Inborn errors of nucleic acid sensing and type I interferon signaling determine viral susceptibility in humans

Leslie Naesens[1,2,3,4], Steven Callens[1,2,4], Tessa Kerre[1,4,5], Simon J. Tavernier[3,4,6,7], Filomeen Haerynck[1,3,4]

[1]Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium
[2]Department of Internal Medicine and Infectious Diseases, Ghent University Hospital, Ghent, Belgium.
[3]Primary Immune Deficiency Research Lab (PIRL), Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium
[4]Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Center, ERN-RITA center, Ghent University Hospital, Ghent, Belgium.
[5]Department of Hematology, Ghent University Hospital, Ghent, Belgium
[6]Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium
[7]Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

Corresponding author: Filomeen Haerynck. Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium. Filomeen.Haerynck@UGent.be.

Abstract

The innate immune system relies on nucleic acid (NA) sensors to detect viral infections and trigger type I interferon (IFN-I) responses, which are crucial for antiviral defense. NA pattern recognition receptors detect viral RNA or DNA within various cellular compartments, initiating antiviral signaling pathways. However, inherited deficiencies in these NA sensing mechanisms can result in increased susceptibility to severe viral infections. This review explores key genetic mutations affecting NA sensing and IFN-I pathways that predispose individuals to life-threatening viral diseases, including herpesviruses, respiratory viruses, enteroviruses, arboviruses, and vaccine-strain disseminated viral diseases. The identification of these monogenic defects in individuals afflicted by severe viral infections, along with the observed incomplete penetrance of these mutations, highlight the intricate interplay of the host's intrinsic, innate and adaptive immune response with invading viral pathogens. These insights into the molecular basis of antiviral immunity not only underscore the clinical challenges associated with viral susceptibility but also offers the opportunity for personalized treatment strategies, including genetic screening, tailored vaccination protocols, and targeted antiviral therapies.

Abbreviations

AD – Autosomal Dominant
AGS – Aicardi-Goutières Syndrome
AMFR – Autocrine Motility Factor Receptor
BCG – Bacille Calmette-Guérin
CARD – Caspase Activation and Recruitment Domain
cGAMP – Cyclic GMP-AMP
cGAS – Cyclic GMP-AMP Synthase
CNS – Central Nervous System
CMV – Cytomegalovirus
DBR1 – Debranching RNA Lariats 1
ds – Double-stranded
EBV – Epstein-Barr Virus
eIF2α – eukaryotic translation Initiation Factor 2α
HSE – Herpes Simplex Encephalitis
HSV – Herpes Simplex Virus
IAV – Influenza A Virus
IEIs – Inborn Errors of Immunity
IFN – Interferon
IFN-I – Type I Interferon
IFN-III– Type III Interferon
IFNAR1 – Interferon Alpha and Beta Receptor Subunit 1
IFNAR2 – Interferon Alpha and Beta Receptor Subunit 2
IFNLR – Interferon Lambda Receptor
IL – Interleukin
IRF – Interferon Regulatory Factor
ISG – Interferon-Stimulated Gene
ISRE – Interferon-Sensitive Response Element
JAK1 – Janus Kinase 1
MAVS – Mitochondrial Antiviral Signaling Protein
MDA5 – Melanoma Differentiation-Associated Protein 5
MMR – Measles, Mumps, and Rubella
MyD88 – Myeloid Differentiation primary response gene 88
NA – Nucleic Acid
NGS – Next-Generation Sequencing
NFKB1 – Nuclear Factor Kappa B Subunit 1
PAMP – Pathogen-Associated Molecular Pattern
PKR – Protein Kinase R
Pol III – RNA Polymerase III
PRR – Pattern Recognition Receptor
RIG-I – Retinoic Acid-Inducible Gene I
RIPK1 – Receptor-Interacting Protein Kinase 1
RIPK3 – Receptor-Interacting Protein Kinase 3
RSV – Respiratory Syncytial Virus
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
SLE – Systemic Lupus Erythematosus
STAT1 – Signal Transducer and Activator of Transcription 1
STAT2 – Signal Transducer and Activator of Transcription 2
STING – Stimulator of Interferon Genes
TBK1 – TANK-Binding Kinase 1
TFIIIA – Transcription Factor IIIA
TLR – Toll-Like Receptor
TRAF3 – TNF Receptor-Associated Factor 3
TRIF – TIR-Domain-Containing Adapter-Inducing Interferon-β
TYK2 – Tyrosine Kinase 2
UNC93B1 – Unc-93 Homolog B1
VZV – Varicella-Zoster Virus
WES – Whole-Exome Sequencing
WGS – Whole-Genome Sequencing
WWP2 – WW Domain Containing E3 Ubiquitin Protein Ligase 2
YF – Yellow Fever
ZBP1 – Z-DNA-Binding Protein 1

Activation of antiviral responses by nucleic acid sensors

Our innate immune system relies on a limited number of germline-encoded receptors known as pattern recognition receptors (PRRs) to identify foreign and potentially harmful cells and organisms (1). The innate immune recognition of viruses presents a particular challenge, as viral proteins are highly mutable and can evade detection by PRRs. Consequently, innate antiviral immunity heavily depends on a diverse set of immune receptors capable of detecting viral nucleic acids (NAs), as viruses cannot replicate without introducing their genome into a host cell. The recognition of foreign NAs initiates proinflammatory responses and induces the production of antiviral interferons (IFNs), which in turn drive the expression of IFN-stimulated genes (ISGs) to inhibit viral replication (**Figure 1**).

NA sensors can be classified based on their ligand specificity (e.g., DNA or RNA motifs) and their location within the cell (**Figure 2**). A limited set of PRRs patrols distinct cellular compartments, scanning for atypical or foreign DNA and RNA. Viral evasion strategies exert evolutionary pressure on the host immune system, driving the development of multiple NA sensors capable of detecting a single virus. For instance, DNA viruses such as herpes simplex virus type 1 (HSV-1) produce RNA intermediates during their replication cycle, which can be detected by RNA-specific sensors. As a result, NA sensing provides a broadly effective mechanism for identifying invading viruses. However, this system requires tight regulation to prevent inappropriate recognition of the abundant self-derived NAs present during normal cellular homeostasis.

The **NA sensing Toll-like receptors (NA TLRs)** are localized in the endolysosomal compartment, where they detect pathogen-derived NAs that are internalized and degraded through endocytosis or phagocytosis (2, 3). This subcellular localization is strategically important for recognizing engulfed viruses and bacteria while simultaneously providing a mechanism to prevent self-recognition and, consequently, autoimmunity. Different classes of pathogens are detected by four types of NA TLRs, each with distinct ligand specificity: double-stranded (ds) RNA (TLR3), single-stranded (ss) RNA or RNA breakdown products (TLR7 and TLR8), and ssDNA containing unmethylated CpG motifs (TLR9) (4–10) (**Figure 2**). MyD88 (myeloid differentiation primary response gene 88) is the central adaptor protein for all TLRs except TLR3 and is critical for promoting the production of inflammatory cytokines as well as type I interferons (IFN-Is) in the case of endosomal TLR7, TLR8, and TLR9 (11, 12). In contrast, TLR3 signaling operates independently of MyD88 and is instead driven by the adaptor protein TIR-domain-containing adapter-inducing interferon-β (TRIF).

