

# Unlocking life-threatening COVID-19 through two types of inborn errors of type I IFNs

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Since 2003, rare inborn errors of human type I IFN immunity have been discovered, each underlying a few severe viral illnesses. Autoantibodies neutralizing type I IFNs due to rare inborn errors of autoimmune regulator (AIRE)-driven T cell tolerance were discovered in 2006, but not initially linked to any viral disease. These two lines of clinical investigation converged in 2020, with the discovery that inherited and/or autoimmune deficiencies of type I IFN immunity accounted for approximately 15%–20% of cases of critical COVID-19 pneumonia in unvaccinated individuals. Thus, insufficient type I IFN immunity at the onset of SARS-CoV-2 infection may be a general determinant of life-threatening COVID-19. These findings illustrate the unpredictable, but considerable, contribution of the study of rare human genetic diseases to basic biology and public health.

## Introduction

Are there rare and common diseases, or just a myriad of unique expressions of disease in individual patients? The debate between “lumpers,” who favor broad classifications, ranged characteristics, and few divisions, and “splitters,” who favor recognition of nuanced differences, specific characteristics, and many divisions, is long-standing and probably never-ending, but the splitters have gained considerable ground in the last decade, with the impact of the next-generation sequencing of human exomes (1–4). This trend had already become clear by 2010, with the number of known medical conditions expanding from a handful to almost 5,000 in just two centuries. This should come as no surprise to physicians or biologists, as the names we give to diseases are mere labels; the use of words is a fragile attempt to describe a transiently unified perception of a highly heterogeneous and evolving biological reality. Patients are unique, idiosyncratic entities, different not only from each other, but also from themselves at different time points. Even identical twins are not phenotypically identical, and elderly people are different from the youngsters they used to be. The determinism of health and disease operates in living organisms, each of which differs from inert objects in consisting of a unique and diverse collection of cells with somatic genomes evolving both genetically and epigenetically in response to, and with selection due to, the continually changing environment.

**Conflict of interest:** JLC is an inventor on patent application PCT/US2021/042741, filed July 22, 2021 by The Rockefeller University, that covers the diagnosis of susceptibility to and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. JLC serves on the scientific advisory boards of ADMA Biologics Inc., Kymera Therapeutics, and Elixiron Immunotherapeutics. MSA holds stock in Medtronic and Merck.

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Nevertheless, most governments and substantial segments of medical academia insist on categorizing, and even prioritizing medical research, on what they refer to as “common diseases,” as opposed to “rare diseases” (5). Rare diseases are typically defined as conditions affecting fewer than 1 in 2,000 people (in the European Union) or 1 in 1,650 people (in the United States), with common diseases having a frequency above these arbitrary thresholds. Paradoxically, there are many more “rare” than “common” diseases, and it remains unclear whether the total number of patients with “common” disease actually exceeds the number with “rare” diseases. In the industrialized world, this dichotomy both stems from and reinforces a bias toward the study of a few diseases of the elderly, most of which are “common,” at the expense of the many diseases of childhood, most of which are “rare.” COVID-19 constitutes a recent example of a “common disease.” We review here how the enigma of “common” COVID-19, which is essentially a geriatric problem, was cracked at the molecular and cellular levels through the convergence in 2020 of hitherto separate lines of pediatric research on two “rare” genetic conditions: inborn errors of antiviral type I IFN immunity (variants of genes governing type I IFN immunity) and inborn errors underlying the production of autoantibodies against type I IFNs (variants of the *AIRE* gene governing T cell tolerance).

## Inborn errors of type I IFN immunity to viruses

There are currently 21 human inborn errors of type I IFN immunity (Table 1 and Figure 1).

*Inborn errors of ISGF3 (STAT1, STAT2, and IRF9).* The first human inborn error of type I IFN immunity was reported in 2003, in a child with autosomal recessive (AR) complete STAT1 deficiency presenting with herpes simplex virus encephalitis (HSE) (6). The role of inborn errors of type I IFNs in HSE was not unequivocally demonstrated until almost 20 years later, when a child with HSE due to AR IFN- $\alpha/\beta$  receptor chain 1 (IFNAR1) deficiency was identified (7). AR complete STAT1 deficiency abolishes both GAS-

**Table 1. Twenty-one inborn errors of type I IFN immunity**

Gene	Year	Inheritance	Viral infections					
			YFV-17D	MMR/MMRV	HSE	Influenza	COVID-19	Other
<i>IFNAR1</i>	2019	AR	Yes (20, 21)	Yes (22)	Yes (7)	No	Yes (23–25)	No
<i>IFNAR2</i>	2015	AR	Yes (28)	Yes (26, 29)	No	No	No	No
<i>TYK2</i>	2006	AR	NA	Yes (16, 41)	Yes (41)	No	Yes (16, 41)	HSV, VZV, PI3, MC, CMV, RSV, AIV, EBV (39–41)
<i>JAK1</i>	2018	AR	NA	No	No	No	No	No
<i>STAT1</i>	2003	AR	NA	Yes (8)	Yes (6)	Yes (8)	No	PIV, CMV, EBV, HSV, EV, HHV6, RV, VZV, RSV, rotavirus, AIV, MC (6, 8, 9)
<i>STAT2</i>	2012	AR	NA	Yes (10, 13, 14, 72)	No	Yes (14)	Yes (16)	No
<i>IRF9</i>	2018	AR	NA	No	No	Yes (17)	Yes (19)	VZV, EV (18)
<i>IRF7</i>	2015	AR	NA	No	No	Yes (42, 43)	Yes (23, 43)	RSV, TBE virus, AIV (43)
<i>TLR3</i>	2007	AR, AD	NA	No	Yes (50, 51, 172, 173)	Yes (128)	Yes (23)	VZV (53), EV (174)
<i>TRIF/TICAM1</i>	2011	AR, AD	NA	No	Yes (52)	No	No	No
<i>UNC93B1</i>	2006	AR	NA	No	Yes (49)	No	No	No
<i>TBK1</i>	2012	AR, AD	NA	No	Yes (45, 46)	No	Yes (128)	No
<i>IRF3</i>	2015	AD	NA	No	Yes (44)	No	No	No
<i>NEMO</i>	2005	XR	NA	Yes (175, 176)	Yes (47)	No	No	CMV, HSV, MV, AV (175, 176)
<i>TLR7</i>	2021	XR	NA	No	No	No	Yes (16, 64, 177–179)	No
<i>MYD88</i>	2008	AR	NA	No	No	No	Yes (65)	No
<i>IRAK4</i>	2003	AR	NA	No	No	No	Yes (65)	HHV6 (61)
<i>MDA5</i>	2017	AR, AD	NA	No	No	Yes (57)	No	RV, EV, RSV (55, 56)
<i>POLR3A</i>	2017	AD	NA	No	No	No	No	VZV (58)
<i>POLR3C</i>	2017	AD	NA	No	No	No	No	VZV (58)
<i>MX1</i>	2021	AD	NA	No	No	Yes (H7N9) (76)	No	No

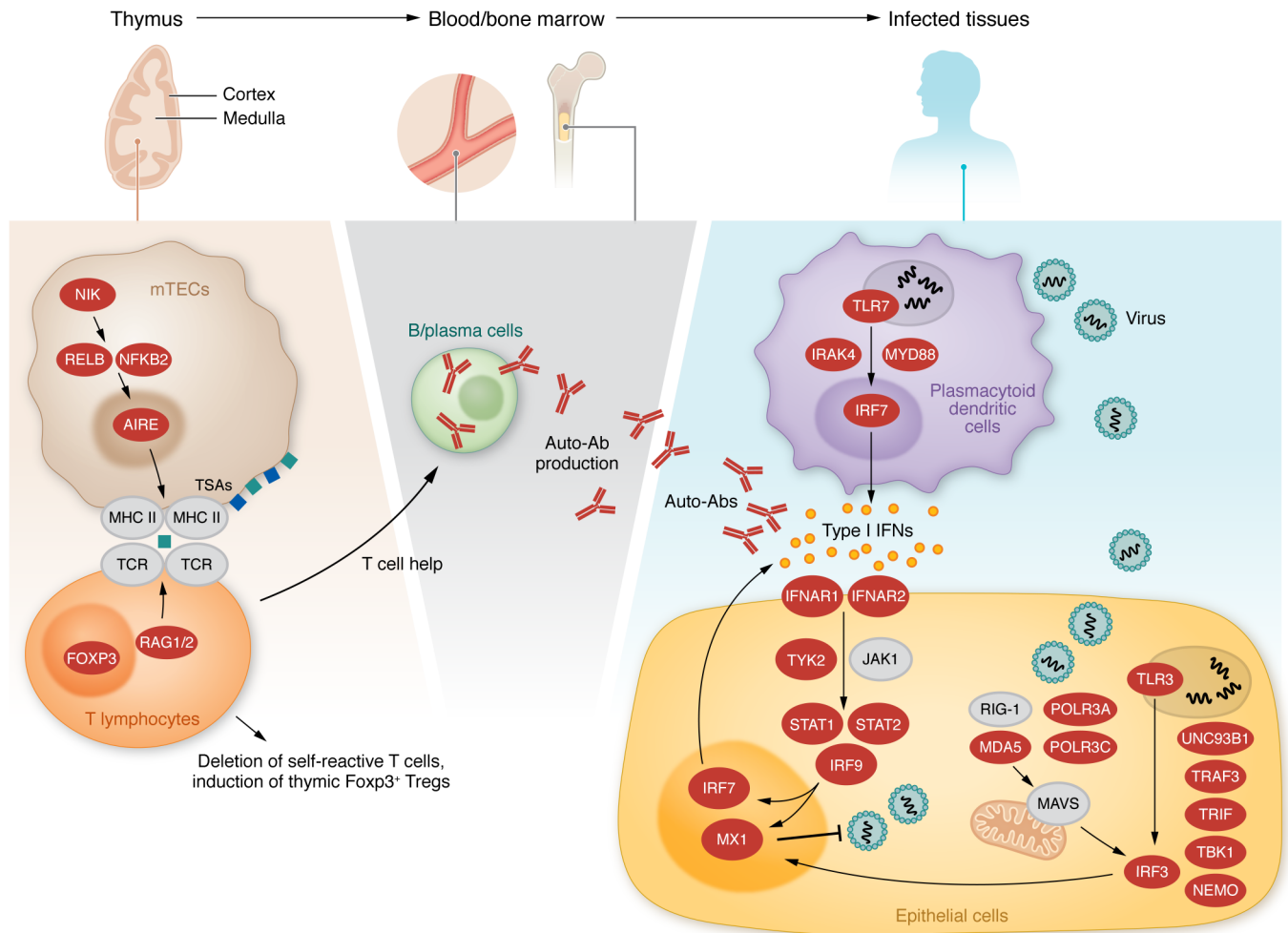
AIV, avian influenza virus; AV, adenovirus; EBV, Epstein-Barr virus; EV, enterovirus; CMV, cytomegalovirus; HHV6, human herpesvirus 6; HSV, herpes simplex virus; MC, molluscum contagiosum; MV, measles virus; PI3, parainfluenza virus 3; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus; TBE, tick-borne encephalitis; VZV, varicella zoster virus; XR, X-linked recessive.

