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# Journal Pre-proof



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## The Monogenic Landscape of Human Infectious Diseases

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### Abstract

The spectrum of known monogenic inborn errors of immunity is growing, with certain disorder underlying a specific and narrow range of infectious diseases. These disorders reveal the core mechanisms by which these infections occur in various settings, including inherited and acquired immunodeficiencies, thereby delineating the essential mechanisms of protective immunity to the corresponding pathogens. These findings also have medical implications, facilitating diagnosis and improving the management of individuals at risk of disease.

**Keywords:** Mendelian and monogenic infections, Inborn errors of immunity, infections, protection against common pathogens

### Abbreviations:

IEI: inborn errors of immunity

GWAS: genome-wide association studies

MSMD: Mendelian susceptibility to mycobacterial disease

EM: environmental mycobacteria

AR: autosomal recessive  
XL: X-linked recessive  
TB: Tuberculosis  
*Mtb*: *Mycobacterium tuberculosis*  
ROS: Reactive oxygen species  
CMC: Chronic mucocutaneous candidiasis  
AD: Autosomal dominant  
GOF: gain-of-function  
IFD: Invasive fungal diseases  
auto-Abs: autoantibodies  
MAC: membrane attack complex  
TLR: Toll-like receptor  
TIR: Toll-like and IL-1 receptor  
LTA: lipoteichoic acid  
CRP: C reactive protein  
EV: Epidermodysplasia verruciformis  
HPV: Human papillomavirus  
NMSC: non-melanoma skin cancer  
APC: antigen-presenting cell  
DC: dendritic cells  
RW: Recalcitrant warts  
HSV-1: Herpes simplex virus 1  
HSE: Herpes simplex encephalitis  
h- and i- PSC: human and induced pluripotent stem cell  
CNS: central nervous system  
EBV: Epstein Barr virus  
WD: Whipple's disease  
DARC: Duffy antigen receptor for chemokines  
HBGA: histo-blood group antigens

## Introduction

Inborn errors of immunity (IEI) were initially thought to affect all leukocyte subsets and to predispose individuals to a wide range of pathogens <sup>[1, 2]</sup>. IEI have been classified into combined immunodeficiency groups (see Tables 1 and 2 of the classification of IEI) <sup>[3]</sup>. However, with the increasing number of IEIs being discovered, some exhibit a very narrow spectrum of susceptibility, often limited to a single pathogen <sup>[4-8]</sup>. In this review, susceptibility is defined as the unusual recurrence or severity of infection with a given pathogen that necessitates medical intervention or hospitalization. These patients are often cared for by specialized centers and undergo ancillary investigations (e.g., immunophenotyping, biopsy, etc.). For monogenic disorders, susceptibility arises from defects having a strong individual effect in increasing the risk of developing a specific infectious disease. This risk is classically measured by odds ratio (OR) or relative risk, with monogenic defects associated with high ORs (e.g. >10) <sup>[9]</sup>. Although these disorders are more common than previously thought and can manifest with a full spectrum of clinical manifestations, ranging from localized symptoms to severe and potentially lethal conditions in otherwise healthy individuals, they highlight the specific involvement of and impact on distinct immunological pathways, and therefore underscore redundant pathways for other pathogens. However, we define a syndromic disorder as a clinical phenotype characterized by the association of a primary infectious disease with additional clinical manifestations, whether infectious or not. The advent of next-generation sequencing has significantly improved our ability to provide a genetic diagnosis for an ever-growing number of these conditions, allowing for more precise and tailored medical interventions <sup>[10]</sup>. In this review, we will attempt to highlight the most important IEIs conferring a predisposition to narrow infectious diseases, focusing particularly on susceptibility to mycobacterial diseases (caused by both weakly virulent non-tuberculous and highly virulent tuberculous species), and certain bacterial, fungal, and viral diseases, and highlighting the genes recently implicated in IEI and the cellular and molecular functions affected in patients. Conversely, we also highlight genetic variants important for resistance to infection. We will not discuss genetic investigations based on genome-wide association studies (GWAS), which are more commonly used to identify common variants for complex traits through large-scale comparisons of patients and controls, scanning the entire genome, and detecting several loci with possible small independent effects on the disease. These approaches have been previously reviewed <sup>[11-13]</sup>. Instead, we focus here on the genetic investigation of patients (and their relatives)

to identify pathogenic causal variants with a strong effect (Table 1). We will deal, in particular, with monogenic predispositions, in which the causal relationship between the genotype and phenotype has been demonstrated.

- **Inborn errors of immunity underlying mycobacterial diseases**

- **Mendelian susceptibility to mycobacterial disease (MSMD)**

MSMD is a rare group of IEL characterized by a selective predisposition to clinical disease caused by weakly virulent mycobacterial species, such as *Mycobacterium bovis*-BCG vaccines and environmental mycobacteria (EM), in otherwise healthy individuals normally resistant to other microbes [14, 15]. MSMD occurs in ~ 1/50,000 individuals of diverse ancestries. About half the patients are also particularly susceptible to *Salmonella* and a significant proportion of MSMD patients also suffer from mucocutaneous infection with *Candida* species [16]. The genetic dissection of MSMD has identified deleterious variants in 22 genes underlying 46 different genetic etiologies [14, 17-23], considering factors such as mode of inheritance, whether the defect is complete or partial, whether the mutant protein being expressed, and the specific function affected (e.g. phosphorylation)(Figure 1). They are all physiologically related and impair the activity of interferon-gamma (IFN- $\gamma$ ), the “macrophage-activating factor” [24, 25]. *ZNF1* is the only gene implicated in MSMD for which the underlying mechanism has yet to be determined [26]. The essential role of IFN- $\gamma$  in protective immunity to mycobacteria was confirmed with the identification of the first patients with complete IFN- $\gamma$  deficiency in 2020 [27], showing that IFN- $\gamma$  is the only agonist of its receptor. The last four years have revealed four new molecular players in MSMD: *TBX21*, *MCTS1*, *IRF1*, and *CCR2*. Patients with autosomal recessive (AR) T-bet/*TBX21* deficiency display impaired development of the NK, iNKT, MAIT, V $\delta$ 2+  $\gamma\delta$  T and TH1 lymphoid cell subsets and impaired IFN- $\gamma$  production by innate and innate-like lymphocytes [19]. X-linked recessive (XL)-*MCTS1* deficiency impairs JAK2 synthesis, leading to impaired IL-23-dependent IFN- $\gamma$  production [18]. AR *IRF1* deficiency highlights the essential role of this protein in IFN- $\gamma$  dependent macrophagic immunity to mycobacteria and its probable redundancy in type I IFN-mediated immunity in humans [22]. Finally, AR *CCR2* deficiency may underlie MSMD in some patients due to migration of too few peripheral blood monocytes to tissues [17]. The identification of new genetic disorders of MSMD should extend the list of molecules known to be involved in the control of human IFN- $\gamma$  immunity.