The recognition of viral RNA in the cytoplasm is primarily mediated by sensors belonging to the retinoic acid-inducible gene I **(RIG-I)-like receptor (RLR) family**, which includes RIG-I and melanoma differentiation-associated protein 5 (MDA5) (13) (**Figure 2**). RLR family proteins consist of a central helicase domain and a carboxy-terminal domain responsible for binding immunostimulatory RNAs. RIG-I and MDA5 share significant homology in their domain architecture, as both contain two amino-terminal caspase activation and recruitment domains (CARDs) (13). The mitochondria play a crucial role as a platform for antiviral signaling, initiated when RIG-I and MDA5 bind to the mitochondrial antiviral signaling protein (MAVS) through CARD-CARD interactions. This signaling cascade activates interferon-regulatory factors (IRFs) and NF-κB, ultimately driving the transcriptional induction of IFN-I and proinflammatory cytokines. In parallel, the **dsRNA-dependent protein kinase (PKR)** plays a key antiviral role through an IFN-independent mechanism (**Figure 2**). Upon binding viral

dsRNA, PKR is activated and phosphorylates eukaryotic translation initiation factor 2α (eIF2α), halting protein synthesis and limiting viral replication (14). Additionally, PKR induces apoptosis, further restricting viral spread (14).

The recognition of microbial DNA is a fundamental mechanism of host defense, enabling the detection of a broad range of pathogens. The presence of DNA in the cytosol induces a robust IFN-I response that is independent of endosomal TLR9. In 2013, Zhijian Chen's group identified **cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS)** as the key receptor governing the cytosolic immune response to DNA (15). Upon binding dsDNA, cGAS is activated to synthesize cGAMP, a second messenger that activates the adaptor protein STING (stimulator of interferon genes). This activation triggers a signaling cascade that drives the production of IFN-I, along with other inflammatory cytokines and chemokines (15, 16) (**Figure 2**). Lastly, **Z-DNA-binding protein 1 (ZBP1)** is a cytosolic NA sensor that can detect both dsDNA and dsRNA, albeit in a Z conformation (17) (**Figure 2**). ZBP1 initiates cell death pathways through interactions with receptor-interacting protein kinase 1 (RIPK1) and RIPK3. Apoptosis is induced through the cooperation of RIPK1 and RIPK3, leading to caspase-8 activation, whereas in necroptosis, ZBP1 engages RIPK3, which in turn activates mixed lineage kinase domain-like protein (MLKL), resulting in membrane rupture (17). Beyond its role in cell death, ZBP1 also drives antiviral immunity through proinflammatory and IFN-I signaling, serving as a critical hub in antiviral defense.

Inherited deficiencies in nucleic acid sensing linked to viral susceptibility

Primary immunodeficiency disorders, described as "experiments of nature" by Robert A. Good, have provided critical insights into the human immune system (18). The study of patients with inborn errors of immunity (IEIs) serves as a valuable in vivo model for understanding immune function and offers an unbiased approach to discover novel disease-associated genes. The advent of next-generation sequencing (NGS), including whole-exome sequencing (WES) and whole-genome sequencing (WGS), has dramatically accelerated the identification of genetic defects underlying various immune disorders over the past decade. Currently, mutations in approximately 504 genes have been associated with a total of 555 distinct inborn errors of immunity (IEIs) (19).

The clinical spectrum of IEIs can involve susceptibility to infections, autoimmunity, autoinflammation, allergy, bone marrow failure, and/or malignancy. Seminal studies by Jean-Laurent Casanova's group established the concept of inborn errors in innate immune sensing and type I interferon immunity as underlying causes of severe, sporadic viral infections, including herpesvirus encephalitis, influenza pneumonia, and severe COVID-19 (20). These findings primarily emerged from genetic studies of young children who experienced life-threatening disease during primary infection with common viruses, despite having no other signs of infection susceptibility or general immunodeficiency.

Impaired innate sensing of herpes viruses

HSV-1 is one of the most common human pathogens, infecting 40–80% of the global population (21). It is associated with mucocutaneous infections, most notably recurrent orolabial lesions (21). The role of HSV-1 in encephalitis was first recognized in 1941, and it is now the most common cause of sporadic viral encephalitis in the Western world (22). Herpes simplex encephalitis (HSE) is a rare complication, with an incidence of 1 per

250,000 person-years (22), but it is a severe and potentially fatal manifestation of HSV-1 infection, primarily affecting children between 6 months and 3 years of age (23). Delayed diagnosis is associated with a high mortality rate, and despite treatment with acyclovir, most patients suffer from long-term neurological sequelae, including recurrent seizures and cognitive impairment (24).

HSV-1 is a neurotropic dsDNA virus that initially infects the oral or nasal epithelium and then gains access to the central nervous system (CNS) via the trigeminal or olfactory nerves. Herpesviruses establish lifelong latency in the host, with viral DNA persisting in the nucleus of infected cells and viral gene expression being largely limited to latency-associated transcripts. Periodic reactivation of the virus leads to a lytic replication cycle, potentially causing symptomatic disease. Approximately 30% of HSE cases occur during primary HSV-1 infection, while 70% result from viral reactivation (25).

Interestingly, only a small fraction of HSV-1-infected children develop HSE, and the disease is typically localized to the temporal lobe and orbitofrontal region (24, 26). There is no significant correlation between HSE and neurovirulent HSV-1 strains or epidemic outbreaks, indicating that viral pathogenicity alone does not explain CNS invasion (23). Furthermore, the incidence of HSE is not linked to geographic or seasonal patterns, suggesting that environmental factors are unlikely to be the sole contributors to disease development (23). These observations highlight the potential role of host-specific factors, such as IEIs, in determining susceptibility to HSE.

The host innate immune surveillance system is critical for controlling HSV-1 infection and determining its clinical outcome (27). Landmark studies have demonstrated that monogenic defects can predispose humans to sporadic, life-threatening viral infections, with genetic mutations in key RNA sensing and metabolizing molecules identified in patients with HSE. Single-gene inborn errors affecting TLR3 pathway components, such as UNC93B1, TLR3, TRIF, and TRAF3, as well as downstream signaling molecules TBK1 and IRF3, have been implicated in HSE susceptibility (28–35) (**Figure 3**). The TLR3 pathway appears to be especially important in defending CNS cells against HSV-1 infection. Additionally, the absence of systemic viral dissemination during HSE suggests that leukocyte-mediated immunity remains largely intact in these cases (36).

