection is not the result of a specific molecular interaction, as for most forms of specificity in immunity. Instead, it reflects the broad redundancy of the genetic defect for host defense, with only a hole in protective immunity being clinically visible. These defects can be seen as lacunar inborn errors of immunity to infection.

**Topics covered in this special issue**

We have assembled, in this special issue of *Human Genetics*, a collection of reviews covering specific aspects of this area of biomedical research. Some chapters review recent progress in related fields, such as human evolutionary genetics (Lluis Quintana-Murci and Luis Barreiro) (Barreiro and Quintana-Murci 2020), human immunology (Petter Brodin) (Brodin 2020), human non-protein coding variants (Amalio Telenti) (Telenti and di Iulio 2019), the question of penetrance (Dusan Bogunovic) (Gruber and Bogunovic 2020), and computational approaches in human genetics (Yuval Itan) (Bayrak and Itan 2020). Most chapters cover the human genetic basis of specific infections: (i) mycobacterial infections, including MSMD (Jacinta Bustamante) (Bustamante 2020), tuberculosis (Stéphanie Boisson-Dupuis) (Boisson-Dupuis 2020), leprosy (Erwin Schurr) (Fava et al. 2019), and Buruli ulcer (Jérémy Manry) (Manry 2020); (ii) other bacterial infections, including those caused by *Neisseria* (Vanessa Sancho-Shimizu and Mike Levin) (Hodeib et al. 2020), and pyogenic bacteria (Bertrand Boisson) (Boisson 2020); (iii) viral infections, including those caused by Epstein–Barr virus (Stuart Tangye) (Tangye 2020), human papilloma viruses (Vivien Béziat) (Beziat 2020), human immunodeficiency virus (Paul McLaren) (Gingras et al. 2020), and viruses causing encephalitis (Shen-Ying Zhang) (Zhang 2020b), chronic hepatitis (Aurélie Cobat) (Nahon and Cobat 2020), and fulminant hepatitis (Emmanuelle Jouanguy) (Jouanguy 2020); (iv) peripheral and invasive candidiasis (Anne Puel) (Puel 2020); (v) parasitic infections, including malaria (Tom Williams) (Kariuki and Williams 2020), leishmaniasis (Jennifer Blackwell) (Blackwell et al. 2020), and schistosomiasis (Alain Dessein) (Dessein et al. 2020); and (vi) fetal and neonatal infections (Alessandro Borghesi) (Borghesi et al. 2020). Unfortunately, a few monogenic infectious diseases described in Table 1 are not reviewed here, including Whipple’s disease (*Tropheryma whipplei*) due to IRF4 deficiency (Guerin et al. 2018), Kaposi sarcoma (human herpes virus 8) due to OX40 deficiency (Byun et al. 2013), lethal cyto-megalovirus infection due to NOS2 deficiency (Drutman et al. 2020), and trypanosomiasis (*Trypanosoma evansi*) due to APOL1 deficiency (Vanhollebeke et al. 2006). One chapter addresses the timely question of interaction between the human genome and the viral genome (Jacques Fellay).
Human Genetics (2020) 139:681–694

(Fellay and Pedergnana 2019); whereas, another reviews autoimmune phenocopies of monogenic infections due to autoantibodies against cytokines (Cheng-Lung Ku and Rainer Doffinger) (Ku et al. 2020). Finally, we have invited colleagues outside the field of the human genetics of infectious diseases to contribute to this issue with reviews about the genetic basis of infections in other species. In particular, Otto Haller reviews the Mx saga (Haller and Kochs 2019), concerning the first animal/human gene conferring predisposition to a specific infection to be identified (Staeheli et al. 1986), and Philippe Gros, who had discovered the molecular basis of the Bcg locus by performing the first positional cloning in mice (Vidal et al. 1993), reviews the complex role of IRF8 in mice and humans (Salem et al. 2020).

Concluding remarks

In assembling this collection of reviews, we intend to provide a broad overview of the vitality of this nascent field. We think the field has an enormous potential for growth, as the vast majority of human infections have not been studied from a human genetic and immunological angle. Moreover, for the infections that have been studied, no genetic defects have yet been identified for the vast majority of patients. This field is important medically, as most microbes will inevitably become resistant to current anti-infectious agents, and the development of novel anti-infectious agents is likely to be slower than in the past. Restoring the immunity of immunodeficient patients with recombinant cytokines or other molecules will become an alternative and timely approach. Moreover, infections are the only conditions that can kill a sizeable proportion of humans in a short period of time, as dramatically reminded by the recent Ebola epidemics and the current SARS-CoV-2 pandemics. We will not be wiped out by malignant, metabolic, or neurodegenerative conditions. Emerging and re-emerging microbes, and microbes resistant to anti-infectious agents pose a fundamental threat to mankind, the magnitude of which is difficult to oversize. Finally, the study of host defense in natural conditions is a fundamental biological problem. Indeed, bacteria and archaea inhabited the planet alone for about one billion years, before the arrival of unicellular eukaryotes, with which they cohabited for another billion years. Phages and other viruses accompanied them. Understanding how multicellular eukaryotes, including plants and animals, and, of course humans, developed in this ocean of unicellular organisms and viruses is a fundamental biological problem (Futuyma 1998; Woese et al. 1990). The immunity of multicellular organisms to unicellular organisms and viruses, and even to other multicellular organisms, is both primordial and essential. It can be studied by means of genetics, and ideally by human genetics.