activating factor–dependent (GAF-dependent) and IFN-stimulated gene factor 3–dependent (ISGF3-dependent) responses to type I, II, and III IFNs, and to IL-27. In total, 24 patients with AR complete *STAT1* deficiency have now been reported (8). This condition is the most clinically severe inborn error of type I IFN immunity, with much more serious consequences than AR partial *STAT1* deficiency, which has been reported in eight other patients (8). Clinical presentation occurs early in life, and mortality is high. It predisposes patients to a broad range of viral diseases (Table 1). However, it was soon noted that these patients were, paradoxically, not particularly vulnerable to certain common viral infections (9). Only 13 patients with AR complete *STAT2* deficiency (10–16) and two with AR complete IFN regulatory factor 9 (*IRF9*) deficiency (17–19) have been reported. The selective impairment of downstream ISGF3-dependent type I and III IFN responses, with intact GAF-dependent type I, II, and III IFN immunity, probably accounts for the milder clinical phenotype of these patients. They present with a globally and individually narrower range of viral diseases (Table 1).

**Inborn errors of *IFNAR1* and *IFNAR2*.** Evidence that the viral diseases of *STAT2*- and *IRF9*-deficient patients result from deficiencies of type I IFN immunity is provided by the similarity of their viral infections to those seen in patients with AR *IFNAR1* (7, 20–25) or *IFNAR2* (26–29) deficiency. As many as 18 patients with AR *IFNAR1* deficiency, and eight with AR *IFNAR2* deficiency,

have been reported. These patients are rare globally, but about 1 in 1,000 individuals of Western Polynesian or Inuit ancestry are *IFNAR1* or *IFNAR2* deficient, respectively, owing to the presence of null *IFNAR1* and *IFNAR2* alleles, which are surprisingly “common” (defined as a minor allele frequency greater than 1%) in the Pacific and Arctic regions (22, 29, 30). Surprisingly, only a few viral diseases have been reported in patients with *IFNAR1* or *IFNAR2* deficiency (Table 1). The most striking wild-type viral illnesses in these patients prior to the COVID-19 pandemic have been HSE and critical influenza. Remarkably, the patients are resistant to most common viruses. The number of patients, their diversity, the small range of viral diseases, their incomplete penetrance, and the occurrence of common deleterious alleles in at least three ancestries all converge to suggest that human type I IFNs are essential for host defense against only a small range of viruses. This observation suggests that there are type I IFN-independent mechanisms of cell-intrinsic antiviral immunity, which may include tissue- and virus-specific restriction factors (31–33).

**Inborn errors of *JAK1* and *TYK2*.** *IFNAR1* is constitutively associated with *JAK1* and *IFNAR2* is constitutively associated with tyrosine kinase 2 (*TYK2*) (15) in their respective signaling pathways, and patients with AR deficiencies of *JAK1* or *TYK2* have been reported. AR *JAK1* deficiency has been reported only as a partial form in a single patient, who presented a few viral diseases-



**Figure 1. Inborn errors of type I IFN immunity or tolerance.** Left, middle: Variants in genes expressed in thymic medullary epithelial cells, indicated in red, are linked to a defect in T cell selection and the production of type I IFN autoantibodies. Right: Variants in genes indicated in red alter type I IFN induction and response pathways.

es due to its impact on type I IFNs (34, 35). In total, 40 patients with AR TYK2 deficiency have been reported since 2006 (36–41). Two of these patients had a partial defect across pathways, 25 had a complete defect (with or without expression), 3 had a rare selective defect of the IL-23 pathway, and about 1 in 500 individuals of European descent were homozygous for the *TYK2* P1104A variant, which also selectively impairs responses to IL-23. All had severe mycobacterial disease due to impaired responses to IL-23. The cellular response to type III IFN of these AR TYK2-deficient patients appears to be maintained, and responses to type I IFNs are only partially affected, and only in patients with complete or partial TYK2 deficiency, 60% of whom had viral disease (41). Residual type I IFN signaling probably accounts for the relative rarity and benign nature of their viral diseases (Table 1) (16, 41).

**Inborn errors of *NEMO*, *TBK1*, *IRF3*, and *IRF7*.** Type I IFNs are induced when cells are stimulated or infected, with or without viral replication, and rely on a family of transcription factors and regulators for their production. An AR deficiency in *IRF7*, a key transcriptional regulator of type I IFNs, was first reported in a 3-year-old child with critical influenza pneumonia (42). AR *IRF7* deficiency was recently reported in six other patients from five families

(43). Intriguingly, the viral infection phenotype of these patients was restricted to the respiratory tract (Table 1). It is possible that residual IFN- $\beta$  levels account for the better control of viruses in these patients than in patients with *IFNAR1* or *IFNAR2* deficiency, despite the lack of *IRF7*-dependent induction of type I and III IFNs. Adaptive immunity to viruses may also compensate for the defects of type I IFN immunity in these patients (43). In contrast, a child with an autosomal dominant (AD) and partial form of *IRF3* deficiency has been reported to have HSE (44). A defect further upstream in the type I IFN-inducing cascade, AD TANK-binding kinase 1 (*TBK1*) deficiency, also underlies HSE (45). Paradoxically, AR *TBK1* deficiency was found to underlie an autoinflammatory condition in four patients aged 7 to 32 years with no history of severe viral disease (46). Finally, a boy with HSE and a specific variant in *NEMO*, encoding the regulatory component of the IKK complex in the canonical NF- $\kappa$ B pathway, has also been reported (47, 48). The mechanism probably involves the disruption of the induction of type I IFN, probably via its impact on IFN- $\beta$ .

**Inborn errors of *TLR3*, *TRIF*, *UNC93B*, *MDA5*, and *POLR3A/C*.** The triggering of type I IFN production frequently relies on viral sensing receptors and their regulators. AR defects of *TLR3*, *TRIF*/

**Table 2. Seven inborn errors of type I IFN tolerance**

Gene	Year	Inheritance	Viral infections					
			YFV-17D	MMR/MMRV	HSE	Influenza	COVID-19	Other
<i>AIRE</i>	1998	AR, AD	NA	No	No	No	Yes (109, 116, 129–131)	VZV (110)
<i>NIK</i>	2017	AR	NA	No	No	No	Yes (180)	No
<i>NFKB2</i>	2013	AD	NA	No	No	Yes	Yes (180)	VZV (180)
<i>RELB</i>	2015	AR	NA	No	No	No	Yes (180)	VZV (180)
<i>FOXP3</i>	2000	XR	NA	No	No	No	NA	No
<i>RAG1</i> and <i>RAG2</i>	1998	AR	NA	Yes	No	Yes (180)	NA	VZV, CMV, RV, RSV (121)

TICAM1, or UNC93B underlie forebrain HSE (Table 1) (49–52) with a penetrance higher than that of the corresponding AD forms of TLR3 and TRIF deficiency (49, 51–53). TLR3 is an endosomal sensor of double-stranded RNA (dsRNA), which is generated as an intermediate or by-product of viral infection. It also controls the tonic, baseline levels of type I IFN in fibroblasts and cortical neurons, and possibly also in respiratory epithelial cells, with the potential involvement of hitherto unknown endogenous agonists (54). TRIF/TICAM1 is an adaptor and UNC93B is a binding partner in the secretory pathway. TRIF binds almost exclusively to TLR3 (and TLR4), whereas UNC93B is also required for responses to the other three endosomal sensors of nucleic acids, TLR7, TLR8, and TLR9. AR MDA5 deficiency is less rare in the general population, as at least one loss-of-function (LOF) allele has a frequency of almost 1%. However, only four patients with this deficiency have been reported (55–57); three of these unrelated patients presented with respiratory viral diseases other than influenza (55, 57), and the fourth presented with brainstem enterovirus encephalitis (56). TLR3 senses dsRNA in endosomes, whereas MDA5 senses dsRNA in the cytosol. Finally, variants of the genes encoding the dsDNA sensor subunits A and C of RNA polymerase III (POLR3A and POLR3C) have been reported in patients with varicella zoster virus encephalitis (58).