Experimental studies using various cellular models have provided key insights into this mechanism. For instance, leukocytes derived from an autosomal recessive (AR) TLR3-deficient patient showed normal responses to extracellular poly(I:C) stimulation or HSV-1 infection, whereas dermal fibroblasts from the same patient exhibited an impaired response (31). Moreover, induced pluripotent stem cell (iPSC)-derived CNS cells, including neurons and oligodendrocytes, from TLR3-deficient patients demonstrated increased susceptibility to HSV-1 infection (37). Further investigations revealed that both dermal fibroblasts and cortical neurons rely on TLR3 for producing constitutive levels of IFN-I during homeostasis, which serve to restrict viral replication during the early stages of infection (38). These findings emphasize the critical role of the TLR3 pathway in CNS-specific antiviral defense and underscore the importance of IFN-I production in early viral containment.

The discovery of monogenic susceptibility to isolated HSE highlights key aspects of human antiviral immunity. Unlike most IEIs, patients with HSE are not particularly susceptible to other microorganisms, including most viruses. This narrow clinical presentation suggests that innate immune sensors may be differentially regulated across cell types. Conversely, HSE is rarely observed in IEIs involving severe T and/or B cell disorders (39, 40), indicating a specific and crucial role for the innate immune response against HSV-1 in the human forebrain. Genetic variants linked to HSE have also been identified in asymptomatic family members, who exhibit

reduced IFN responses to viral infections and increased virus-induced cell death at the cellular level. Incomplete clinical penetrance may depend on host factors (e.g., age of infection, modifying genes), viral factors (e.g., load, strain), or non-viral environmental influences, although their precise contributions remain unclear. Furthermore, impaired TLR3 signaling has been detected in only ~10% of patients with isolated HSE (28, 41), suggesting the involvement of additional genetic variants in either known or novel pathways. For example, a recent case of a 14-month-old girl with HSE revealed impaired TLR3 responses due to a mutation in the E3 ubiquitin ligase WWP2, which regulates TRIF ubiquitination (42). Studies in patients with brainstem or forebrain HSE also identified genetic defects in TLR3-independent pathways, including biallelic defects in genes like *DBR1*, *GTF3A* and *TMEFF1* or heterozygous pathogenic variants in *SNORA31* (43–46) (**Figure 3**). Further supporting the role of alternative antiviral mechanisms, a recent case of HSE in a patient with RIPK3 deficiency demonstrated impaired cell-death-dependent control of HSV-1 in cortical neurons (47). Despite these advances, the genetic basis of many HSE cases remains unknown, and the diagnostic evaluation of cell-intrinsic immunity remains an important unmet need.

Varicella-zoster virus (VZV) infections are highly prevalent in the general population and typically manifest as varicella (chickenpox) during primary infection or zoster (shingles) during reactivation from latency in sensory ganglia. In some cases, VZV can lead to severe invasive disease, including encephalitis, cerebellitis, or pneumonitis. The critical role of VZV sensing by RNA polymerase III (Pol III) in vivo was highlighted by the discovery of rare pathogenic heterozygous missense variants in the POLR3A and POLR3C subunits of Pol III, which were found to underlie severe VZV infections (48). Similar findings of Pol III deficiency have been observed in adult patients with VZV-induced (meningo)encephalitis or recurrent CNS vasculitis, associated with pathogenic variants in the *POLR3A*, *POLR3E*, or *POLR3F* genes (49, 50). Pol III-generated RNAs lack a 5′ cap and often form complex secondary structures, two characteristics known to have RIG-I-immunostimulatory potential (51). Pol III has been shown to transcribe viral genomic sequences, generating RIG-I ligands that trigger antiviral immune responses (52–54).

Pol III has also been implicated in the detection of **cytomegalovirus (CMV)**, further highlighting its broader role in antiviral immunity. Similar to VZV, the CMV genome contains several AT-rich regions, which serve as targets for Pol III-mediated transcription and immune activation. Notably, a father with digenic heterozygous mutations in *POLR3A* and *POLR3C*, the same mutations identified in his child with invasive VZV infection, developed CMV encephalitis at the age of 20 (48). Additionally, homozygous missense mutations in *POLR3E* were identified in a child with recurrent systemic viral infections, including CMV. Fibroblasts from this patient demonstrated an impaired IFN-I response upon CMV infection, underscoring the importance of Pol III in initiating antiviral defenses (55). These findings suggest that genetic defects in Pol III subunits can result in susceptibility to multiple viral pathogens, extending beyond VZV to include CMV and potentially other viruses with AT-rich genomes.

A recent paradigm shift in innate sensing of virus infections was the discovery of host non-coding RNAs activating RIG-I during herpesvirus infection. These host RNAs are liberated from specific RNA binding proteins during virus infection (a process dubbed ‘viral unmasking’) and can trigger antiviral defenses. Functional analysis indicated that in particular 5S ribosomal pseudogene transcripts (i.e., *RNA5SP141*) served as RIG-I agonists (56) and stimulated cytokine (e.g., IFN-I) responses. These recent findings showed that ‘unmasking’ of self-RNA ligands during viral infection can induce antiviral immunity analogously to virus-derived PAMP recognition. We identified that TFIIIA (encoded by the gene *GTF3A*) enabled Pol III-mediated *RNA5SP141* transcription by investigating

compound heterozygous hypomorphic *GTF3A* mutations in a patient with HSV-1 encephalitis exhibiting impaired viral control (46) (**Figure 3**). TFIIIA comprises nine cysteine/histidine zinc fingers and is a co-factor for Pol III in type I promoters, unique to *5S rRNA* and its paralog *RNA5SPs* (54, 57). In this patient, the mutations in one of the highly conserved cysteine residues of TFIIIA conferred reduced DNA-binding ability. *GTF3A* mutant primary fibroblasts showed impaired *RNA5SP141* upregulation during HSV-1 infection, which resulted in abrogated RIG-I activation, reduced innate immune responses and enhanced viral replication.

Impaired innate sensing of respiratory viruses

Influenza, commonly known as "the flu," is an infectious respiratory disease caused by influenza A (IAV) and influenza B (IBV) viruses (58). While most infections are self-limiting, some can lead to severe complications, such as pneumonia and even acute respiratory distress syndrome (ARDS) (58). Genetic analysis in a 7-year-old girl with life-threatening ARDS during IAV infection revealed AR IRF7 deficiency due to compound heterozygous pathogenic variants (59). Impaired IFN-I responses were observed in plasmacytoid dendritic cells (pDCs) and iPSC-derived pulmonary epithelial cells (PECs) following viral infection (59). As shown in knockout (KO) mice, IRF7 is essential for governing local and systemic IFN responses that support innate antiviral immunity (60). pDCs, which express high basal levels of IRF7, produce large quantities of IFN-I/III upon viral infection (61). In human lung epithelial cells, IRF7, but not IRF3, is strongly induced during IAV infection and is critical for IFN production during the later stages of infection (62). Pathogenic heterozygous *TLR3* variants have also been linked to severe ARDS in influenza. Three unrelated patients with these variants developed ARDS following IAV infection (63). Although patient leukocytes exhibited normal responses to poly(I:C) and IAV, fibroblasts and iPSC-derived PECs showed increased viral replication, suggesting that autosomal dominant (AD) TLR3 deficiency affects PEC-intrinsic immunity (63). A fourth patient with a heterozygous *TLR3* mutation presented with IAV infection and bacterial co-infection (64). In vitro studies have previously demonstrated a TLR3-dependent inflammatory response to IAV in human lung epithelial cells (65, 66).