Acknowledgements We thank Isabelle Meyts, Claire Fieschi, Paul Bastard, Eduardo Garcia Reino, Jérémie Rosain, the senior researchers and other members of the Laboratory of Human Genetics of Infectious Diseases for helpful discussions and critical reading of this introduction to this issue of Human Genetics. On behalf of all authors, the corresponding author states that there is no conflict of interest. The Laboratory of Human Genetics of Infectious Diseases is supported in part by institutional grants from INSERM, Paris Descartes University, St. Giles Foundation, the French Foundation for Medical Research (FRM) (EQU201903007798), the SCOR Corporate Foundation for Science, The Rockefeller University Center for Clinical and Translational Science grant number 8UL1TR001866 from the National Center for Research Resources and the National Center for Advancing Sciences (NCATS), National Institutes of Health grants (R01AI088364, R01NS072381, R37AI095983, P01AI061093, R21AI137371, R01AI127564, and U19AI111143), and grants from the French National Research Agency (ANR) under the “Investments for the future” program (ANR-10-IAHU-01).

References

Alangari AA, Al-Zamil F, Al-Mazrou A, Al-Muhsen S, Boisson-Dupuis S, Awadallah S, Kambal A, Casanova JL (2011) Treatment of disseminated mycobacterial infection with high-dose IFN-gamma in a patient with IL-12Rbeta1 deficiency. Clin Dev Immunol 2011:691956. https://doi.org/10.1155/2011/691956

Alcais A, Quintana-Murci L, Thaler DS, Schurr E, Abel L, Casanova JL (2010) Life-threatening infectious diseases of childhood: single-gene inborn errors of immunity? Ann N Y Acad Sci 1214:18–33

Allison AC (1954) Protection afforded by sickle cell trait against subterranean malarian infection. BMJ 1:290–294

Allison AC (2009) Genetic control of resistance to human malaria. Curr Opin Immunol 21:499–505. https://doi.org/10.1016/j.coi.2009.04.001

Barreiro LB, Quintana-Murci L (2010) From evolutionary genetics to human immunology: how selection shapes host defence genes. Nat Rev Genet 11:17–30. https://doi.org/10.1038/nrg2698

Barreiro LB, Quintana-Murci L (2020) Evolutionary and population (epi)genetics of immunity to infection. Hum Genet. https://doi.org/10.1007/s00439-020-02167-x

Bayrak CS, Istan Y (2020) Identifying disease-causing mutations in genomes of single patients by computational approaches. Hum Genet. https://doi.org/10.1007/s00439-020-02179-7

Bearn AG (1993) Archibald Garrod and the Individuality of Man. Clarion Press, Oxford

Bernard C (1865) An introduction to the study of experimental medicine. Dover Publications, New York

Berzati V (2020) Human genetic dissection of papillomavirus-driven diseases: new insight into their pathogenesis. Hum Genet. https://doi.org/10.1007/s00439-020-02183-x

Blackwell JM, Fakiola M, Castellucci LC (2020) Human genetics of leishmania infections. Hum Genet. https://doi.org/10.1007/s00439-020-02130-w

Boisson B (2020) The genetic basis of pneumococcal and staphylococcal infections: inborn errors of human TLR and IL-1R immunity. Hum Genet. https://doi.org/10.1007/s00439-020-02111-z

