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Human genetics of infectious diseases: Unique insights into immunological redundancy

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Abstract

For almost any given human-tropic virus, bacterium, fungus, or parasite, the clinical outcome of primary infection is enormously variable, ranging from asymptomatic to lethal infection. This variability has long been thought to be largely determined by the germline genetics of the human host, and this is increasingly being demonstrated to be the case. The number and diversity of known inborn errors of immunity is continually increasing, and we focus here on autosomal and X-linked recessive traits underlying complete deficiencies of the encoded protein. Schematically, four types of infectious phenotype have been observed in individuals with such deficiencies, each providing information about the redundancy of the corresponding human gene, in terms of host defense in natural conditions. The lack of a protein can confer vulnerability to a broad range of microbes in most, if not all patients, through the disruption of a key immunological component. In such cases, the gene concerned is of *low redundancy*. However, the lack of a protein may also confer vulnerability to a narrow range of microbes, sometimes a single pathogen, and not necessarily in all patients. In such cases, the gene concerned is *highly redundant*. Conversely, the deficiency may be apparently neutral, conferring no detectable predisposition to infection in any individual. In such cases, the gene concerned is *completely redundant*. Finally, the lack of a protein may, paradoxically, be advantageous to the host, conferring resistance to one or more infections. In such cases, the gene is considered to display *beneficial redundancy*. These findings reflect the current state of evolution of humans and microbes, and should not be considered predictive of redundancy, or of a lack of redundancy, in the distant future. Nevertheless, these

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observations are of potential interest to present-day biologists testing immunological hypotheses experimentally and physicians managing patients with immunological or infectious conditions.

1. Introduction

For almost all human-tropic viruses, bacteria, fungi, and parasites, the clinical outcome of primary infection varies enormously, from asymptomatic to lethal infection. At one extreme, the most common infections with weakly pathogenic microbes can kill rare patients with the most severe forms of immunodeficiency. At the other extreme, rare and highly pathogenic microbes can be harmless in rare individuals with constitutive resistance [1]. In the vast majority of cases, the clinical outcome of infection is unexplained. This “infection enigma” is arguably the most important problem in the fields of immunology and microbiology [2]. There is also great interindividual variability in the course of secondary infection or reactivation from latency, but this should be treated as a separate problem, due to the strong influence of adaptive, somatic, immunological memory of the previous, primary infection [3, 4]. Acquired immunity (i.e. somatic memory) may also play a key role in governing interindividual variability in the course of primary infection. For example, vaccination with an attenuated pathogen or infection with a related pathogen can prevent diseases caused by deadly pathogens, mimicking immunity to secondary or latent infection. Moreover, an acquired immunodeficiency of adaptive immunity can precipitate various severe primary infections. For example, therapeutic immunosuppression or HIV infection renders patients highly vulnerable to both common and “opportunistic” primary infections, the latter being defined as infections occurring preferentially or exclusively in patients with overt immunodeficiency. Host genetic make-up is an additional mechanism contributing to interindividual variability in the response to primary infection [5]. Obviously, host germline genome can influence both the quality of adaptive immunity and the severity of acquired immunodeficiency, both of which play important roles in primary infection. However, the strongest effect of germline genetic variation is predicted to be that on innate and intrinsic immunity to infection [6]. In broader terms, inborn errors of host defense can affect innate or adaptive hematopoietic cells, and the immunity controlled by non-hematopoietic cells, through the secretion of molecules involved in host defense or cell-intrinsic immunity. These inborn errors can be immunologically overt or covert, and may underlie diverse common and opportunistic infections following primary contact with a microbe.

The notion that some infections have a genetic basis dates back to the start of the 20th century. We previously reviewed the history and philosophy of this field [2, 5, 7]. Briefly, plant, mammalian, and human geneticists proposed, at the start of the 20th century, that infectious diseases had a strong host genetic component. They documented this notion with elegant classical genetics studies. For example, a fungal infection of wheat was shown to segregate as a Mendelian trait as early as 1905. From the 1930s onward, different strains of laboratory animals were shown to have different outcomes when challenged with various infectious agents. Likewise, twin studies have shown that concordance for some infectious diseases is much greater for monozygotic than for dizygotic twins. Indeed, the idea that infectious diseases had a strong genetic component can be dated back to Pasteur’s formulation of the germ theory itself. Pasteur proved that microbes were involved in disease

development in his classic studies of two diseases of silkworm, *pébrine* and the *flacherie*. He convincingly made the case that *flacherie* also has an inherited element, in the sense that predisposition to the disease is transmitted, rather than the microbe being transmitted from the parents to the offspring [8, 9]. Despite the publication of Mendel's discoveries in 1866, there was no real genetic theory in the 1865–1870 period, so Pasteur did not literally attribute *flacherie* to genetic variation. Nevertheless, the idea of a predisposition transmitted from the parents to the offspring was both proposed and documented. The first primary immunodeficiencies (PIDs) were described in the 1950s, at the beginning of the modern era of molecular genetics, with the description of molecules, cells, and mechanisms [10–13]. PIDs were then defined as Mendelian traits combining a rare immunological phenotype with a rare infectious phenotype. It was possible to detect such rare and artificial phenotypes thanks to the advent of antibiotics and the development of new immunological techniques facilitating the recognition of rare children with multiple, recurrent infections (who would previously have died during their first life-threatening infection) and of immunological defects (which would previously have been missed). A further major advance in elucidation of the emerging genetic architecture of infectious diseases was made in 1996, when life-threatening infectious diseases striking otherwise healthy individuals in the course of primary infection were shown to result from single-gene inborn errors of immunity that rarely display full penetrance [6, 7]. Monogenic forms of resistance to infection were also characterized genetically during this period.