Pathogenic variants in MDA5 have been associated with severe respiratory disease caused by **human rhinovirus (HRV)** and **respiratory syncytial virus (RSV)**. In a cohort of 120 previously healthy children admitted to pediatric intensive care units with respiratory failure, seven children were found to carry heterozygous *MDA5* mutations, while one child carried a homozygous loss-of-function mutation (67). A 5-year-old child with life-threatening, recurrent respiratory tract infections caused by HRV, influenza virus, and RSV was found to have homozygous loss-of-function mutations in *MDA5* (68). Similarly, AR IRF7 deficiency results in susceptibility to multiple respiratory viruses beyond influenza, including RSV and adenovirus (69).

The emergence of **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)** has caused a devastating global pandemic. COVID-19 severity ranges from mild cases to life-threatening pneumonia and ARDS, with outcomes influenced by factors such as gender, age, and co-morbidities (70). The COVID Human Genetic Effort investigated the role of inborn errors of IFN-I immunity by performing targeted genetic analysis on 659 patients with severe COVID-19 pneumonia. Disease-causing variants were identified in 3.5% of cases and included pathogenic variants in *TLR3*, *UNC93B1*, *TRIF*, *TBK1*, *IRF3* and *IRF7* (71). To address the observed male predominance of severe COVID-19, genetic analysis of the X chromosome in male patients under 60 years old with critical disease identified X-linked recessive TLR7 deficiency as a highly penetrant cause (72). Leukocytes from

affected patients did not respond to TLR7 stimulation, and pDCs produced low levels of IFN-I in response to SARS-CoV-2 infection (72). In contrast to adults, children with COVID-19 typically experience mild or asymptomatic cases, with severe disease being rare (73). Genetic analysis of 112 hospitalized children under the age of 16 with COVID-19 pneumonia revealed AR deficiencies in TLR7 (74).

Interestingly, SARS-CoV-2 has also been shown to cause isolated brainstem encephalitis, with inherited DBR1 deficiency identified as the underlying monogenic cause (75). Inborn errors in *DBR1*, which impair neuron-intrinsic antiviral immunity, predispose individuals to a range of viral infections, including SARS-CoV-2, HSV-1, influenza B, and norovirus. The molecular mechanism underlying DBR1-associated brainstem viral encephalitis involves the accumulation of RNA lariats, disrupting stress granule assembly and PKR-mediated viral control (76).

In conclusion, human IEIs that compromise innate immune sensors or downstream signaling are clearly associated with heightened clinical susceptibility to viral disease. The precise contribution of IFN signaling cascades can be dissected by studying specific IEIs located in the IFN-I signaling pathway.

Inherited deficiencies in type I IFN signaling linked to viral susceptibility

Human deficiencies in IFN-I signaling reveal the essential role in antiviral immunity, but with a strikingly narrow clinical phenotype reflecting signaling network redundancy, complementation by adaptive immunity or other host/environmental factors.

Patients with complete **IFNAR1 or IFNAR2 deficiency** were initially diagnosed after experiencing serious adverse reactions following vaccination with live attenuated viruses such as measles, mumps and rubella (MMR) or yellow fever (YF) (77, 78). Another report highlighted the variable clinical penetrance of IFNAR1 deficiency in a family where three members were affected (79). One family member died of HSE at the age of 2 years, a 12-month-old cousin died following vaccination against MMR, and another 17-year-old cousin, who was homozygous for the same variant, experienced other, less severe viral illnesses. Similar observations were made in AR IFNAR1 deficiency in five unrelated kindreds of Western Polynesian ancestry and IFNAR2 deficiency in five children of Inuit ancestry, who exhibited severe complications from the MMR and varicella vaccines, as well as severe viral disease following respiratory virus infections (80, 81). Both IFNAR1 and IFNAR2 deficiencies have also been associated with severe COVID-19 pneumonia in both adults and children (71, 74). Recently, IFNAR1 deficiency has also been reported as autosomal dominant that impairs, but does not abolish, responses to IFN-α and IFN-ω while sparing responses to IFN-β. This deficiency also reveals a broad susceptibility spectrum to viral diseases, including respiratory tract infections (COVID-19), CNS infections (HSE, Japanese encephalitis virus, enterovirus), and adverse reactions to live attenuated vaccines (MMR and YF) (82).

Analogous findings of heterogeneous clinical disease were observed with **autoantibodies (autoAbs) neutralizing IFN-I**, which can be considered a partial phenocopy of genetic IFN-I receptor deficiencies (83). The pathogenicity of pre-existing autoAbs against IFN-ω, IFN-β, and the 13 types of IFN-α was demonstrated during the SARS-CoV-2 pandemic, with these autoAbs found in approximately 15% of patients with critical COVID-19 infections (84–86). The prevalence of these autoAbs showed a strong male predominance, increased sharply with age, and accounted for about 20% of COVID-19 deaths (85). A follow-up analysis of patients with life-threatening IAV infection revealed that autoAbs neutralizing IFN-I accounted for approximately 5% of cases of life-threatening influenza pneumonia in patients under 70 years old (87). Additionally, a retrospective analysis of plasma samples from patients hospitalized with Middle East respiratory syndrome (MERS) pneumonia identified IFN-Is autoAbs

in approximately 25% of cases (88).

Similar to IFNAR1 deficiency, susceptibility to the yellow fever live attenuated vaccine has been observed in patients with autoAbs against IFN-Is (89). Several studies have also reported more severe herpesviral disease in patients with these antibodies (90–92). Moreover, neutralizing IFN-I antibodies have been implicated in severe arboviral infections, including those caused by West Nile virus (WNV) and tick-borne encephalitis (TBE), as well as rarer arboviral infections, such as Powassan virus, Usutu virus, and Ross River virus (93–95).