Boisson-Dupuis S (2020) The monogenic basis of human tuberculosis. Hum Genet. https://doi.org/10.1007/s00439-020-02126-6
Bustamante J, Boisson-Dupuis S, Ramirez-Alejo N, Li Z, Patin E, Rao G, Kerner G, Lim CK, Kremenkov DN, Hernandez N, Ma CS, Zhang Q, Markle J, Martinez–Barricarte R, Payne K, Fisch R, Deswarte C, Halpern J, Bouaziz M, Mulwa J, Sivanesan D, Lazarov T, Naves R, Garcia I, Itan Y, Boisson B, Checchi A, Jabot–Hanin F, Cobat A, Guennoun A, Jackson CC, Pekcan S, Caliskaner Z, Inostroza J, Costa–Carvalho BT, de Albuquerque JAT, Garcia–Ortiz H, Orozco L, Ozcelik T, Abid A, Rhorfi I, Souhi H, Amrani HN, Zegmout A, Geissmann F, Michnick SW, Muller-Fleckenstein I, Fleckenstein B, Puel A, Ciancanelli MJ, Marr N, Abolhassani H, Balcels ME, Condino-Neto A, Strickler A, Abarca K, Teuscher C, Ochs HD, Reishi I, Sayar EH, El-Baghdadi J, Bustamante J, Hammarsrom L, Tangye SG, Pellegrini S, Quintana-Murci L, Abel L, Casanova JL (2018) Tuberculosis and impaired IL-23–dependent IFN-γamma immunity in humans homozygous for a common TRYK2 missense variant. Sci Immunol. https://doi.org/10.1126/sciimmunol.aau8714

Borghesi A, Marzollo A, Michev A, Fellay J (2020) Susceptibility to infection in early life: a growing role for human genetics. Hum Genet. https://doi.org/10.1007/s00439-019-01209-2

Brodin P (2020) New approaches to the study of immune responses in humans. Hum Genet. https://doi.org/10.1007/s00439-020-01219-3

Brodin P, Jovic V, Gao T, Bhattacharya S, Angel CJ, Furman D, Shen-Orr S, Dekker CL, Swan GE, Butte AJ, Maecher HT, Davis MM (2015) Variation in the human immune system is largely driven by non-heritable influences. Cell 160:37–47. https://doi.org/10.1016/j.cell.2014.12.020

Bustamante J (2020) Mendelian susceptibility to mycobacterial disease: recent discoveries. Hum Genet. https://doi.org/10.1007/s00439-020-01210-y

Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL (2014) Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol 26:454–470. https://doi.org/10.1016/j.smim.2014.09.008

Byun M, Ma CS, Aklay A, Pedergnana V, Palendira U, Myong J, Avery DT, Liu Y, Abhyankar A, Lorenzo L, Schmidt M, Lim HK, Cassar O, Migaud M, Rozenberg F, Canpolat N, Aydogan A, Picard C, Gessain A, Jouanguy E, Cesaran E, Olivier M, Gros P, Abel L, Croft M, Tangye SG, Casanova JL (2013) Inherited human OX40 deficiency underlying classic Kaposi sarcoma of childhood. J Exp Med 210:1743–1759. https://doi.org/10.1084/jem.20130592

Cairns J (1997) Matters of life and death: perspectives on public health, molecular biology, cancer, and the prospects for the human race. Princeton University Press, Princeton

Cardona PJ (2016) Reactivation or reinfection in adult tuberculosis: is that the question? Int J Mycobacteriol 5:400–407. https://doi.org/10.1016/j.ijmyco.2016.09.017

Casanova JL (2016a) Human genetic basis of interindividual variability in the course of infection. Proc Natl Acad Sci USA 112:E7118–E7127. https://doi.org/10.1073/pnas.1521644112

Casanova JL (2015b) Severe infectious diseases of childhood as monogenic inborn errors of immunity. Proc Natl Acad Sci USA 112:E7128–E7137. https://doi.org/10.1073/pnas.1521651112

Casanova JL, Abel L (2002) Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol 20:581–620

Casanova JL, Abel L (2004) The human model: a genetic dissection of immunity to infection in natural conditions. Nat Rev Immunol 4:55–66

Casanova JL, Abel L (2005) Inborn errors of immunity to infection: the rule rather than the exception. J Exp Med 202:197–201

Casanova JL, Abel L (2007a) Human genetics of infectious diseases: a unified theory. EMBO J 26:915–922

Casanova JL, Abel L (2007b) Primary immunodeficiencies: a field in its infancy. Science 317:617–619

Casanova JL, Abel L (2013) The genetic theory of infectious diseases: a brief history and selected illustrations. Annu Rev Genomics Hum Genet 14:215–243. https://doi.org/10.1146/annurev-genom-091212-153448

Casanova JL, Abel L (2018) Human genetics of infectious diseases: unique insights into immunological redundancy. Semin Immunol 36:1–12. https://doi.org/10.1016/j.smim.2017.12.008

Casanova JL, Abel L (2020) Lethal infectious diseases as inborn errors of immunity: toward a synthesis of the germ and genetic theories. Annu Rev Pathol. https://doi.org/10.1146/annurev-pathol-031920-101429

Casanova JL, Abel L, Quintana-Murci L (2011) Human TLRs and IL-1Rs in host defense: natural insights from evolutionary, epidemiological, and clinical genetics. Annu Rev Immunol 29:447–491

Casanova JL, Abel L, Quintana-Murci L (2013) Immunology taught by human genetics. Cold Spring Harb Symp Quant Biol 78:157–172. https://doi.org/10.1101/sqb.2013.78.019968