## Tuberculosis (TB)

Tuberculosis, caused by the highly virulent *Mycobacterium tuberculosis* (*Mtb*), remains a devastating disease [28, 29]. However, building on the discoveries made for MSMD, rare patients suffering solely from TB and homozygous for variants causing deficiencies of IL-12R $\beta$ 1 and TYK2, for example, have been identified [5, 8, 15, 16, 30, 31], providing the first proof-of-principle that TB can be a monogenic disorder, upon infection with *Mtb* that acts as a trigger [9, 30] (Figure 1). New genetic etiologies, such as AR ITK and PD1 deficiencies, have been shown to underlie TB [32-34] through the impairment of IFN- $\gamma$ -mediated immunity [35]. The latter has been corroborated by the susceptibility to mycobacterial disease observed in patients treated with anti-PD1/PDL1 antibodies [36, 37]. Impaired IFN- $\gamma$  production was also observed in the first two PDL1-deficient patients [38]. In addition, five forms of AR TYK2 deficiency were characterized, based on expression, pathway affected and minor allele frequency of the deleterious variants [39, 40], all affecting IL-23-dependent IFN- $\gamma$ -mediated immunity and underlying susceptibility to mycobacterial diseases, highlighting the role of IL-23 in anti-TB immunity [39, 40]. Moreover, homozygosity for a common missense *TYK2* variant (P1104A) was identified as the first common monogenic cause of tuberculosis in two different patient cohorts [41, 42]. P1104A has been subject to negative selection over the last 4,000 years in Europe, probably due to the selective pressure exerted by TB [43, 44]. Homozygosity for this variant was probably responsible for 10 million deaths (1%) from TB over the last 2,000 years [42]. Homozygosity for P1104A specifically impairs (but does not abolish) IL-23-mediated IFN- $\gamma$ -dependent immunity, which is exerted mostly by MAIT and V $\delta$ 2<sup>+</sup>  $\gamma\delta$  T cells [23], challenging the conventional doctrine and demonstrating that IL-23 is predominantly an antimycobacterial cytokine. Two patients with complete AR TNF deficiency and recurrent TB were recently identified (Figure 1). Reactive oxygen species (ROS) production is impaired in the patients' alveolar-like macrophages but not in other myeloid cells, explaining the narrow clinical phenotype of the patients [45] and revealing the redundant nature of TNF for other infectious diseases. The discovery of additional IEL underlying TB is anticipated, with different genetic architectures depending on ethnicity and inheritance.

- **Inborn errors of immunity underlying fungal diseases**

### Non-invasive fungal diseases

Chronic mucocutaneous candidiasis (CMC) manifests as persistent or recurrent infections of the skin, mucosa, and nails with *Candida* spp. Severe CMC disease is associated with weight loss, failure to thrive, and complications, such as esophageal stricture, squamous cell carcinoma, and cerebral aneurysms in some cases [46, 47]. The first IEI of the IL-17A/F signaling pathway were identified in 2011 [48, 49]. Autosomal dominant (AD) IL-17F, and AR IL-17RA, IL-17RC, and ACT1 deficiencies were described in patients with CMC who were otherwise healthy apart from mucocutaneous diseases caused by *Staphylococcus aureus* in some patients (Figure 2). In parallel, IEI affecting the production alone or both the production of and response to IL-17A/F were progressively described and deciphered, mostly in patients with syndromic CMC (ie: CMC and additional symptoms, infectious or not). AD JNK1 or IL6ST deficiency, AR IL-23R, ROR $\gamma$ /ROR $\gamma$ T, ZNF341, or cRel deficiency, and AD STAT1 gain-of-function (GOF) have all been described in patients with mild or severe CMC and other infectious and/or autoimmune features. These IEI were shown to impair the production of IL-17A/F, probably underlying the CMC observed in the patients [48-51]. CMC was recently reported in a third of the patients from a cohort of individuals with complete AR IL-23R deficiency and abolished responses to IL-23, a cytokine reported to be essential for the maintenance of Th17 cells in mice [23]. These findings suggest that human IL-23 plays a crucial role in IL-17A/F-mediated protection against mucocutaneous *Candida* disease in a subset of affected individuals, whereas it appears to be redundant in most individuals [23]. None of the patients with IEI of IL-17-mediated immunity reported (except for a few of the patients with AD STAT1 GOF and most patients with AR CARD9 deficiency) have been documented to have invasive candidiasis, suggesting that IL-17A/F play a redundant role in protection against invasive *C. albicans* disease.

### **Invasive fungal diseases (IFD)**

The second emblematic example of an IEI underlying fungal diseases is AR CARD9 deficiency [52, 53]. Over 90 patients have now been reported, all suffering from mucocutaneous or invasive diseases caused exclusively by fungal pathogens, with a disease onset ranging from early childhood to late adulthood. CARD9 is expressed primarily by myeloid cells and serves as an adaptor downstream from C-type lectin receptors (e.g. dectin-1), promoting the production of proinflammatory cytokines and chemokines upon fungal infection [53]. The fungal diseases concerned include superficial and deep dermatophytosis,



superficial and invasive *Candida* infections, subcutaneous and invasive phaeohyphomycosis caused by fungi such as *Exophiala* spp., *Corynespora cassiicola*, and *Phialophora verrucosa*. Rare cases of mucormycosis or aspergillosis have been reported<sup>[49]</sup>. By contrast, no cases of cryptococcosis “reported in some patients with neutralizing autoantibodies (auto-Abs) against GM-CSF”, *Pneumocystis jirovecii* pneumonia “frequently reported in patients with IEI of the IKAROS zinc finger transcription factor family”, or cases following dimorphic fungal infections have yet been reported in patients with AR CARD9 deficiency. Impaired CARD9-dependent induction of Th17 cytokines and neutrophil-recruiting chemokines (CXCL1, CXCL2 or CXCL5<sup>[54]</sup>) has been identified as a potentially important mechanism underlying superficial and invasive fungal diseases, respectively, in patients with CARD9 deficiency (Figure 2). Biallelic deleterious variants of *CLEC7A*, encoding dectin-1 (a  $\beta$ -glucan-binding receptor), which signals through CARD9, have recently been reported in patients with severe *C. cassiicola* phaeohyphomycosis<sup>[55]</sup>. However, human dectin-1 deficiency is a frequent condition, with the p.Y238\* allele present at a frequency of about 7% in European populations and up to 40% in the San population of South Africa, suggesting that it cannot be considered *per se* as an IEI underlying rare *C. cassiicola* phaeohyphomycosis, but should instead be seen as a risk factor. Further studies of the molecular and cellular bases of isolated CMC and IFD in humans with inherited CARD9 deficiency should shed light on the mechanisms of antifungal immunity in humans.

- **Inborn errors of immunity underlying pyogenic bacterial diseases**

- ***Neisseria* disease**

Diseases due to *Neisseria* result in an estimated 600,000 deaths worldwide<sup>[56]</sup>. Complement deficiencies, first identified in the early 1970s, confer a predisposition to *Neisseria* infections<sup>[57]</sup>. The complement system — discovered by Bordet in 1896 and shown to have antibacterial properties — is a proteolytic cascade of multiple proteins<sup>[58, 59]</sup> defining three activation pathways: the classical, mannose, and alternative complement pathways. All these pathways can cleave C3, the central component, and activate the terminal pathway<sup>[58, 59]</sup>. Genetic studies of patients with a particularly susceptibility only to *Neisseria* infections revealed AR deficiencies of terminal pathway components (C5, C6, C7, C8 and C9) as the main cause<sup>[60-62]</sup>. These terminal components form the membrane attack complex (MAC) on the surface of the bacterium, creating a pore that kills it by osmolysis<sup>[63]</sup>. In 2023, two studies suggested a role for C5 in human immunity

to fungi<sup>[64, 65]</sup>, but these studies were unable to explain the absence of fungal infections in hundreds of previously reported C5-deficient patients. Inherited deficiencies of early alternative pathway components (XLR properdin, AR factor D, AR factor B deficiencies)<sup>[60, 62]</sup> and classical pathway components (AR C1q, AR C1r, AR C1s, AR C2, AR C3, AR C4, AR, AR factor H, AR factor I deficiencies) increase susceptibility to *Neisseria*, but also to pneumococcal diseases, and such deficiencies may also be associated with autoimmune conditions<sup>[60, 62]</sup>. Investigations of complement are therefore essential in child and adult patients who have suffered from invasive infections due to encapsulated bacteria, even after a single episode<sup>[66, 67]</sup>. Deficiencies of components of the mannose pathway do not cause Mendelian disorders<sup>[68]</sup>. Interestingly, alleles underlying deficiencies of C2, C6, and C9 are present in the European, African and Asian populations, respectively, each with a minor allele frequency close to 1%<sup>[69]</sup>. The high frequencies of these deleterious alleles, at least in certain populations, are intriguing and warrant further investigation through population and evolutionary genetics.