JAK1 and **TYK2** are essential activating signaling proteins that bind to the intracellular domains of the IFN-I receptors, initiating downstream signaling cascades (96). Upon ligating of IFN-I with its cognate receptor complex comprising IFNAR1 and 2, JAK1 and TYK2 phosphorylate **STAT1** and **STAT2** proteins, leading to the transcription of ISGs critical for antiviral immunity (96). Given that NA sensing pathways ultimately trigger the production of IFN-I and that JAK/STAT proteins regulate downstream signaling, a broad spectrum of viral susceptibility has been identified. These include herpesviruses (HSV-1, VZV, CMV, EBV), respiratory viruses (SARS-CoV-2, IAV, RSV, adenovirus), and enteroviruses, as well as cases of disseminated vaccine-strain measles and varicella following routine immunization (97–108)(**Table 1**).

JAK/STAT signaling complexes participate in various cytokine signaling cascades, contributing to broader infection susceptibility, as evidenced by patients with TYK2 and STAT1 deficiencies. Patients with these deficiencies are particularly vulnerable to mycobacteria, as shown by affected children developing disseminated disease caused by the Bacille Calmette-Guérin (BCG) vaccine strain (97, 100–103, 106, 108, 109). Patients with TYK2 and STAT1 deficiencies exhibit additional susceptibility to these intracellular bacteria due to impaired IL-23-dependent induction of IFN-γ in TYK2 deficiency or disrupted type II IFN signaling in STAT1 deficiency (97, 104, 106, 109, 110). The level of viral susceptibility in STAT1 deficiency varies based on residual STAT1 function, as AD STAT1 deficiencies preserve IFN-I signaling, resulting in a more selective predisposition to mycobacterial disease (111). Similar findings are reported in TYK2 deficiency, which has a relatively mild impact on antiviral immunity, manifesting as cutaneous herpesviral infections (100–103).

A compensatory role for other IFN signaling cascades may help partially preserve antiviral immune responses and explain the milder disease presentation. For instance, STAT2 and **IRF9** mediate downstream signaling of IFN-I/III, contributing to a clinical phenotype largely restricted to invasive viral diseases. The protective role of IFN-III at mucosal and epithelial barriers likely explains the more severe clinical spectrum of viral infections observed in patients with STAT2 and IRF9 deficiencies (81, 98, 105, 107, 108). For example, IRF9 deficiency has been associated with invasive viral diseases caused by HSV-1, VZV, IAV, and SARS-CoV-2, as well as enterovirus-induced encephalitis and severe infections with arboviruses, including Dengue and Zika (112, 113). Additionally, IRF9 deficiency has been linked to infections with vaccine strains of measles and yellow fever (112, 113).

In conclusion, IFN-I receptor signaling plays a crucial role in antiviral immunity, as demonstrated by human inborn errors affecting this pathway. While IFN-I signaling defects lead to heightened susceptibility to certain viral diseases, especially following vaccination with live attenuated viruses, the clinical impact can vary significantly due to redundancy in immune signaling, compensation by other IFN pathways, and contributions from adaptive immunity. These findings emphasize the essential, yet context-dependent, role of IFN-I signaling in protect against viral infections.

Conclusions

The study of human inborn errors in both NA sensing and IFN-I signaling has provided crucial insights into the molecular mechanisms underlying antiviral immunity. Deficiencies in this pathway lead to increased susceptibility to severe viral infections or complications following vaccination with live attenuated viruses, such as varicella, measles and yellow fever. These findings underscore the importance of considering genetic variants when administering vaccines, particularly live attenuated ones, to minimize the risk of adverse reactions in genetically predisposed individuals.

Promising therapeutic strategies are emerging to address these genetic susceptibilities. For example, recombinant IFN therapy has been explored in conditions with impaired IFN-I responses, such as IFNAR1 or STAT2 deficiency. Antiviral gene therapy is also gaining traction, utilizing rationally designed NAs to disable viral replication by targeting viral genomes and essential host factors. Key advancements in RNA interference and CRISPR/Cas9 technologies have been pivotal, enabling precise gene inactivation and therapeutic gene transfer for immunostimulation. Ongoing research aims to develop targeted small molecules to enhance antiviral pathways, such as small-molecule RIG-I agonists that are designed to boost innate immune responses and provide broad-spectrum protection against viral infections.

However, the spectrum of clinical manifestations resulting from genetic defects in NA sensing and IFN-I signaling extends beyond the described viral susceptibility, reflecting a much greater complexity. Notably, genes central to NA sensing and IFN-I production are also implicated in type I interferonopathies, including systemic lupus erythematosus (SLE) and Aicardi-Goutières syndrome (AGS). This dual involvement emphasizes the delicate balance between protective antiviral immunity and the risk of immune dysregulation, calling for cross-disciplinary research to better understand and address both infectious and autoimmune diseases.

Moving forward, genetic screening for IEIs should be integrated into clinical practice to enable early identification of at-risk individuals and guide personalized therapeutic strategies. Tailoring interventions, including vaccine administration and antiviral treatments, to a patient's specific genetic and immunological profile will help reduce morbidity and mortality from both viral infections and immune-related complications. Ongoing research into the molecular mechanisms underlying these susceptibilities will continue to drive the development of targeted therapies, improve vaccine efficacy, and open new avenues for intervention in both infectious and autoimmune diseases.

Acknowledgements

Leslie Naesens is a beneficiary of FWO PhD fellowship. Tessa Kerre is a senior clinical researcher at FWO. Simon J. Tavernier is a beneficiary of a postdoctoral FWO grant. Filomeen Haerynck is supported by a BOF tenure track (UGent). Figures were created with BioRender illustration software.

Conflict of interest

The authors declare that the review was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors alone are responsible for the content and writing of the paper.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions

L.N. wrote the first draft of the manuscript. S.C, T.K., S.J.T. and F. H. reviewed and edited the manuscript.

References

1. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol. 1994;12:991-1045.
2. Barton GM, Kagan JC. A cell biological view of Toll-like receptor function: regulation through compartmentalization. Nat Rev Immunol. 2009;9:535-542.
3. Lind NA, Rael VE, Pestal K, Liu B, Barton GM. Regulation of the nucleic acid-sensing Toll-like receptors. Nat Rev Immunol. 2022;22:224-235.
4. Greulich W, Wagner M, Gaidt MM et al. TLR8 Is a Sensor of RNase T2 Degradation Products. Cell. 2019;179:1264-1275.e13.
5. Heil F, Hemmi H, Hochrein H et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science. 2004;303:1526-1529.
6. Hemmi H, Kaisho T, Takeuchi O et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol. 2002;3:196-200.
7. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature. 2001;413:732-738.
8. Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science. 2004;303:1529-1531.
9. Hemmi H, Takeuchi O, Kawai T et al. A Toll-like receptor recognizes bacterial DNA. Nature. 2000;408:740-745.
10. Krüger A, Oldenburg M, Chebrolu C et al. Human TLR8 senses UR/URR motifs in bacterial and mitochondrial RNA. EMBO Rep. 2015;16:1656-1663.
11. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140:805-820.
12. Tan Y, Kagan JC. Innate Immune Signaling Organelles Display Natural and Programmable Signaling Flexibility. Cell. 2019;177:384-398.e11.
13. Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. Nat Rev Immunol. 2020;20:537-551.
14. Cesaro T, Michiels T. Inhibition of PKR by Viruses. Front Microbiol. 2021;12:757238.
15. Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science. 2013;339:786-791.
16. Ablasser A, Goldeck M, Cavlar T et al. cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING. Nature. 2013;498:380-384.
17. Maelfait J, Rehwinkel J. The Z-nucleic acid sensor ZBP1 in health and disease. J Exp Med. 2023;220:e20221156.
18. Good RA. Experiments of nature in the development of modern immunology. Immunol Today. 1991;12:283-286.
19. IJspeert H, Edwards ESJ, O'Hehir RE, Dalm VASH, van Zelm MC. Update on inborn errors of immunity. J Allergy Clin Immunol. 2024S0091-6749(24)02407.
20. Casanova JL, Abel L. The human genetic determinism of life-threatening infectious diseases: genetic heterogeneity and physiological homogeneity [editorial]. Hum Genet 2020;139(6-7):681.