**Inborn errors of TLR7, IRAK4, and MyD88.** Other inborn errors of type I IFN immunity affect the sensing of single-stranded RNA (ssRNA) rather than dsRNA. Almost all patients with AR IRAK4 or MyD88 deficiency described between 2003 and 2019 exhibited pyogenic bacterial infections, but not viral infections (59, 60). Two exceptions were patients with human herpesvirus 6 encephalitis (61, 62). This led to the suggestion that human TLR7, TLR8, and TLR9, which are endosomal sensors of nucleic acids and which all depend on IRAK4 and MyD88 for their signaling, were redundant for host defense against most current and common viruses (59, 60). Moreover, patients with AR UNC93B deficiency, whose cells cannot respond to TLR3, TLR7, TLR8, and TLR9, were found to be prone to HSE, like patients with TLR3 deficiency (49). This further suggested that TLR7, TLR8, and TLR9 were largely redundant in host defense (49). This idea was paradoxical, because the genes encoding the four endosomal TLRs sensing nucleic acids, including TLR3, were under stronger negative selection than those encoding the other TLRs (63). As detailed below, this riddle was solved when X-linked recessive TLR7 deficiency was found to be a genetic etiology of critical COVID-19 pneumonia (64). Patients

with IRAK4 or MyD88 deficiency were subsequently found to be at very high risk of life-threatening COVID-19 pneumonia (65). These findings are consistent with the demonstration that plasmacytoid dendritic cells (pDCs) are dependent on IRAK4 and TLR7 for SARS-CoV-2 sensing and type I IFN production (64, 66) and with the observation that patients with chronic lymphocytic leukemia have diminished counts of pDCs and are prone to hypoxemic COVID-19 pneumonia (67).

**Inborn errors of MX1.** The first human inborn error of an IFN-stimulated gene (ISG) to be described was AR ISG15 deficiency (68). The patients did not have viral disease, and their cells were even found to be unusually resistant to viral infection (69). These cells have abnormally high levels of type I IFN activity in vivo, and the patients present a type I interferonopathy manifesting with brain calcifications (69). The underlying mechanism involves unchecked USP18- and STAT2-dependent regulation of the type I IFN response pathway, as confirmed by the identification of patients homozygous for *STAT2* variants disrupting the interaction of STAT2 with USP18 (70–72) and of patients with complete or partial AR USP18 deficiency (73–75), who also have a type I interferonopathy. Paradoxically, the first two recessive disorders of ISGs (ISG15 and USP18 deficiencies) underlie a type I interferonopathy that can potentially increase resistance to viruses. It was not until 2021 that an AD form of MX1 deficiency was reported in Chinese patients with critical disease due to avian influenza virus (76). The IFN-induced GTPase MX1 was first identified by complementation studies in 1986 as essential for immunity to influenza virus in various mouse strains (77). This seminal discovery launched the search for susceptibility genes for host infection (78). Thirty-five years later, an enrichment in rare germline variants of *MX1* was found in Chinese patients with severe avian influenza (76). Most of these LOF variants are also dominant negative.

### Inborn errors of type I IFN tolerance

**APS-1: clinical features and history.** A separate line of research led to the discovery of autoantibodies (auto-Abs) against type I IFNs that impair their activity (Table 2 and Figure 1). Most if not all patients with autoimmune polyglandular syndrome type 1 (APS-1; OMIM #240300), also known as autoimmune polyendocrinopathy ectodermal dystrophy (APECED), develop a defect of type I IFN immunity through an acquired autoimmune response to type I IFNs (79). APS-1 was first described clinically in 1943 (80). It is characterized by the development of multiple

organ-specific autoimmune diseases in a single patient, and its inheritance is typically AR. It is globally rare (1 in 200,000), but with a prevalence at least 10 times higher in Scandinavia (1 in 14,000), due to founder effects (81). Autoimmune features vary between individual patients, but the most common clinical features are Addison's disease, hypoparathyroidism, and an unusually selective susceptibility to chronic mucocutaneous candidiasis (CMC). This core triad is seen in about 75% of patients. Even within families, the autoimmune conditions that develop may differ between affected relatives. The management of APS-1 patients typically involves supportive care and, frequently, replacement therapy for affected organs, with immunosuppression occasionally used to treat more severe features, such as autoimmune hepatitis (82). The overall clinical outcome of APS-1 patients is highly variable, but mortality reaches 50% by the age of 45 years, typically due to the cumulative effect of multiple disease features and their sequelae (83).

*The discovery linking AIRE to APS-1.* Given the typical AR pattern of inheritance for APS-1, physical linkage approaches mapped the defective gene to human chromosome 21 in 1994 (84). Continuing with this laborious linkage approach, two groups simultaneously reported the identification of the defective gene in 1997. It was agreed to name the gene "autoimmune regulator" (*AIRE*), given the clinical phenotype of APS-1 patients (85, 86). This new gene displayed no marked sequence similarity to any known gene and was thought to encode a 545-amino acid protein with at least four distinct domains. Analysis of the sequence of the *AIRE* gene indicated that it contained a nuclear localization domain (85, 86). In addition, staining for the protein resulted in a speckled nuclear pattern in cells actively expressing the gene (87). This critical gene hunt paved the way for the unlocking of a critical regulator of immune tolerance, because patients with this disease harbored variants predicted to be loss-of-function (e.g., nonsense variants) when homozygous. It was not until 2014 that heterozygous and dominant-negative variants of *AIRE* were found to underlie an AD form of APS-1, in both multiplex and sporadic families (88–90), typically with a milder phenotype.

*Immunological role of the AIRE gene product.* Major clues to the function of *AIRE* were initially provided by studies mapping its expression to the thymus and, particularly, to the medullary thymic epithelial cells (mTECs) (91). A knockout mouse model was developed that also presented multiple autoimmune conditions (91). A detailed analysis of mTECs in the knockout mouse gave rise to a model in which *AIRE* promotes the expression of a wide array (i.e., thousands) of tissue-specific self-antigens (TSAs), all expressed in isolated tissues (91, 92). Another interesting picture of gene expression is being unraveled in mTECs, a fraction of which further differentiate after *AIRE* expression and acquire a gene expression program reflective of some peripheral tissues, including enteroendocrine, respiratory epithelium, mature skin epithelium, and tuft cells, that also contribute to TSA expression (93–96). During development, thymocytes traffic through the medullary compartment, where these cells undergo a critical negative selection step in which self-reactive T cells are eliminated by the recognition of self-antigens in the medulla. *AIRE* controls T cell immune tolerance by driving the expression of "self" within the medulla such that self-reactive T cells that develop by chance

can recognize self and be eliminated from the developing T cell pool (Figure 1). *AIRE* can also promote the development of a fraction of CD4<sup>+</sup> Foxp3<sup>+</sup> Tregs protective against autoimmunity in the periphery (97). Studies in mice have clearly established that this elegant thymic selection process is remarkably efficient and frequently results in the deletion of tissue-specific T cells (98). Interestingly, recent single-cell studies of the human thymus have also demonstrated that TSAs are expressed in *AIRE*-expressing cells within the thymus and that these cells frequently express the targets of the autoimmune response in APS-1 patients (94).

*Mechanisms of autoimmune endocrine and fungal diseases.* The core mechanism of disease in APS-1 patients is T cell driven, but tissue damage is often associated with tissue-specific auto-Abs. Endocrine disease in APS-1 patients is mostly driven by a T cell-mediated destruction of the affected organ, and mouse models have provided support for a prominent Th1-like response in affected tissues (99). APS-1 patients can develop a wide array of autoimmune responses, but, unexpectedly, some of these responses were found to be directed against cytokines. As mentioned above, CMC is an intriguing prominent condition in APS-1 patients. CMC develops in these patients due to an autoimmune response directed against crucial Th17 cytokines, such as IL17A and IL17F, with auto-Abs neutralizing both these cytokines detected in most patients (100, 101). This autoimmune connection is further bolstered by data showing that candidiasis frequently develops in patients with germline variants affecting IL-17A/F and its IL17RA/RC receptor (102) and in patients treated with blocking antibodies against these cytokines for inflammatory conditions (103). These findings suggest that most if not all of the clinical features of APS-1 patients, including their characteristic isolated fungal infection, are of an autoimmune nature.