Attempts have been made to use the standard vocabulary of immunology to draw immunological conclusions from the observation of infectious phenotypes for categories of monogenic disorders [14, 15]. However, this enterprise is somewhat risky. Indeed, host defense genes do not easily fall into immunology textbook dichotomies, such as innate vs. adaptive, hematopoietic vs. non-hematopoietic, or cell-intrinsic vs. cell-extrinsic immunity. A first problem with the innate/adaptive dichotomy is that it ignores key components of host defense, at least when the term "innate" is used to refer to leukocytes other than T and B cells. Indeed, cells other than leukocytes are involved in immunity. Each and every cell type of the body, not just tissue macrophages, which may be formed before hematopoiesis, contributes to host defense, by secreting molecules (e.g. hepatocytes secreting complement components) or through cell-intrinsic immunity (e.g. keratinocytes controlling papillomaviruses). More importantly, few, if any genes are expressed exclusively in any given cell type, rendering such binary classifications derived from cellular immunology fundamentally irrelevant to genetics, particularly for the innate/adaptive dichotomy. Only a handful of genes can be attributed purely to adaptive immunity (i.e. exclusively to T and B cells): those encoding the BCR and TCR chains. Likewise, very few host defense genes are not expressed at all in any T or B cells, not only because some of these cells, such as NKT and MAIT cells, which have a low level of TCR diversity, have "innate" features, but also more generally because T and B cells belong to the lymphoid lineage, which includes cells that do not express TCRs and BCRs, known as innate lymphoid cells (ILCs). The pattern of expression of human genes thus indicates that the vast majority of genes are expressed, to at least detectable levels, in at least some types of T and B cells and some other cells. For example, the most basic housekeeping genes can contribute to host defense, as illustrated by the immunological impact of inborn errors of metabolism (e.g. ADA and PNP deficiency).

Last, but not least, adaptive immunity cannot be attributed solely to T and B cells, because the core players of the system, the α/β T cells, recognize antigens presented by HLA molecules on other cells, with $CD8^+$ T cells recognizing HLA-I molecules on nucleated cells and $CD4^+$ T cells recognizing HLA-II molecules on antigen-presenting cells (including B cells, which in early vertebrates also have phagocytic properties [16]). Deficiencies of HLA-I and HLA-II are therefore immunologically more "adaptive" than disorders of genes expressed both in T/B and other cells, even though $CD8^+$ and $CD4^+$ T cells are only indirectly afflicted by the lack of expression of HLA molecules. Moreover, the HLA molecules themselves are also not purely adaptive, because they play a key role in target recognition by NK cells.

By contrast, leaving these traditional notions of cellular immunology aside, human carriers of knockout mutations provide a unique opportunity to delineate the function of the corresponding genes in host defense more precisely. The number and diversity of inborn errors of immunity are increasing, and we will focus here on recessive traits causing a complete defect. We will not consider dominant disorders, partial defects, and gain-of-function mutations. With a mutation rate of 1.2×10^{-8} per nucleotide per generation, and seven billion people worldwide exposed to diverse microbes, the human population provides a unique resource for investigations of the impact of gene knockouts on host defense [17, 18]. In particular, the study of humans with complete deficiencies of a particular gene can provide information about the function of the gene concerned in host defenses in natural conditions (*in natura*), *i.e.* its ecologically relevant and evolutionarily selected functions [18–20]. Since the identification of the first PID gene in 1985 [21], hemizygous and biallelic null mutations of various genes have been found to underlie multiple infections. Since the mid-1990s, complete deficiencies of other gene products have been found to underlie infections with a narrow range of microbes [7, 22]. Also since the mid-1990s, biallelic null mutations of a few genes have been shown to confer protection against specific infections [7, 22]. The last two decades have thus been marked by the discovery that monogenic lesions confer the protection or predisposition of otherwise healthy individuals to specific infections. With the more recent advent of large-scale next-generation sequencing (NGS), a fourth category of host defense genes was discovered, as several knockouts were found in humans with no overt infectious phenotype [23]. Some of these studies were conducted in specific contexts, such as bottle-necked [24, 25] or consanguineous [26, 27] populations, but the availability of large public databases, such as ExAC [28], and its extended version, gnomAD (http://gnomad.broadinstitute.org), has made it possible to search for common knockouts in the general population. These common knockouts can be defined as recessive defects caused by loss-of-function (LOF) variants with a minor allele frequency (MAF) >1%. Some of these knockouts may be associated with hitherto unknown resistances or predispositions to infection. Not all human genes involved in host defense fall into these four categories of genes, for which the role in host defense can be analyzed by studying the phenotype of human beings with a complete recessive defect. Indeed, hemizygous or biallelic null mutations of some genes are embryonic lethal, and the proportion of such genes is unknown. The role in host defense of genes essential for embryonic development can be inferred only from studies of partial defects, as illustrated by autosomal recessive, partial MCM4 or GINS1 deficiency [29, 30], or autosomal dominant, partial STAT3 or

GATA2 deficiency [31–35]. Indeed, homozygous null mutations of the mouse orthologs of these genes have been shown to be embryonic lethal.