Casanova JL, Su H, on behalf of the COVID Human Genetic Effort (2020) A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection. Cell. https://doi.org/10.1016/j.cell.2020.05.016

Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, Picard C, Mahfoult N, Nicolas N, Lorenzo L, Plancoulaine S, Senechal B, Geissmann F, Tabeta K, Hoebe K, Du X, Miller RL, Heron B, Mignot C, de Villemeur TB, Lebon P, Dulac O, Rozenberg F, Beutler B, Tardieu M, Abel L, Casanova JL (2006) Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 314:308–312

Ciancanelli MJ, Abel L, Zhang SY, Casanova JL (2016) Host genetics of severe influenza: from mouse Mx1 to human IRF7. Curr Opin Immunol 38:109–120. https://doi.org/10.1016/j.coi.2015.12.002

Cooper MD (2010) A life of adventure in immunobiology. Annu Rev Immunol 28:1–19. https://doi.org/10.1146/annurev-immunol-030409-101248

Dangl JL, Jones JD (2001) Plant pathogens and integrated defence responses to infection. Nature 411:826–833. https://doi.org/10.1038/35081161

Darwin C (1993) The origin of species by means of natural selection, or, the preservation of favored races in the struggle for life. Modern Library, New York

Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E, Donfield S, Vlahos D, Kaslow R, Saah A, Rinaldo C, Detels R, O'Brien SJ (1996) Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CRK5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science 273:1856–1862

Dessein H, Duflot N, Romano A, Opio C, Pereira V, Mola C, Kabaterene N, Coutinho A, Dessein A (2020) Genetic algorithms identify individuals with high risk of severe liver disease caused by schistosomes. Hum Genet. https://doi.org/10.1007/s00439-020-02160-4

Drutman SB, Mansouri D, Mahdaviani SA, Neelhus AL, Hum D, Bryk R, Hernandez N, Belkaya S, Rapaport F, Bigio B, Fisch R, Rahman M, Khan T, Al Ali F, Marjani M, Mansouri N, Lorenzo-Diaz L, Emile JF, Marr N, Jouanguy E, Bustamante J, Abel L, Boisson-Dupuis S, Beziet V, Nathan C, Casanova JL (2020) Fatal cytomegalovirus infection in an adult with inherited NOS2 deficiency. N Engl J Med 382:437–445. https://doi.org/10.1056/NEJMoa1910640
Fava VM, Dallmann-Sauer M, Schurt E (2019) Genetics of leprosy: today and beyond. Hum Genet. https://doi.org/10.1007/s00439-019-02087-5

Feigin RD, Cherry JD (1998) Textbook of pediatric infectious diseases, 4th edn. W.B. Saunders Company, Philadelphia

Fellay J, Pedergnana V (2019) Exploring the interactions between the human and viral genomes. Hum Genet. https://doi.org/10.1007/s00439-019-02089-3

Flor HH (1942) Inheritance of pathogenicity in a cross between physiological races 22 and 24 of Melampsora lini. Phytopathology 32:5

Fortin A, Abel L, Casanova JL, Gros P (2007) Host genetics of mycobacterial diseases in mice and men: forward genetic studies of BCG-osis and tuberculosis. Annu Rev Genomics Hum Genet 8:163–192

Fox GJ, Orlova M, Schurr E (2016) Tuberculosis in newborns: the lessons of the “Lubeck Disaster” (1929–1933). PLoS Pathog 12:e1005271. https://doi.org/10.1371/journal.ppat.1005271

Futuyma DJ (1998) Evolutionary biology, 3rd edn. Sinauer Associates, Sunderland

Garske T, Cori A, Ariyarajah A, Blake IM, Dorigatti I, Eckmanns T, Fraser C, Hinsley W, Jombart T, Mills HL, Nedjati-Gilani G, Newton E, Nouvellet P, Perkins D, Riley S, Schumacher D, Shah A, Van Kerkhove MD, Dye C, Ferguson NM, Donnelly CA (2017) Heterogeneities in the case fatality ratio in the West African Ebola outbreak 2013–2016. Philos Trans R Soc Lond B Biol Sci. https://doi.org/10.1098/rstb.2016.0308

Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Geoghegan JL, Holmes EC (2018) The phylogenomics of evolvability. Nature 551:435–438. https://doi.org/10.1038/nature24677

Hodeib S, Herberg JA, Levin M, Sancho-Shimizu V (2020) Human genetics of meningococcal infections. Hum Genet. https://doi.org/10.1007/s00439-020-02128-4

Holland SM (2001) Immunotherapy of mycobacterial infections. Semin Respir Infect 16:47–59

