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Human inborn errors of immunity to herpes viruses

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Abstract

Infections with any of the nine human herpes viruses (HHV) can be asymptomatic or life-threatening. The study of patients with severe diseases caused by HHVs, in the absence of overt acquired immunodeficiency, has led to the discovery or diagnosis of various inborn errors of immunity. The related inborn errors of adaptive immunity disrupt α/β T-cell rather than B-cell immunity. Affected patients typically develop HHV infections in the context of other infectious diseases. However, this is not always the case, as illustrated by inborn errors of SAP-dependent T-cell immunity to EBV-infected B cells. The related inborn errors of innate immunity disrupt leukocytes other than T and B cells, non-hematopoietic cells, or both. Patients typically develop only a single type of infection due to HHV, although, again, this is not always the case, as illustrated by inborn errors of TLR3 immunity resulting in HSV-1 encephalitis in some patients and influenza pneumonitis in others. Most severe HHV infections in otherwise healthy patients remains unexplained. The forward human genetic dissection of isolated and syndromic HHV-

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driven illnesses will establish the molecular and cellular basis of protective immunity to HHVs, paving the way for novel diagnosis and management strategies.

Keywords

Inborn errors of immunity; Herpes viruses

Introduction

Nine human herpes viruses (HHVs) have been identified, all with strict human tropism and a capacity to alternate latent and lytic phases (reactivation). The first isolation and characterization of a herpes virus was performed in 1919, and two serotypes (HSV1 and HSV2) were distinguished in 1962 (1). Other herpes viruses were subsequently isolated. Varicella zoster virus (VZV or HHV3) was isolated in 1953 from human embryonic tissue infected with the chickenpox virus (2, 3). Human cytomegalovirus (HCMV or HHV5) was isolated in 1956 from the salivary gland of an infected child (4). Epstein-Barr virus (EBV or HHV4) was isolated in 1964 from cultured tumor cells derived from an African case of Burkitt's lymphoma (5); this virus was the first human oncogenic virus to be discovered (6). HHV6 was isolated in 1986 from leukocytes of patients with lymphoproliferative disorders, including lymphoma (7). Two variants of HHV6, 6A and 6B, have been defined since 2014; these variants are closely related but have different molecular and epidemiological characteristics (8). In 1990, HHV7 was isolated from activated T cells from a healthy individual (9), and, finally, in 1994, HHV8 was isolated from a Kaposi sarcoma lesion from a patient with HIV-induced acquired immune deficiency (AIDS) (10).

The classification of HHVs into three subfamilies is based on multiples features, including DNA sequence similarity, site of latent infection, cytopathologic effect, and replicative cycle (short or long). HSV1, HSV2, and VZV belong to the α-herpes subfamily, HCMV, HHV6 and HHV7 belong to the β-herpes subfamily, and EBV and HHV8 constitute the oncogenic γ-herpes subfamily. During the latent phase of infection, the cellular reservoir is sensory ganglia neurons for α-herpesviruses (11), bone marrow progenitors, including those of the myeloid lineage, for HCMV, HHV6A and HHV6B, CD4 T cells for HHV7 (12, 13), and B lymphocytes for γ-herpesviruses (14). In all cases, the viral genome is maintained as an episome (15). These viruses display human-to-human transmission, through saliva (HSV1, EBV, HCMV, HHV6, HHV7 and HHV8), skin lesions (HSV1, VZV), respiratory droplets (VZV, HCMV), sexual contact (HSV2 and HHV8), or from infected mother to child in utero (HCMV) or during delivery (HSV1 and 2, VZV and HCMV). Breast milk transmission has been documented for HCMV (16). HHV6 is the only herpes virus for which chromosomal integration has been observed as a mechanism of congenital infection (17). With the exception of HSV2 and HHV8, HHVs are almost ubiquitous in the general population, with seroprevalence rates exceeding 80–90% by the age of 20 years for HSV1, VZV, and EBV, and reaching 100% by the age of 10 years for HHV6 and HHV7, and more than 50% by the age of 45 years for HCMV (18).

The vast majority of herpesvirus infections are asymptomatic. Furthermore, efficient antiviral drugs, such as acyclovir and ganciclovir, have improved the treatment of symptomatic HHV infections since their first clinical use in 1977 (19, 20). A very small proportion of infected individuals develop life-threatening disease. These individuals are frequently patients with acquired immune deficiencies, due to AIDS or following organ or hematopoietic stem cell transplantation (HSCT) (21–31). EBV-induced lymphoproliferative diseases and HHV8-associated Kaposi sarcoma can affect individuals with acquired immunodeficiencies or otherwise healthy people, but its frequency is much higher among those with acquired immunodeficiencies. The clinical manifestations of infection with other HHVs tend to differ between individuals with acquired immunodeficiencies and the general population. HHV infection may cause only benign manifestations (e.g. labial herpes) or no manifestations at all in the general population. However, in patients with acquired immunodeficiencies, infection frequently leads to the development of invasive diseases potentially affecting multiple tissues, such as encephalitis, hepatitis, retinitis, pneumonitis or cancers. In rare cases, life-threatening diseases are reported in otherwise healthy individuals, in which case the clinical course may resemble that in patients with acquired immunodeficiency. Some otherwise healthy patients present a unique clinical course, such as HSV1 encephalitis (HSE) not associated with acquired immunodeficiency in children. Here, we review the inherited genetic defects associated with severe HHV infections, either isolated or syndromic (i.e. in combination with other infections), and discuss how the study of primary immunodeficiencies (PIDs) has defined the requirements of adaptive, innate and tissue-intrinsic immune responses to HHV.

HSV1/HSV2 immunity

The genome sequences of HSV1 and HSV2 are 70% identical (32, 33). The seroprevalence of HSV1 in the general population reaches about 80% by adolescence, and that of HSV2 reaches about 30% in young adults. Both these viruses cause diverse diseases, including cutaneous herpes, keratitis, retinitis, cold sores, genital herpes, hepatitis, meningitis, and encephalitis. HSV1 is usually associated with orofacial infections and encephalitis, whereas HSV2 usually causes genital infections (33, 34). However, the clinical syndromes of HSV1 and HSV2 overlap, and infection severity (i.e. cutaneous infection *vs.* encephalitis) has not been associated with particular HSV strains. Recurrent or severe HSV infection is relatively rare among infected individuals and prognosis remains poor, particularly for encephalitis, due to neurological sequelae (35–37). The causal link to the virus is clear, but the pathogenesis of the various HSV diseases otherwise remains largely unknown. The observation of patients with PIDs and severe HSV infection (mostly due to HSV1), whether syndromic or isolated, has shed light on host protective immune responses to HSV.

Patients with various inborn errors of immunity affecting the development and/or function of various leukocytes frequently present severe/recurrent cutaneous/mucous HSV1 infection (Table 1). These conditions include, but are not limited to, autosomal recessive (AR) deficiencies of MCM4 (38, 39), GINS1 (40), DOCK8 (41–43), and STK4 (MST1) (44), autosomal dominant (AD) GATA2 deficiencies (45–49), gain-of-function (GOF) *CXCR4* mutations (50), and X-linked recessive (XR) Wiskott-Aldrich syndrome (51, 52). The most common immunological abnormality in these PIDs is numerical and/or functional deficiency

of natural killer (NK) and/or T cells. These observations suggested a potentially important role of NK cells and αβ T cells in HSV1 control in the skin. Severe/recurrent cutaneous/mucous HSV infection has also been reported in patients with PIDs affecting both adaptive and innate immunity, including IFNγ-R deficiencies (due to mutations of *IFNGR1* or *IFNGR2*), AR TYK2 deficiency, XR NEMO deficiency (*IKBKG* mutations), and immune deficiency due to AD GOF STAT1 mutations (53–59). These observations suggested an involvement of immune responses mediated by IFNγ-R and/or TYK2/STAT1 signaling pathways in skin-resident cells, leukocytes or both, in the progression of HSV1 skin infection. Interestingly, STAT1 GOF mutations impair NK cell proliferation and function, in addition to Th17 differentiation (60). Several patients with these PIDs can develop life-threatening clinical forms of HSV1 infection, manifesting as systemic HSV infection in a patient with AD GATA2 deficiency characterized by monocytopenia together with B, NK and dendritic cell (DC) lymphopenia (48), or HSE in one patient with XR NEMO deficiency and one patient with AR complete STAT1 deficiency (61, 62). Further molecular and cellular characterization of these PIDs in the context of HSV1 infection will clarify the contributions of T, NK and tissue-resident cells in host defense against HSV1. Interestingly, patients with leukocyte deficiencies, including severe combined immunodeficiencies (SCID), do not develop childhood HSE, even if they develop severe/recurrent cutaneous/mucous HSV1 infections or meningitis (63). These observations raise questions about the host specific immune factors protecting against HSV infection, either systemically or in a specific tissue (i.e. the skin) or organ (i.e. the central nervous system).

Since 2006, HSE has been studied as an example of inborn errors of immunity conferring a predisposition to isolated severe viral infection affecting a specific organ in otherwise healthy children. In about 1 in 10,000 infected individuals, HSV1 invades the central nervous system (CNS) via the olfactory bulb, causing forebrain HSE (~95% of cases) or, more rarely, via the trigeminal nerves, causing brainstem HSE (~5% of cases)(37, 64–66). HSE typically strikes otherwise healthy individuals, who are not particularly susceptible to other clinical forms of HSV infection, and no viral dissemination has been reported during the course of HSE (35, 37). Genetic studies of isolated HSE of the forebrain led to the discovery of single-gene inborn errors of the Toll-like receptor 3 (TLR3)/IFN-α/β and -λ pathway, due to mono- or biallelic mutations of six TLR3 pathway genes (*TLR3*, *UNC93B1*, *TRIF*, *TRAF3*, *TBK1* or *IRF3*) (67–77) (Table 1). These findings, together with the previous observation of HSE in patients with either XR NEMO deficiency (impairing IFN-α/β and -λ production upon viral infection)(78) and AR complete STAT1 deficiency (61) (impairing IFN-α/β and -λ responses), suggested that TLR3-dependent IFN-α/β and/or -λ immunity is crucial for host defense against HSV1 in the CNS. It has been suggested that other mutations of these and other TLR3 or IFN pathway genes probably underlie HSE in adults or children (79–81). It has been further shown in a series of experiments that TLR3 pathway-deficient fibroblasts (68–74) and induced pluripotent stem cell (iPSC)-derived cortical neurons and oligodendrocytes (75) are much more susceptible to HSV1 infection than control cells, probably due to impaired TLR3-dependent IFN-β and IFN-λ production. By contrast, TLR3-mediated antiviral immunity is redundant in most other TLR3-expressing cell types, including leukocytes, iPSC-derived peripheral nervous system trigeminal neurons and CNS neural stem cells and astrocytes (75, 82). These data suggested that TLR3-dependent, IFN-

mediated cortical neuron- and oligodendrocyte-autonomous anti-HSV1 immunity is critical for host defense against HSV1 infection of the human forebrain. Other, distinctive molecular mechanisms may also underlie forebrain HSE, as suggested by the more recent discovery of AD snoRNA31 deficiency, which impairs the control of HSV1 infection in iPSC-derived cortical neurons despite normal responses via TLR3 and the IFN-α/β receptor (83).