In this context, we will focus here on biallelic or hemizygous LOF mutations. Some caution is required, because it is easier to predict than to prove that a mutant allele is LOF [36–39]. We will refer, when possible, to alleles experimentally demonstrated to be LOF, at least in the first three sections of this review focusing on monogenic forms of broad and narrow susceptibility to infection, and resistance to infection. In the fourth section, dealing with human knockout mutations associated with no particular infectious phenotype, we will be more inclusive and consider mutations that are predicted to be LOF, but not necessarily validated as such experimentally. We are well aware that the impact of mutations cannot be predicted with certainty and that experimental validation is required, although not always sufficient, to conclude that a mutation is LOF. For example, a premature stop mutation may lead to the re-initiation of translation, read-through, or the truncation of a protein segment not required for protein production and function. Moreover, many genes encode multiple isoforms, some of which have multiple functions. Not all the isoforms encoded by a given gene may be known, not all the functions of any isoform may be known, and the expression patterns of most isoforms are not known for most tissues and developmental stages. Rigorously speaking, there is, therefore, no such thing as a LOF allele. A devil's advocate would say that it is impossible to prove *in vivo*, even with strong evidence *in vitro*, and therefore to predict with confidence *in silico*, that a mutation is LOF in general, or *per se*. In our opinion, many studies have drawn conclusions from predictions with a flimsy scientific basis, particularly in the field of computational, population-based genetics, as opposed to experimental, patient-based genetics. We will, however, use LOF as a reasonable proxy, as at least a sizeable proportion of homozygous premature stop mutations, whether due to nonsense, indel, or splice variants, are likely to result in a complete deficiency of all encoded isoforms in all tissues. We will review the autosomal and X-linked recessive traits responsible for complete protein deficiencies interfering with host defense. Similar mutations in RNA genes have not yet been described, but are likely to be discovered in the future. As shown in Table 1, complete protein deficiencies underlie four types of phenotypes — five, if we consider genes for which homozygous or hemizygous lesions are embryonic lethal. In this review, we will focus on the four categories that can be distinguished in individuals after birth: complete recessive defects can precipitate multiple infections, they can underlie a single infection, they can be neutral, or they may protect against one or several types of infection. Each of these four categories provides unique information about the level of redundancy of the gene in question for protective immunity to infection *in natura* – a hallmark of human studies.

2. Human genes for which disruption underlies multiple infections: *low redundancy*

Many disorders underlie multiple infections by disrupting an immunological component, a cell or a molecule essential for host defense in all humans. In the most striking examples, the development of a major leukocyte subset, such as granulocytes, B cells, or T cells, is prevented. These disorders have complete penetrance, not only immunologically but also for

the occurrence of severe infections, after sufficient time has passed for infection to occur. In the absence of B cells, infections do not occur during the neonatal period and are rare during the first three months of life, thanks to the passage of maternal antibodies across the placenta [40]. The first infections can occur earlier in the absence of T cells [41], and even earlier in the absence of granulocytes [42]. Given enough time, and provided that each life-threatening infection is cured, these patients invariably suffer from multiple recurrent infections. This extraordinary infectious phenotype became apparent only after the advent of anti-infectious agents in the late 1940s. Affected children would have died during their first life-threatening bacterial infection before the massive distribution of antibiotics. This “artificial” phenotype actually led to the recognition of PIDs as Mendelian traits defined by the segregation of both unusual infectious and immunological phenotypes. There are many more immunological phenotypes than those defined by the isolated lack of granulocytes, B cells, or T cells. Collectively, at least 300 of the >350 PID genes known correspond to classical PIDs with little redundancy [12, 13], and our conservative estimate is that another 300 will be discovered in the next two decades. The corresponding genes are essential for host defense against various infectious agents, but, surprisingly, affected patients can cope with other infectious agents. These genes therefore display little redundancy when all potential infections are considered. Moreover, penetrance is incomplete for any given infection. There is probably no single infectious disease that has affected all patients with any given PID, even for infectious agents that are ubiquitous and have infected every patient. In other words, these defects display variable expressivity. There is no redundancy for the generic infectious phenotype (infection due to any infectious agent), but there is redundancy for individual infectious phenotypes (infections caused by a given infectious agent). We will illustrate this notion with the three classical disorders mentioned above.

Most genetic defects displaying little or no redundancy disrupt at least one branch of adaptive immunity. X-linked agammaglobulinemia is characterized by an almost complete lack of B cells due to mutations of *BTK* [43–46]. Patients with this condition typically suffer from various bacterial infections, including infections caused by many extracellular (e.g. pyogens) and some intracellular (e.g. mycoplasmas) bacteria, but they are also vulnerable to a few viruses and parasites. They do not appear to be particularly susceptible to fungal infections. Thousands of patients from most ethnicities have been diagnosed, and have benefited from IgG substitution. Autosomal recessive forms of agammaglobulinemia have also been described [47]. In all cases of recessive complete deficiency, the immunological phenotype has nearly complete penetrance, attesting to its robustness across genetic backgrounds. It is, however, striking that a lack of B cells does not result in infections caused by a very large group of microbes. Severe combined immunodeficiency (SCID) constitutes another related group of PIDs characterized by an almost complete lack of autologous T cells. Multiple genetic etiologies have been identified, some associated with B-cell defects, and others with NK-cell defects. Patients with SCID have no T-cell subsets, with complete penetrance, and the causal genes are therefore not redundant immunologically. A good example is provided by the *RAG1* and *RAG2* genes, biallelic LOF mutations of which underlie SCID in almost all cases. Hypomorphic mutations encoding proteins with residual enzymatic activity underlie various other phenotypes [48, 49]. Interestingly, one family has been reported to suffer from selective α/β T-cell deficiency due

to a homozygous mutation of the TCR alpha constant (*TRAC*) gene [50], suggesting that α/β T cells and the *TRAC* and *TRBC* genes are also essential. Again, these patients lacking T-cell immunity are prone to multiple infections, but can nevertheless cope with some infections. There is therefore little redundancy in host defense. An important enigma concerns the possible redundancy of γ/δ T cells. These cells are unlikely to be redundant, as the three lineages of adaptive immunity have emerged twice, through convergent evolution [51]. The discovery of a selective disorder of γ/δ T cells underlying an infectious phenotype would solve this enigma.