### **Pneumococcal disease**

Pneumococcal diseases cause an estimated 800,000 deaths annually worldwide<sup>[56]</sup>. In 1953, Bruton reported that immunoglobulins play an important role in controlling *S. pneumoniae* infection<sup>[1]</sup>. Studies of patients with agammaglobulinemia led to the discovery of the most common genetic etiology underlying this condition: X-recessive BTK deficiency<sup>[70, 71]</sup>. It is now well established that IEI affecting the development, differentiation or maturation of B cells confer a predisposition to *S. pneumoniae*<sup>[72]</sup>. More than 50 genetic etiologies with an impact on the quantity or quality of immunoglobulins have now been identified and recently reviewed<sup>[73]</sup>. Complement studies revealed that the classical complement pathway and antibodies binding to the polysaccharide on the surface of *S. pneumoniae* cooperate to initiate opsonization of the bacteria (see above). Patients with AR deficiencies of C2, C3 and C4 may therefore develop severe pneumococcal disease, but they may also present autoimmunity. From 2001 onwards, studies of a series of patients with Toll-like receptor (TLR)-IL-1R (TIR)-NF- $\kappa$ B pathway deficiencies (XLR-IKBKG, AD NFKBIA, AR HOIL-1 and AR HOIP deficiencies)<sup>[74-79]</sup>, in addition to the identification of IRAK-4<sup>[80]</sup> and MyD88<sup>[81]</sup> deficiencies, highlighted the crucial role of TLR/IL-1R pathway in the myeloid lineage for controlling pneumococcal infections in humans and defining narrow non-redundant antibacterial immunity.

However, the effector mechanism remains unknown. These three key non-redundant mechanisms-complement and myeloid cells (both innate immunity) and anti-polysaccharide antibodies (humoral immunity)-are required to protect humans against pneumococcal disease. The absence of a genetic diagnosis for most people suffering from pneumococcal disease<sup>[66]</sup> despite active vaccination, suggests the presence of other immune mechanisms capable of controlling this disease.

### **Staphylococcal disease**

Staphylococcal diseases lead to an estimated 1,000,000 deaths annually worldwide<sup>[56]</sup>. Human phagocytes play a key role in defenses against *S. aureus* infection<sup>[82]</sup>. Indeed, IELI such as congenital neutropenia<sup>[83]</sup> and phagocytosis defects<sup>[84, 85]</sup> confer a predisposition to *S. aureus* infections. Disorders of the TLR/IL-1R-NF- $\kappa$ B pathway (XLR-*IKBK*G, AD *NFKBIA*, AR *IRAK4* and AR *MyD88* deficiencies)<sup>[74-81]</sup>, confer a predisposition to severe *S. aureus* and a few other infections. The description of inherited *TIRAP* deficiency, which is an adaptor protein interacting with TLR2 and TLR4, and acts upstream of *MyD88* and *IRAK-4*, has narrowed the search for the main player in selective predisposition to *S. aureus* infection to TLR1/2 and TLR2/6<sup>[86]</sup>. The incomplete penetrance of staphylococcal infection among individuals with AR *TIRAP* deficiency in this kindred was explained by the production of anti-lipoteichoic acid antibody in all relatives tested but not in the patient, which rescue TLR2-dependent immunity to staphylococcal LTA. Studies of patients with human *OTULIN* haploinsufficiency have recently shed light on the essential role of toxin receptor expression in immunity. *OTULIN* haploinsufficiency in fibroblasts dysregulates *CAVEOLIN/ADAM10* expression on the cell surface, increasing the cells' sensitivity to  $\alpha$ -toxin. It has indicated that other, non-hematopoietic immune cells also play crucial roles in controlling pyogenic infections through intrinsic mechanisms<sup>[87]</sup>. Incomplete penetrance for staphylococcal infection in individuals with *OTULIN* haploinsufficiency has been shown to be due to the presence of anti- $\alpha$ -toxin antibody<sup>[87]</sup>. Finally, further investigations into patients suffering from staphylococcal diseases and hyper-IgE syndrome ultimately led to the discovery of the first patients with AR *IL-6* receptor deficiency<sup>[88-90]</sup>. The studies of these patients have revealed the importance of *IL-6* in T-cell differentiation (circulating follicular helper cells and Th17 T cells) confirming the observation described in patients with AD *STAT3*, or AD or AR *GP130* deficiency (encoded by *IL6ST*), who are characterized by a deficit of *STAT3*-dependent *IL-6*

response<sup>[91-93]</sup>. Since 2008, a few patients with recurrent subcutaneous staphylococcal abscesses or other severe pyogenic infections have been reported to have neutralizing auto-Abs against IL-6<sup>[94-96]</sup>. Similarly, severe bacterial infections have been reported in patients treated with Tocilizumab<sup>[97]</sup>. Auto-Abs against IL-6 should therefore be considered in patients, particularly adults, with unexplained bacterial infections, especially when there is no adequate increase in CRP levels during the infection. Together, these discoveries demonstrate the key role of IL-6 in immunity to staphylococci and highlight the contribution of adaptive immunity.

- **Inborn errors of immunity underlying viral diseases of the skin**

- **Epidermodysplasia verruciformis (EV)**

Human papillomaviruses (HPVs) are small DNA viruses, each with a specific tropism to mucosal ( $\alpha$ -) or cutaneous ( $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\mu$ - and  $\nu$ -) tissues. In the general population, the  $\alpha$ -,  $\gamma$ -,  $\mu$ - and  $\nu$ -HPVs cause benign cutaneous common and plantar warts<sup>[98]</sup>. The  $\alpha$ -HPVs also cause anogenital and oropharyngeal cancers, whereas  $\beta$ -HPVs generally cause asymptomatic infections. Some  $\beta$ -HPVs are responsible for flat wart-like lesions and non-melanoma skin cancer (NMSC) in rare patients with epidermodysplasia verruciformis (EV)<sup>[99, 100]</sup>. In 1946, EV was the first Mendelian IEI described, characterized by a narrow range or “isolated” form of infections<sup>[99-101]</sup>. Three IEI have been identified in patients with isolated EV: EVER1, EVER2 and CIB1 deficiencies<sup>[101-103]</sup> (Figure 3). CIB1, EVER1, and EVER2 form a complex that binds E5 and E8, governing keratinocyte-intrinsic immunity to  $\beta$ -HPVs and potentially acting as a viral restriction factor<sup>[104]</sup>. Rare patients with EV and other phenotypes, mostly infectious, referred to as atypical, or “syndromic” forms of EV<sup>[101]</sup> present various inherited disorders of T cells, including RhoH, CORO1A, DOCK8, LCK, TPP2, STK4, and ITK deficiencies<sup>[32, 105-110]</sup>. Complete AR FLT3L deficiency was recently reported in a multiplex family with syndromic EV or recalcitrant warts. FLT3L deficiency induces a severe deficit of antigen-presenting cells (APCs) of all kinds, including dendritic cells. FLT3L-deficient individuals have a similar skin composition to healthy donor, with the presence of Langerhans cells and macrophages, but with much lower levels of dermal DCs. These findings strongly suggest a non-redundant role of dermal DCs in the control of cutaneous HPVs<sup>[111]</sup>. Together, these data demonstrate that both isolated and syndromic EV display genetic heterogeneity but physiological homogeneity. Both cellular and intrinsic immune responses

are therefore involved in cutaneous immunity to EV-HPVs. Disorders of T-cell responses underlie syndromic EV and other HPV-related skin infections, whereas disorders of keratinocytes underlie isolated EV.