Human genetic studies of forebrain HSE paved the way for investigations of inborn errors of immunity conferring a predisposition to other types of isolated viral encephalitis (VE). In this context, AR partial DBR1 deficiency - due to biallelic hypomorphic mutations of *DBR1* - has recently been reported in five otherwise healthy children with brainstem VE (BVE) due to various viruses, including HSV1 in two patients (84) (Table 1). In most patients with devastating BVE, the brainstem is the only region of the CNS affected, suggesting that, if there is an inborn error of immunity underlying BVE, it may affect brainstem-specific immunity. *DBR1* encodes the only known RNA lariat-debranching enzyme (84, 85). DBR1 protein levels are highest in the brainstem and spinal cord, strongly suggesting that DBR1 deficiency disrupts immunity in brainstem-resident cells (84). DBR1-deficient fibroblasts from the patients, whose TLR3 and IFN-α/β responsive pathways were intact, were found to contain higher RNA lariat levels than control cells, this difference becoming even more marked during HSV1 infection. Moreover, DBR1-deficient fibroblasts were highly susceptible to HSV1 and vesicular stomatitis virus (VSV), like TLR3- and STAT1-deficient fibroblasts (84). Inherited DBR1 deficiency probably underlies viral infection of the brainstem through the disruption of brainstem-specific and cell-intrinsic immunity to viruses, including HSV1. Human genetic studies of HSE have thus provided proof-of-principle that TLR3 governs cell-intrinsic immunity to HSV1 in the forebrain, whereas DBR1 governs cell-intrinsic immunity to various viruses, including HSV1, in the brainstem, paving the way for further investigations of CNS tissue-specific cell-intrinsic, as opposed to hematopoietic cell-mediated, immunity to HSV1 in humans.

VZV immunity

In the general population, the seroprevalence of VZV reaches about 80% by adulthood (86–88). VZV causes two different diseases: chickenpox (varicella) upon primary infection and shingles (herpes zoster) following reactivation. In rare cases, primary VZV infection or a reactivation of VZV infection may be complicated by severe clinical outcomes, including hemorrhagic varicella, pneumonitis, gastroenterological infection (ulcers, pancreatitis, hepatitis), eye infection (retinitis, keratitis), CNS infection (encephalitis, cerebellitis, meningitis, cranial nerve palsies, and vasculopathy), or systemic multiorgan infection (86, 89). In developed countries, ~5 in 1,000 people with varicella are hospitalized, and 2–3 per 100,000 patients die (86–88). However, the precise immunological correlates of human protective immunity to VZV are incompletely understood. Antibody-mediated humoral immunity is not generally thought to make a major contribution, as suggested by the absence of VZV infection as a prominent clinical phenomenon in individuals with antibody deficiencies (90). In this setting, as in other HHV infections, severe or recurrent VZV infection has been observed in some patients with various PIDs, often in combination with other infections.

Cellular immunity, exerted by T and NK cells, clearly plays an important role in host defense against VZV (90). In addition to severe infections caused by other pathogens, several PIDs confer a predisposition to severe disseminated primary varicella and frequent and extensive zoster or varicella pneumonia (Table 1). The most classic example is SCID, in which severe disseminated VZV infection is frequently documented (91). Severe VZV infection, including VZV-induced hemophagocytic lymphohistiocytosis (HLH), has also been reported in patients with AD GATA2 deficiency (92–94). Moreover, disseminated cutaneous VZV infection has been observed in other PIDs, including, but not restricted to, CORONIN1A, DOCK8, MCM4 and GINS1 deficiencies (38–40, 95, 96). Hemorrhagic or invasive VZV infection (including CNS infection) has been reported in patients with STAT5B (97–99) or DOCK2 deficiencies (100), respectively. Impaired activation of αβ T and NK cells due to STAT5B, DOCK8 or DOCK2 deficiency probably underlies severe cutaneous VZV infection in these patients. DOCK2 deficiency also compromises IFN-α/β and -λ production by peripheral blood cells upon viral infection, and cell-intrinsic antiviral immunity in fibroblasts. Thus, the severe invasive VZV infection observed in DOCK2-deficient children may result from defective adaptive (T cells) and/or innate (NK cells, IFN immunity in non-hematopoetic cells) immunity (100). Like cutaneous HSV infection, other PIDs affecting both adaptive and innate immunity (AD/AR IFNγ-R, AR TYK2 deficiencies) confer a predisposition to severe/recurrent cutaneous VZV infection in combination with mycobacterial diseases (56, 101). IFNγ-R and TYK2 deficiencies interfere with macrophage function and defense against intracellular pathogens, and with IFNγ-R/TYK2 signaling, suggesting a role of IFNs in restricting VZV replication and spread, as also suggested by some *in vitro* studies of VZV infection (86, 89, 90).

Further investigations of molecular and cellular mechanisms are required to confirm or clarify the role of IFN-mediated immunity in VZV infection. Recurrent zoster ophthalmicus has recently been reported in a patient with AD TLR3 deficiency, providing additional support for this hypothesis (102). Moreover, RNA polymerase III (POL III) deficiency has been added to the list of PIDs conferring predisposition to isolated severe VZV infection of specific organs, following the identification and characterization of an AD POL III defect in four otherwise healthy children with severe CNS or pulmonary VZV infection (103). POL III is a protein complex comprising 17 subunits organized into different subcomplexes involved in DNA/RNA binding, the initiation of transcription, enzymatic activity, and the termination of transcription (104). POL III is a cytosolic DNA sensor recognizing and transcribing AT-rich DNA to RNA, and then triggering IFN induction through the RIG-I pathway (105, 106). The four affected children were found to have rare heterozygous missense mutations of *POLR3A*, *POLR3C*, or both. Leukocytes from all four patients displayed poor induction of IFN-α/β and -λ in response to synthetic or VZV-derived AT-rich DNA. Moreover, leukocytes from three patients displayed defective IFN-α/β and -λ production upon VZV infection and poor control of VZV replication (103). This work suggested an important contribution of innate immunity to antiviral defenses against VZV through the recognition of the AT-rich VZV genome, and demonstrated a major role of type I and III IFNs. AD *POLR3F* mutations were subsequently reported in monozygotic adult twins experiencing repeated CNS vasculitis presenting in a stroke-like manner with hemiparesis, sensory deficits, and headache, clinically diagnosed as being caused by

recurrent VZV reactivation (107). Collectively, these recent findings suggested POL III may be important not only in protection against VZV CNS and pulmonary disease during primary infection, but also during reactivation, by controlling VZV latency in sensory ganglia (104, 107, 108). Future studies will clarify whether POL III is a VZV-specific antiviral immune sensor.

EBV immunity

EBV seroprevalence has been estimated at more than 90% in the general adult population (31, 109). The vast majority (>90%) of EBV-exposed individuals remain asymptomatic, or experience only mild self-limited disease. EBV causes infectious mononucleosis, which mostly affects adolescents. EBV was also oncogenic, causing several malignancies of lymphoid (non-Hodgkin lymphoma, Hodgkin's lymphoma, NK/T-cell lymphoma) and epithelial (nasopharyngeal carcinoma) origin (31, 110). However, in the setting of acquired immunodeficiencies, EBV infection can have dire consequences. For example, post-transplant lymphoproliferative disease due to the EBV-induced transformation of donor B cells is a frequent adverse event in immunocompromised patients undergoing organ transplantation or HSCT for various conditions (23, 31). Similarly, AIDS patients frequently develop EBV-related diseases, including EBV encephalitis (31). Many inborn errors of immunity predisposing affected individuals to EBV diseases, such as viremia, encephalitis, meningitis, and pneumonia, or EBV-induced diseases, such as lymphoproliferation, HLH, and B-cell lymphoma, have been identified. Severe EBV infection has frequently been reported in patients with PIDs that affect the development and/or function of various leukocytes (Table 1), including SCID (i.e. RAG2 deficiency (111)), CID (i.e. DOCK8 deficiency (112, 113)), syndromic CID (i.e. CARMIL2 deficiency (114)), AR IRF8 deficiency (115, 116), and GOF mutations in CARD11 (117, 118). These clinical observations revealed a strict balance between host and pathogen, as alterations to this homeostatic relationship were sufficient to cause disease.

X-linked lymphoproliferative disease (XLP) is the textbook example of a PID with a selective inability to generate effective immunity against EBV infection in otherwise healthy individuals. XLP1 and XLP2 are caused by inactivating mutations of *SH2D1A*, encoding SAP (SLAM-associating protein) and *XIAP*, encoding XIAP (X-linked inhibitor of apoptosis), respectively (119, 120). SAP is a cytoplasmic adaptor protein that links SLAM-family surface receptors to intracellular signaling pathways, to regulate T and NK cell function. In the absence of SAP, cytotoxicity of $CD8^+$ T and NK cells induced by the engagement of the SLAM-family receptors CD244 (2B4) and NTB-A is abolished. However, the cytotoxic effects of these cells following signaling through other activating receptors remain intact, potentially accounting for specific susceptibility to EBV but not to other HHVs (120, 121). Analyses of responses of SAP-deficient and SAP-sufficient $CD8^+$ T cells specific for the same antigenic peptide presented on different APCs confirmed this hypothesis. The killing of Ag-presenting DCs, monocytes or fibroblasts is unaffected by SAP deficiency, but responses of Ag-specific $CD8^+$ T cells to Ag-presenting B cells are strictly SAP-dependent (122). CD244 and NTB-A therefore play non-redundant roles in SLAM/SAP-mediated costimulation of Ag-specific $CD8^+$ T cells. Consistently, SLAM family ligands (CD48, NTB-A) are strongly expressed on B cells, but not fibroblasts or DCs

(122). Other receptor-ligand pairs would therefore serve this costimulatory function in the setting of Ag presentation by non-B cells. EBV is B-cell tropic, whereas many other viruses infect more than one type of host cell. These findings therefore account for the unique inability of XLP patients to control EBV infection, rendering them specifically vulnerable to EBV-induced disease.