Mutations of other genes disrupt the development of specific myeloid cells. Severe congenital neutropenia can be caused by defects of various genes. *HAX1* provides a perfect illustration, as mutations of this gene were identified in the Swedish families reported by Kostmann in 1950 [52–54], before the description of X-linked agammaglobulinemia by Bruton in 1952. The *HAX1* gene is clearly not redundant for the development of neutrophils and protection against various bacterial and fungal infections. However, there are two isoforms of HAX1. Germline biallelic mutations underlie neutropenia alone if they affect the first isoform, which is expressed in hematopoietic cells, whereas they underlie neutropenia and a profound neurological defect if they affect both isoforms, the second isoform being expressed in the brain [55, 56]. This example highlights the inappropriateness of considering protein-coding genes as a unique entity, as these genes can encode multiple isoforms endowed with different functions in different tissues or at different stages of development. Recessive defects of mononuclear phagocytes have also been described, including a lack of monocytes and dendritic cells in a patient with AR IRF8 deficiency [57]. No disorder characterized by a selective lack of monocytic or dendritic cell subsets due to a recessive disorder has yet been described. Likewise, there is no known tissue-specific deficiency of macrophages, probably because of the potential severity of such conditions *in utero*. Finally, no mutation disrupting the development of a non-hematopoietic cell lineage involved in host defense has ever been described, to our knowledge. By contrast, mutations disrupting the development of a lymphoid organ (e.g. thymus, spleen) have been identified, although not all lymphoid organs are essential (e.g. the appendix, which may even be seen as deleterious, as appendicitis kills 1–10% of humans in the absence of surgery, and appendectomy seems to have no deleterious consequences). Paradoxically, the lack of a lymphoid organ is not always life-threatening or even associated with a risk of infection. Isolated congenital asplenia displays incomplete penetrance in this respect [58]. Moreover, symptomatic individuals display narrow, selective susceptibility to pneumococcus. Finally, mutations that disrupt the function of a normally developed tissue or myeloid cell subset can also be recessive and underlie many infections with complete penetrance. It would go beyond the limited scope of this paper to review such disorders. Suffice it to say that the genes for which mutations underlie PIDs, as defined in the 1950s, are typically non-redundant, as the corresponding disorders are Mendelian traits underlying multiple early-onset infections with complete penetrance, when infections are considered collectively and managed correctly.

3. Human genes for which disruption underlies a single type of infection: *high redundancy*

Over the last two decades, a number of severe infections striking otherwise healthy children, adolescents, and young adults have been attributed to single-gene inborn errors of immunity [6, 7]. As discussed in the previous section, PIDs were historically defined as fully penetrant, familial, Mendelian traits underlying both an overt immunological phenotype and multiple, recurrent, and opportunistic infections. Work conducted in the complement field from the 1970s onward remained largely ignored for many years, but profoundly challenged this view. Indeed, mutations of the genes encoding certain components of complement result in a very narrow range of infections, such as defects of the membrane attack complex, properdin, factor H, or factor D, underlying severe infections caused by *Neisseria*, and only *Neisseria* [59–66]. Complement protein defects were discovered in the 1970s, the associated phenotypes almost as a follow-up and consequence, but the underlying genetic lesions were not identified until the 1990s. Similarly, the discovery of APOL1 as the key trypanosome lytic factor in 2003 [67] paved the way for the discovery of its autosomal recessive deficiency in a patient who had suffered from trypanosomiasis due to a poorly virulent trypanosome, which can be killed by APOL1 in other individuals [68]. In 1996, reverse genetic investigations of complement were finally recognized, when forward genetic studies of infectious diseases that had long been known to be both idiopathic and Mendelian bore fruit. Five such infections were identified and their genetic basis was gradually elucidated. Mendelian susceptibility to mycobacterial disease (MSMD) was first described in the 1950s and was shown in various studies, from 1996 onward, to be caused by inborn errors of IFN-γ immunity, including AR complete defects of either chain of the IFN-γ receptor [69–71]. Chronic mucocutaneous candidiasis (CMC) was described in the late 1960s and shown, from 2011 onward, to be due to inborn errors of other lymphokines, IL-17A and IL-17F, including AR complete defects of IL-17RA and IL-17RC [72–74]. Another fungal infection, invasive dermatophytic disease, first described in the 1950s, was shown to be due to AR CARD9 deficiency in 2013 [75, 76]. Its cellular basis remains elusive, although CARD9 is mostly expressed in phagocytes. X-linked lymphoproliferation is a specific vulnerability to Epstein-Barr virus. It was shown in 1998 to be caused by hemizygous LOF mutations of *SAP*, a gene later shown to be essential for $CD8^+$ cytotoxic T cells to kill EBV-infected B cells [77–81]. This work led to the exciting discovery of a number of other, X-linked and autosomal recessive genetic etiologies of severe EBV disease [82–85]. Finally, epidermodysplasia verruciformis (EV) deserves a particular mention, as it was, with hindsight, the first PID to be described, in 1946; it was by then known to be both a genodermatosis and a virosis. Nevertheless, it was not considered to be a PID for five decades after its discovery, due to both the absence of an immunological phenotype and the narrow infectious phenotype. In 2002, it was shown to be caused by bi-allelic truncating mutations of *EVER1* and *EVER2*, which probably control keratinocyte-intrinsic immunity to beta-human papillomavirus (HPV) in the absence of a detectable leukocyte phenotype [86–88].

These experimental studies confirmed that these five “Mendelian infections” had a molecular genetic basis. The surprise was not that mutations were actually found, but that

the genes concerned were so highly redundant. IFN-γ and IL-17, two emblematic lymphokines, were both thought to be the signature cytokines of Th lineages critical for defense against a broad range of microbes — intracellular microbes for IFN-γ-producing Th1 cells and mucosal microbes for IL-17A- and IL-17F–producing Th17 cells [89, 90]. It was also surprising to find that SAP and CARD9, two important proteins of lymphoid and myeloid cells, were so redundant in host defense. For these four disorders, the corresponding knockout mice have broader susceptibility to infection, probably reflecting the lower redundancy for protective immunity against experimental infections in mice. As EVER1 and EVER2 were discovered by a genome-wide approach to tackling the problem of EV, for which there is no mouse model, there was no surprise concerning the function of these proteins. In fact, the apparent selectivity of infections in patients with these inborn errors attests to the high redundancy of the corresponding human genes. These are two sides of the same coin. The observation that some inborn errors cause a narrow infectious phenotype does not attest to specificity in the structural sense of the term, as used for enzyme-substrate or antibody-antigen specificity. On the contrary, these observations indicate that the apparent specificity of the infections seen in patients with such inborn errors result from the corresponding gene being redundant for host defense against other microbes. These genes display high levels of redundancy in host defense. These studies showed that some PIDs were Mendelian traits underlying idiopathic and isolated infections, striking otherwise healthy individuals, at odds with the definition from the 1950s based on the discovery of severe congenital neutropenia and agammaglobulinemia, but in line with the definition of 1946, when EV was described. However, if severe infectious diseases in general, or even if a sizeable group of infectious diseases were Mendelian traits, i.e. both monogenic and fully penetrant, then life-threatening infectious diseases would long have been shown to be genetic.