### **Recalcitrant warts (RW)**

In rare cases, common warts, mostly due to  $\alpha$ -HPVs, can spread and persist, in which case they are described as recalcitrant warts (RW)<sup>[112]</sup>. Unlike EV, RW often present as a syndromic form, with multiple HPV types or manifestations (cutaneous, mucosal). The best characterized of these genetic defects are those in patients with monoallelic mutations of *CXCR4*<sup>[113-115]</sup> and *GATA2*<sup>[116-119]</sup>, and biallelic mutations of *DOCK8*<sup>[120-122]</sup>, who suffer from RW in 80, 50 and 40%, respectively, of cases<sup>[105, 123]</sup>. These IEI with a high penetrance for HPV diseases may selectively affect APCs counts, as recently reported for *FLT3L* deficiency<sup>[111]</sup>, or both APCs and T lymphocytes counts, migration or function (Figure 3). Other IEI affecting mostly T lymphocytes have also been reported in patients with severe HPV infection<sup>[105, 123]</sup>. Many of these IEI impair  $\alpha\beta$  T-cell counts, as reported for *TRAC* and *IL-7* deficiencies<sup>[124-126]</sup>, or primarily *CD4*<sup>+</sup> T-cell counts, as reported for *STK4* deficiency or the recently described *SASH3* deficiency<sup>[127-132]</sup>. Other IEI conferring a predisposition to RW are associated with normal or near-normal T-cell counts and differentiation. *CD28* deficiency has been reported in patients with isolated RW, including one patient with tree man syndrome<sup>[133]</sup>. Interestingly multiple IEI conferring predisposition to HPV underlie a *CD28* signaling defect. Deficiencies of *CARMIL2*, a cytoplasmic signaling molecule, impair NF- $\kappa$ B activation downstream from *CD28*<sup>[134-136]</sup>. *MAGT1* deficiency results in a glycosylation defect, the effects of which include an impairment of *CD28* expression on T lymphocytes<sup>[137]</sup>. AD *CARD11* dominant-negative variants impair NF- $\kappa$ B activation upon *CD3/CD28* costimulation<sup>[138]</sup>, and *CARD11* is a direct partner of *CARMIL2*<sup>[139, 140]</sup>. Together, these findings suggest a major role of the NF- $\kappa$ B pathway downstream from *CD28* in the control of skin papillomavirus infection by T cells. Furthermore, deficiencies of *CD4*<sup>[141]</sup>, another T cell-costimulating molecule, have recently been shown to underlie RW<sup>[142]</sup> by an as yet unclear mechanism, possibly involving *CD28* and *LCK*<sup>[143]</sup>. Thus, studies of IEI have shown that impairments of the numbers or functions of APCs and T cells can confer a predisposition to severe RW.

#### **• Inborn errors of immunity underlying viral encephalitis**

Herpes simplex virus 1 (HSV-1) encephalitis (HSE) is the most common sporadic viral encephalitis in Western countries and, perhaps, worldwide. The causal role of HSV in HSE was established in 1941<sup>[144]</sup>, and HSV-1 was distinguished from HSV-2 in 1977<sup>[145]</sup>. About 1-2/10,000 infected individuals develop life-threatening HSE. In the early 2000s, it was hypothesized that childhood HSE might result from single-gene IEL to HSV-1 in the central nervous system (CNS)<sup>[146-148]</sup>. The evidence supporting genetic susceptibility to HSE came from two very rare cases of “syndromic” HSE observed in combination with mycobacterial diseases, in a child with AR complete STAT1 deficiency<sup>[149]</sup>, and a child with a *NEMO* mutation<sup>[150-152]</sup>. From 2006 onwards, 12 IEL underlying the typical form of isolated childhood HSE were progressively discovered. Most of the HSE-causing IEL identified to date affect type I IFN-mediated antiviral immunity through mutations of genes encoding proteins involved in type I IFN production (TLR3, UNC93B1, TRIF, TRAF3, TBK1, IRF3, NEMO, GTF3A) or responsiveness (IFNAR1, STAT1, STAT2, TYK2)<sup>[6, 149, 152-162]</sup> pathways (Figure 4). HSE-causing IEL disrupting novel type I IFN-independent antiviral mechanisms have also recently been shown to underlie HSE in other HSE patients, the genes encode DBR1<sup>[163]</sup>, snoRNA31<sup>[164]</sup>, RIPK3<sup>[165]</sup> and TMEFF1<sup>[166]</sup>. Unlike deficits of the type I IFN circuit that impair type I IFN-mediated first line antiviral responses in a broad range of tissues and cells, hence underlying various severe viral infections in humans including those resulted from live attenuated virus vaccination<sup>[40, 167, 168]</sup>, the four HSE-causing IEL impairing type I IFN-independent antiviral immunity have been found only in patients with isolated HSE so far. Regardless of the molecular mechanisms, human pluripotent stem cell (hPSC)-derived forebrain neurons harboring HSE-causing IELs display defective cell-intrinsic immunity to HSV-1, resulting in unrestricted HSV-1 replication in neurons. Such IEL therefore presumably underlie HSE pathogenesis *in vivo*, with incomplete clinical penetrance, accounting for up to 10% of the cases studied. The last two decades of human genetic and immunological studies have, therefore, progressively established a new paradigm that childhood HSE can result from inborn errors of CNS-specific, cell-intrinsic immunity to HSV-1, expanding the concept of host defense *in natura* from the immune system to the whole organism.

#### • Inborn errors of immunity underlying viral pneumonia

The first IEL identified to cause life-threatening viral pneumonia was IRF7-deficiency in a patient with influenza<sup>[169]</sup>. IRF7-deficient plasmacytoid DCs (pDCs) and induced pluripotent stem cell (iPSC)-derived

pulmonary epithelial cells (PECs) from this patient produced abnormally small amounts of type I and III IFNs in response to influenza A viruses (IAVs), promoting IAV proliferation<sup>[169]</sup>. AD deficiencies of TLR3, and AR deficiencies of IRF9, STAT1, TYK2 and STAT2- have been identified in patients with life-threatening influenza pneumonia, further demonstrating that the type I IFN response in PECs is essential to control influenza infection<sup>[40, 167, 168, 170-172]</sup> (Figure 4). Studies of critical COVID-19 pneumonia led to the discovery of a new IEI, XR TLR7 deficiency, accounting for more than 1% of cases of critical COVID-19 in men, especially those under 60 years of age<sup>[173]</sup>. The blood B-cell lines and myeloid cell subsets of these patients did not respond to TLR7 stimulation and their pDCs produced low levels of type I IFNs in response to SARS-CoV-2 <sup>[173]</sup>. TLR7 is a MyD88/IRAK-4-dependent endosomal receptor for single-stranded RNA in pDCs. Patients with AR MyD88 or IRAK-4 deficiency have been shown to be at high risk of life-threatening COVID-19 due to impaired TLR7-dependent type I IFN production by pDCs<sup>[174]</sup>. The discoveries of IE of TLR3- and IRF7-dependent type I IFN immunity, including AR deficiencies of IRF7, IRF9, IFNAR1, IFNAR2, STAT2, TYK2 and TBK1-, and AD deficiencies of TLR3 in patients with critical COVID-19 pneumonia suggested that influenza and COVID-19 pneumonia are allelic on five loci (IRF7, IRF9, STAT2, TYK2, and TLR3)<sup>[175-180]</sup>, where variants on the same loci underlie both diseases. AR deficiencies of IFIH1, a RIG-I-like receptor involved in the sensing of viral RNA leading to the induction of type I interferons, have been reported in children suffering of severe respiratory illness due to respiratory syncytial virus, human rhinovirus or influenza <sup>[181, 182]</sup>. Intriguingly, the penetrance of all these inborn errors of type I IFN immunity is far from complete, even for the most virulent pathogen, SARS-CoV-2.