Biallelic deleterious mutations of *ITK* (IL-2 inducible T cell kinase), *CD27*, *CD70, CTPS1* (CTP synthase 1) or *TNFRSF9* (4–1BB), and hemizygous mutations of *MAGT1* (encoding a magnesium transporter) all result in PIDs characterized by susceptibility to EBV diseases (viremia) or EBV-induced diseases (lymphoproliferation, lymphoma)(121, 123–127). Patients with these mutations also suffer from infections with other viral and bacterial pathogens, but investigations of their immune cell defects have shed more light on the molecular requirements for host defense against EBV. MAGT1 plays an important role in regulating TCR signaling, and maintaining expression of the activating receptor NKG2D on cytotoxic cells. Low levels of NKG2D on T and NK cells of MAGT1-deficient individuals is sufficient to compromise the ability of these cells to respond to EBV-transformed B cells (128). Remarkably, CD70-deficient memory $CD8^+$ T cells have abnormally low levels of expression for both NKG2D and 2B4, and are also unable to undergo activation by and to respond to autologous EBV-B cell targets (129). As CD70 is the counterpart structure of CD27, similar defects would be predicted to occur in CD27 deficiency. CD70 expression by B cells is required for the engagement of CD27 on responding $CD8^+$ T cells to induce activation and subsequent effector function (130). Given the important roles of 2B4 and NKG2D in $CD8^+$ T cell-mediated anti-EBV immunity, deduced from studies of XLP1 and MAGT1 deficiency, it has been suggested that impaired expression of these activating receptors underlies the inability of CD70-deficient (and CD27-deficient) $CD8^+$ T cells to kill EBV-infected B cells (121, 129). The recent discovery of *TNFRSF9* mutations in eight individuals with EBV viremia, lymphoproliferation and malignancy revealed that 4–1BB-deficient $CD8^+$ T cells had impairments of IFNγ and perforin production and of the killing of MHC class I-matched EBV-transformed B cells (123, 125, 131). As 4–1BB appears to have similar functions to CD27 (132), it will be important to determine whether the expression of CD244, NKG2D and even CD27 are affected by 4–1BB deficiency.

Thus, different genetic etiologies underlie these specific PIDs (Table 1), but the mechanisms resulting in susceptibility to EBV disease or EBV-induced disease all affect the expression or function of key receptors providing EBV-specific T cells with costimulatory signals in the context of Ag presentation by B cells. These observations, together with the preferential expression of ligands for CD244 (CD48), NTB-A (NTB-A), NKG2D (MIC-A/B), CD27 (CD70) and 4–1BB (4–1BBL) by B cells – the host cell for EBV – highlight the differences in molecular interactions between cognate $CD8^+$ T cells and APCs as a function of the nature of the invading pathogen and the APC itself, and the selective impairment of immunity to EBV infection in this group of specific PIDs.

HCMV immunity

The seroprevalence of HCMV ranges between 45 and 100% of the population (133, 134). Acute infection is usually asymptomatic in healthy individuals, or is associated with a

mononucleosis syndrome (135). HCMV infection has a profound impact on the immune repertoire in healthy individuals, influencing >50% of measured immune parameters in a large cohort of serodiscordant monozygotic twins (136). HCMV infection in pregnant women can lead to congenital infection, causing stillbirth or severe sequelae in the newborn, such as sensorineural hearing loss in particular (137, 138). HCMV infection or reactivation is also a major health problem in immunocompromised patients, such as AIDS patients, and patients on immunosuppression for HSCT or solid organ transplantation (22). Severe clinical manifestations, including encephalitis, colitis, hepatitis, retinitis, pneumonitis and vasculitis, have been reported in these patients (22, 27). The pathogenesis of these various HCMV diseases remains largely unclear. The same HCMV diseases have also been observed in some patients with various PIDs, with and without other infections (Table 1).

HCMV infection can be fatal in patients with SCID, who completely lack T cells (e.g. *IL2RG*, *JAK3*, *RAG*, and *ADA* mutations)(139). Similarly, patients with CID due to LOF recessive mutations broadly impairing T-cell immunity (e.g. *CARD11*, *IL2RB*, *IL12RB*, *ORAI1*, *STIM1*) are vulnerable to HCMV infection (140–143). However, some CID patients may have CMV viremia without clinical manifestations, as observed in CARMIL2 (144), DOCK2 (100, 145, 146) and ICOS deficiencies (147). In addition, inborn errors of immunity leading to an isolated absence of B cells (e.g. BTK deficiency)(148), complement deficiency (e.g. C3 deficiency)(149) or phagocyte deficiency (e.g. CYBA, NCF1 or NCF4 deficiencies) (150) are not associated with a specific risk of HCMV disease. Inborn errors of immunity reveal the crucial role of T cells in defense against HCMV. $CD4^+$ T cells have been shown to have a non-redundant role, based on the high susceptibility to HCMV of patients with MHC class II and CD40L deficiencies, which impair $CD4^+$ T-cell activation (151, 152). This finding is consistent with susceptibility to this virus of AIDS patients with low $CD4^+$ T-cell counts (153, 154). The lack of inborn errors resulting in isolated complete $CD8^+$ T-cell or NK cell deficiency makes it impossible to draw firm conclusion about the absolute requirements for these lymphocyte subsets in anti-HCMV immunity. MHC class I and CD8A deficiencies, which specifically impair, but do not abolish, $CD8^+$ T-cell and/or NK cell function, do not result in susceptibility to HCMV (155–157). However, GINS1 deficiency, which results in very low NK cell counts, neutropenia and a modest decrease in T-cell counts, is associated with fatal HCMV infection in one patient (40, 158).

Isolated susceptibility to HCMV is exceedingly rare, but there have been many reports of otherwise healthy patients with severe or life-threatening HCMV infection (159–162). Infection is usually restricted to a single organ in these patients. To date, only patients with hypomorphic *RAG1* mutations have been reported to suffer from isolated multivisceral and recurrent HCMV infection and autoimmunity (163). The immunological phenotype of these patients is characterized by low levels of $\alpha\beta$ T lymphocytes, normal levels of NK cells and a clonal expansion of the $\gamma\delta$ T-cell population (163). Analyses of patients with isolated HCMV infection will undoubtedly refine our understanding of anti-HCMV immunity. Interestingly, HCMV colitis or enteritis has mostly been reported in elderly individuals, although some teenagers or young adults have also been reported to be affected, in the absence of known morbidity cofactors (162, 164). Finally, fetal HCMV infection is common, with a prevalence of 0.7% worldwide, but its pathogenesis is unclear. It is diagnosed on the basis of clinical and/or laboratory abnormalities. The symptoms are

diverse, and include hearing loss, microcephaly and hepatitis. Fetal morbidity is not correlated with primary or secondary infection of the mother, suggesting that genetic factors may be involved (165). Based on restricted organ involvement, it seems likely that, as for HSE or severe influenza virus pneumonitis (75, 166), these patients are likely to have inherited cell-intrinsic immune defects with incomplete penetrance.

Immunity to HHV6 and HHV7

More than 90% of adults are seropositive for HHV6A, HHV6B and HHV7, with primary infection occurring between the ages of one and five years, depending on the virus (18). HHV6A and HHV6B have genomes that are 90% identical and about 50% identical to that of HHV7 (167). HHV6A and 6B can infect many different cell types, including $CD4^+$ and $CD8^+$ T lymphocytes, myeloid cells, some epithelial cells and neuronal cells, such as microglial cells, oligodendrocytes and astrocytes. By contrast, HHV7 has a narrow tropism, restricted to $CD4^+$ T cells, with CD4 playing a crucial role in virus entry (167). Primary infection with these three viruses is usually asymptomatic. The main clinical expression of HHV6B primary infection is exanthema subitum (ES), or roseola infantum, a benign childhood infection. Clinical expression following primary infection with HHV6A and HHV7 is less well documented, but some cases of ES have been reported.

Severe manifestations are extremely rare. Cases of encephalitis and hepatitis due to reactivation have been reported in patients with acquired immune deficiency, either due to AIDS or immunosuppression for HSCT or solid organ transplantation (26, 29, 30). HHV6 reactivation and detectable viremia are common, with a frequency of 40 to 60% after HSC or solid organ transplantation, but only a few patients develop encephalitis (28). Diagnosis is based on electroencephalography and the detection of replicative HHV6 by immunochemistry or PCR in brain tissue and/or peripheral blood, together with antibody detection in CSF (29). HHV7 reactivation associated with encephalitis has been observed in patients post-HSCT (24, 29). One patient with X-linked SCID developed HLH due to activation of the integrated HHV6 genome (168). Finally, one ICOS-deficient patient with colitis and mild chronic hepatitis was found to be HHV6-positive by PCR on colon, duodenum and liver biopsy specimens. Her hepatitis symptoms improved, but those of colitis did not, following intravenous ganciclovir and oral valganciclovir treatments (169). However, some cases of encephalitis associated with HHV6 or HHV7 (170–174), and fulminant hepatitis due to HHV6 (175–178) have been reported in otherwise healthy individuals based on serology tests and/or the detection of viral DNA in CSF and/or whole blood. Patients who developed meningoencephalitis following HHV6 infection may also have ES manifestations (179, 180). Interestingly, no known inherited immunodeficiency has yet been associated with isolated severe HHV6 or HHV7 infections causing encephalitis or fulminant hepatitis. Novel inborn errors of immunity might explain these phenotypes. The identification of genetic etiologies responsible for severe clinical manifestations will facilitate the dissection of anti-HHV6 and anti-HHV7 immunity.