*"Silent" auto-Abs against type I IFNs.* It was reported from 2006 onward that more than 90% of patients with APS-1 develop auto-Abs against type I IFNs (104). They have also been found in patients with myasthenia gravis, thymoma, and systemic lupus erythematosus, and in individuals treated with IFN- $\alpha$ 2 or IFN- $\beta$  (105–108). The clinical significance of these auto-Abs generally, and in APS-1 patients in particular, remained unknown, as patients with these auto-Abs displayed no consistent susceptibility to viral infections. The auto-Abs against type I IFNs observed in individuals with APS-1 are almost exclusively directed against the 13 IFN- $\alpha$  forms and the single  $\omega$  form, rarely against IFN- $\beta$ , and apparently not against  $\epsilon$  and  $\kappa$  (104). This pattern was identified as a possible reason for the lack of overt association of these antibodies with a viral susceptibility phenotype. IFN- $\beta$ , in particular, is the first type I IFN induced by viruses in most cells. As detailed below, it was not until 2020 that APS-1 patients were found to be at very high risk of critical COVID-19 pneumonia and even other viral diseases (109, 110). The high prevalence of auto-Abs against type I IFNs in patients with APS-1 and thymoma suggests that defects of thymus function may trigger this specific autoimmune response. In support of this notion, *AIRE* expression has been shown to be impaired in thymoma, connecting the mechanism of autoimmunity in patients with inherited APS-1 with acquired thymoma (111).

*Other mTEC etiologies of auto-Abs against type I IFNs.* *AIRE* expression in mouse mTECs is driven by RANK via the alternative NF- $\kappa$ B pathway (Figure 1) (111–114). Consistently, auto-Abs

against type I IFNs were found in patients with AR NIK or RELB deficiencies, and patients with a specific form of AD NF- $\kappa$ B deficiency due to C-terminal variants preventing the cleavage of p100 into p52, resulting in a loss of p52 activity but a gain of inhibitory function for p100 (115). Moreover, *AIRE* expression in the thymus was found to be impaired in the patients with *RELB* or *NFKB2* variants studied. Deficiencies of the alternative NF- $\kappa$ B pathway can, therefore, underlie the production of auto-Abs against type I IFNs through an impairment of *AIRE* expression in mTECs. By contrast, the patients with inborn errors of canonical NF- $\kappa$ B immunity tested had no auto-Abs against type I IFNs. However, most women with incontinentia pigmenti due to heterozygosity for LOF *NEMO* variants do have such auto-Abs, possibly due to the apoptosis of mTECs expressing the mutated *NEMO* allele during thymic development (116). Collectively, these findings suggest that *AIRE*-dependent thymic dysfunctions (deleterious variants of *AIRE* or the genes encoding components of the *AIRE*-inducing pathway in mTECs, or locally, within a thymoma) may underlie the production of auto-Abs against type I IFNs.

**Other T cell etiologies of auto-Abs against type I IFNs.** Several T cell-intrinsic inborn errors have also been found to underlie auto-Abs against type I IFNs. Male patients with deleterious variants of the X-linked gene *FOXP3*, who display a loss of functional Tregs, often carry auto-Abs against type I IFNs (117). They present with a condition known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) (118, 119), which has autoimmune and clinical features partly overlapping with those of APS-1 (120). They have not been reported to have severe viral disease, at least before immunosuppressive therapy for hematopoietic stem cell transplantation. Patients with *RAG1* or *RAG2* deleterious variants and combined immunodeficiency may also produce auto-Abs against type I IFNs (121). These patients frequently have herpes virus diseases, due to the presence of these auto-Abs against type I IFNs alone or together with the combined T and B cell deficiency. The known etiologies of auto-Abs against type I IFN thus affect T cell tolerance, in a T cell-intrinsic manner (*RAG*, *FOXP3*) or via mTECs (*AIRE* and the pathway that induces it). *AIRE* defects are linked to impairment of the correct selection of Tregs (97), and defects of *RAG1* and *RAG2* are linked to impairment of the expression of *AIRE* (122). Together, these data again link the generation of auto-Abs against type I IFNs to thymic selection.

## Critical COVID-19 pneumonia and type I IFN deficiency

**The problem, hypothesis, and approach.** The key problem posed by COVID-19 in 2020 is common to all human pathogens: what drives the vast interindividual clinical variability observed during infection (78, 123)? The global infection fatality rate (IFR) of COVID-19 in unvaccinated individuals was about 1% across all ages and sexes. The risk of death was found to double every 5 years of age, from childhood onward, accounting for the risk of death being 10,000 times greater at age 85 than at age 5 (124). We hypothesized that critical COVID-19 pneumonia might result from single-gene inborn errors of immunity, at least in some patients (125). The identification of a causal inborn error, even in a single patient, might be sufficient to pull the mechanistic thread to reveal other causes disrupting the same physiological mechanisms in other patients (78).

The COVID Human Genetic Effort ([www.covidhge.com](http://www.covidhge.com)) was set up to follow this approach and to enroll as many patients as possible worldwide, such that even low levels of genetic homogeneity could be detected (125). The phenotypes and genotypes of the patients were made available to all the teams of the consortium, facilitating coordinated and synergistic research into the human genetic and immunological determinants of critical COVID-19.

**Inborn errors of immunity to influenza and candidate genes.** The first hypothesis tested was that critical pneumonia due to seasonal influenza virus and critical pneumonia due to SARS-CoV-2 might be allelic. Patients with AR IRF7 deficiency, AR IRF9 deficiency, and AR or AD TLR3 deficiency were prone to severe influenza (126). Another ten genes were considered, with (a) products biochemically and immunologically connected to the three core influenza susceptibility genes and (b) germline variants already shown to underlie other severe viral illnesses (Figure 1). The genes considered included those encoding STAT1 and STAT2, which were soon confirmed to be influenza susceptibility genes (8, 14). Rare and deleterious variants of 8 of the 13 candidate genes were found in 23 patients with critical COVID-19 pneumonia. Eleven patients had known dominant disorders, whereas eight had potentially new dominant disorders. These findings were replicated in a larger cohort (127). Germline variants affecting the TLR3 pathway suggested that tonic type I IFN levels in respiratory epithelial cells (RECs) played an important role in host defense against SARS-CoV-2 (54). Four patients with AR defects provided unique insight into the pathogenesis of COVID-19. Two unrelated adults were found to have AR IFNAR1 deficiency, while another two had AR IRF7 deficiency (23). Other patients with critical COVID-19 due to AR IFNAR1 (16, 24, 25) or AR IRF7 (43) deficiency were later reported, as well as a patient with AR TBK1 deficiency (128). Remarkably, the young and even middle-aged adults with such profound AR deficits identified had remained well until they developed COVID-19.

**Genome-wide search: TLR7 and type I IFN again.** A burden test on the X chromosome found an enrichment in rare non-synonymous variants at a single locus encoding the endosomal RNA sensor TLR7 (64). The lack of enrichment at the X-linked *TLR8* locus suggested not only that most TLR7 variants were deleterious and pathogenic, but also that the mechanism of disease involved a disruption of the TLR7-dependent induction of type I IFN by pDCs. Indeed, TLR7 and TLR8 are both endosomal sensors of overlapping RNAs, and both signal via the MyD88- and IRAK4-dependent signaling pathway, which had already been shown to be essential for SARS-CoV-2 sensing in pDCs; however, TLR7 is expressed in pDCs, whereas TLR8 is not (66). Further experiments showed that most TLR7 variants in patients with critical COVID-19, but none of those in mildly infected individuals, were LOF. Penetrance was incomplete among relatives of index cases. TLR7-deficient pDCs had profoundly impaired responses to SARS-CoV-2 (64). X-linked recessive TLR7 deficiency was found in about 1% to 2% of male patients with critical COVID-19. The proportion of adults with critical pneumonia due to these 14 inborn errors, including autosomal defects, was about 3% to 5%, while about 10% of children with COVID-19 pneumonia had recessive deficiencies not only of TLR7 and IRF7, but also of STAT2 and TYK2 (16). An unbiased, genome-wide approach yet again implicated defects of type I IFN immunity. TLR3 pathway variants had implicated resident RECs, but TLR7 variants implicat-

ed circulating pDCs, implying that the recruitment of these cells to the respiratory tract during SARS-CoV-2 infection was essential for type I IFN-mediated protective immunity.