Attempts were thus made to test the hypothesis that common and/or sporadic infectious diseases could be monogenic, but not Mendelian. This notion would have obvious implications for the analysis of gene redundancy in host defense. A first step forward was made when tuberculosis was shown to be due to IL-12Rβ1 deficiency in some patients with no personal or familial history of MSMD [91–95]. This implied that the IL-12 and IL-23 receptor chain was redundant against weakly virulent mycobacteria in some individuals, but essential for defense against the more virulent mycobacterium responsible for tuberculosis. Both IL-12 and IL-23 were identified as possible signature cytokines inducing Th1 and Th17 immunity in mice. Invasive pneumococcal disease was subsequently shown to be caused by inborn errors of the TLR and IL-1R pathway in some children, with biallelic null mutations of *IRAK4* and *MYD88* [96–98]. This was surprising, because immunological theories and the conclusions of experiments in mouse models of infection suggested that the proteins encoded by these genes played a broad role in host defense, especially the various TLRs other than TLR3 that signal through this pathway, and three IL-1 cytokines, IL-1β, IL18, and IL-33, had been suggested to play a broad role in immune responses. Herpes simplex encephalitis (HSE) was then shown to be due to mutations affecting the TLR3-dependent control of IFN-α/β production in cells resident in the central nervous system, such as cortical neurons and oligodendrocytes in particular [99–101]. AR defects of TLR3, TRIF, and UNC93B abolish this pathway and, surprisingly, underlie HSE, with incomplete

penetrance in the case of UNC93B. Kaposi sarcoma, caused by HHV8, was found to be caused by AR OX40 deficiency in an otherwise healthy patient, suggesting that this T-cell signaling pathway is otherwise redundant [102]. Finally, severe influenza was attributed to AR complete IRF7 deficiency, implying that the IRF7-dependent amplification of antiviral IFNs across the cells and tissues of the organism is largely redundant in host defense [103]. More recent examples include mutations of *MDA5* underlying severe rhinovirus infections [104], mutations of the RNA polymerase III gene underlying severe varicella-zoster virus infection [105], and mutations of the TIRAP gene underlying invasive staphylococcal disease [106]. The molecular basis of the incomplete penetrance of TIRAP gene mutations was explained when antibodies against staphylococcal LTA rescued its recognition by TLR2 in healthy relatives lacking TIRAP, whereas the patient with staphylococcal disease lacked both TIRAP and antibodies against LTA. Collectively, these studies provided proof-of-principle that severe, isolated, common, sporadic infections could be due to single-gene inborn errors of immunity that rarely display complete penetrance. It remains surprising that genes thought to control fundamental immunological pathways are largely redundant in host defense. For some genes, more patients are required before firm conclusions can be drawn, as different infectious diseases might be caused the same AR disorder in different patients; in other words, different infections may be allelic. This is neatly illustrated by CARD9 deficiency, which underlies various invasive fungal diseases, each patient suffering from a single infection. Some mutations underlying sporadic infections disrupt intrinsic (e.g. TLR3) or innate immunity (e.g. MYD88 and IRAK4), whereas many mutations, surprisingly, disrupt an effector function common to innate and adaptive immunity (e.g. IFN-γ, IL-17, SAP, OX40). The narrow range of infection attests to the nature of the deficit, which is both antigen-independent and highly redundant for host defense.

4. Human genes for which disruption is apparently neutral: *complete redundancy*

Genes harboring LOF alleles that are common in the healthy general population are very unlikely to play a substantial role in host survival, particularly during infection, and are presumably redundant. Recent systematic studies based on NGS, focusing mostly on bottlenecked or consanguineous populations, have revealed the prevalence of knockout mutations to be high in humans. With sample sizes of 3,000 to 104,000 individuals, the number of genes homozygous for mutations predicted to be LOF ranged from 781 to 1,317 [24–27]. Only a few of these knockouts (the rare ones in particular) are likely to be associated with a phenotype, e.g. homozygosity for *PLA2G7* LOF mutations, resulting in an absence of soluble lipoprotein-associated phospholipase A2 [27]. The reality of most defects, if any, remains to be experimentally established. Interestingly, in a study of 3,222 British adults of Pakistani heritage with high levels of parental relatedness, 781 genes were found to carry homozygous LOF variants in at least one individual [26]. A comparison of the group of subjects carrying at least one of these knockouts with those carrying no knockouts revealed an absence of significant association with clinical consultation or prescription rate, including for infectious diseases. In addition, redundancy for fertility was demonstrated for *PRDM9*, a gene involved in meiotic recombination events, based on the identification of a healthy mother with *PRDM9* knockout [26]. Large public databases, such

as ExAC and gnomAD, can be used to search for knockouts in populations of more diverse ethnic origins. In 60,706 individuals from the ExAC database, a mean of 35 homozygous variants resulting in protein truncation were found per individual, the vast majority of which (34.81 on average) had a MAF > 1% [28]. In 123,136 individuals with exome data in the gnomAD database, 903 genes carrying homozygous mutations predicted to be LOF and with a MAF > 1% were identified in at least one of the five main subpopulations of this database (African, East Asian, South Asian, European, and American) (A. Rausell, J.L. Casanova, L. Abel, unpublished data). All these observations indicate that a large number of knockouts, especially those that are common, may have no detectable effect. Obviously, these conclusions are tentative and further investigations are required. We cannot exclude the possibility that these common deficiencies underlie a deleterious or beneficial phenotype upon specific infectious challenges, such as the emergence of a new pathogen, now or in the future.