HHV8 immunity

The seroprevalence of HHV8 is variable worldwide, ranging from <20% in non-endemic areas, (eg North America, Northern Europe, most of Asia), to > 40% in parts of Africa and

South America (181). HHV8 causes Kaposi sarcoma (KS) or B-cell lymphoproliferative disorders, such as multicentric Castleman's disease and primary effusion lymphoma. The vast majority of individuals exposed to HHV8 remain asymptomatic, or experience mild self-limited disease. KS has been classified into four epidemiological forms: epidemic and iatrogenic KS, both related to acquired immune deficiencies, due to HIV and following immunosuppression for solid organ transplantation, respectively; classic KS, which is observed in elderly men from Mediterranean countries and Eastern Europe; and endemic KS in sub-Saharan Africa. The histological features of the four forms of KS are identical, with spindle-shaped cells, inflammation, and angioproliferation with erythrocyte extravasation, suggesting a similar pathogenic mechanism. With the exception of epidemic KS, KS is very rare in children, suggesting that affected patients may suffer from an inherited immunodeficiency (182, 183).

Two inherited PIDs have been associated with KS in combination with other infectious diseases: AR *IFNGR1* and XR *WASP* mutations. Complete AR IFNγR1 deficiency affects both adaptive and innate immunity, and is associated with life-threatening mycobacterial infections (53). In addition to such recurrent infections, one IFNγR1-deficient patient developed disseminated cutaneous and systemic KS. This patient presented a low $CD4^+$ T-cell count, probably due to recurrent infections with mycobacteria, HHV8, or both. He died at 12 years of age (184). XR WAS affects cells involved in both innate and adaptive immunity, including myeloid cells, NK cells, B and T cells. Two cases of XR WAS with KS have been reported: one in a child and one in an adult with concomitant T-cell lymphoma (185, 186). The adult case was diagnosed with WAS in early childhood, but had a mild clinical phenotype. The child developed many infections during his two years of life. He received systemic steroid treatment in the month before onset of KS, which might have contributed to the development of KS. KS remission was complete after non-T cell-depleted allogeneic HSCT (186). The observation of KS in patients with acquired immunodeficiencies and these two PIDs suggested a role for T cells, probably $CD4^+$ T cells, in anti-HHV8 immunity.

AR complete deficiencies of STIM1 and OX40 have recently been shown to be associated with isolated KS (187, 188). For both deficiencies, patients have aggressive, disseminated, cutaneous and systemic KS. The patient with STIM1 deficiency died at two years of age from pulmonary KS lesions, and would probably have developed the many infections seen in other STIM1-deficient patients had she lived long enough (182, 187). By contrast, complete remission was observed in the patient with OX40 deficiency after drug treatment. With the exception of leishmaniasis at the age of nine years, she has not suffered from other unusual infections, and is now 25 years old (188). Interestingly, in both these PIDs, T-cell immunity was impaired, but T-cell counts were normal. STIM1 is involved in the Ca^{2+} release-activated Ca^{2+} channel, which is essential for Ca^{2+} influx in T lymphocytes following TCR stimulation, leading to proliferation and production of the cytokines required for T-cell effector function and differentiation (189). Similarly, OX40 is highly expressed on activated T cells and functions as a costimulatory molecule for inducing proliferation, survival and cytokine production by T cells (190). OX40 deficiency is associated with impaired $CD4^+$ T-cell responses to recall antigens in terms of proliferation and IFNγ production (188). Studies of acquired and inherited immunodeficiencies have, thus, highlighted the crucial role of

OX40-dependent $CD4^+$ T-cell immunity in the control of HHV8 infection (Table 1). Further studies are required to define the immune responses to HHV8 crucial for preventing KS, multicentric Castleman's disease and primary effusion lymphoma.

Conclusions

The first herpes virus was identified 100 years ago, and the last 25 years ago. Due to high seroprevalence, the lack of an effective vaccine, and the emergence of antiviral drug-resistant strains, HHV infections continue to be a public health problem (191). Despite a century of virological studies, our understanding of human immunity to HHVs remains partial. HHVs are associated with diverse clinical manifestations, involving different cells and tissues. Interestingly, PIDs of leukocytes conferring a predisposition to HHV infection, including even the most severe forms of SCID, although are frequently associated with severe HHV infections of peripheral tissues (i.e. skin, lung), may, only in rarer cases, be associated with invasive infections of internal organs (i.e. brain, liver). The discovery of the molecular basis of severe HHV infections in some patients has shed light on the contribution of leukocytes and other cells to protective immunity to HHVs. Some HHV infections can be attributed, at least partly, to abnormally small numbers or impaired functions of leukocyte subsets, such as $CD4^+$ T, $CD8^+$ T, and NK cells ($CD8^+$ T cells in anti-EBV immunity, $CD4^+$ T cells in anti-HCMV and HHV8 immunity, NK cells in anti-HSV, VZV and possibly EBV immunity). IFN-α/β or -λ-mediated immunity provided by leukocytes, including DCs in particular, may be crucial in some infections, as suggested by the observation of severe VZV infection in POL III-deficient or DOCK2-deficient patients (whose leukocyte IFN-α/β and -λ responses to VZV-related stimulations are impaired) and in GATA2-deficient patients (whose leukocyte IFN immunity is impaired due to DC lymphopenia). Other HHV infections can be attributed to deficiencies of cells other than leukocytes, as illustrated by the role of forebrain neuron and oligodendrocyte cell-intrinsic immunity in forebrain defense against HSV1 infection, and brainstem cell-intrinsic immunity at this anatomical site. These studies highlight the importance of studying the human genetic and immunological basis of severe HHV disease restricted to a specific cell, tissue, or organ, in otherwise healthy individuals.

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References

1. Schneweis K. Serological relations of types 1 and 2 of herpesvirus hominis to herpesvirus simiae. Z Immun Exp Ther. 1962;124:337–41. [PubMed: 13992215]
2. Weller TH, Stoddard MB. Intranuclear inclusion bodies in cultures of human tissue inoculated with varicella vesicle fluid. J Immunol. 1952;68(3):311–9. [PubMed: 14938547]
3. Weller TH, Stoddard MB. Intranuclear inclusion bodies in tissue cultures inoculated with varicella vesicle fluid. AMA Am J Dis Child. 1952;83(1):75–6. [PubMed: 14884741]
4. Smith MG. Propagation in tissue cultures of a cytopathogenic virus from human salivary gland virus (SGV) disease. Proc Soc Exp Biol Med. 1956;92(2):424–30. [PubMed: 13350368]
5. Epstein MA, Achong BG, Barr YM. Virus Particles in Cultured Lymphoblasts from Burkitt's Lymphoma. Lancet. 1964;1(7335):702–3. [PubMed: 14107961]
6. Pattengale PK, Smith RW, Gerber P. Selective transformation of B lymphocytes by E.B. virus. Lancet. 1973;2(7820):93–4.
7. Salahuddin SZ, Ablashi DV, Markham PD, Josephs SF, Sturzenegger S, Kaplan M, et al. Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science. 1986;234(4776):596–601. [PubMed: 2876520]
8. Ablashi D, Agut H, Alvarez-Lafuente R, Clark DA, Dewhurst S, DiLuca D, et al. Classification of HHV-6A and HHV-6B as distinct viruses. Arch Virol. 2014;159(5):863–70. [PubMed: 24193951]
9. Frenkel N, Schirmer EC, Wyatt LS, Katsafanas G, Roffman E, Danovich RM, et al. Isolation of a new herpesvirus from human CD4+ T cells. Proc Natl Acad Sci U S A. 1990;87(2):748–52. [PubMed: 2153965]
10. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266(5192):1865–9. [PubMed: 7997879]
11. Hill TJ. Herpes simplex virus latency In: Roizman, ed. 1985;The Herpesviruses, Vol 3, New York: Plenum Press:175–240.
12. Kondo K, Kondo T, Okuno T, Takahashi M, Yamanishi K. Latent human herpesvirus 6 infection of human monocytes/macrophages. J Gen Virol. 1991;72 (Pt 6):1401–8. [PubMed: 1646280]
13. Luppi M, Barozzi P, Morris C, Maiorana A, Garber R, Bonacorsi G, et al. Human herpesvirus 6 latently infects early bone marrow progenitors in vivo. J Virol. 1999;73(1):754–9. [PubMed: 9847383]
14. Rickinson AB, Kieff E. Epstein-Barr virus In Field's Virology, ed Fields BN, Knipe DM, Howley PM 2001;Philadelphia: Lippincott-Raven:2397–446.
15. Roizman B, Pellet PE. The family Herpesviridae : A brief introduction Fields' Virology, 4th edition, editors Knipe DM and Howley PM. 2007;Part II:2381–98.
16. Stagno S, Reynolds DW, Pass RF, Alford CA. Breast milk and the risk of cytomegalovirus infection. N Engl J Med. 1980;302(19):1073–6. [PubMed: 6245360]
17. Arbuckle JH, Medveczky MM, Luka J, Hadley SH, Luegmayr A, Ablashi D, et al. The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes in vivo and in vitro. Proc Natl Acad Sci U S A. 2010;107(12):5563–8. [PubMed: 20212114]
18. Ward KN, Turner DJ, Parada XC, Thiruchelvam AD. Use of immunoglobulin G antibody avidity for differentiation of primary human herpesvirus 6 and 7 infections. J Clin Microbiol. 2001;39(3):959–63. [PubMed: 11230411]
19. Elion GB, Furman PA, Fyfe JA, de Miranda P, Beauchamp L, Schaeffer HJ. Selectivity of action of an antiherpetic agent, 9-(2-hydroxyethoxymethyl) guanine. Proc Natl Acad Sci U S A. 1977;74(12):5716–20. [PubMed: 202961]
20. Whitley J, Gnann W Jr., Acyclovir: a decade later. N Engl J Med. 1992;327(11):782–9. [PubMed: 1288525]
21. Grulich AE, Vajdic CM. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. Semin Oncol. 2015;42(2):247–57. [PubMed: 25843729]
22. Boeckh M, Geballe AP. Cytomegalovirus: pathogen, paradigm, and puzzle. J Clin Invest. 2011;121(5):1673–80. [PubMed: 21659716]