#### • Inborn errors of immunity underlying EBV diseases

Epstein Barr virus (EBV) belongs to the  $\gamma$ -herpes family <sup>[183]</sup>. Most EBV infections are benign and symptom-free, with about 90% of adults worldwide experiencing infection at some time in their lives, but this virus has been implicated in about 1% of all cancer cases <sup>[184]</sup>. EBV primarily infects epithelial cells and B lymphocytes, establishing latency within B cells. Uncontrolled EBV infections can manifest as infectious mononucleosis (IM), hemophagocytic lymphohistiocytosis (HLH), and various B-cell proliferative disorders. CD8<sup>+</sup> T-cell responses play a key role in immunity to EBV <sup>[183, 185, 186]</sup>. Two types of IEI corresponding to different lymphoproliferative disorders have been identified. The first group, characterized by variants of

*PRF1*, *RAB27A*, *UNC13D*, *SYT11*, *LYST* and *SH2D1A*, impairs the granule-dependent cytotoxicity function of NK and CD8<sup>+</sup> T cells, leading to EBV-induced HLH. The second group comprises IEI in which EBV infection predominantly drives B-cell lymphoproliferative disorders, including B-cell lymphomas. Patients with IEI of this type present an impaired activation and expansion of EBV-specific T cells due to deficiencies of RASGRP1, ITK, MAGT1, DEF6, CTPS1, TNFRSF9, CD27 or its ligand CD70 [187, 188]. Patients with ITK deficiency are also susceptible to TB [32]. For this group of IEI, a recent report identified patients homozygous for loss-of-function variants of *IL27RA* displaying selective vulnerability to EBV [189]. The phosphorylation of STAT1 and STAT3 by IL-27 was abolished in the T cells of these patients. This deficiency impairs the expansion of potent anti-EBV effector cytotoxic CD8<sup>+</sup> T cells, probably due to the lack of a synergistic effect on T-cell receptor-dependent T-cell proliferation. In addition, a specific allele of *IL27RA* (rs201107107) for which enrichment has been detected in the Finish population is associated with a higher risk of developing IM when present in the homozygous state. Finally, neutralizing auto-Abs against IL-27 have also been reported in patients with sporadic IM and chronic EBV infection. These findings demonstrate the crucial role of IL27-IL27RA in immunity to EBV [189].

#### • Autoimmune phenocopies of inborn errors of immunity

Some autoimmune disorders can phenocopy IEIs, resulting in an almost undistinguishable infectious phenotype [190]. Auto-Abs against a component of the complement system (C3 convertase) has been shown to enhance its activity (thus being an “enhancing” auto-Ab), lowering complement levels and underlying severe bacterial infections such as meningitis due to *Neisseria* [191], pneumonia due to *Streptococcus pneumoniae* [192] or *Haemophilus influenzae* [193]. Autoimmune phenocopies of at least four cytokines have also been described [72, 194, 195]: IL-6 and staphylococcal disease [94], IFN- $\gamma$  and MSMD [194, 196-199], IL-17A/F and autoimmune polyendocrinopathy syndrome type I (APS-1 or APECED syndrome) /CMC [200, 201] and GM-CSF and idiopathic pulmonary alveolar proteinosis and cerebral/pulmonary nocardiosis [202-204] or cryptococcosis [205-216]. More recently, auto-Abs neutralizing IFN- $\alpha$  and/or  $\omega$  were detected in about 15% of cases of life-threatening COVID-19 pneumonia [217], 20% of the fatal COVID-19 cases tested [218-220], and 20% of individuals suffering from ‘breakthrough’ hypoxemic COVID-19 pneumonia despite an appropriate Ab response to mRNA vaccine [221, 222]. The risk of critical disease increases with the



number and concentration of type I IFNs neutralized. These auto-Abs were also found to underlie about one third of the rare cases of severe adverse reactions to yellow fever YFV-17D live-attenuated viral vaccine [223], 5% of cases of critical influenza pneumonia [176], 20% of cases of critical Middle East respiratory syndrome (MERS) pneumonia [224], 40% of cases of West Nile virus encephalitis [225], and various herpes viral infections [226-231]. They can be detected in 0.3-1% of individuals under the age of 65 years (including 0.2-2% of children), after which their prevalence increases sharply, reaching 4-8% in individuals over 70 years of age. Auto-Abs neutralizing type I IFNs are present before infection and are causal for severe viral diseases. Patients with neutralizing anti-IL-27 auto-Abs have recently been reported to be prone to Epstein-Barr virus diseases, like patients with AR IL-27RA deficiency [189]. It remains unknown why they are produced, but their production can be genetically driven, as in patients with anti-IFN- $\gamma$  auto-Abs and specific HLA class II haplotypes, or in a few patients with IEL of T-cell thymic selection and auto-Abs against type I IFNs [232, 233]. The clinical consequences may be much broader than initially thought, such as high titers of neutralizing auto-Abs against IL-10 recently reported in children with mild to severe colitis, phenotypically mimicking inborn errors of the IL-10 pathway [234].

#### **Other infections studied from a monogenic angle**

Other infectious diseases have also been investigated to identify the human genetic component involved. Whipple's disease (WD), caused by the bacterium *Tropheryma whippelii*, is associated with chronic or acute infections [235, 236]. Two genetic etiologies have been identified: AD IRF4 deficiency due to haploinsufficiency [237] and CD4 deficiency in patients with WD among other symptoms [141]. However, the pathophysiology of this disease remains unknown. Two mycobacterial diseases, Buruli ulcer, caused by *M. ulcerans* and recently shown to be transmitted by mosquitoes in Australia [238] and leprosy, caused by *M. leprae*, have been studied. A monogenic contribution to Buruli ulcer was recently reported, with the identification of a microdeletion on chromosome 8 encompassing a long non-coding (lnc) RNA gene expressed in the skin and located close to a cluster of defensin genes [239, 240], in a familial form of severe Buruli ulcer [241]. Recent studies of twins with early-onset leprosy led to identification of three rare variants of two genes (*LRRK2* and *NOD2*), with deleterious and additive effects on disease development [242]. Kaposi sarcoma is caused by infection with HHV8, a  $\gamma$ -herpes virus with oncogenic properties, the seroprevalence of which varies

considerably worldwide, from 20 to 40 % [243]. Three AR genetic etiologies have been linked to susceptibility to KS (IFNGR1, STIM1 and OX40), and three XL genetic etiologies have been linked to cutaneous KS (WAS, MAGT1 and CTLA4), highlighting the crucial role of T cells, and of OX40-dependent T-cell immunity in particular, for protection against HHV8 [244-246]. In addition, fulminant viral hepatitis, caused by hepatitis A virus (HAV) is a rare life-threatening disease, for which two genetic etiologies have been discovered: IL10RB [247] and IL18BP deficiencies [248]. These findings suggest that the molecular basis of FVH in these patients may involve excessive IFN- $\gamma$  activity during HAV infections of the liver [249]. Finally, NOS2 deficiency was found to be associated with fatal CMV disease in an otherwise healthy adult [250]. Altogether, these studies suggest that human genetic determinants play an important role in the course of infectious diseases.