Some of the genes with common knockouts are well known to immunologists and deserve closer attention. *IFNA10* and *IFNE*, which are located in the cluster of IFN-α-encoding genes on chromosome 9, provide examples of this situation. *IFNA10*, encoding IFN-α 10, may carry a nonsense mutation, C20X, introducing a termination of translation in the signal peptide. This mutation is very frequent in all populations, with frequencies ranging from 15.5% in South Asia to 50.6% in East Asia, and more than 8,000 homozygotes in the gnomAD database. *IFNE*, encoding IFN-ε, also has a common nonsense mutation, Q71X, decreasing the length of the protein by two thirds, with a worldwide frequency of 4.4%, increasing to 18.6% in East Asia, with a total of 762 homozygotes in gnomAD. A large evolutionary genetic study of human interferons showed that selective constraints have been relaxed for both *IFNA10* and *IFNE*, by contrast to several other IFN-α-encoding genes and the IFN-γ-encoding gene, which has been subject to strong purifying selection [107]. This suggests that *IFNA10* and *IFNE* are largely redundant in host defense. Four other examples concern receptors recognizing various types of microbes. The cell surface TLR5 is a receptor for bacterial flagella. The *TLR5* nonsense allele R392X, which abolishes cellular responses to flagellin and acts in a dominant-negative manner [108, 109], is found at high frequency in all populations in the gnomAD database (from 2% in the Latino and African samples of this database to 10% in the South Asian sample). This variant has been reported to increase susceptibility to Legionnaire's disease in heterozygous subjects [108]. However, two healthy controls exposed to *Legionella* (but none of the patients) were homozygous for this LOF allele in this study. The gnomAD database includes 497 homozygous individuals, clearly indicating that humans can live a normal life with AR complete TLR5 deficiency. This conclusion is consistent with the lack of evidence of selection acting on *TLR5* in human populations, contrary to the findings for endosomal TLRs (TLR3, TLR7, TLR8, TLR9), which are subject to strong selective constraints [98, 110]. These observations also suggest that additional mechanisms of flagellin recognition, such as those involving the NAIP-NLRC4 inflammasome [111, 112], may provide sufficient protection in the absence of TLR5. A similar picture is observed for the *CLEC7A* gene encoding Dectin-1, a β-glucan receptor recognizing several fungal species, including *Candida*. CMC with an unclear mode of inheritance was reported in a family bearing the nonsense Y238X mutation of *CLEC7A* [113]. However, the high frequency of this variant reported in some populations at the time

(7% in Europeans and up to 40% in the South Africa San population) strongly suggested that this mutation was not causal [114]. Analysis of the gnomAD database confirmed that this mutation was common in almost all populations (from 2.3% in the African sample to 9.4% in South Asian sample), with the exception of the East Asian population, with a total of 662 homozygotes (0.5% of the individuals tested), indicating that Dectin-1 is largely redundant in antifungal defense in natural conditions of infection.

More debatable patterns have been observed for mannose-binding lectin (MBL) and CD36, which are involved in the recognition of a broader range of microbes than TLR5 and Dectin-1. MBL, encoded by *MBL2*, is a member of the collectin protein family that binds a large range of microorganisms, ranging from viruses to parasites, and activates the lectin complement pathway [115]. About 5% of individuals lack functional serum MBL, mostly because they are homozygous or compound heterozygous for any of three common missense mutations (R52C, G54D, G57Q) in exon 1 of *MBL2* [116]. For example, the most common mutation, G54D, has a frequency in gnomAD of 13 to 17% for all populations other than the African population (3%), in which the G57Q mutation is present at a higher frequency (23%). The role of MBL deficiency in predisposition to severe infections, such as meningococcal disease in particular [117], has been subject of heated debate, with conflicting results reported [116, 118]. Overall, the results seem to suggest that MBL may play a minor role in children of a narrow age range (6–18 months), who no longer have maternal antibodies and have not yet developed a fully mature antibody response. In addition, population genetic analyses have shown that the observed pattern of variation is consistent with neutral evolution, strongly supporting the view that MBL is largely redundant in human defenses [119]. CD36 is a scavenger receptor that is also involved in the phagocytic uptake of multiple pathogens, including *Plasmodium* [120]. CD36 deficiency results from the nonsense variant Y325X, which is common in Africa (allele frequency of 9% in the gnomAD database, with 103 homozygous) and much rarer (<0.3%) in other populations. Several association studies investigating the role of CD36 deficiency in susceptibility/resistance to malaria have provided conflicting results [121–123], and initial population genetic studies suggested that the Y325X variant was under recent positive selection [124]. However, a subsequent large population study challenged these initial findings, as no association was found between severe malaria and CD36 variants, and evidence for recent positive selection was obtained only for the Yoruba population, and not in the Gambian population [125]. The consequences of AR CD36 deficiency for resistance and/or susceptibility to pathogens therefore remain to be determined. Complete CD36 deficiency remains compatible with a healthy life in Africa, indicating that this receptor displays redundancy in host defense.