23. Bollard CM, Rooney CM, Heslop HE. T-cell therapy in the treatment of post-transplant lymphoproliferative disease. Nat Rev Clin Oncol. 2012;9(9):510–9. [PubMed: 22801669]
24. Chan PK, Chik KW, To KF, Li CK, Shing MM, Ng KC, et al. Case report: human herpesvirus 7 associated fatal encephalitis in a peripheral blood stem cell transplant recipient. J Med Virol. 2002;66(4):493–6. [PubMed: 11857527]
25. Chrétien F, Bélec L, Hikton DA, Flament-Saillour M, Guillon F, Wingerstmann L, et al. Herpes simplex virus type 1 encephalitis in acquired immunodeficiency syndromes. Neuropathol Appl Neurobiol. 1996;22(5):394–404. [PubMed: 8930949]
26. Clark DA, Griffiths PD. Human herpesvirus 6: relevance of infection in the immunocompromised host. Br J Haematol. 2003;120(3):384–95. [PubMed: 12580952]
27. Golden MP, Hammer SM, Wanke CA, Albrecht MA. Cytomegalovirus vasculitis. Case reports and review of the literature. Medicine (Baltimore). 1994;73(5):246–55. [PubMed: 7934809]
28. Ogata M, Satou T, Kawano R, Takakura S, Goto K, Ikewaki J, et al. Correlations of HHV-6 viral load and plasma IL-6 concentration with HHV-6 encephalitis in allogeneic stem cell transplant recipients. Bone Marrow Transplant. 2010;45(1):129–36. [PubMed: 19465942]
29. Ongradi J, Ablashi DV, Yoshikawa T, Stercz B, Ogata M. Roseolovirus-associated encephalitis in immunocompetent and immunocompromised individuals. J Neurovirol. 2017;23(1):1–19. [PubMed: 27538995]
30. Singh N, Paterson DL. Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus. Transplantation. 2000;69(12):2474–9. [PubMed: 10910264]
31. Taylor GS, Long HM, Brooks JM, Rickinson AB, Hislop AD. The immunology of Epstein-Barr virus-induced disease. Annu Rev Immunol. 2015;33:787–821. [PubMed: 25706097]
32. Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet. 2001;357(9267):1513–8. [PubMed: 11377626]
33. Widener RW, Whitley RJ. Herpes simplex virus. Handb Clin Neurol. 2014;123:251–63. [PubMed: 25015489]
34. Chentoufi AA, Benmohamed L. Mucosal herpes immunity and immunopathology to ocular and genital herpes simplex virus infections. Clin Dev Immunol. 2012;2012:149135.
35. Gnann JW Jr., Whitley RJ. Herpes Simplex Encephalitis: an Update. Curr Infect Dis Rep. 2017;19(3):13. [PubMed: 28251511]
36. Whitley R, Baines J. Clinical management of herpes simplex virus infections: past, present, and future. F1000Res. 2018;7.
37. Whitley RJ. Herpes Simplex Virus Infections of the Central Nervous System. Continuum (Minneap Minn). 2015;21(6 Neuroinfectious Disease):1704–13. [PubMed: 26633784]
38. Gineau L, Cognet C, Kara N, Lach FP, Dunne J, Veturi U, et al. Partial MCM4 deficiency in patients with growth retardation, adrenal insufficiency, and natural killer cell deficiency. J Clin Invest. 2012;122(3):821–32. [PubMed: 22354167]
39. Hughes CR, Guasti L, Meimaridou E, Chuang CH, Schimenti JC, King PJ, et al. MCM4 mutation causes adrenal failure, short stature, and natural killer cell deficiency in humans. J Clin Invest. 2012;122(3):814–20. [PubMed: 22354170]
40. Cottineau J, Kottemann MC, Lach FP, Kang YH, Vely F, Deenick EK, et al. Inherited GINS1 deficiency underlies growth retardation along with neutropenia and NK cell deficiency. J Clin Invest. 2017;127(5):1991–2006. [PubMed: 28414293]
41. Aydin E, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, et al. DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. J Clin Immunol. 2015;35(2):189–98. [PubMed: 25627830]
42. Engelhardt KR, Gertz ME, Keles S, Schaffer AA, Sigmund EC, Glocker C, et al. The extended clinical phenotype of 64 patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol. 2015;136(2):402–12. [PubMed: 25724123]
43. Zhang Q, Davis JC, Dove CG, Su HC. Genetic, clinical, and laboratory markers for DOCK8 immunodeficiency syndrome. Dis Markers.29(3–4):131–9. [PubMed: 21178272]
44. Abdollahpour H, Appaswamy G, Kotlarz D, Diestelhorst J, Beier R, Schaffer AA, et al. The phenotype of human STK4 deficiency. Blood. 2012;119(15):3450–7. [PubMed: 22294732]

45. Delgado-Marquez AM, Zarco C, Ruiz R, Simarro A, Vanaclocha F. Severe disseminated primary herpes simplex infection as skin manifestation of GATA2 deficiency. J Eur Acad Dermatol Venereol. 2016;30(7):1248–50. [PubMed: 25955867]
46. Donadieu J, Lamant M, Fieschi C, de Fontbrune FS, Caye A, Ouachee M, et al. Natural history of GATA2 deficiency in a survey of 79 French and Belgian patients. Haematologica. 2018;103(8):1278–87. [PubMed: 29724903] * This paper report a large cohort of 79 AD GATA2-deficient patients from 53 families from France and Belgium. Known and novel clinical features are reported. This report further highlights the complex genetic, immunological and clinical features of AD GATA2 deficiency.
47. Hsu AP, McReynolds LJ, Holland SM. GATA2 deficiency. Curr Opin Allergy Clin Immunol. 2015;15(1):104–9. [PubMed: 25397911]
48. Spinner MA, Ker JP, Stoudenmire CJ, Fadare O, Mace EM, Orange JS, et al. GATA2 deficiency underlying severe blastomycosis and fatal herpes simplex virus-associated hemophagocytic lymphohistiocytosis. J Allergy Clin Immunol. 2016;137(2):638–40. [PubMed: 26395816]
49. Spinner MA, Sanchez LA, Hsu AP, Shaw PA, Zerbe CS, Calvo KR, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood. 2014;123(6):809–21. [PubMed: 24227816]
50. Heusinkveld LE, Yim E, Yang A, Azani AB, Liu Q, Gao JL, et al. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. Expert Opin Orphan Drugs. 2017;5(10):813–25. [PubMed: 29057173]
51. Albert MH, Notarangelo LD, Ochs HD. Clinical spectrum, pathophysiology and treatment of the Wiskott-Aldrich syndrome. Curr Opin Hematol. 2011;18(1):42–8. [PubMed: 21076297]
52. Ochs HD, Thrasher AJ. The Wiskott-Aldrich syndrome. J Allergy Clin Immunol. 2006;117(4):725–38; quiz 39. [PubMed: 16630926]
53. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol. 2014;26(6):454–70. [PubMed: 25453225]
54. Dorman SE, Picard C, Lammas D, Heyne K, van Dissel JT, Baretto R, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet. 2004;364(9451):2113–21. [PubMed: 15589309]
55. Dorman SE, Uzel G, Roesler J, Bradley JS, Bastian J, Billman G, et al. Viral infections in interferon-gamma receptor deficiency. J Pediatr. 1999;135(5):640–3. [PubMed: 10547254]
56. Kreins AY, Ciancanelli MJ, Okada S, Kong XF, Ramirez-Alejo N, Kilic SS, et al. Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. J Exp Med. 2015;212(10):1641–62. [PubMed: 26304966]
57. Picard C, Casanova JL, Puel A. Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IkappaBalpha deficiency. Clin Microbiol Rev. 2011;24(3):490–7. [PubMed: 21734245]
58. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra C, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood. 2016;127(25):3154–64. [PubMed: 27114460]
59. Vargas-Hernandez A, Mace EM, Zimmerman O, Zerbe CS, Freeman AF, Rosenzweig S, et al. Ruxolitinib partially reverses functional natural killer cell deficiency in patients with signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations. J Allergy Clin Immunol. 2018;141(6):2142–55 e5. [PubMed: 29111217]
60. Tabellini G, Vairo D, Scomodon O, Tamassia N, Ferraro RM, Patrizi O, et al. Impaired natural killer cell functions in patients with signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations. J Allergy Clin Immunol. 2017;140(2):553–64 e4. [PubMed: 28069426]
61. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet. 2003;33(3):388–91. [PubMed: 12590259]
62. Puel A, Reichenbach J, Bustamante J, Ku CL, Feinberg J, Doffinger R, et al. The NEMO mutation creating the most-upstream premature stop codon is hypomorphic because of a reinitiation of translation. Am J Hum Genet. 2006;78(4):691–701. [PubMed: 16532398]

63. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018;38(1):96–128. [PubMed: 29226302]
64. Abel L, Plancoulaine S, Jouanguy E, Zhang SY, Mahfoufi N, Nicolas N, et al. Age-dependent Mendelian predisposition to herpes simplex virus type 1 encephalitis in childhood. J Pediatr. 2010;157(4):623–9, 9 e1. [PubMed: 20553844]
65. Whitley RJ. Herpes simplex encephalitis: adolescents and adults. Antiviral Res. 2006;71(2–3):141–8. [PubMed: 16675036]
66. Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis / brainstem encephalitis. Curr Neurol Neurosci Rep. 2011;11(6):543–52. [PubMed: 21956758]
67. Casanova J, Abel L. The genetic theory of infectious diseases: brief history and selected illustrations. Ann Rev Genomics. 2013;14:215–43.
68. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science. 2006;314(5797):308–12. [PubMed: 16973841]
69. Guo Y, Audry M, Ciancanelli M, Alsina L, Azevedo J, Herman 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(10):2083–98. [PubMed: 21911422]
70. Herman M, Ciancanelli M, Ou YH, Lorenzo L, Klaudel-Dreszler M, Pauwels E, et al. Heterozygous TBK1 mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood. J Exp Med. 2013;209(9):1567–82.
71. Perez de Diego R, Sancho-Shimizu V, Lorenzo L, Puel A, Plancoulaine S, Picard C, et al. Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. Immunity. 2010;33(3):400–11. [PubMed: 20832341]
72. Sancho-Shimizu V, Perez de Diego R, Lorenzo L, Halwani R, Alangari A, Israelsson E, et al. Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. J Clin Invest. 2011;121(12):4889–902. [PubMed: 22105173]
73. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, et al. TLR3 deficiency in patients with herpes simplex encephalitis. Science. 2007;317(5844):1522–7. [PubMed: 17872438]
74. Lim HK, Seppänen M, Hautala T, Ciancanelli M, Itan Y, Lafaille FG, et al. TLR3 deficiency in herpes simplex encephalitis: high allelic heterogeneity and recurrence risk. Neurology. 2014;83(21):1888–97. [PubMed: 25339207]
75. Lafaille G, Pessach M, Zhang Y, Ciancanelli J, Herman M, Abhyankar A, et al. Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. Nature. 2012;491(7426):769–73. [PubMed: 23103873]
76. Zhang SY, Casanova JL. Inborn errors underlying herpes simplex encephalitis: From TLR3 to IRF3. J Exp Med. 2015;212(9):1342–3. [PubMed: 26304982]
77. Andersen LL, Mork N, Reinert LS, Kofod-Olsen E, Narita R, Jorgensen SE, et al. Functional IRF3 deficiency in a patient with herpes simplex encephalitis. J Exp Med. 2015;212(9):1371–79. [PubMed: 26216125]
78. Audry M, Ciancanelli M, Yang K, Cobat A, Chang HH, Sancho-Shimizu V, et al. NEMO is a key component of NF-kappaB- and IRF-3-dependent TLR3-mediated immunity to herpes simplex virus. J Allergy Clin Immunol. 2011;128(3):610–7 e1–4. [PubMed: 21722947]
79. Garcia-Morato B, Apalategi CA, Bravo-Galego L, Blaquez Moreno A, Soimon-Fuentes M, Garmendia J, et al. Impaired control of multiple viral infections in a family with complete IRF9 deficiency. J Allergy Clin Immunol. 2019;144(1):309–12. [PubMed: 30826365]
80. Mork N, Kofod-Olsen E, Sorensen KB, Bach E, Orntoft TF, Ostergaard L, et al. Mutations in the TLR3 signaling pathway and beyond in adult patients with herpes simplex encephalitis. Genes Immun. 2015;16(8):552–66. [PubMed: 26513235]
81. Armangue T, Baucells BJ, Vlagea A, Petit-Pedrol M, Esteve-Sole A, Deya-Martinez A, et al. Toll-like receptor 3 deficiency in autoimmune encephalitis post-herpes simplex encephalitis. Neurol Neuroimmunol Neuroinflamm. 2019;6(6).
82. Zimmer B, Ewaleifoh O, Harschnitz O, Lee YS, Peneau C, McAlpine JL, et al. Human iPSC-derived trigeminal neurons lack constitutive TLR3-dependent immunity that protects cortical