*APS-1 patients and hypoxemic COVID-19 pneumonia.* Early in the COVID-19 pandemic, several patients with APS-1 developed critical COVID-19 pneumonia (116, 129). Given this knowledge and the identification of inborn errors of type I IFNs in other patients with critical COVID-19, a unifying hypothesis developed according to which the susceptibility to critical COVID-19 pneumonia of APS-1 patients was due to their preexisting auto-Abs against type I IFN. In an international series of 22 APS-1 patients aged 8 to 48 years, 86% had hypoxemic pneumonia, including 68% with severe disease and 18% who died (109). A smaller, single-center study of four patients confirmed that not all patients with APS-1 infected with SARS-CoV-2 developed hypoxemic pneumonia (130), while a more recent study reported several other APS-1 patients with critical COVID-19 (131). Importantly, the auto-Abs against type I IFNs were present in the APS-1 patients before their infection with SARS-CoV-2 and the development of COVID-19 pneumonia. Given that inborn errors of type I IFN immunity have been shown to be causal for critical pneumonia, these findings provided proof of principle that auto-Abs neutralizing type I IFN may also be causal for critical pneumonia. This rare disease therefore provided a key insight into one of the possible mechanisms underlying the development of severe course of COVID-19 in some subjects.

*Auto-Abs against type I IFNs in patients with critical COVID-19.* Remarkably, about 10% of patients with critical COVID-19 carried circulating auto-Abs neutralizing high concentrations of IFN- $\alpha$  and/or IFN- $\omega$  (116). This proportion was subsequently found to be higher (15%) if patients whose plasma neutralized lower concentrations were considered (132). Auto-Abs neutralizing IFN- $\beta$  were rarely found. Patients with auto-Abs against type I IFNs collectively accounted for 20% of deaths across age groups and 20% of critical cases among patients over 70 years of age. The risk of critical disease increased with both the number of forms of type I IFN and the concentration of IFN neutralized (132, 133). These findings have been replicated in 29 independent populations worldwide (109, 130, 131, 134–159). These auto-Abs have also been shown to underlie a delayed type I IFN ISG response in leukocytes, as shown by single-cell RNA sequencing (156), and in the nasal mucosae, as shown by RNA-Seq (160). These auto-Abs were detected in blood samples drawn very early during hospitalization (156) and even in pre-COVID-19 samples for the small number of patients for whom such samples were available. Their levels in the blood may increase during COVID-19 (136, 161). Their prevalence was studied in 33,000 individuals aged 20 to 100 years for whom samples collected before 2019 were available (132). Their prevalence remained stable until the age of 65 years, between 0.3% and 1% depending on the concentrations neutralized, subsequently increasing to reach 4% and 7%, respectively, after the age of 80 years (132). The prevalence of auto-Abs neutralizing IFN- $\beta$  remained stable, at about 0.2%, across age groups. These findings suggest that the IFR is much greater in individuals with auto-Abs than in those without these antibodies (133).

*Developing a clinical test: risk stratification and treatment approaches.* The presence of these auto-Abs is the second most important common risk factor for critical COVID-19 after age. If the risk associated with age and the risk associated with the pres-

ence of auto-Abs against type I IFNs are combined, the effective mortality rate for COVID-19 can reach levels well over 50% in subjects over 80 years old carrying auto-Abs against type I IFNs (133). This provides a strong argument for testing for these antibodies in the initial assessment of patients diagnosed with COVID-19, especially, but not exclusively, in those who have not been vaccinated. We recently found that about 20% of cases of “breakthrough” hypoxemic pneumonia were due to auto-Abs neutralizing high concentrations of both IFN- $\alpha$  and - $\omega$ , despite good antibody responses to the RNA vaccine and a normal capacity to neutralize the virus (162, 163). The development of a simple screening test in the clinical setting for widespread deployment with a quick turnaround time is warranted. A positive result on such a test in healthy individuals would have implications for vaccination (influenza, COVID-19) and follow-up, and would contraindicate certain other vaccinations (e.g., the yellow fever vaccine YFV-17D). It would also have implications for rapid correct treatment in patients diagnosed with specific viral infections. For example, it will be interesting to see whether IFN- $\beta$  treatment is a feasible approach (116). Recent trials with IFN- $\beta$  revealed little evidence of the benefit of such treatment in hospitalized patients (164), but trials in an ambulatory setting are warranted.

*A general mechanism of viral disease.* Auto-Abs neutralizing type I IFN were recently shown to underlie severe herpes simplex or zoster virus disease in patients hospitalized for COVID-19 (137). These findings are consistent with the seminal report by Ion Gresser and colleagues of auto-Abs against type I IFN in a 77-year-old woman with disseminated shingles (165) and with the occurrence of such viral infections in patients bearing deleterious genotypes of *RAG1* or *RAG2* or carrying such auto-Abs (121). A similar observation was recently made in a large cohort of patients with systemic lupus erythematosus (SLE) (148). Moreover, one-third of the small series of patients with adverse reactions to the live attenuated YFV-17D vaccine had such auto-Abs (28). Remarkably, these patients included a young woman subsequently diagnosed with SLE, an elderly woman, and an elderly man. These three groups are at risk of producing auto-Abs against type I IFNs and had already been shown to be at greater risk of adverse reactions to YFV (166). Finally, about 5% of patients under 70 years of age carried such auto-Abs, and the estimated risk of critical influenza increased with the concentration and number of IFNs neutralized (167). Other candidate viral diseases for which auto-Abs against type I IFNs increase susceptibility include the viral infections seen in patients with inborn errors of type I IFN immunity. The evidence of a role of auto-Abs against type I IFNs is already clear for at least four viral illnesses: critical COVID-19 pneumonia, influenza pneumonia, adverse reactions to the YFV-17D vaccine, and recurrent or disseminated shingles.

## Concluding remarks

The discovery of inborn errors of type I IFNs and auto-Abs against these cytokines in at least 15% to 20% of patients with critical COVID-19 pneumonia suggested a unifying general mechanism of disease (78, 124). The “common” COVID-19 enigma was cracked thanks to previous studies conducted over several decades on two groups of patients with “rare” and seemingly opposite Mendelian phenotypes: infectious and autoimmune (78). This rare-to-common, patient-to-population, genetic-to-mechanism approach (78,

124, 168) contrasts with other approaches. The population-based approach to COVID-19, in which this “common disease” is tackled via purely mathematical (genetic association studies) or purely immunological (blood or mucosal multi-omics) approaches, met with less success. Rather than detecting the immunological causes of viral disease, the latter studies analyzed immune responses to the virus (124). Rather than detecting the genetic causes of viral disease in individual patients, the former studies detected common modifiers of disease at the population level. We argue that, with the splitters’ approach, focusing on individual patients and “rare diseases,” particularly in young patients, with individual human beings seen as single organisms, it can be possible subsequently to lump patients with different causes of disease via shared mechanisms together. By contrast, with the lumpers’ approach, focusing on large populations and “common diseases,” mostly in elderly populations, it is not easy to split patients into different groups later, owing to the lack of unambiguously identified causes and mechanisms of disease. Studies of “rare” outliers constitute a powerful approach that can be used to guide the exploration of “common” diseases, whether viral or otherwise (78, 168–171).

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- Conley ME. Genetic immunodeficiencies: both the lumpers and the splitters can claim victory. *Curr Opin Immunol.* 1992;4(4):490–493.
- Endersby J. Lumpers and splitters: Darwin, Hooker, and the search for order. *Science.* 2009;326(5959):1496–1499.
- McKusick VA. On lumpers and splitters, or the nosology of genetic disease. *Perspect Biol Med.* 1969;12(2):298–312.
- Smith CIE, et al. Estimating the number of diseases — the concept of rare, ultra-rare, and hyper-rare. *iScience.* 2022;25(8):104698.
- Chung BHY, et al. Rare versus common diseases: a false dichotomy in precision medicine. *NPJ Genom Med.* 2021;6(1):19.
- Dupuis S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet.* 2003;33(3):388–391.
- Bastard P, et al. Herpes simplex encephalitis in a patient with a distinctive form of inherited IFNAR1 deficiency. *J Clin Invest.* 2021;131(1):e139980139980.
- Le Voyer T, et al. Genetic, immunological, and clinical features of 32 patients with autosomal recessive STAT1 deficiency. *J Immunol.* 2021;207(1):133–152.
- Chaggier A, et al. Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. *J Immunol.* 2006;176(8):5078–5083.
- Hambleton S, et al. STAT2 deficiency and susceptibility to viral illness in humans. *Proc Natl Acad Sci U S A.* 2013;110(8):3053–3058.
- Moens L, et al. A novel kindred with inherited STAT2 deficiency and severe viral illness. *J Allergy Clin Immunol.* 2017;139(6):1995–1997.
- Shahni R, et al. Signal transducer and activator of transcription 2 deficiency is a novel disorder of mitochondrial fission. *Brain.* 2015;138(pt 10):2834–2846.
- Alosaimi MF, et al. A novel variant in STAT2 presenting with hemophagocytic lymphohistiocytosis. *J Allergy Clin Immunol.* 2019;144(2):611–613.
- Freij BJ, et al. Life-threatening influenza, hemophagocytic lymphohistiocytosis and probable vaccine-strain varicella in a novel case of homozygous STAT2 deficiency. *Front Immunol.* 2020;11:624415.
- Meys I, Casanova JL. Viral infections in humans and mice with genetic deficiencies of the type I IFN response pathway. *Eur J Immunol.* 2021;51(5):1039–1061.
- Zhang Q, et al. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. *J Exp Med.* 2022;219(8):e20220131.
- Hernandez N, et al. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. *J Exp Med.* 2018;215(10):2567–2585.
- Bravo Garcia-Morato M, et al. Impaired control of multiple viral infections in a family with complete IRF9 deficiency. *J Allergy Clin Immunol.* 2019;144(1):309–312.
- Levy R, et al. Monoclonal antibody-mediated neutralization of SARS-CoV-2 in an IRF9-deficient child. *Proc Natl Acad Sci U S A.* 2021;118(45):e2114390118.
- Hernandez N, et al. Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. *J Exp Med.* 2019;216(9):2057–2070.
- Gothé F, et al. A novel case of homozygous IFNAR1 deficiency with haemophagocytic lymphohistiocytosis. *Clin Infect Dis.* 2022;74(1):136–139.
- Bastard P, et al. A loss-of-function IFNAR1 allele in Polynesia underlies severe viral diseases in homozygotes. *J Exp Med.* 2022;219(6):e20220028.
- Zhang Q, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science.* 2020;370(6515):eabd4570.
- Abolhassani H, et al. Inherited IFNAR1 deficiency in a child with both critical COVID-19 pneumonia and multisystem inflammatory syndrome. *J Clin Immunol.* 2022;42(3):471–483.
- Khanmohammadi S, et al. A case of autosomal recessive interferon alpha/beta receptor alpha chain (IFNAR1) deficiency with severe COVID-19. *J Clin Immunol.* 2022;42(1):19–24.
- Duncan CJ, et al. Human IFNAR2 deficiency: lessons for antiviral immunity. *Sci Transl Med.* 2015;7(307):307ra154.
- Passarelli C, et al. IFNAR2 deficiency causing dysregulation of NK cell functions and presenting with hemophagocytic lymphohistiocytosis. *Front Genet.* 2020;11:937.
- Bastard P, et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. *J Exp Med.*