### **Mendelian resistance to infection**

Mendelian susceptibility to infectious disease is indissociable from Mendelian resistance to infection. The role of Duffy antigen receptor for chemokines (DARC)-expressing erythrocytes in protection against *Plasmodium vivax* infection was first reported in the 1970s [251]. In *Plasmodium vivax* malaria, the parasite makes use of the interaction between its Duffy binding protein and DARC to invade reticulocytes. AR DARC deficiency, due to a single-nucleotide variant, inhibits *DARC* transcription in erythroid cells [252]. Natural selection, in areas in which *Pv* is endemic, led to an increase in the prevalence of resistance associated with an absence of the Duffy binding protein [253]. Similarly, FUT2-expressing intestinal epithelial cells play a key role in resistance to norovirus and rotavirus infections, which cause diarrheal diseases [254]. *FUT2* controls the secretion of ABO histo-blood group antigens (HBGAs) at the surface of the gut, where they act as receptors for norovirus and rotavirus. AR loss-of-function *FUT2* variants confer a non-secretor phenotype, preventing the expression of HBGAs on the surface of the gut, making it more difficult for the virus to bind [255, 256]. However, the idea that HBGAs function as receptors is controversial and some authors have suggested that these antigens may simply enhance viral replication and disease development without being essential for infection *per se* [257]. *FUT2* non-secretor status has also been linked to susceptibility to various diseases. Consistently, a complex pattern of natural selection has been described for *FUT2*, with most variants displaying a long history of balancing selection in Eurasian and African populations [258]. These advances in our understanding of monogenic resistance have highlighted the importance of non-

professional immune cells in protective immunity. Human genotypes at the DARC and FUT2 loci blocking the entry of parasites and viruses into non-professional immune cells have demonstrated how genetic variants in erythrocytes and the intestinal epithelium can have a life-saving effect. Finally, AR CCR5 deficiency, which has been found to confer resistance to HIV-1, illustrates the role of complete deficiencies of pathogen entry receptors in mechanisms of Mendelian resistance <sup>[259-261]</sup>. The most common loss-of-function variant of CCR5 is a 32-base pair deletion with a minor allele frequency of 10% in the European population. The genetic mechanisms of protection against severe infectious outcomes and resistance to infection are subject to positive selection, providing a survival advantage.

### **Future directions**

The human genetic basis of infectious diseases remains elusive in most affected individuals, driving ongoing efforts to unravel the genetic determinants underlying diseases, including those occurring sporadically. In large cohorts of patients with narrow infectious phenotypes, the identification of causal genetic etiologies depends largely on the disease itself and its prevalence (ranging from 50% for MSMD to 1% for tuberculosis) <sup>[8]</sup>. Other genetic hypotheses (e.g. weak clinical penetrance, digenic or oligogenic models) have not yet been thoroughly tested and might explain many infectious phenotypes. Recent discoveries of common monogenic alleles in the general population — such P1104A TYK2 and the role of this allele in the homozygous state in TB <sup>[41]</sup> through a selective biochemical effect on IL-23-mediated IFN- $\gamma$  immunity, or D31N PTCRA <sup>[262]</sup>, which increase the risk of autoimmunity — indicate promising future directions for IEL research. Digenic or oligogenic models with strong effects will probably shape the future of this field. Nevertheless, many patients still have no known genetic etiology, particular for the more frequent diseases. Widespread access to WES has already resolved many genetic cases, and the possibility of performing WGS combined with long-read technology may soon make it possible to determine not only the role of non-coding variants but also that of more complex variants involved in chromosome architecture, such as short and long repeats, CNVs, inversions, or translocations. The computing challenges posed by the large amounts of data generated are gradually being resolved. The bottleneck is not currently the identification of variants, but substantiating the deleterious nature of the variants identified and their causal role in the disease studied. Diagnosis based on the identification of a variant without functional validation persists and

poses inherent risks<sup>[173, 262-264]</sup>. The ongoing elucidation of interindividual variability in responses to specific pathogens is improving our genetic understanding and providing deeper insight into the phenomenon of incomplete penetrance (Table 1). Furthermore, the identification of novel genetic causes of specific infectious diseases is enriching our knowledge of cellular, immunological, and pathophysiological processes in an unbiased manner. This should help to define the cell subsets and pathways crucial for the control of particular infections *in vivo* and will serve as a basis for the development of preventive and therapeutic strategies based on physiological mechanisms. These discoveries will also facilitate the development of genetic counseling for affected families.

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**Figure 1: Schematic representation of the cooperation between phagocytic cells and T and NK cells during bacterial invasion.**

Molecules for which the genes are found mutated in patients with MSMD are represented in pink. Molecules for which the genes are found mutated in patients with TB are represented with a red surrounding. Molecules in pink with a red surrounding indicate that patients were found to suffer from MSMD or TB or both. Autoantibodies to IFN- $\gamma$  in patients with MSMD are also represented.

**Figure 2: Schematic representation of the signaling pathways activated during *C. albicans* infection.**

Molecules for which the genes are mutated and responsible for syndromic chronic mucocutaneous candidiasis (CMC) are represented in pink. Molecules for which the genes are mutated and responsible for isolated CMC are represented with red surroundings. Autoantibodies neutralizing IL-17A and/or IL-17F in patients with syndromic CMC (APS-1/APECED patients) are also represented.

**Figure 3: Schematic representation of the skin and the cooperation between target cells (keratinocytes), antigen-presenting cells (APCs) et T lymphocytes in the cutaneous anti-HPV immune response.**

Mutated genes found mutated in patients with isolated EV are in red. Molecules for which the genes are found mutated in patients with syndromic EV or recalcitrant warts are represented in pink.

**Figure 4: Schematic representation of the cooperation between Epithelial/neuron cells sand plasmacytoid dendritic cells during viral invasion.**

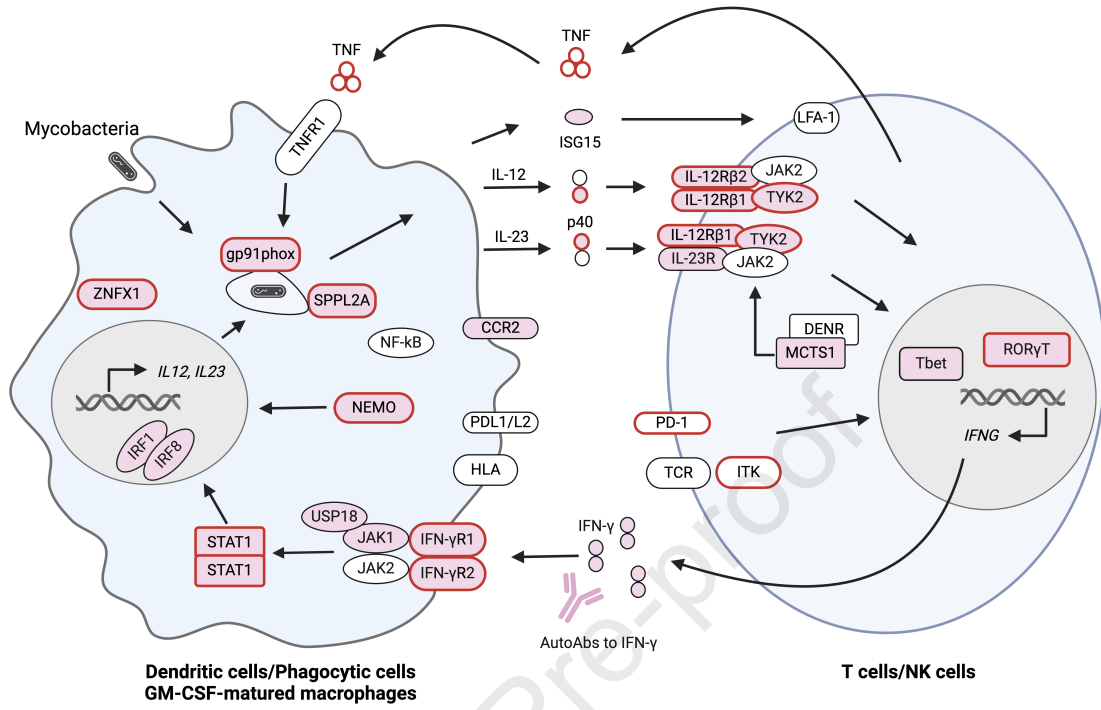
Molecules for which the genes are found mutated in patients with viral encephalitis are represented in pink. Molecules for which the genes are found mutated in patients with viral pneumonia are represented with a red surrounding. Molecules in pink with a red surrounding indicate that patients were found to suffer from HSE or viral pneumonia or both. Autoantibodies to IFN- $\alpha$  and  $\omega$  in patients with pneumonia are also represented.