21. Kelly BJ, Fraefel C, Cunningham AL, Diefenbach RJ. Functional roles of the tegument proteins of herpes simplex virus type 1. Virus Res. 2009;145:173-186.
22. Whitley RJ, Kimberlin DW. Herpes simplex encephalitis: children and adolescents. Semin Pediatr Infect Dis. 2005;16:17-23.
23. Abel L, Plancoulaine S, Jouanguy E et al. Age-dependent Mendelian predisposition to herpes simplex virus type 1 encephalitis in childhood. J Pediatr. 2010;157:623-9, 629.e1.
24. KL T. Update on herpes simplex encephalitis. Rev Neurol Dis. 2004;169
25. Gnann JW, Whitley RJ. Herpes Simplex Encephalitis: an Update. Curr Infect Dis Rep. 2017;19:13.
26. Whitley RJ. Herpes simplex encephalitis: adolescents and adults. Antiviral Res. 2006;71:141-148.
27. Paludan SR, Bowie AG, Horan KA, Fitzgerald KA. Recognition of herpesviruses by the innate immune system. Nat Rev Immunol. 2011;11:143-154.
28. Lim HK, Seppänen M, Hautala T et al. TLR3 deficiency in herpes simplex encephalitis: high allelic heterogeneity and recurrence risk. Neurology. 2014;83:1888-1897.
29. Andersen LL, Mørk N, Reinert LS et al. Functional IRF3 deficiency in a patient with herpes simplex encephalitis. J Exp Med. 2015;212:1371-1379.
30. Zhang SY, Jouanguy E, Ugolini S et al. TLR3 deficiency in patients with herpes simplex encephalitis. Science. 2007;317:1522-1527.
31. Guo Y, Audry M, Ciancanelli M et al. Herpes simplex virus encephalitis in a patient with complete TLR3 deficiency: TLR3 is otherwise redundant in protective immunity. J Exp Med. 2011;208:2083-2098.
32. Casrouge A, Zhang SY, Eidenschenk C et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science. 2006;314:308-312.
33. Herman M, Ciancanelli M, Ou YH et al. Heterozygous TBK1 mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood. J Exp Med. 2012;209:1567-1582.
34. Sancho-Shimizu V, Pérez de Diego R, Lorenzo L et al. Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. J Clin Invest. 2011;121:4889-4902.
35. Pérez de Diego R, Sancho-Shimizu V, Lorenzo L et al. Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. Immunity. 2010;33:400-411.
36. Zhang SY. Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity. Hum Genet. 2020;139:911-918.
37. Lafaille FG, Pessach IM, Zhang SY et al. Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. Nature. 2012;491:769-773.
38. Gao D, Ciancanelli MJ, Zhang P et al. TLR3 controls constitutive IFN-β antiviral immunity in human fibroblasts and cortical neurons. J Clin Invest. 2021;131
39. Buckley RH. Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. Annu Rev Immunol. 2004;22:625-655.
40. Bousfiha A, Moundir A, Tangye SG et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. J Clin Immunol. 2022;42:1508-1520.
41. Zhang SY, Casanova JL. Inborn errors underlying herpes simplex encephalitis: From TLR3 to IRF3. J Exp Med. 2015;212:1342-1343.
42. Bibert S, Quinodoz M, Perriot S et al. Herpes simplex encephalitis due to a mutation in an E3 ubiquitin ligase. Nat Commun. 2024;15:3969.
43. Zhang SY, Clark NE, Freije CA et al. Inborn Errors of RNA Lariat Metabolism in Humans with Brainstem Viral Infection. Cell. 2018;172:952-965.e18.
44. Lafaille FG, Harschnitz O, Lee YS et al. Human SNORA31 variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis. Nat Med. 2019;25:1873-1884.
45. Chan YH, Liu Z, Bastard P et al. Human TMEFF1 is a restriction factor for herpes simplex virus in the brain. Nature. 2024;632:390-400.
46. Naesens L, Muppala S, Acharya D et al. GTF3A mutations predispose to herpes simplex encephalitis by disrupting biogenesis of the host-derived RIG-I ligand RNA5SP141. Sci Immunol. 2022;7:eabq4531.
47. Liu Z, Garcia Reino EJ, Harschnitz O et al. Encephalitis and poor neuronal death-mediated control of herpes simplex virus in human inherited RIPK3 deficiency. Sci Immunol. 2023;8:eade2860.
48. Ogunjimi B, Zhang SY, Sørensen KB et al. Inborn errors in RNA polymerase III underlie severe varicella zoster virus infections. J Clin Invest. 2017;127:3543-3556.
49. Carter-Timofte ME, Hansen AF, Christiansen M, Paludan SR, Mogensen TH. Mutations in RNA Polymerase III genes and defective DNA sensing in adults with varicella-zoster virus CNS infection. Genes Immun. 2019;20:214-223.
50. Carter-Timofte ME, Hansen AF, Mardahl M et al. Varicella-zoster virus CNS vasculitis and RNA polymerase III gene mutation in identical twins. Neurol Neuroimmunol Neuroinflamm. 2018;5:e500.
51. Dieci G, Conti A, Pagano A, Carnevali D. Identification of RNA polymerase III-transcribed genes in eukaryotic genomes. Biochim Biophys Acta. 2013;1829:296-305.
52. Ablasser A, Bauernfeind F, Hartmann G, Latz E, Fitzgerald KA, Hornung V. RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nat Immunol. 2009;10:1065-1072.
53. Chiu YH, Macmillan JB, Chen ZJ. RNA polymerase III detects cytosolic DNA and induces type I interferons through the RIG-I pathway. Cell. 2009;138:576-591.
54. Naesens L, Haerynck F, Gack MU. The RNA polymerase III-RIG-I axis in antiviral immunity and inflammation. Trends Immunol. 2023;44:435-449.
55. Ramanathan A, Weintraub M, Orlovetskie N et al. A mutation in POLR3E impairs antiviral immune response and RNA polymerase III. Proc Natl Acad Sci U S A. 2020;117:22113-22121.
56. Chiang JJ, Sparrer KMJ, van Gent M et al. Viral unmasking of cellular 5S rRNA pseudogene transcripts induces RIG-I-mediated immunity. Nat Immunol. 2018;19:53-62.