5. Human genes for which disruption is beneficial: *beneficial redundancy*

Paradoxically, the knockout of some human genes may have beneficial effects. The advantageous effects of heterozygous lesions is well known, as exemplified by the HbS mutation protecting against severe *Plasmodium falciparum* infection, which has led, over time, to the natural selection of high frequencies of the HbS allele in African regions (up to 30%) [126]. Homozygous lesions can also be beneficial. For example, another hemoglobin variant, HbC, also enhances resistance to *P. falciparum* malaria, this effect being strongest in

HbC homozygotes (who have a relatively mild form of hemolytic anemia) [127]. This recessive resistance may account for the specific spread of the HbC allele in West Africa [128, 129]. These effects of HbS and HbC have provided fascinating insights into population genetics and evolutionary biology, with molecular proof that natural selection operates in humans and that infection is one of the main drivers of this selection [130]. Accordingly, the evolutionary dissection of the pattern of selection of LOF variants can provide major insights into their levels of redundancy [14, 131]. Typically, the genes displaying low or high redundancy described in the first two sections would be expected to be targeted by purifying selection or more commonly its milder form, negative selection, resulting in the gradual and selective removal of deleterious alleles at these loci from the population. Complete redundancy is consistent with neutral evolution. Finally, genes displaying beneficial redundancy should be subject to positive selection, which gradually increases the frequency of the advantageous allele. In particular, LOF variants that are common in at least some populations raise interesting questions about the factors that led to and maintained such high frequencies of these variants. The best documented examples of beneficial complete knockouts to date are those providing resistance to infection described in the next two sections. Other examples are provided by genes involved in lipid metabolism, although fewer complete knockouts have been reported for these genes to date. LOF mutations of *PCSK9* are known to decrease LDL-C levels and to protect against coronary heart disease (CHD) in heterozygous individuals [132], and a healthy subject compound heterozygous for two inactivating mutations and with very low levels of LDL-C has been described [133]. Similarly, heterozygous *APOC3* deficiency has been shown to protect against CHD, and several homozygous LOF *APOC3* variants were recently found to enhance the clearance of plasma triglycerides after a fatty meal [27]. The number of known beneficial knockouts will probably increase with the investigation of genes homozygous for common LOF variants identified in large-scale NGS studies.

The first emblematic example of a beneficial complete knockout in the context of infection was provided by the protection against infection with *Plasmodium vivax* conferred by a lack of expression of DARC, a coreceptor for the parasite on the surface of erythrocytes [134]. The resistance trait is autosomal recessive and the causal single-nucleotide mutation affects the GATA-1 binding site in the promoter of the *DARC* gene, thereby preventing gene transcription in erythroid cells [135]. This allele is, therefore, not strictly speaking a LOF allele, as DARC is expressed normally in cells other than erythrocytes. It is, however, LOF in erythrocytes. This mutation, also known as FY*O (Duffy null), is not found in European populations, whereas the mutant allele has become fixed in some African populations [136], suggesting that *P. vivax* has exerted strong selective pressure on the human genome. A recent study also confirmed the positive selection of a FY*O null mutation, by showing that this mutation swept to fixation in Africa from a very low initial frequency (0.1%), with a selection coefficient among the strongest estimated in the human genome [137]. The importance of the interaction between *P. vivax-DBL* and DARC for the invasion of human erythrocytes by *P. vivax* provides a rationale for novel therapeutic approaches specifically blocking interactions between the parasite and erythrocytes [138]. In particular, Duffy binding protein region II (DBPII) is an important candidate vaccine under clinical evaluation [139], as anti-DBPII antibodies have been shown to inhibit the invasion of human

erythrocytes by *P. vivax* [140], and to confer protection against blood-stage infection [141]. The discovery that individuals homozygous for LOF mutations of *CCR5* are strongly protected against infection with CCR5-tropic HIV-1 [142–144] also had a major effect on HIV research, particularly for the development of new treatment strategies [145]. The most common deleterious *CCR5* mutation is a 32 bp deletion (Δ32) with a MAF in gnomAD of more than 1% in all populations other than the East Asian population, and a maximum MAF of 13.4% in Europe. In a remarkable study, an HIV-1-infected patient with acute myeloid leukemia received hematopoietic stem cells from a homozygous Δ32 donor [146]. After four years of follow-up and in the absence of antiretroviral treatment, HIV levels have remained undetectable in this patient [147]. Based on this initial finding, further research has focused on the development of CCR5 antagonists [148, 149], and, more recently, on the search for other non-essential HIV host-dependence factors. In this context, a genome-wide CRISPR screen identified four host factors in addition to CCR5 that were required for HIV infection and dispensable for cell viability (CD4, TPST2, SLC35B2, and ALCAM) [150]. None of the four genes encoding these molecules had common LOF mutations in the gnomAD database.

Another example of resistance to viral infection is provided by LOF mutations of the fucosyltransferase 2 (*FUT2*) gene [151]. This gene encodes an α(1,2)-fucosyltransferase that regulates the expression of histo-blood group antigens (HBGAs) on the surface of epithelial cells and mucosal secretions, and is responsible for the secretor phenotype [152]. Several inactivating *FUT2* mutations lead to the non-secretor phenotype, and the W154X nonsense mutation (rs601338) is by far the most common (> 95%) in populations of European and African descent [153]. This mutation is highly prevalent in Europe, as ~20 % of the population is homozygous for the LOF allele, resulting in a non-secretor phenotype. A complex pattern of natural selection is observed for *FUT2*, with most variants displaying a long history of balancing selection in Eurasian and African populations [153]. Non-secretor individuals have been shown to be resistant to infections with norovirus [154, 155], and rotavirus [156, 157], two common enteric viruses that recognize and bind to HBGA [158, 159]. A recent large meta-analysis showed that this resistance to these two viruses can be strain specific [160], indicating that genetic studies of resistance to enteric viruses and the evaluation of candidate vaccines should be conducted within specific populations. These results also suggest that it may be useful to envisage pharmaceutical interventions blocking the binding of these enteric viruses to HBGA glycans [160]. Finally, another illustration of a knockout gene with beneficial effects is provided by the *CASP12* gene encoding caspase-12, a cysteine protease generally considered to be a negative regulator of the inflammatory response [161]. Most individuals are homozygous for the R125X stop codon of *CASP12*, leading to the expression of a truncated inactive form of caspase-12, and only about 20% of subjects of African origin produce the full-length active caspase-12 protein [162]. This active form has been shown to decrease cytokine production after stimulation with LPS, and to increase the risk of severe sepsis and mortality [163]. These findings are consistent with data for mice, in which caspase-12 was found to exert a dominant-negative suppressive effect on caspase 1, increasing susceptibility to bacterial infection and mortality from sepsis, whereas caspase-12 deficiency confers resistance to septic shock [164]. An elegant population genetics study found that the truncated form arose before the migration out of Africa, and was then subject to positive selection pressure, probably due to an advantage for

dealing with pathogens encountered in Asia and Europe, driving the mutation to near fixation [165]. Overall, *CASP12* is probably the best example of a gene that has been almost completely lost in the human species, due to the selection exerted by pathogens [130], resulting in AR CASP12 deficiency in most humans.