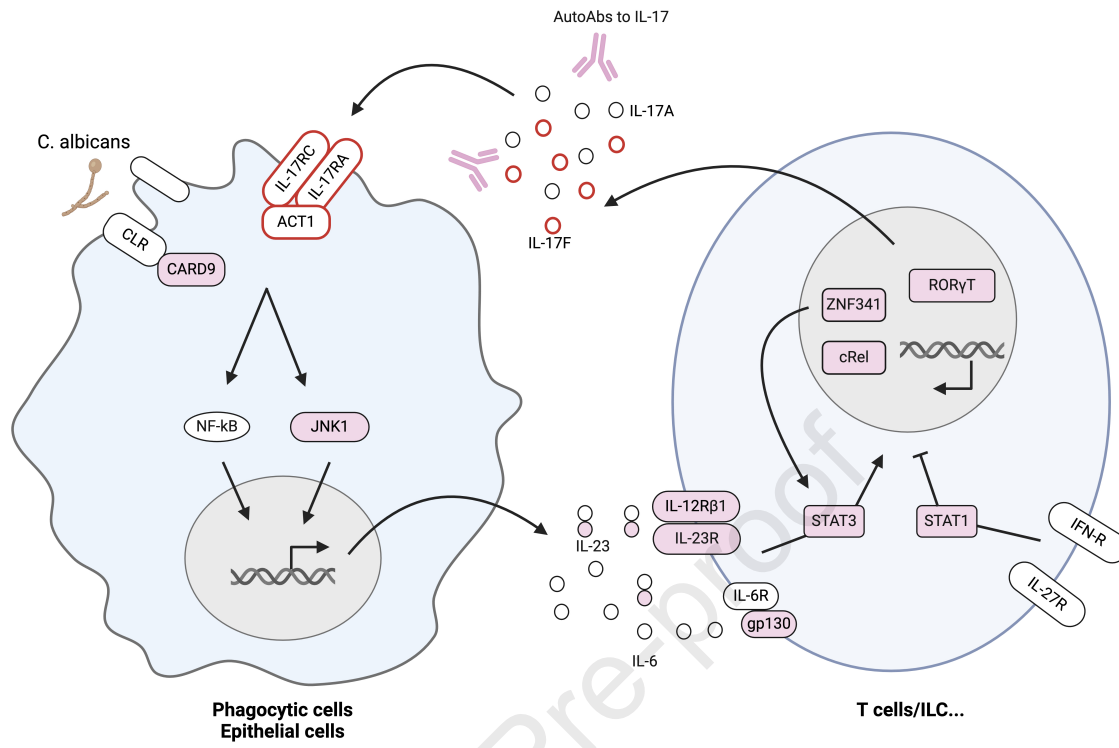
	Infectious agent	Clinical phenotype	Immunological phenotype	Gene	Inheritance #	
<b>Mycobacterial diseases</b>	BCG vaccines and environmental mycobacteria	Mendelian Susceptibility to Mycobacterial Diseases (MSMD)	IFN- $\gamma$ deficiency	<i>IFNGR1, IFNGR2, IL12RB1, IL12B, NEMO, STAT1, CYBB, IRF8, ISG15, TYK2, RORC, IL12RB2, IL23R, SPPL2A, JAK1, IFNG, CCR2, IRF1, MCTS1, ZNFX1, TBX21, USP18</i>	Mendelian or monogenic	AR, AD, XR
	<i>Mycobacterium tuberculosis</i>	Tuberculosis (TB)	IFN- $\gamma$ or TNF deficiency	<i>IL12RB1, TYK2, ITK, PDCD1, TNF</i>	Monogenic	AR
	<i>Mycobacterium ulcerans</i>	Buruli ulcer	Defensin deficiency	Chr. 8 microdeletion	Monogenic	AR
	<i>Mycobacterium leprosy</i>	Leprosy	LRRK2 and NOD2 deficiency	LRRK2 and NOD2	Digenic	AR, AD
<b>Fungal diseases</b>	<i>Candida sp.</i>	Chronic Mucocutaneous Candidiasis (CMC)	IL-17 deficiency	<i>IL17F, IL17RA, IL17RC, TRAP3IP2, STAT1, JNK1, IL6ST, CARD9, IL12B, IL12RB1, IL23R, STAT3, REL, ZNF341, RORC</i>	Mendelian	AR, AD
	Dermatophytes	Invasive fungal diseases	CARD9 deficiency	<i>CARD9</i>	Mendelian	AR
<b>Bacteria disease</b>	<i>Neisseria</i>	Meningitis	Complement deficiency	<i>C1QA, C1QB, C1QC, C1S, C2, C3, C4A, C4B, CFH, CFI, C5, C6, C7, C8A, C8B, C9, CFB, CFD, CFP</i>	Monogenic	AR, XR
	<i>Streptococcus pneumoniae</i> (and other encapsulated bacteria)	Meningitis, pneumonia, ENT	Complement deficiency	<i>C1QA, C1QB, C1QC, C1S, C2, C3, C4A, C4B, CFH, CFI, CFP</i>	Monogenic	AR
			TIR response deficiency	<i>IRAK4, MYD88, NEMO, HOIL1, HOIP</i>	Monogenic	AR, XR
			Specific antibody defect/asplenia	<i>RPSA</i>	Monogenic	AD
	<i>Staphylococcus aureus</i>	Severe and recurrent pneumonia, skin infection (CMC, Abscesses)	TLR2 response deficiency or IL-6 deficiency	<i>TIRAP, IL6RA, ZNF341, STAT3, IL6ST</i>	Mendelian or monogenic	AR, AD
		Increase sensitivity to $\alpha$ -toxin in non-hematopoietic cells	<i>OTULIN</i>	Monogenic	AD	
	<i>Tropheryma whipplei</i>	Whipple's disease	IRF4 or CD4 deficiency	<i>IRF4, CD4</i>	Monogenic	AD, AR
<b>Viral diseases of the skin</b>	Human papillomavirus (HPV)	Epidermodysplasia verruciformis	EVER-CIB1 deficiency and APC and/or T cells deficiency	<i>EVER1, EVER2, CIB1, RhoH, CORO1A, DOCK8, LCK, TPP2, STK4, ITK, FLT3L</i>	Monogenic	AR