- 2021;218(4):e20202486.
29. Duncan CJA, et al. Life-threatening viral disease in a novel form of autosomal recessive IFNAR2 deficiency in the Arctic. *J Exp Med.* 2022;219(6):e20212427.
  30. Meyts I. Null IFNAR1 and IFNAR2 alleles are surprisingly common in the Pacific and Arctic. *J Exp Med.* 2022;219(6):e20220491.
  31. Nathan C. Rethinking immunology. *Science.* 2021;373(6552):276–277.
  32. Paludan SR, et al. Constitutive immune mechanisms: mediators of host defence and immune regulation. *Nat Rev Immunol.* 2021;21(3):137–150.
  33. Zhang SY, et al. Human inborn errors of immunity to infection affecting cells other than leukocytes: from the immune system to the whole organism. *Curr Opin Immunol.* 2019;59:88–100.
  34. Eletto D, et al. Biallelic JAK1 mutations in immunodeficient patient with mycobacterial infection. *Nat Commun.* 2016;7:13992.
  35. Daza-Cajigal V, et al. Partial human Janus kinase 1 deficiency predominantly impairs responses to interferon gamma and intracellular control of mycobacteria. *Front Immunol.* 2022;13:888427.
  36. Boisson-Dupuis S, et al. Tuberculosis and impaired IL-23-dependent IFN- $\gamma$  immunity in humans homozygous for a common *TYK2* missense variant. *Sci Immunol.* 2018;3(30):eaau8714.
  37. Fuchs S, et al. Tyrosine kinase 2 is not limiting human antiviral type III interferon responses. *Eur J Immunol.* 2016;46(11):2639–2649.
  38. Kerner G, et al. Homozygosity for *TYK2* P1104A underlies tuberculosis in about 1% of patients in a cohort of European ancestry. *Proc Natl Acad Sci U S A.* 2019;116(21):10430–10434.
  39. Minegishi Y, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity.* 2006;25(5):745–755.
  40. Kreins AY, et al. Human *TYK2* deficiency: mycobacterial and viral infections without hyper-IgE syndrome. *J Exp Med.* 2015;212(10):1641–1662.
  41. Ogishi M, et al. Impaired IL-23-dependent induction of IFN- $\gamma$  underlies mycobacterial disease in patients with inherited *TYK2* deficiency. *J Exp Med.* 2022;219(10):e20220094.
  42. Ciancanelli MJ, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human *IRF7* deficiency. *Science.* 2015;348(6233):448–453.
  43. Campbell TM, et al. Respiratory viral infections in otherwise healthy humans with inherited *IRF7* deficiency. *J Exp Med.* 2022;219(12):e2022020210282022c.
  44. Andersen LL, et al. Functional *IRF3* deficiency in a patient with herpes simplex encephalitis. *J Exp Med.* 2015;212(9):1371–1379.
  45. Herman M, et al. Heterozygous *TBK1* mutations impair *TLR3* immunity and underlie herpes simplex encephalitis of childhood. *J Exp Med.* 2012;209(9):1567–1582.
  46. Taft J, et al. Human *TBK1* deficiency leads to autoinflammation driven by TNF-induced cell death. *Cell.* 2021;184(17):4447–4463.
  47. Audry M, et al. NEMO is a key component of NF- $\kappa$ B- and *IRF-3*-dependent *TLR3*-mediated immunity to herpes simplex virus. *J Allergy Clin Immunol.* 2011;128(3):610–617.
  48. Casanova JL, et al. Guidelines for genetic studies in single patients: lessons from primary immunodeficiencies. *J Exp Med.* 2014;211(11):2137–2149.
  49. Casrouge A, et al. Herpes simplex virus encephalitis in human *UNC-93B* deficiency. *Science.* 2006;314(5797):308–312.
  50. Guo Y, et al. Herpes simplex virus encephalitis in a patient with complete *TLR3* deficiency: *TLR3* is otherwise redundant in protective immunity. *J Exp Med.* 2011;208(10):2083–2098.
  51. Lim HK, et al. Recurrent herpes in herpes simplex encephalitis: high allelic heterogeneity and recurrence risk. *Neurology.* 2014;83(21):1888–1897.
  52. Sancho-Shimizu V, et al. Herpes simplex encephalitis in children with autosomal recessive and dominant *TRIF* deficiency. *J Clin Invest.* 2011;121(12):4889–4902.
  53. Liang F, et al. Recurrent herpes zoster ophthalmicus in a patient with a novel toll-like receptor 3 variant linked to compromised activation capacity in fibroblasts. *J Infect Dis.* 2020;221(8):1295–1303.
  54. Gao D, et al. *TLR3* controls constitutive IFN- $\beta$  antiviral immunity in human fibroblasts and cortical neurons. *J Clin Invest.* 2021;131(1):e134529134529.
  55. Asgari S, et al. Severe viral respiratory infections in children with *IFIH1* loss-of-function mutations. *Proc Natl Acad Sci U S A.* 2017;114(31):8342–8347.
  56. Chen J, et al. Inborn errors of *TLR3*- or *MDA5*-dependent type I IFN immunity in children with enterovirus rhombencephalitis. *J Exp Med.* 2021;218(12):e20211349.
  57. Lamborn IT, et al. Recurrent rhinovirus infections in a child with inherited *MDA5* deficiency. *J Exp Med.* 2017;214(7):1949–1972.
  58. Ogunjimi B, et al. Inborn errors in RNA polymerase III underlie severe varicella zoster virus infections. *J Clin Invest.* 2017;127(9):3543–3556.
  59. Picard C, et al. Pyogenic bacterial infections in humans with *IRAK-4* deficiency. *Science.* 2003;299(5615):2076–2079.
  60. von Bernuth H, et al. Pyogenic bacterial infections in humans with *MyD88* deficiency. *Science.* 2008;321(5889):691–696.
  61. Nishimura S, et al. *IRAK4* deficiency presenting with anti-NMDAR encephalitis and HHV6 reactivation. *J Clin Immunol.* 2021;41(1):125–135.
  62. Tepe ZG, et al. Inherited *IRAK-4* deficiency in acute human herpesvirus-6 encephalitis [published online October 7, 2022]. *J Clin Immunol.* <https://doi.org/10.1007/s10875-022-01369-4>.
  63. Quach H, et al. Different selective pressures shape the evolution of Toll-like receptors in human and African great ape populations. *Hum Mol Genet.* 2013;22(23):4829–4840.
  64. Asano T, et al. X-linked recessive *TLR7* deficiency in ~1% of men under 60 years old with life-threatening COVID-19. *Sci Immunol.* 2021;6(62):eabl4348.
  65. García-García A, et al. Inherited *MyD88* and *IRAK-4* deficiencies confer a predisposition to hypoxemic COVID-19 pneumonia. *J Exp Med.* In press.
  66. Onodi F, et al. SARS-CoV-2 induces human plasmacytoid dendritic cell diversification via *UNC93B* and *IRAK4*. *J Exp Med.* 2021;218(4):e20201387.
  67. Smith CIE, et al. Do reduced numbers of plasmacytoid dendritic cells contribute to the aggressive clinical course of COVID-19 in chronic lymphocytic leukaemia? *Scand J Immunol.* 2022;95(4):e13153.
  68. Bogunovic D, et al. Mycobacterial disease and impaired IFN- $\gamma$  immunity in humans with inherited *ISG15* deficiency. *Science.* 2012;337(6102):1684–1688.
  69. Zhang X, et al. Human intracellular *ISG15* prevents interferon- $\alpha/\beta$  over-amplification and autoinflammation. *Nature.* 2015;517(7532):89–93.
  70. Duncan CJA, et al. Severe type I interferonopathy and unrestrained interferon signaling due to a homozygous germline mutation in *STAT2*. *Sci Immunol.* 2019;4(42):eaav7501.
  71. Gruber C, et al. Homozygous *STAT2* gain-of-function mutation by loss of *USP18* activity in a patient with type I interferonopathy. *J Exp Med.* 2020;217(5):e20192319.
  72. Duncan CJA, Hambleton S. Human disease phenotypes associated with loss and gain of function mutations in *STAT2*: viral susceptibility and type I interferonopathy. *J Clin Immunol.* 2021;41(7):1446–1456.
  73. Martin-Fernandez M, et al. A partial form of inherited human *USP18* deficiency underlies infection and inflammation. *J Exp Med.* 2022;219(4):e20211273.
  74. Meuwissen ME, et al. Human *USP18* deficiency underlies type I interferonopathy leading to severe pseudo-TORCH syndrome. *J Exp Med.* 2016;213(7):1163–1174.
  75. Alshime F, et al. JAK inhibitor therapy in a child with inherited *USP18* deficiency. *N Engl J Med.* 2020;382(3):256–265.
  76. Chen Y, et al. Rare variant *MX1* alleles increase human susceptibility to zoonotic H7N9 influenza virus. *Science.* 2021;373(6557):918–922.
  77. Staeheli P, et al. Mx protein: constitutive expression in 3T3 cells transformed with cloned Mx cDNA confers selective resistance to influenza virus. *Cell.* 1986;44(1):147–158.
  78. Casanova JL, Abel L. From rare disorders of immunity to common determinants of infection: following the mechanistic thread. *Cell.* 2022;185(17):3086–3103.
  79. Ahonen P, et al. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med.* 1990;322(26):1829–1836.
  80. Sutphin A, et al. Five cases (three in siblings) of idiopathic hypoparathyroidism associated with moniliasis. *J Clin Endocrinol Metab.* 1943;3(12):625–634.
  81. Constantine GM, Lionakis MS. Lessons from primary immunodeficiencies: autoimmune regulator and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *Immunol Rev.* 2019;287(1):103–120.
  82. Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab.* 2006;91(8):2843–2850.
  83. Borchers J, et al. Patients with APECED have increased early mortality due to endocrine causes, malignancies and infections. *J Clin Endocrinol Metab.* 2020;105(6):e2207–e2213.
  84. Aaltonen J, et al. An autosomal locus causing autoimmune disease: autoimmune polyglandular