neurons from HSV-1 infection. Proc Natl Acad Sci U S A. 2018;115(37):E8775–E82. [PubMed: 30154162]

83. Lafaille FG, Harschnitz O, Lee YS, Zhang P, Hasek ML, Kerner G, et al. Human SNORA31 variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis. Nat Med. 2019;25(12):1873–84. [PubMed: 31806906] * This paper reports the discovery of autosomal dominant snoRNA31 deficiency in patients with Herpes simplex virus 1 (HSV1) encephalitis. This study suggests that molecular mechanisms independent of the activation of TLR3 and IFN pathways may also be involved in central nervous system neuron-intrinsic immunity to HSV1.
84. Zhang SY, Clark NE, Freije CA, Pauwels E, Taggart AJ, Okada S, et al. Inborn Errors of RNA Lariat Metabolism in Humans with Brainstem Viral Infection. Cell. 2018;172(5):952–65 e18. [PubMed: 29474921] * This paper reports the discovery of autosomal recessive partial DBR1 deficiency in children with viral infections of the brainstem. DBR1 is the only known RNA lariat-debranching enzyme and its expression normally peaks in the brainstem. Inborn errors of RNA lariat debranching underlie viral infection of the brainstem by disrupting brainstem-specific and cell-intrinsic immunity to viruses.
85. Chapman KB, Boeke JD. Isolation and characterization of the gene encoding yeast debranching enzyme. Cell. 1991;65(3):483–92. [PubMed: 1850323]
86. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, et al. Varicella zoster virus infection. Nat Rev Dis Primers. 2015;1:15016. [PubMed: 27188665]
87. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,. 2015;8th Edition, Elsevier:1731–7.
88. Whitley RJ. Varicella-Zoster Virus Infections. Harrison's principles of internal Medecine. 2014;19e New York, NY:McGraw-Hill.
89. Zerboni L, Sen N, Oliver SL, Arvin AM. Molecular mechanisms of varicella zoster virus pathogenesis. Nat Rev Microbiol. 2014;12(3):197–210. [PubMed: 24509782]
90. Duncan CJ, Hambleton S. Varicella zoster virus immunity: A primer. J Infect. 2015;71 Suppl 1:S47–53.
91. Brooks EG, Schmalstieg FC, Wirt DP, Rosenblatt HM, Adkins LT, Lookingbill DP, et al. A novel X-linked combined immunodeficiency disease. J Clin Invest. 1990;86(5):1623–31. [PubMed: 2243135]
92. Biron CA, Byron KS, Sullivan JL. Severe herpesvirus infections in an adolescent without natural killer cells. N Engl J Med. 1989;320(26):1731–5. [PubMed: 2543925]
93. Hsu AP, Sampaio EP, Khan J, Calvo KR, Lemieux JE, Patel SY, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. Blood. 2011;118(10):2653–5. [PubMed: 21670465]
94. Prader S, Felber M, Volkmer B, Truck J, Schwieger-Briel A, Theiler M, et al. Life-Threatening Primary Varicella Zoster Virus Infection With Hemophagocytic Lymphohistiocytosis-Like Disease in GATA2 Haploinsufficiency Accompanied by Expansion of Double Negative T-Lymphocytes. Front Immunol. 2018;9:2766. [PubMed: 30564229]
95. Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, et al. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med. 2009;361(21):2046–55. [PubMed: 19776401]
96. Yee CS, Massaad MJ, Bainter W, Ohsumi TK, Foger N, Chan AC, et al. Recurrent viral infections associated with a homozygous CORO1A mutation that disrupts oligomerization and cytoskeletal association. J Allergy Clin Immunol. 2016;137(3):879–88 e2. [PubMed: 26476480]
97. Bezrodnik L, Di Giovanni D, Caldirola MS, Azcoiti ME, Torgerson T, Gaillard MI. Long-term follow-up of STAT5B deficiency in three argentinian patients: clinical and immunological features. J Clin Immunol. 2015;35(3):264–72. [PubMed: 25753012]
98. Bernasconi A, Marino R, Ribas A, Rossi J, Ciaccio M, Oleastro M, et al. Characterization of immunodeficiency in a patient with growth hormone insensitivity secondary to a novel STAT5b gene mutation. Pediatrics. 2006;118(5):e1584–92. [PubMed: 17030597]
99. Scaglia PA, Martinez AS, Feigerlova E, Bezrodnik L, Gaillard MI, Di Giovanni D, et al. A novel missense mutation in the SH2 domain of the STAT5B gene results in a transcriptionally inactive

STAT5b associated with severe IGF-I deficiency, immune dysfunction, and lack of pulmonary disease. J Clin Endocrinol Metab. 2012;97(5):E830–9. [PubMed: 22419735]

100. Dobbs K, Dominguez Conde C, Zhang SY, Parolini S, Audry M, Chou J, et al. Inherited DOCK2 Deficiency in Patients with Early-Onset Invasive Infections. N Engl J Med. 2015;372(25):2409–22. [PubMed: 26083206]
101. Roesler J, Kofink B, Wendisch J, Heyden S, Paul D, Friedrich W, et al. Listeria monocytogenes and recurrent mycobacterial infections in a child with complete interferon-gamma-receptor (IFNgammaR1) deficiency: mutational analysis and evaluation of therapeutic options. Exp Hematol. 1999;27(9):1368–74. [PubMed: 10480427]
102. Liang F, Glans H, Enoksson SL, Kolios AGA, Lore 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. 2019.
103. Ogunjimi B, Zhang SY, Sorensen KB, Skipper KA, Carter-Timofte M, Kerner G, et al. Inborn errors in RNA polymerase III underlie severe varicella zoster virus infections. J Clin Invest. 2017;127(9):3543–56. [PubMed: 28783042] * This paper reports the identification and characterization of AD POL III deficiency in four otherwise healthy children with severe CNS or pulmonary VZV infection. POL III is a cytosolic DNA sensor recognizing and transcribing AT-rich DNA to RNA, and then triggering IFN induction through the RIG-I pathway. The four otherwise healthy children carry heterozygous missense mutations of POLR3A, POLR3C, or both. Leukocytes from the patients display poor induction of IFN-α/β and -λ in response to synthetic or VZV-derived AT-rich DNA or VZV infection, and poor control of VZV replication. POL III-mediated type I and III IFNs are therefore crucial for human antiviral defenses against VZV.
104. Carter-Timofte ME, Paludan SR, Mogensen TH. RNA Polymerase III as a Gatekeeper to Prevent Severe VZV Infections. Trends Mol Med. 2018;24(10):904–15. [PubMed: 30115567]
105. 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(10):1065–72. [PubMed: 19609254]
106. 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(3):576–91. [PubMed: 19631370]
107. Carter-Timofte ME, Hansen AF, Mardahl M, Fribourg S, Rapaport F, Zhang SY, et al. Varicella-zoster virus CNS vasculitis and RNA polymerase III gene mutation in identical twins. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e500.
108. 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(3):214–23. [PubMed: 29728610]
109. Rickinson AB, Long HM, Palendira U, Munz C, Hislop AD. Cellular immune controls over Epstein-Barr virus infection: new lessons from the clinic and the laboratory. Trends Immunol. 2014;35(4):159–69. [PubMed: 24589417]
110. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer. 2004;4(10):757–68. [PubMed: 15510157]
111. Schuetz C, Huck K, Gudowius S, Megahed M, Feyen O, Hubner B, et al. An immunodeficiency disease with RAG mutations and granulomas. N Engl J Med. 2008;358(19):2030–8. [PubMed: 18463379]
112. Buchbinder D, Kirov I, Danielson J, Shah NN, Freeman AF, Chavan RS, et al. Compound Heterozygous DOCK8 Mutations in a Patient with B Lymphoblastic Leukemia and EBV-Associated Diffuse Large B Cell Lymphoma. J Clin Immunol. 2019.
113. Dimitriades VR, Devlin V, Pittaluga S, Su HC, Holland SM, Wilson W, et al. DOCK 8 Deficiency, EBV+ Lymphomatoid Granulomatosis, and Intrafamilial Variation in Presentation. Front Pediatr. 2017;5:38. [PubMed: 28293550]
114. Schober T, Magg T, Laschinger M, Rohlfs M, Linhares ND, Puchalka J, et al. A human immunodeficiency syndrome caused by mutations in CARMIL2. Nat Commun. 2017;8:14209. [PubMed: 28112205] * This paper reports four human patients with EBV+ disseminated smooth muscle tumours carrying two homozygous loss-of-function mutations in CARMIL2. This is the first report of CARMIL2 deficiency as an autosomal recessive primary immunodeficiency

disorder associated with defective CD28-mediated TCR co-signaling and impaired cytoskeletal dynamics.