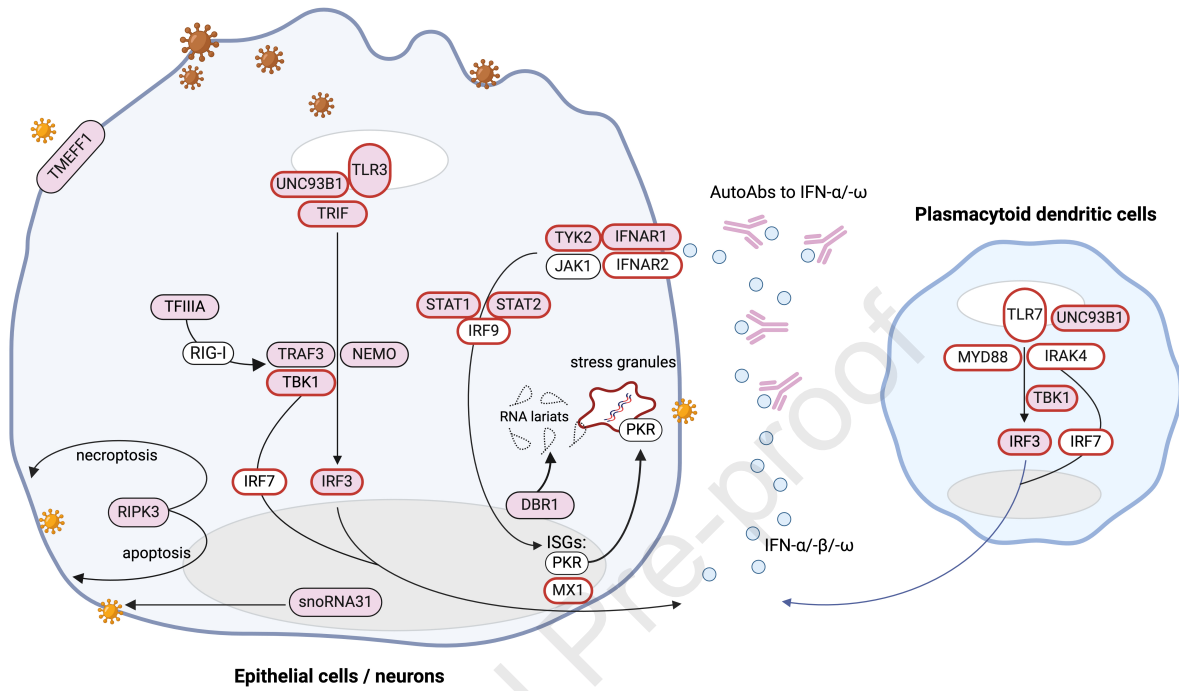
		Recurrent warts	APC and/or T cells deficiency	<i>STK4, DOCK8, GATA2, CXCR4, FLT3L, CD4, ICOSLG, CARMIL2, IL7, CD28, CARD11, MAGT1, TRAC</i>	Monogenic	AR, AD, XLR
	Human herpes virus 8	Kaposi sarcoma	T cells and OX40-dependent T cell immunity	<i>OX40, IFNGR1, CTLA4, MAGT1, STIM1</i>	Monogenic	AR, AD
<b>Viral encephalitis</b>	Herpes simplex virus (HSV)	Encephalitis	TLR3-IFN- $\alpha/\beta$ deficiency, TFIIIA-RIG-I-IFN- $\alpha/\beta$ deficiency	IFN- $\alpha/\beta$ -independent deficiency	Monogenic	AR, AD
<b>Viral pneumonia</b>	SARS-CoV-2	COVID-19 pneumonia	Type I and III IFN deficiency	<i>IRF7, IRF9, STAT2, TYK2, TLR3, STAT1</i>	Mendelian	AR, AD, XR
	Influenza virus	Severe influenza	Type I and III IFN deficiency	<i>IRF7, IRF9, TLR3, TLR7, IFNAR1, IFNAR2, STAT2, TYK2, TBK1</i>	Monogenic	AR, AD
	Rhinovirus, Respiratory syncytial virus (RSV)	Recurrent/severe infections	MDA5 deficiency	<i>IFIH1</i>	Monogenic	AR, AD
<b>EBV diseases</b>	Epstein-Barr virus (EBV)	X-linked lymphoproliferative disease; severe infection; B-cell lymphoma	Cytotoxic T/NK cell deficiency	<i>PRF1, RAB27A, UNC13D, SYT11, LYST, SH2D1A, RASGRP1, ITK, MAGT1, DEF6, CTPS1, THFRSF9, CD27, CD70, IL27RA</i>	Mendelian or monogenic	AR, XR
	Cytomegalovirus (CMV)	Lethal infection	NOS2 deficiency	<i>NOS2</i>	Mendelian	AR
<b>Hepatitis</b>	Hepatitis A virus	Fulminant hepatitis	Increased IFN- $\gamma$ activity	<i>IL18BP, IL10RB</i>	Monogenic	AR
<b>Resistance to infection</b>	Human immunodeficiency virus-1	Resistance to infection	Lack of receptor for pathogen in CD4 <sup>+</sup> T cells	<i>CCR5</i>	Mendelian	AR
	<i>Plasmodium vivax</i>	Resistance to infection	Lack of receptor for pathogen in erythrocytes	<i>DARC</i>	Mendelian	AR
	Norovirus	Resistance to infection	Lack of receptor for pathogen in intestinal epithelium	<i>FUT2</i>	Mendelian	AR

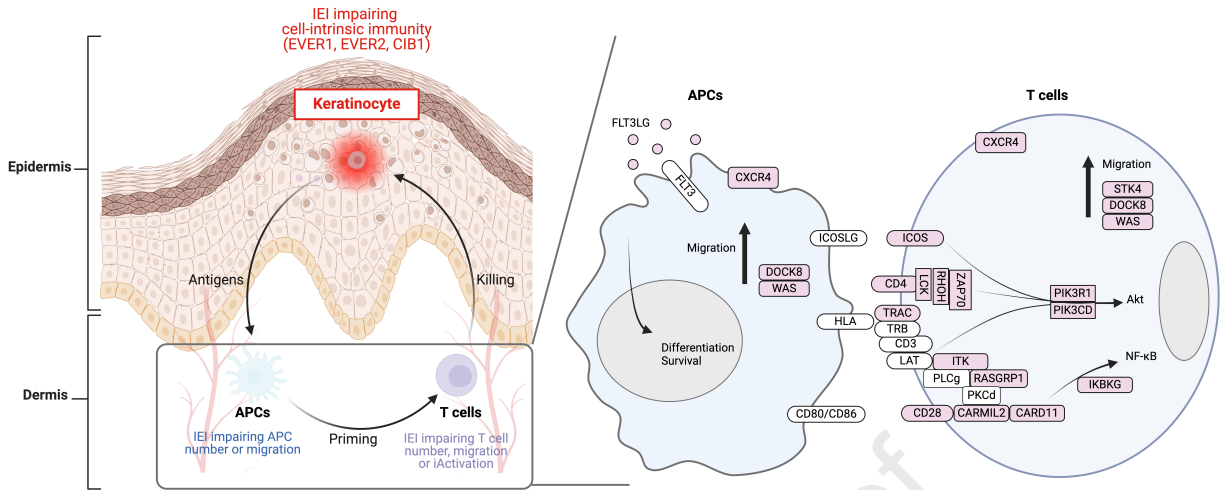
Table 1 : Genetic etiologies of infectious diseases categorized by infectious agents, clinical, and immunological phenotypes.

Footnote: # Mendelian refers to complete concordance between the genotype and phenotype, with full penetrance of the trait. In contrast, monogenic diseases may exhibit incomplete penetrance.









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