- disease type I assigned to chromosome 21. *Nat Genet.* 1994;8(1):83–87.
85. Aaltonen J, et al. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet.* 1997;17(4):399–403.
  86. Nagamine K, et al. Positional cloning of the APECED gene. *Nat Genet.* 1997;17(4):393–398.
  87. Heino M, et al. Autoimmune regulator is expressed in the cells regulating immune tolerance in thymus medulla. *Biochem Biophys Res Commun.* 1999;257(3):821–825.
  88. Oftedal BE, et al. Dominant mutations in the autoimmune regulator AIRE are associated with common organ-specific autoimmune diseases. *Immunity.* 2015;42(6):1185–1196.
  89. Cetani F, et al. A novel mutation of the autoimmune regulator gene in an Italian kindred with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, acting in a dominant fashion and strongly cosegregating with hypothyroid autoimmune thyroiditis. *J Clin Endocrinol Metab.* 2001;86(10):4747–4752.
  90. Su MA, et al. Mechanisms of an autoimmunity syndrome in mice caused by a dominant mutation in Aire. *J Clin Invest.* 2008;118(5):1712–1726.
  91. Anderson MS, et al. Projection of an immunological self shadow within the thymus by the Aire protein. *Science.* 2002;298(5597):1395–1401.
  92. Sansom SN, et al. Population and single-cell genomics reveal the Aire dependency, relief from Polycomb silencing, and distribution of self-antigen expression in thymic epithelia. *Genome Res.* 2014;24(12):1918–1931.
  93. Michelson DA, et al. Thymic epithelial cells co-opt lineage-defining transcription factors to eliminate autoreactive T cells. *Cell.* 2022;185(14):2542–2558.
  94. Bautista JL, et al. Single-cell transcriptional profiling of human thymic stroma uncovers novel cellular heterogeneity in the thymic medulla. *Nat Commun.* 2021;12(1):1096.
  95. Miller CN, et al. Thymic tuft cells promote an IL-4-enriched medulla and shape thymocyte development. *Nature.* 2018;559(7715):627–631.
  96. Bornstein C, et al. Single-cell mapping of the thymic stroma identifies IL-25-producing tuft epithelial cells. *Nature.* 2018;559(7715):622–626.
  97. Malchow S, et al. Aire-dependent thymic development of tumor-associated regulatory T cells. *Science.* 2013;339(6124):1219–1224.
  98. Taniguchi RT, et al. Detection of an autoreactive T-cell population within the polyclonal repertoire that undergoes distinct autoimmune regulator (Aire)-mediated selection. *Proc Natl Acad Sci U S A.* 2012;109(20):7847–7852.
  99. Devoss JJ, et al. Effector mechanisms of the autoimmune syndrome in the murine model of autoimmune polyglandular syndrome type 1. *J Immunol.* 2008;181(6):4072–4079.
  100. Puel A, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med.* 2010;207(2):291–297.
  101. Kisand K, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med.* 2010;207(2):299–308.
  102. Puel A, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science.* 2011;332(6025):65–68.
  103. Saunte DM, et al. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol.* 2017;177(1):47–62.
  104. Meager A, et al. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Med.* 2006;3(7):e289.
  105. Mogensen KE, et al. Patient with circulating antibodies to alpha-interferon. *Lancet.* 1981;318(8257):1227–1228.
  106. Meager A, et al. Spontaneous neutralising antibodies to interferon- $\alpha$  and interleukin-12 in thymoma-associated autoimmune disease. *Lancet.* 1997;350(9091):1596–1597.
  107. Suit BE, et al. Detection of anti-interferon antibodies in systemic lupus erythematosus. *Clin Exp Rheumatol.* 1983;1(2):133–135.
  108. Vallbracht A, et al. Interferon-neutralizing antibodies in a patient treated with human fibroblast interferon. *Nature.* 1981;289(5797):496–497.
  109. Bastard P, et al. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J Exp Med.* 2021;218(7):e20210554.
  110. Hetemaki I, et al. Patients with autoimmune polyendocrine syndrome type 1 have an increased susceptibility to severe herpesvirus infections. *Clin Immunol.* 2021;231:108851.
  111. Cheng MH, et al. Acquired autoimmune polyglandular syndrome, thymoma, and an AIRE defect. *N Engl J Med.* 2010;362(8):764–766.
  112. Rossi SW, et al. RANK signals from CD4(+)3(-) inducer cells regulate development of Aire-expressing epithelial cells in the thymic medulla. *J Exp Med.* 2007;204(6):1267–1272.
  113. Akiyama T, et al. The tumor necrosis factor family receptors RANK and CD40 cooperatively establish the thymic medullary microenvironment and self-tolerance. *Immunity.* 2008;29(3):423–437.
  114. Hikosaka Y, et al. The cytokine RANKL produced by positively selected thymocytes fosters medullary thymic epithelial cells that express autoimmune regulator. *Immunity.* 2008;29(3):438–450.
  115. Ramakrishnan KA, et al. Anticytokine autoantibodies in a patient with a heterozygous NFKB2 mutation. *J Allergy Clin Immunol.* 2018;141(4):1479–1482.
  116. Bastard P, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science.* 2020;370(6515):eabd4585.
  117. Rosenberg JM, et al. Neutralizing anti-cytokine autoantibodies against interferon- $\alpha$  in immunodysregulation polyendocrinopathy enteropathy X-linked. *Front Immunol.* 2018;9:544.
  118. Chatila TA, et al. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic dysregulation syndrome. *J Clin Invest.* 2000;106(12):R75–R81.
  119. Bennett CL, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet.* 2001;27(1):20–21.
  120. Bennett CL, Ochs HD. IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena. *Curr Opin Pediatr.* 2001;13(6):533–538.
  121. Walter JE, et al. Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. *J Clin Invest.* 2015;125(11):4135–4148.
  122. Cavadini P, et al. AIRE deficiency in thymus of 2 patients with Omenn syndrome. *J Clin Invest.* 2005;115(3):728–732.
  123. Casanova JL, Abel L. Lethal infectious diseases as inborn errors of immunity: toward a synthesis of the germ and genetic theses. *Annu Rev Pathol.* 2021;6:23–50.
  124. Zhang Q, et al. Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature.* 2022;603(7902):587–598.
  125. Casanova JL, et al. A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection. *Cell.* 2020;181(6):1194–1199.
  126. Lim HK, et al. Severe influenza pneumonitis in children with inherited TLR3 deficiency. *J Exp Med.* 2019;216(9):2038–2056.
  127. Matuozzo D, et al. Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19 [preprint]. <https://doi.org/10.1101/2022.10.22.22281221>. Posted on medRxiv October 25, 2022.
  128. Schmidt A, et al. TBK1 and TNFRSF13B mutations and an autoinflammatory disease in a child with lethal COVID-19. *NPJ Genom Med.* 2021;6(1):55.
  129. Beccuti G, et al. A COVID-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy, Italy: letter to the editor. *J Endocrinol Invest.* 2020;43(8):1175–1177.
  130. Meisel C, et al. Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1. *J Clin Invest.* 2021;131(14):e150867.
  131. Schidlowski L, et al. Diagnosis of APS-1 in two siblings following life-threatening COVID-19 pneumonia. *J Clin Immunol.* 2022;42(4):749–752.
  132. Bastard P, et al. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. *Sci Immunol.* 2021;6(62):eabl4340.
  133. Manry J, et al. The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies. *Proc Natl Acad Sci U S A.* 2022;119(21):e2200413119.
  134. Abers MS, et al. Neutralizing type-I interferon autoantibodies are associated with delayed viral clearance and intensive care unit admission in patients with COVID-19. *Immunol Cell Biol.* 2021;99(9):917–921.
  135. Acosta-Ampudia Y, et al. COVID-19 convalescent plasma composition and immunological effects in severe patients. *J Autoimmun.* 2021;118:102598.
  136. Akbil B, et al. Early and rapid identification of COVID-19 patients with neutralizing type I interferon auto-antibodies. *J Clin Immunol.* 2022;42(6):1111–1129.
  137. Busnadiego I, et al. Critically ill COVID-19 patients with neutralizing autoantibodies against type I interferons have increased risk of herpesvirus disease. *PLoS Biol.* 2022;20(7):e3001709.