115. Mace EM, Bigley V, Gunesch JT, Chinn IK, Angelo LS, Care MA, et al. Biallelic mutations in IRF8 impair human NK cell maturation and function. J Clin Invest. 2017;127(1):306–20. [PubMed: 27893462]
116. Adams NM, Lau CM, Fan X, Rapp M, Geary CD, Weizman OE, et al. Transcription Factor IRF8 Orchestrates the Adaptive Natural Killer Cell Response. Immunity. 2018;48(6):1172–82 e6. [PubMed: 29858012]
117. Arjunaraja S, Angelus P, Su HC, Snow AL. Impaired Control of Epstein-Barr Virus Infection in B-Cell Expansion with NF-kappaB and T-Cell Anergy Disease. Front Immunol. 2018;9:198. [PubMed: 29472930]
118. Brohl AS, Stinson JR, Su HC, Badgett T, Jennings CD, Sukumar G, et al. Germline CARD11 Mutation in a Patient with Severe Congenital B Cell Lymphocytosis. J Clin Immunol. 2015;35(1):32–46. [PubMed: 25352053]
119. Latour S, Aguilar C. XIAP deficiency syndrome in humans. Semin Cell Dev Biol. 2015;39:115–23. [PubMed: 25666262]
120. Tangye SG. XLP: clinical features and molecular etiology due to mutations in SH2D1A encoding SAP. J Clin Immunol. 2014;34(7):772–9. [PubMed: 25085526]
121. Tangye SG, Palendira U, Edwards ES. Human immunity against EBV-lessons from the clinic. J Exp Med. 2017;214(2):269–83. [PubMed: 28108590]
122. Palendira U, Low C, Chan A, Hislop AD, Ho E, Phan TG, et al. Molecular pathogenesis of EBV susceptibility in XLP as revealed by analysis of female carriers with heterozygous expression of SAP. PLoS Biol. 2011;9(11):e1001187.
123. Alosaimi MF, Hoenig M, Jaber F, Platt CD, Jones J, Wallace J, et al. Immunodeficiency and EBV-induced lymphoproliferation caused by 4–1BB deficiency. J Allergy Clin Immunol. 2019.* This paper reports 4–1BB deficiency as a novel immunodeficiency associated with recurrent sinopulmonary infections, persistent EBV viremia, and EBV-induced lymphoproliferation in two unrelated patients. It demonstrates the critical role of 4–1BB costimulation in host immunity to EBV infection.
124. Latour S, Winter S. Inherited Immunodeficiencies With High Predisposition to Epstein-Barr Virus-Driven Lymphoproliferative Diseases. Front Immunol. 2018;9:1103. [PubMed: 29942301]
125. Rodriguez R, Fournier B, Jorge Cordeiro D, …, Latour S. Concomitant PIK3CD and TNFRSF9 deficiencies cause chronic active Epstein-Barr virus infection of T cells. J Exp Med. 2019;In press.
126. Tangye SG, Latour S. Primary immunodeficiencies reveal the molecular requirements for effective host defense against EBV infection. Blood. 2019;In press.
127. Martin E, Palmic N, Sanquer S, Lenoir C, Hauck F, Mongellaz C, et al. CTP synthase 1 deficiency in humans reveals its central role in lymphocyte proliferation. Nature. 2014;510(7504):288–92. [PubMed: 24870241]
128. Chaigne-Delalande B, Li FY, O'Connor GM, Lukacs MJ, Jiang P, Zheng L, et al. Mg2+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science. 2013;341(6142):186–91. [PubMed: 23846901]
129. Abolhassani H, Edwards ES, Ikinciogullari A, Jing H, Borte S, Buggert M, et al. Combined immunodeficiency and Epstein-Barr virus-induced B cell malignancy in humans with inherited CD70 deficiency. J Exp Med. 2017;214(1):91–106. [PubMed: 28011864] * This paper reports AR CD70 deficiency as a novel primary immunodeficiency in four patients from two unrelated families of different ethnicities. The expression of 2B4 and NKG2D, receptors implicated in controlling EBV infection, on memory CD8+ T cells from CD70-deficient individuals was reduced, consistent with the impaired killing of EBV-infected cells. AD CD70 deficiency is, therefore, a novel cause of combined immunodeficiency and EBV-associated diseases.
130. Izawa K, Martin E, Soudais C, Bruneau J, Boutboul D, Rodriguez R, et al. Inherited CD70 deficiency in humans reveals a critical role for the CD70-CD27 pathway in immunity to Epstein-Barr virus infection. J Exp Med. 2017;214(1):73–89. [PubMed: 28011863] * This is a report of a patient suffering from recurrent EBV-induced B-cell proliferation, including Hodgkin's

lymphoma, due to an AR deficiency of CD70, the ligand of CD27. The proliferation of T cells triggered by CD70-expressing B cells was dependent on CD27 and CD3 on T cells. The CD70-CD27 pathway is thus crucial for EBV-specific T-cell immunity.

131. Somekh I, Thian M, Medgyesi D, Gulez N, Magg T, Gallon Duque A, et al. CD137 deficiency causes immune dysregulation with predisposition to lymphomagenesis. Blood. 2019;134(18):1510–6. [PubMed: 31501153]
132. Nolte MA, van Olffen RW, van Gisbergen KP, van Lier RA. Timing and tuning of CD27-CD70 interactions: the impact of signal strength in setting the balance between adaptive responses and immunopathology. Immunol Rev. 2009;229(1):216–31. [PubMed: 19426224]
133. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010;20(4):202–13. [PubMed: 20564615]
134. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988–2004. Clin Infect Dis. 2010;50(11):1439–47. [PubMed: 20426575]
135. Taylor GH. Cytomegalovirus. Am Fam Physician. 2003;67(3):519–24. [PubMed: 12588074]
136. Brodin P, Jojic V, Gao T, Bhattacharya S, Angel CJ, Furman D, et al. Variation in the human immune system is largely driven by non-heritable influences. Cell. 2015;160(1–2):37–47. [PubMed: 25594173]
137. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol. 2007;17(5):355–63. [PubMed: 17542052]
138. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. J Pediatr. 2008;153(1):84–8. [PubMed: 18571542]
139. Fischer A, Notarangelo LD, Neven B, Cavazzana M, Puck JM. Severe combined immunodeficiencies and related disorders. Nat Rev Dis Primers. 2015;1:15061. [PubMed: 27189259]
140. Feske S, Picard C, Fischer A. Immunodeficiency due to mutations in ORAI1 and STIM1. Clin Immunol. 2010;135(2):169–82. [PubMed: 20189884]
141. Fuchs S, Rensing-Ehl A, Pannicke U, Lorenz MR, Fisch P, Jeelall Y, et al. Omenn syndrome associated with a functional reversion due to a somatic second-site mutation in CARD11 deficiency. Blood. 2015;126(14):1658–69. [PubMed: 26289640]
142. Zhang Z, Gothe F, Pennamen P, James JR, McDonald D, Mata CP, et al. Human interleukin-2 receptor beta mutations associated with defects in immunity and peripheral tolerance. J Exp Med. 2019;216(6):1311–27. [PubMed: 31040185]
143. Fernandez IZ, Baxter RM, Garcia-Perez JE, Vendrame E, Ranganath T, Kong DS, et al. A novel human IL2RB mutation results in T and NK cell-driven immune dysregulation. J Exp Med. 2019;216(6):1255–67. [PubMed: 31040184] * This is a report of AR IL-2Rβ deficiency as a novel primary immune deficiency, in two infant siblings with a homozygous IL2RB mutation affecting the WSXWS motif. The patients presented with CMV infection and other clinical phenotypes. This finding highlights the possible link between altered IL-2Rβ expression and signaling in T and NK cells and the early-onset autoimmunity and immunodeficiency iobserved in these two affected children.
144. Wang Y, Ma CS, Ling Y, Bousfiha A, Camcioglu Y, Jacquot S, et al. Dual T cell- and B cell-intrinsic deficiency in humans with biallelic RLTPR mutations. J Exp Med. 2016;213(11):2413–35. [PubMed: 27647349]
145. Alizadeh Z, Mazinani M, Shakerian L, Nabavi M, Fazlollahi MR. DOCK2 Deficiency in a Patient with Hyper IgM Phenotype. J Clin Immunol. 2018;38(1):10–2. [PubMed: 29204803]
146. Moens L, Gouwy M, Bosch B, Pastukhov O, Nieto-Patlan A, Siler U, et al. Human DOCK2 Deficiency: Report of a Novel Mutation and Evidence for Neutrophil Dysfunction. J Clin Immunol. 2019;39(3):298–308. [PubMed: 30838481]

147. Schepp J, Chou J, Skrabl-Baumgartner A, Arkwright PD, Engelhardt KR, Hambleton S, et al. 14 Years after Discovery: Clinical Follow-up on 15 Patients with Inducible Co-Stimulator Deficiency. Front Immunol. 2017;8:964. [PubMed: 28861081]

148. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore). 2006;85(4):193–202. [PubMed: 16862044]

149. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010;23(4):740–80. [PubMed: 20930072]

150. Rosenzweig SD, Holland SM. Phagocyte immunodeficiencies and their infections. J Allergy Clin Immunol. 2004;113(4):620–6. [PubMed: 15100664]

151. Hanna S, Etzioni A. MHC class I and II deficiencies. J Allergy Clin Immunol. 2014;134(2):269–75. [PubMed: 25001848]

152. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, et al. Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr. 1997;131(1 Pt 1):47–54. [PubMed: 9255191]

153. Gianella S, Letendre S. Cytomegalovirus and HIV: A Dangerous Pas de Deux. J Infect Dis. 2016;214 Suppl 2:S67–74. [PubMed: 27625433]

154. Deeks SG, Overbaugh J, Phillips A, Buchbinder S. HIV infection. Nat Rev Dis Primers. 2015;1:15035. [PubMed: 27188527]

155. Zimmer J, Andres E, Donato L, Hanau D, Hentges F, de la Salle H. Clinical and immunological aspects of HLA class I deficiency. QJM. 2005;98(10):719–27. [PubMed: 16087697]