Jones JD, Vance RE, Dangl JL (2016) Intracellular innate immune surveillance devices in plants and animals. Science. https://doi.org/10.1126/science.aaf6395

Jouanguy E (2020) Human genetic basis of fulminant viral hepatitis. Hum Genet. https://doi.org/10.1007/s00439-020-02166-y

Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, Levin M, Blanche S, Seboun E, Fischer A, Casanova JL (1996) Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. N Engl J Med 335:1956–1961

Kallmann MJ, Reisner D (1943) Twin studies on the significance of genetic factors in tuberculosis. Am Rev Tuberc 47:549–574

Kariuki SN, Williams TN (2020) Human genetics and malaria resistance. Hum Genet. https://doi.org/10.1007/s00439-020-02142-6

Kash JC, Taubenberger JK (2015) The role of viral, host, and secondary bacterial factors in influenza pathogenesis. Am J Pathol 185:1528–1536. https://doi.org/10.1016/j.ajpath.2014.08.030

Kerner G, Ramiez-Alejo N, Seeleuthner Y, Yang R, Ogishi M, Cobat A, Patin E, Quintana-Murci L, Boisson-Dupuis S, Casanova JL, Abel L (2019) Homozygosity for TYK2 P1104A underlies tuberculosis in about 1% of patients in a cohort of European ancestry. Proc Natl Acad Sci USA 116:10430–10434. https://doi.org/10.1073/pnas.1903561116

Khandaker G, Raynes-Greenow C, Smithers-Sheedy H, Booy R, Menzies R, Jones C (2014) Mortality from herpes simplex virus (HSV) infection in Australian children, 1999–2011 using national datasets. Infect Disord Drug Targets 14:89–92

Kindt TJ, Capra JD (1984) The antibody enigma. Plenum Press, New York

Koo S, Marty FM, Baden LR (2011) Infectious complications associated with immunomodulating biologic agents. Hematol Oncol Clin North Am 25:117–138. https://doi.org/10.1016/j.hoc.2010.11.009

Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, Doherty PC, Palese P, Shaw ML, Treanor J, Webster RG, Garcia-Sastre A (2018) Influenza. Nat Rev Dis Primers 4:3. https://doi.org/10.1038/nrdp.2018.37

Ku CL, von Bernuth H, Picard C, Zhang SY, Chang HH, Yang K, Chrabieh M, Issekutz AC, Cunningham CK, Gallin J, Holland SM, Roifman C, Ehl S, Smart J, Tang M, Barratt FJ, Levy O, McDonald D, Day-Good NK, Miller R, Takada H, Hara T, Al-Hajjar S, Al-Ghonaum A, Speert D, Sanlaville D, Li X, Geissmann F, Vivier E, Marodi L, Garty BZ, Chapel H, Rodriguez-Gallego C, Bossuyt X, Abel L, Puel A, Casanova JL (2007) Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependentTLRs are otherwise redundant in protective immunity. J Exp Med 204:2407–2422

Ku CL, Chi CY, Von Bernuth H, Doffinger R (2020) Autoantibodies against cytokines: Phenocopies of primary immunodeficiencies? Hum Genet. https://doi.org/10.1007/s00439-020-02180-0

Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, Doherty PC, Palese P, Shaw ML, Treanor J, Webster RG, Garcia-Sastre A (2018) Influenza. Nat Rev Dis Primers 4:3. https://doi.org/10.1038/nrdp.2018.37

Laemmle L, Goldstein RS, Kinchington PR (2019) Modeling varicella zoster virus persistence and reactivation—closer to resolving a perplexing persistent state. Front Microbiol 10:1634. https://doi.org/10.3389/fmicb.2019.01634

Lafaille FG, Pessach IM, Zhang SY, Ciancanelli MJ, Herman M, Abhyankar A, Ying SW, Keros S, Goldstein PA, Mostoslavsky G, Ordonez-Montanes J, Jouanguy E, Plancoulaine S, Tu E, Elkahtet Y, Al-Muhsen S, Tardieu M, Schlaeger TM, Daley GQ,
Abel L, Casanova JL, Studer L, Notarangelo LD (2012) Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. Nature 491:769–773. https://doi.org/10.1038/nature11583

Lafaille FG, Harschnitz O, Lee YS, Zhang P, Hasek ML, Kerner G, Itan Y, Ewaleifoh O, Rapaport F, Carlile TM, Carter-Timefo ME, Paquet D, Dobbs K, Zimmer B, Gao D, Rojas-Duran MF, Kwart D, Rattina V, Ciancanneli MJ, McAlpine JL, Lorenzo L, Boucherit S, Rozenberg F, Halwani R, Henry B, Amenzouzi N, Alsim Z, Marques L, Church JA, Al-Muhsen S, Tardieu M, Bousfiha AA, Paludan SR, Mogensen TH, Quintana-Murci L, Tessier-Lavigne M, Smith GA, Notarangelo LD, Studer L, Gilbert W, Abel L, Casanova JL, Zhang SY (2019) Human SNORA31 variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis. Nat Med 25:1873–1884. https://doi.org/10.1038/s41591-019-0672-3

Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Lindesmith L, Moe C, Marionneau S, Ruvoen N, Jiang X, Lindblad L, Manry J (2020) Human genetics of Buruli ulcer. Hum Genet. https://doi.org/10.1007/s00439-020-02163-1

Marbeit LS, Hershfield MS (2004) Principles and practice of infectious diseases, 6th edn. Elsevier Health Sciences, Philadelphia

Martinez-Barricarte R, Markle JG, Ma CS, Deenick EK, Ramirez-Alejo N, Mele F, Latorre D, Mahdadaviani SA, Aytekin C, Mansouri D, Bryant VL, Jabot-Hanin F, Deswarte C, Nieto-Pathan A, Surace L, Kerner G, Itan Y, Jovic S, Avery DT, Wong N, Rao G, Patin E, Okada S, Bigio B, Boisson B, Rapaport F, Seeleutner Y, Schmidt M, Ikincigullari A, Dogu F, Tanir G, Tabarsi P, Bloursaz MR, Joseph JK, Heer A, Kong XF, Migaud M, Lazarov T, Geissmann F, Fleckenstein B, Arlehamn CL, Sette A, Puel A, Emile JF, van de Vosse E, Quintana-Murci L, Di Santo JP, Abel L, Boisson-Dupuis S, Bustamante J, Tangey SG, Sallusto F, Casanova JL (2018) Human IFN-gamma immunity to mycobacteria is governed by both IL-12 and IL-23. Sci Immunol. https://doi.org/10.1126/sciimmunol.aau6759

Maye E (1988) Toward a new philosophy of biology. Harvard University Press, Cambridge

McChesney MB, Oldstone MB (1989) Virus-induced immunosuppression: infections with measles virus and human immunodeficiency virus. Adv Immunol 45:335–380

Meyts I, Bosch B, Bolze A, Boisson B, Itan Y, Belkadi A, Pedergnana V, Moens L, Picard C, Cobat A, Bossuyt X, Abel L, Casanova JL (2016) Exome and genome sequencing for inborn errors of immunity. J Allergy Clin Immunol 138:957–969. https://doi.org/10.1016/j.jaci.2016.08.003

Miller LH, Mason SJ, Clyde DF, McGinniss MH (1976) The resistance factor to Paramyxoviruses in blacks. The Duffy-blood-group genotype, FYf, Engl J Med 295:302–304

Mina MJ, Kula T, Leng Y, Li M, de Vries RD, Knip M, Siljander H, Rewers M, Choy DF, Wilson MS, Larman HB, Nelson AN, Griffin DE, de Swart RL, Elledge SJ (2019) Measles viruses infection diminishes preexisting antibodies that offer protection from other pathogens. Science 366:599–606. https://doi.org/10.1126/science.aay6485

Nahon P, Cobat A (2020) Human genetics of HCV infection phenotypes in the era of direct-acting antivirals. Hum Genet. https://doi.org/10.1007/s00439-020-02136-4

Naniche D, Oldstone MB (2000) Generalized immunosuppression: how viruses undermine the immune response. Cell Mol Life Sci 57:1399–1407. https://doi.org/10.1007/PL00000625

Newport MJ, Huxley CM, Huston S, Haryawanicz CM, Oostra BA, Williamson R, Levin M (1996) A mutation in the interferon-gamma receptor gene and susceptibility to mycobacterial infection. N Engl J Med 335:1941–1949

Panzer C, Amemiya CT, Erhardt GR, Cetlin J, Gurtler GL, Cooper MD (2004) Somatic diversification of variable lymphocyte receptors in the agnathan sea lamprey. Nature 430:174–180. https://doi.org/10.1038/nature02740

Pasteur L (1926) Etudes sur la maladie des vers à soie. In: Vallery-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic infections of the agnathan sea lamprey. Nature 430:174–180. https://doi.org/10.1038/nature02740

Piat J, Ewaleifoh O, Deenick EK, Ramirez-Alejo N, Mele F, Latorre D, Mahdadaviani SA, Aytekin C, Mansouri D, Bryant VL, Jabot-Hanin F, Deswarte C, Nieto-Pathan A, Surace L, Kerner G, Itan Y, Jovic S, Avery DT, Wong N, Rao G, Patin E, Okada S, Bigio B, Boisson B, Rapaport F, Seeleutner Y, Schmidt M, Ikincigullari A, Dogu F, Tanir G, Tabarsi P, Bloursaz MR, Joseph JK, Heer A, Kong XF, Migaud M, Lazarov T, Geissmann F, Fleckenstein B, Arlehamn CL, Sette A, Puel A, Emile JF, van de Vosse E, Quintana-Murci L, Di Santo JP, Abel L, Boisson-Dupuis S, Bustamante J, Tangey SG, Sallusto F, Casanova JL (2018) Human IFN-gamma immunity to mycobacteria is governed by both IL-12 and IL-23. Sci Immunol. https://doi.org/10.1126/sciimmunol.aau6759

Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaum A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299:2076–2079

Springer
Puel A (2020) Human inborn errors of immunity underlying superficial or invasive candidiasis. Hum Genet. https://doi.org/10.1007/s00439-020-02141-7

Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL (2012) Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 12:616–622. https://doi.org/10.1097/ACI.b013e328358cc0b

Quintana-Murci L (2019) Human immunology through the lens of evolutionary genetics. Cell 177:184–199. https://doi.org/10.1016/j.cell.2019.02.033

Quintana-Murci L, Clark AG (2013) Population genetic tools for dissecting innate immune in humans. Nat Rev Immunol 13:280–293. https://doi.org/10.1038/nri3421

Quintana-Murci L, Alcais A, Abel L, Casanova JL (2007) Immunology in nature: clinical, epidemiological and evolutionary genetics of infectious diseases. Nat Immunol 8:1165–1171

Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Quintas C, Ramírez-Alejo N, Markle J, Okada S, Boisson-Dupuis S, Casanova JL, Bustamante J (2019) Mendelian susceptibility to mycobacterial disease: 2014-2018 update. Immunol Cell Biol 97:360–367. https://doi.org/10.1007/s10555-019-00220-3

Salem S, Salem D, Gros P (2020) Role of IRF8 in immune cell functions, protection against infections, and susceptibility to inflammatory diseases. Hum Genet. https://doi.org/10.1007/s00439-020-02154-2

Samsom M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cogniaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M (1996) Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 382:722–725

Skamene E, Gros P, Forget A, Kongshavn PA, St Charles C, Taylor BA (1982) Genetic regulation of resistance to intracellular pathogens. Nature 297:506–509

Sorensen TI, Nielsen GG, Andersen PK, Teadsale TW (1988) Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 318:727–732

Staal JP, Haller O, Boll W, Lindenmann J, Weissmann C (1982) Genetic regulation of resistance to intracellular pathogens. Nature 297:506–509

Staal GP, Robertson JD, Young DB (2003) Tuberculosis: a problem with persistence. Nat Rev Microbiol 1:97–105

Suppiah V, Moldovan M, Ahlenstiel G, Vertel T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheriess, N, van der Heijden M, Nakamura H, Ioannou D, Boll W, Mokri M, Ghandil P, Camcioglu Y, Vasconcelos J, Sirvent N, Guedes M, Vitor AB, Herrero-Mata MJ, Arostegui JI, Rodrigo C, Alsina L, Ruiz-Ortiz E, Juan M, Fortunya C, Yague J, Anton J, Pascal M, Chang HH, Janniere L, Rose Y, Garty BZ, Chapel H, Isskutz A, Marodi L, Rodríguez-Gallego C, Banchereau J, Abel L, Li X, Chauvassel D, Puel A, Casanova JL (2008) Pyogenic bacterial infections in humans with MyD88 deficiency. Science 321:691–696

S vortex, B, Picard C, Puel A, Casanova JL (2012) Experimental and natural infections in MyD88- and IRAK-4-deficient mice and humans. Eur J Immunol 42:3126–3135. https://doi.org/10.1002/eji.201242683

Vogt MA, Greub G (2016) Emerging bacterial pathogens: the past and beyond. Clin Microbiol Infect 22:12–21. https://doi.org/10.1016/j.cmi.2015.10.010

Webster LT (1939) Heredity in infectious disease. J Heredity 30(9):365–370

WHO (1978) Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ 56:271–293

Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM, Infectious Diseases Society of America Emerging Infections N (2008) Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the emerging infections network. Clin Infect Dis 46:1738–1740. https://doi.org/10.1086/587989

Zhang Q (2020a) Human genetics of life-threatening influenza pneumonia. Hum Genet. https://doi.org/10.1007/s00439-019-02108-3

of Immunological Societies Expert Committee. J Clin Immunol 40:24–64. https://doi.org/10.1007/s10475-019-00737-x

Taubenberger JK, Morens DM (2006) 1918 influenza: the mother of all pandemics. Emerg Infect Dis 12:15–22. https://doi.org/10.3201/eid1201.050979

Teleni A, de Iulio J (2019) Regulatory genome variants in human susceptibility to infection. Hum Genet. https://doi.org/10.1007/s00439-019-02091-9

Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O’Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M (2009) Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461:798–801