138. Carapito R, et al. Identification of driver genes for critical forms of COVID-19 in a deeply phenotyped young patient cohort. *Sci Transl Med.* 2022;14(628):eabj7521.
139. Chang SE, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun.* 2021;12(1):5417.
140. Chauvineau-Grenier A, et al. Autoantibodies neutralizing type I interferons in 20% of COVID-19 deaths in a French hospital. *J Clin Immunol.* 2022;42(3):459–470.
141. Credle JJ, et al. Unbiased discovery of autoantibodies associated with severe COVID-19 via genome-scale self-assembled DNA-barcoded protein libraries. *Nat Biomed Eng.* 2022;6(8):992–1003.
142. Eto S, et al. Neutralizing type I interferon autoantibodies in Japanese patients with severe COVID-19. *J Clin Immunol.* 2022;42(7):1360–1370.
143. Frasca F, et al. Anti-IFN- $\alpha$ /- $\omega$  neutralizing antibodies from COVID-19 patients correlate with downregulation of IFN response and laboratory biomarkers of disease severity. *Eur J Immunol.* 2022;52(7):1120–1128.
144. Goncalves D, et al. Antibodies against type I interferon: detection and association with severe clinical outcome in COVID-19 patients. *Clin Transl Immunology.* 2021;10(8):e1327.
145. Koning R, et al. Autoantibodies against type I interferons are associated with multi-organ failure in COVID-19 patients. *Intensive Care Med.* 2021;47(6):704–706.
146. Lamacchia G, et al. Clinical and immunological features of SARS-CoV-2 breakthrough infections in vaccinated individuals requiring hospitalization. *J Clin Immunol.* 2022;42(7):1379–1391.
147. Lemarquis A, et al. Severe COVID-19 in an APS1 patient with interferon autoantibodies treated with plasmapheresis. *J Allergy Clin Immunol.* 2021;148(1):96–98.
148. Mathian A, et al. Lower disease activity but higher risk of severe COVID-19 and herpes zoster in patients with systemic lupus erythematosus with pre-existing autoantibodies neutralising IFN- $\alpha$ . *Ann Rheum Dis.* 2022;81(12):1695–1703.
149. Petrikov SS, et al. Anti-interferon alpha autoantibodies and their significance in COVID-19. *Russ J Infect Immun.* 2022;12(2):279–287.
150. Raadsen MP, et al. Interferon- $\alpha$ 2 auto-antibodies in convalescent plasma therapy for COVID-19. *J Clin Immunol.* 2022;42(2):232–239.
151. Savvateeva E, et al. Microarray-based detection of antibodies against SARS-CoV-2 proteins, common respiratory viruses and type I interferons. *Viruses.* 2021;13(12):2553.
152. Simula ER, et al. Increased presence of antibodies against type I interferons and human endogenous retrovirus W in intensive care unit COVID-19 patients. *Microbiol Spectr.* 2022;e0128022(4):e0128022.
153. Solanich X, et al. Pre-existing autoantibodies neutralizing high concentrations of type I interferons in almost 10% of COVID-19 patients admitted to intensive care in Barcelona. *J Clin Immunol.* 2021;41(8):1733–1744.
154. Soltani-Zangbar MS, et al. A comprehensive evaluation of the immune system response and type-I Interferon signaling pathway in hospitalized COVID-19 patients. *Cell Commun Signal.* 2022;20(1):106.
155. Troya J, et al. Neutralizing autoantibodies to type I IFNs in >10% of patients with severe COVID-19 pneumonia hospitalized in Madrid, Spain. *J Clin Immunol.* 2021;41(5):914–922.
156. van der Wijst MGP, et al. Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. *Sci Transl Med.* 2021;13(612):eab2624.
157. Vazquez SE, et al. Neutralizing autoantibodies to type I interferons in COVID-19 convalescent donor plasma. *J Clin Immunol.* 2021;41(6):1169–1171.
158. Wang EY, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature.* 2021;595(7866):283–288.
159. Ziegler CGK, et al. Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19. *Cell.* 2021;184(18):4713–4733.
160. Lopez J, et al. Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. *J Exp Med.* 2021;218(10):e20211211.
161. Shaw ER, et al. Temporal dynamics of anti-type I interferon autoantibodies in COVID-19 patients. *Clin Infect Dis.* 2021;75(1):e1192–e1194.
162. Bastard P, et al. Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs [published online June 14, 2022]. *Sci Immunol.* <https://doi.org/10.1126/sciimmunol.abp8966>.
163. Sokal A, et al. Human type I IFN deficiency does not impair B cell response to SARS-CoV-2 mRNA vaccination. *J Exp Med.* 2023;220(1):e20220258.
164. Kalil AC, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 2021;9(12):1365–1376.
165. Pozzetto B, et al. Characteristics of autoantibodies to human interferon in a patient with varicella-zoster disease. *J Infect Dis.* 1984;150(5):707–713.
166. Seligman SJ, et al. Defining risk groups to yellow fever vaccine-associated viscerotropic disease in the absence of denominator data. *Am J Trop Med Hyg.* 2014;90(2):267–271.
167. Zhang Q, et al. Autoantibodies against type I IFNs in patients with critical influenza pneumonia. *J Exp Med.* 2022;219(11):e20220514.
168. Casanova JL, Abel L. Mechanisms of viral inflammation and disease in humans. *Science.* 2021;374(6571):1080–1086.
169. Lifton RP. Molecular genetics of human blood pressure variation. *Science.* 1996;272(5262):676–680.
170. Cohen JC, et al. Human fatty liver disease: old questions and new insights. *Science.* 2011;332(6037):1519–1523.
171. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell.* 2015;161(1):161–172.
172. Hautala T, et al. Herpes simplex virus 2 encephalitis in a patient heterozygous for a TLR3 mutation. *Neurol Genet.* 2020;6(6):e532.
173. Zhang SY, et al. TLR3 deficiency in patients with herpes simplex encephalitis. *Science.* 2007;317(5844):1522–1527.
174. Kuo CY, et al. Life-threatening enterovirus 71 encephalitis in unrelated children with autosomal dominant TLR3 deficiency. *J Clin Immunol.* 2022;42(3):606–617.
175. Miot C, et al. Hematopoietic stem cell transplantation in 29 patients hemizygous for hypomorphic *IKBKKG/NEMO* mutations. *Blood.* 2017;130(12):1456–1467.
176. Boisson B. The genetic basis of pneumococcal and staphylococcal infections: inborn errors of human TLR and IL-1R immunity. *Hum Genet.* 2020;139(6-7):981–991.
177. Abolhassani H, et al. X-linked TLR7 deficiency underlies critical COVID-19 pneumonia in a male patient with ataxia-telangiectasia. *J Clin Immunol.* 2022;42(1):1–9.
178. Solanich X, et al. Genetic screening for TLR7 variants in young and previously healthy men with severe COVID-19. *Front Immunol.* 2021;12:719115.
179. van der Made CI, et al. Presence of genetic variants among young men with severe COVID-19. *JAMA.* 2020;324(7):663–673.
180. Le Voyer T, et al. Impaired thymic AIRE expression underlies autoantibodies against type I IFNs in humans with inborn errors of the alternative NF- $\kappa$ B pathway. Authorea. <https://doi.org/10.22541/au.167330741.18394805/v1>. Published January 9, 2023. Accessed January 17, 2023.