6. Concluding remarks

Redundancy for protective immunity to infection varies between genes in the human genome. We describe here four categories of infectious phenotypes, defining four categories of human genes, for which biallelic or hemizygous LOF mutations are not embryonic lethal, and which can display low, high, complete, or beneficial redundancy. Clearly, not all genes are equal in terms of their redundancy for host defense. Genetic defects massively disrupting the development or function of the B- or T-cell branch of adaptive immunity tend to have a major impact, and the corresponding genes have low levels of redundancy. This finding is consistent with the role of adaptive immunity, which has been selected twice by convergent evolution, to protect the host against any type of microbe [166, 167]. However, this is not a general rule, as inborn errors of IFN-γ and IL-17 affect cytokines that are produced by T cells and underlie a narrow range of infections. Indeed, it would be more accurate to state that disorders that impair antigen-specific responses, whether T or B responses, underlie a broad range of infections, consistent with the nature of antigen-specific responses. This view is unlikely to be profoundly modified by the discovery of new disorders of this kind. Indeed, the proportion of such disorders may even decline. Disorders that do not impair antigen-specific responses, including intrinsic, innate, and adaptive defects, and, frequently, combinations of such effects, are currently fewer in number than defects impairing antigen-specific responses, because the corresponding phenotypes have been much less studied. Patients with multiple infections are much more likely than patients with a single infection to suffer from an inborn error that disrupts antigen-specific responses. This trend will probably change, as isolated infections striking otherwise healthy individuals are increasingly being studied from a genetic angle. We can reasonably predict that hundreds of new disorders will be discovered in the next 20 years, most of which will underlie a single type of idiopathic infection, and most of which will not directly disrupt antigen-specific responses, but more specific, antigen-independent pathways in intrinsic, innate, and/or adaptive immunity.

This classification of human genes into four categories, excluding embryonic lethal genes, has at least three limitations. First, most genes compatible with live birth at term have not yet been attributed to these four categories. At least two decades of research may be required to assign these genes to the correct category. Another key limitation is that most findings were obtained for limited samples of the human population, including specific ethnicities living in specific microbial environments. We do not know the impact of many of the disorders identified in other ethnic groups living in other ecological niches. What holds for populations in Bolivia or Saudi Arabia may not hold for Inuits or Pygmies. Only a complete genetic and infectious description of humans would overcome these limitations, and no such description is expected to become available in the foreseeable future. A third limitation is that the current observation probably reflects the current state of interaction of humans and microbes, after generations of co-evolution. What holds now for any given gene may not

hold in 100 or 1,000 years; human genes may switch categories over time. Evolutionary genetic studies constitute an interesting approach to testing the validity and robustness of this classification, despite its inherent limitations. In principle, loci displaying beneficial redundancy would be expected to have undergone positive selection, as shown for *DARC* and *CASP12*. Loci displaying complete redundancy would be expected to display drift, consistent with neutral evolution, as found for *TLR5* and *MBL*. Conversely, although the purging of life-threatening recessive traits is theoretically slow, loci with low levels of redundancy would be expected to have evolved under negative selection. Indeed, key genes, such as *BTK, HAX1*, and *RAG1*, have been found to be subject to negative selection. Highly redundant loci would be expected to evolve under at least negative selection. Negative selection is, understandably, weaker for autosomal recessive than for X-linked recessive traits, and for recessive than for dominant traits, but, remarkably, negative selection has been shown to operate on human genes with high or low redundancy. Purifying selection is more likely to be documented for genes whose heterozygous LOF alleles are life-threatening, especially by haplo-insufficiency [168]. A study of the evolutionary genetics of human genes that can already be attributed to the four defined categories is warranted. If the correlation holds for this small sample of genes, then the evolutionary genetic features of other genes may be predictive of their future assignment to one category or another by the identification of knockouts in humans.

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Table 1

Human genes can be grouped into four categories according to their level of redundancy for protective immunity to infection in natural conditions

	Human gene redundancy for host defense			
Category[a]	**Low**	**High**	**Complete**	**Beneficial**
Null allele frequency (MAF[b])	Very rare ($<10^{-3}$)	Rare ($<10^{-2}$)	Common ($>10^{-2}$)	Common ($>10^{-2}$)
Clinical penetrance[c]	Complete	Incomplete	None	High (resistance)
Infection spectrum	Broad	Narrow	None	Single (resistance)
Natural selection	Negative[d]	Negative	Neutral	Positive
Examples	*BTK, RAG1, HAX1*	*IL12RB1, IRAK4, CARD9*	*TLR5, MBL, CLEC7A*	*DARC, CCR5, CASP12*

[a] The four categories are defined for live-born individuals. There is a fifth category of genes, not considered here, for which complete knockouts are embryonic lethal.

[b] MAF values are indicative. For example, a LOF variant with low redundancy can have a MAF $>10^{-3}$ and a LOF variant with high redundancy may have a MAF $> 10^{-2}$, especially in a context of incomplete penetrance.

[c] The penetrance is indicative. For example, genes with little redundancy can display incomplete penetrance for some of the associated phenotypes; conversely, genes with high redundancy can show complete penetrance.

[d] Purifying selection might be documented for a few genes with low or even high redundancy, due to purging, although this is more likely to occur for genes that underlie autosomal dominant immunodeficiencies.