Thomler L, Schneewind O, Missiakas D (2016) Pathogenesis of Staphylococcus aureus bloodstream infections. Annu Rev Pathol 11:343–364. https://doi.org/10.1146/annurev-pathol-012615-044351

Vournamille C, Colin Y, Cartron JP, Le Van Kim C (1995) Disruption of a GATA motif in the Duffy gene promoter abolishes erythroid gene expression in Duffy-negative individuals. Nat Genet 10:224–228

Vanhollebeke B, Truc P, Poelvoorde P, Pays A, Joshi PP, Katti R, Jannin JG, Pays E (2006) Human Trypanosoma evansi infection linked to a lack of apolipoprotein L-I. N Engl J Med 355:2752–2756. https://doi.org/10.1056/NEJMoa063265

Vidal SM, Malo D, Vogan K, Skamene E, Gros P (1993) Natural resistance to infection with intracellular parasites: isolation of a candidate for Becg. Cell 73:469–485

Vidal SM, Malo D, Marquis JF, Gros P (2008) Forward genetic dissection of immunity to infection in the mouse. Annu Rev Immunol 26:81–132

von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, Charbie M, Mustapha IB, Ghandil P, Camcioglu Y, Vasconcelos J, Sirvent N, Guedes M, Vitor AB, Herrero-Mata MJ, Arostegui JI, Rodrigo C, Alsina L, Ruiz-Ortiz E, Juan M, Fortunya C, Yague J, Anton J, Pascal M, Chang HH, Janniere L, Rose Y, Garty BZ, Chapel H, Isskutz A, Marodi L, Rodríguez-Gallego C, Banchereau J, Abel L, Li X, Chauvassel D, Puel A, Casanova JL (2008) Pyogenic bacterial infections in humans with MyD88 deficiency. Science 321:691–696

von Bernuth H, Picard C, Puel A, Casanova JL (2012) Experimental and natural infections in MyD88- and IRAK-4-deficient mice and humans. Eur J Immunol 42:3126–3135. https://doi.org/10.1002/eji.201242683

Vogt MA, Greub G (2016) Emerging bacterial pathogens: the past and beyond. Clin Microbiol Infect 22:12–21. https://doi.org/10.1016/j.cmi.2015.10.010

Webster LT (1939) Heredity in infectious disease. J Heredity 30(9):365–370

WHO (1978) Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ 56:271–293

Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM, Infectious Diseases Society of America Emerging Infections N (2008) Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the emerging infections network. Clin Infect Dis 46:1738–1740. https://doi.org/10.1086/587989

Woese CR, Kandler O, Wheelis ML (1990) Towards a natural system of organisms: proposal for the domains Archaea, Bacteria, and Eucarya. Proc Natl Acad Sci USA 87:4576–4579. https://doi.org/10.1073/pnas.87.12.4576

Zhang Q (2020a) Human genetics of life-threatening influenza pneumonia. Hum Genet. https://doi.org/10.1007/s00439-019-02108-3
Zhang SY (2020b) Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity. Hum Genet. https://doi.org/10.1007/s00439-020-02127-5

Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, Segal D, Sancho-Shimizu V, Lorenzo L, Puel A, Picard C, Chappier A, Plancoulaine S, Titeux M, Cognet C, von Bernuth H, Ku CL, Casrouge A, Zhang XX, Barreiro L, Leonard J, Hamilton C, Lebon P, Heron B, Vallee L, Quintana-Murci L, Hovnanian A, Rozenberg F, Vivier E, Geissmann F, Tardieu M, Abel L, Casanova JL (2007) TLR3 deficiency in patients with herpes simplex encephalitis. Science 317:1522–1527

Zhang Q, Frange P, Blanche S, Casanova JL (2017) Pathogenesis of infections in HIV-infected individuals: insights from primary immunodeficiencies. Curr Opin Immunol 48:122–133. https://doi.org/10.1016/j.coi.2017.09.002

Zhang SY, Jouanguy E, Zhang Q, Abel L, Puel A, Casanova JL (2019) Human inborn errors of immunity to infection affecting cells other than leukocytes: from the immune system to the whole organism. Curr Opin Immunol 59:88–100. https://doi.org/10.1016/j.coi.2019.03.008

Zimmer B, Ewaleifoh O, Harschnitz O, Lee YS, Peneau C, McAlpine JL, Liu B, Tchieu J, Steinbeck JA, Lafaille F, Volpi S, Notarangelo LD, Casanova JL, Zhang SY, Smith GA, Studer L (2018) Human iPSC-derived trigeminal neurons lack constitutive TLR3-dependent immunity that protects cortical neurons from HSV-1 infection. Proc Natl Acad Sci USA 115:E8775–E8782. https://doi.org/10.1073/pnas.1809853115

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.