57. Miller J, McLachlan AD, Klug A. Repetitive zinc-binding domains in the protein transcription factor IIIA from Xenopus oocytes. EMBO J. 1985;4:1609-1614.
58. Krammer F, Smith GJD, Fouchier RAM et al. Influenza. Nat Rev Dis Primers. 2018;4:3.
59. Ciancanelli MJ, Huang SX, Luthra P et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science. 2015;348:448-453.
60. Honda K, Yanai H, Negishi H et al. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature. 2005;434:772-777.
61. Honda K, Taniguchi T. IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. Nat Rev Immunol. 2006;6:644-658.
62. Wu W, Zhang W, Tian L, Brown BR, Walters MS, Metcalf JP. IRF7 Is Required for the Second Phase Interferon Induction during Influenza Virus Infection in Human Lung Epithelia. Viruses. 2020;12:377.
63. Lim HK, Huang SXL, Chen J et al. Severe influenza pneumonitis in children with inherited TLR3 deficiency. J Exp Med. 2019;216:2038-2056.
64. Bucciol G, Desmet L, Leuven LOIEOI, Corveleyn A, Meyts I. Pathogenic P554S Variant in TLR3 in a Patient with Severe Influenza Pneumonia.[letter]. J Clin Immunol 2022;42(2):430-432.
65. Le Goffic R, Pothlichet J, Vitour D et al. Cutting Edge: Influenza A virus activates TLR3-dependent inflammatory and RIG-I-dependent antiviral responses in human lung epithelial cells. J Immunol. 2007;178:3368-3372.
66. Le Goffic R, Balloy V, Lagranderie M et al. Detrimental contribution of the Toll-like receptor (TLR)3 to influenza A virus-induced acute pneumonia. PLoS Pathog. 2006;2:e53.
67. Asgari S, Schlapbach LJ, Anchisi S et al. Severe viral respiratory infections in children with IFIH1 loss-of-function mutations. Proc Natl Acad Sci U S A. 2017;114:8342-8347.
68. Lamborn IT, Jing H, Zhang Y et al. Recurrent rhinovirus infections in a child with inherited MDA5 deficiency. J Exp Med. 2017;214:1949-1972.
69. Campbell TM, Liu Z, Zhang Q et al. Respiratory viral infections in otherwise healthy humans with inherited IRF7 deficiency. J Exp Med. 2022;219:e20220202.
70. Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med. 2021;27:28-33.
71. Zhang Q, Bastard P, Liu Z et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370:eabd4570.
72. Asano T, Boisson B, Onodi F et al. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. Sci Immunol. 2021;6:eabl4348.
73. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109:1088-1095.
74. Zhang Q, Matuozzo D, Le Pen J et al. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. J Exp Med. 2022;219:e20220131.
75. Chan YH, Lundberg V, Le Pen J et al. SARS-CoV-2 brainstem encephalitis in human inherited DBR1 deficiency. J Exp Med. 2024;221:e20231725.
76. Ru S, Tang S, Xu H et al. Human DBR1 deficiency impairs stress granule-dependent PKR antiviral immunity. J Exp Med. 2025;222:e20240010.
77. Duncan CJ, Mohamad SM, Young DF et al. Human IFNAR2 deficiency: Lessons for antiviral immunity. Sci Transl Med. 2015;7:307ra154.
78. Hernandez N, Bucciol G, Moens L et al. Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. J Exp Med. 2019;216:2057-2070.
79. Bastard P, Manry J, Chen J et al. Herpes simplex encephalitis in a patient with a distinctive form of inherited IFNAR1 deficiency. J Clin Invest. 2021;131
80. Bastard P, Hsiao KC, Zhang Q et al. A loss-of-function IFNAR1 allele in Polynesia underlies severe viral diseases in homozygotes. J Exp Med. 2022;219:e20220028.
81. Duncan CJA, Skouboe MK, Howarth S et al. Life-threatening viral disease in a novel form of autosomal recessive IFNAR2 deficiency in the Arctic. J Exp Med. 2022;219:e20212427.
82. Al Qureshah F, Le Pen J, de Weerd NA et al. A common form of dominant human IFNAR1 deficiency impairs IFN-α and -ω but not IFN-β-dependent immunity. J Exp Med. 2025;222:e20241413.
83. Bastard P, Gervais A, Le Voyer T et al. Human autoantibodies neutralizing type I IFNs: From 1981 to 2023. Immunol Rev. 2024;322:98-112.
84. Bastard P, Orlova E, Sozaeva L et al. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. J Exp Med. 2021;218:e20210554.
85. Bastard P, Gervais A, Le Voyer T 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:eabl4340.
86. Bastard P, Rosen LB, Zhang Q et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370:eabd4585.
87. Zhang Q, Pizzorno A, Miorin L et al. Autoantibodies against type I IFNs in patients with critical influenza pneumonia. J Exp Med. 2022;219:e20220514.
88. Alotaibi F, Alharbi NK, Rosen LB et al. Type I interferon autoantibodies in hospitalized patients with Middle East respiratory syndrome and association with outcomes and treatment effect of interferon beta-1b in MIRACLE clinical trial. Influenza Other Respir Viruses. 2023;17:e13116.
89. Bastard P, Michailidis E, Hoffmann HH et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. J Exp Med. 2021;218
90. Busnadiego I, Abela IA, Frey PM et al. Critically ill COVID-19 patients with neutralizing autoantibodies against type I interferons have increased risk of herpesvirus disease. PLoS Biol. 2022;20:e3001709.
91. Hetemäki I, Laakso S, Välimaa H et al. Patients with autoimmune polyendocrine syndrome type 1 have an increased susceptibility to severe herpesvirus infections. Clin Immunol. 2021;231:108851.

92. Pozzetto B, Mogensen KE, Tovey MG, Gresser I. Characteristics of autoantibodies to human interferon in a patient with varicella-zoster disease. J Infect Dis. 1984;150:707-713.
93. Gervais A, Rovida F, Avanzini MA et al. Autoantibodies neutralizing type I IFNs underlie West Nile virus encephalitis in ~40% of patients. J Exp Med. 2023;220:e20230661.
94. Gervais A, Marchal A, Fortova A et al. Autoantibodies neutralizing type I IFNs underlie severe tick-borne encephalitis in ~10% of patients. J Exp Med. 2024;221:e20240637.
95. Gervais A, Bastard P, Bizien L et al. Auto-Abs neutralizing type I IFNs in patients with severe Powassan, Usutu, or Ross River virus disease. J Exp Med. 2024;221:e20240942.
96. Duncan CJA, Randall RE, Hambleton S. Genetic Lesions of Type I Interferon Signalling in Human Antiviral Immunity. Trends Genet. 2021;37:46-58.
97. Dupuis S, Jouanguy E, Al-Hajjar S et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet. 2003;33:388-391.
98. Hambleton S, Goodbourn S, Young DF et al. STAT2 deficiency and susceptibility to viral illness in humans. Proc Natl Acad Sci U S A. 2013;110:3053-3058.
99. Chapgier A, Kong XF, Boisson-Dupuis S et al. A partial form of recessive STAT1 deficiency in humans. J Clin Invest. 2009;119:1502-1514.
100. Sarrafzadeh SA, Mahloojirad M, Casanova JL et al. A New Patient with Inherited TYK2 Deficiency. J Clin Immunol. 2020;40:232-235.
101. Kreins AY, Ciancanelli MJ, Okada S et al. Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. J Exp Med. 2015;212:1641-1662.
102. Minegishi Y, Saito M, Morio T et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity. 2006;25:745-755.
103. Kilic SS, Hacimustafaoglu M, Boisson-Dupuis S et al. A patient with tyrosine kinase 2 deficiency without hyper-IgE syndrome. J Pediatr. 2012;160:1055-1057.
104. Vairo D, Tassone L, Tabellini G et al. Severe impairment of IFN-γ and IFN-α responses in cells of a patient with a novel STAT1 splicing mutation. Blood. 2011;118:1806-1817.
105. Moens L, Van Eyck L, Jochmans D et al. A novel kindred with inherited STAT2 deficiency and severe viral illness. J Allergy Clin Immunol. 2017;139:1995-1997.e9.
106. Kong XF, Ciancanelli M, Al-Hajjar S et al. A novel form of human STAT1 deficiency impairing early but not late responses to interferons. Blood. 2010;116:5895-5906.
107. Shahni R, Cale CM, Anderson G et al. Signal transducer and activator of transcription 2 deficiency is a novel disorder of mitochondrial fission. Brain. 2015;138:2834-2846.
108. Alosaimi MF, Maciag MC, Platt CD, Geha RS, Chou J, Bartnikas LM. A novel variant in STAT2 presenting with hemophagocytic lymphohistiocytosis. J Allergy Clin Immunol. 2019;144:611-613.e3.
109. Chapgier A, Wynn RF, Jouanguy E 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;176:5078-5083.
110. Ogishi M, Arias AA, Yang R et al. Impaired IL-23-dependent induction of IFN-γ underlies mycobacterial disease in patients with inherited TYK2 deficiency. J Exp Med. 2022;219:e20220094.
111. Boisson-Dupuis S, Kong XF, Okada S et al. Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. Curr Opin Immunol. 2012;24:364-378.
112. Hernandez N, Melki I, Jing H et al. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. J Exp Med. 2018;215:2567-2585.
113. Bravo García-Morato M, Calvo Apalategi A, Bravo-Gallego LY et al. Impaired control of multiple viral infections in a family with complete IRF9 deficiency. J Allergy Clin Immunol. 2019;144:309-312.e10.
114. Audry M, Ciancanelli M, Yang K et al. NEMO is a key component of NF-κB- and IRF-3-dependent TLR3-mediated immunity to herpes simplex virus. J Allergy Clin Immunol. 2011;128:610-7.e1.
115. Bucciol G, Delafontaine S, Moens L, Corveleyn A, Morren MA, Meyts I. Pathogenic TLR3 Variant in a Patient with Recurrent Herpes Simplex Virus 1-Triggered Erythema Multiforme. J Clin Immunol. 2021;41:280-282.
116. Hait AS, Olagnier D, Sancho-Shimizu V et al. Defects in LC3B2 and ATG4A underlie HSV2 meningitis and reveal a critical role for autophagy in antiviral defense in humans. Sci Immunol. 2020;5:eabc2691.
117. Reyahi A, Studahl M, Skouboe MK et al. An IKBKE variant conferring functional cGAS/STING pathway deficiency and susceptibility to recurrent HSV-2 meningitis. JCI Insight. 2023;8:e173066.
118. Thomsen MM, Skouboe MK, Møhlenberg M et al. Impaired STING Activation Due to a Variant in the E3 Ubiquitin Ligase AMFR in a Patient with Severe VZV Infection and Hemophagocytic Lymphohistiocytosis. J Clin Immunol. 2024;44:56.
119. Carter-Timofte ME, Hansen AF, Christiansen M, Paludan SR, Mogensen TH. Mutations in RNA Polymerase III genes and defective DNA sensing in adults with varicella-zoster virus CNS infection. Genes Immun. 2019;20:214-223.
120. Liang F, Glans H, Enoksson SL, Kolios AGA, Loré K, Nilsson J. 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;221:1295-1303.
121. Mandola AB, Sharfe N, Nagdi Z et al. Combined immunodeficiency caused by a novel homozygous NFKB1 mutation. J Allergy Clin Immunol. 2021;147:727-733.e2.
122. Chen J, Jing H, Martin-Nalda A et al. Inborn errors of TLR3- or MDA5-dependent type I IFN immunity in children with enterovirus rhombencephalitis. J Exp Med. 2021;218:e20211349.
123. Chen Y, Graf L, Chen T et al. Rare variant MX1 alleles increase human susceptibility to zoonotic H7N9 influenza virus. Science. 2021;373:918-922.

TLR3
TLR7
TLR8
TLR9
dsRNA
ssRNA
ssRNA
ssDNA
Endosome
cGAS
dsDNA
GTP
ATP
2', 3'-cGAMP
STING
Endoplasmic reticulum
TRIF
MyD88
ZBP-1
Z-dsDNA/
dsRNA
RIPK1
RIPK3
Cell
death
Caspase 8
RIG-I
dsRNA
MDA5
dsRNA
MAVS
Mitochondrion
PKR
dsRNA
P
eIF2α
Protein
translation
P
IκB
NF-κB
P
P
IRF3
IRF7
Nucleus
Proinflammatory
cytokines
NF-κB
Type I/III
interferons
P
P
IRF3
IRF7

Virus

DNA

RNA

Nucleic acid sensors

Proinflammatory cytokines

NF-κB

P

P

IRF3

IRF7

Type I/III interferons

Nucleus

IFN-I

IFN-III

IFNAR1

IFNAR2

IFNLR1

IL-10Rβ

P TYK2

JAK1 P

P JAK1

TYK2 P

STAT1 P

STAT2 P

IRF9

ISGF3

STAT1 P

IRF9

STAT2 P

ISRE

ISGs

Nucleus