156. Hanalioglu D, Ayvaz DC, Ozgur TT, van der Burg M, Sanal O, Tezcan I. A novel mutation in TAP1 gene leading to MHC class I deficiency: Report of two cases and review of the literature. Clin Immunol. 2017;178:74–8. [PubMed: 28161407]

157. de la Calle-Martin O, Hernandez M, Ordi J, Casamitjana N, Arostegui JI, Caragol I, et al. Familial CD8 deficiency due to a mutation in the CD8 alpha gene. J Clin Invest. 2001;108(1):117–23. [PubMed: 11435463]

158. Bernard F, Picard C, Cormier-Daire V, Eidenschenk C, Pinto G, Bustamante JC, et al. A novel developmental and immunodeficiency syndrome associated with intrauterine growth retardation and a lack of natural killer cells. Pediatrics. 2004;113(1 Pt 1):136–41. [PubMed: 14702466]

159. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J. 2008;5:47. [PubMed: 18371229]

160. Grilli E, Galati V, Bordi L, Taglietti F, Petrosillo N. Cytomegalovirus pneumonia in immunocompetent host: case report and literature review. J Clin Virol. 2012;55(4):356–9. [PubMed: 22975082]

161. Lancini D, Faddy HM, Flower R, Hogan C. Cytomegalovirus disease in immunocompetent adults. Med J Aust. 2014;201(10):578–80. [PubMed: 25390262]

162. Sue PK, Salazar-Austin NM, McDonald OG, Rishi A, Cornish TC, Arav-Boger R. Cytomegalovirus Enterocolitis in Immunocompetent Young Children: A Report of Two Cases and Review of the Literature. Pediatr Infect Dis J. 2016;35(5):573–6. [PubMed: 26862673]

163. de Villartay JP, Lim A, Al-Mousa H, Dupont S, Dechanet-Merville J, Coumau-Gatbois E, et al. A novel immunodeficiency associated with hypomorphic RAG1 mutations and CMV infection. J Clin Invest. 2005;115(11):3291–9. [PubMed: 16276422]

164. Karigane D, Takaya S, Seki Y, Mastumoto Y, Onose A, Kosakai A, et al. Cytomegalovirus enteritis in immunocompetent subjects: a case report and review of the literature. J Infect Chemother. 2014;20(5):325–9. [PubMed: 24751234]

165. Leruez-Ville M, Ville Y. Fetal cytomegalovirus infection. Best Pract Res Clin Obstet Gynaecol. 2017;38:97–107. [PubMed: 27923540]

166. Ciancanelli M, Huang S, Luthra P, Garner H, Itan Y, Volpi S, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science. 2015;348(6233):448–53. [PubMed: 25814066]

167. Yamanidhi K, Mori Y, Pellett P. Human herpesvirus 6 and 7 Fields Virology, 6th edition, Knipe DM, howley P (Eds) Wolters Kluwer health, Philadelphia 2013;2:2058.

168. Endo A, Watanabe K, Ohye T, Suzuki K, Matsubara T, Shimizu N, et al. Molecular and virological evidence of viral activation from chromosomally integrated human herpesvirus 6A in a patient with X-linked severe combined immunodeficiency. Clin Infect Dis. 2014;59(4):545–8. [PubMed: 24803376]

169. Robertson N, Engelhardt KR, Morgan NV, Barge D, Cant AJ, Hughes SM, et al. Astute Clinician Report: A Novel 10 bp Frameshift Deletion in Exon 2 of ICOS Causes a Combined Immunodeficiency Associated with an Enteritis and Hepatitis. J Clin Immunol. 2015;35(7):598–603. [PubMed: 26399252]

170. Torigoe S, Koide W, Yamada M, Miyashiro E, Tanaka-Taya K, Yamanishi K. Human herpesvirus 7 infection associated with central nervous system manifestations. J Pediatr. 1996;129(2):301–5. [PubMed: 8765632]

171. Schwartz KL, Richardson SE, Ward KN, Donaldson C, MacGregor D, Banwell B, et al. Delayed primary HHV-7 infection and neurologic disease. Pediatrics. 2014;133(6):e1541–7. [PubMed: 24819578]

172. Ward KN, Kalima P, MacLeod KM, Riordan T. Neuroinvasion during delayed primary HHV-7 infection in an immunocompetent adult with encephalitis and flaccid paralysis. J Med Virol. 2002;67(4):538–41. [PubMed: 12116001]

173. Marseglia L, Manti S, G DA, Stroscio G, Impollonia D, Arena S, et al. Human herpesviruses-6 and −7 encephalitis in immunocompetent infants: are they really so uncommon? J Biol Regul Homeost Agents. 2016;30(4):1131–6. [PubMed: 28078864]

174. Yoshikawa T, Ohashi M, Miyake F, Fujita A, Usui C, Sugata K, et al. Exanthem subitum-associated encephalitis: nationwide survey in Japan. Pediatr Neurol. 2009;41(5):353–8. [PubMed: 19818937]

175. Chevret L, Boutolleau D, Halimi-Idri N, Branchereau S, Baujard C, Fabre M, et al. Human herpesvirus-6 infection: a prospective study evaluating HHV-6 DNA levels in liver from children with acute liver failure. J Med Virol. 2008;80(6):1051–7. [PubMed: 18428148]

176. Charnot-Katsikas A, Baewer D, Cook L, David MZ. Fulminant hepatic failure attributed to infection with human herpesvirus 6 (HHV-6) in an immunocompetent woman: A case report and review of the literature. J Clin Virol. 2016;75:27–32. [PubMed: 26745830]

177. Szewc AM, Taylor S, Cage GD, Jacobsen J, Bulut OP, de Mello DE. Acute Liver Failure in an Adolescent Male Induced by Human Herpesvirus 6 (HHV-6): A Case Report With Literature Review. Lab Med. 2018;49(2):165–74. [PubMed: 29390152]

178. Asano Y, Yoshikawa T, Suga S, Yazaki T, Kondo K, Yamanishi K. Fatal fulminant hepatitis in an infant with human herpesvirus-6 infection. Lancet. 1990;335(8693):862–3. [PubMed: 1969592]

179. Asano Y, Yoshikawa T, Kajita Y, Ogura R, Suga S, Yazaki T, et al. Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection. Arch Dis Child. 1992;67(12):1484–5. [PubMed: 1336954]

180. Yoshikawa T, Nakashima T, Suga S, Asano Y, Yazaki T, Kimura H, et al. Human herpesvirus-6 DNA in cerebrospinal fluid of a child with exanthem subitum and meningoencephalitis. Pediatrics. 1992;89(5 Pt 1):888–90. [PubMed: 1315948]

181. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer. 2010;10(10):707–19. [PubMed: 20865011]

182. Sahin G, Palanduz A, Aydogan G, Cassar O, Ertem AU, Telhan L, et al. Classic Kaposi sarcoma in 3 unrelated Turkish children born to consanguineous kindreds. Pediatrics. 2010;125(3):e704–8. [PubMed: 20156905]

183. Kusenbach G, Rubben A, Schneider EM, Barker M, Bussing A, Lassay L, et al. Herpes virus (KSHV) associated Kaposi sarcoma in a 3-year-old child with non-HIV-induced immunodeficiency. Eur J Pediatr. 1997;156(6):440–3. [PubMed: 9208237]

184. Camcioglu Y, Picard C, Lacoste V, Dupuis S, Akcakaya N, Cokura H, et al. HHV-8-associated Kaposi sarcoma in a child with IFNgammaR1 deficiency. J Pediatr. 2004;144(4):519–23. [PubMed: 15069403]

185. Meropol NJ, Hicks D, Brooks JJ, Siminovitch KA, Fishman NO, Kant JA, et al. Coincident Kaposi sarcoma and T-cell lymphoma in a patient with the Wiskott-Aldrich syndrome. Am J Hematol. 1992;40(2):126–34. [PubMed: 1316718]

186. Picard C, Mellouli F, Duprez R, Chedeville G, Neven B, Fraitag S, et al. Kaposi's sarcoma in a child with Wiskott-Aldrich syndrome. Eur J Pediatr. 2006;165(7):453–7. [PubMed: 16602009]

187. Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, et al. Whole-exome sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. J Exp Med. 2010;207(11):2307–12. [PubMed: 20876309]

188. Byun M, Ma CS, Akçay A, Pedergnana V, Palendira U, Myoung J, et al. inherited human OX40 deficiency underlying classic Kaposi sarcoma in childhood. J Exp Med. 2013;210(9):1743–59. [PubMed: 23897980]

189. Vaeth M, Feske S. Ion channelopathies of the immune system. Curr Opin Immunol. 2018;52:39–50. [PubMed: 29635109]

190. Croft M. Control of immunity by the TNFR-related molecule OX40 (CD134). Annu Rev Immunol. 2010;28:57–78. [PubMed: 20307208]

191. Gilbert C, Bestman-Smith J, Boivin G. Resistance of herpesviruses to antiviral drugs: clinical impacts and molecular mechanisms. Drug Resist Updat. 2002;5(2):88–114. [PubMed: 12135584]

192. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol. 2009;124(6):1289–302 e4. [PubMed: 20004785]

193. Sabry A, Hauk PJ, Jing H, Su HC, Stence NV, Mirsky DM, et al. Vaccine strain varicella–zoster virus-induced central nervous system vasculopathy as the presenting feature of DOCK8 deficiency. J Allergy Clin Immunol. 2014;133(4):1225–7. [PubMed: 24418481]

194. Moshous D, Martin E, Carpentier W, Lim A, Callebaut I, Canioni D, et al. Whole-exome sequencing identifies Coronin-1A deficiency in 3 siblings with immunodeficiency and EBV-associated B-cell lymphoproliferation. J Allergy Clin Immunol. 2013;131(6):1594–603. [PubMed: 23522482]

195. Al-Herz W, Essa S. Spectrum of Viral Infections Among Primary Immunodeficient Children: Report From a National Registry. Front Immunol. 2019;10:1231. [PubMed: 31191561]

196. Imai K, Morio T, Zhu Y, Jin Y, Itoh S, Kajiwara M, et al. Clinical course of patients with WASP gene mutations. Blood. 2004;103(2):456–64. [PubMed: 12969986]

197. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994;125(6 Pt 1):876–85. [PubMed: 7996359]

198. Al-Herz W, Alsmadi O, Melhem M, Recher M, Frugoni F, Notarangelo LD. Major histocompatibility complex class II deficiency in Kuwait: clinical manifestations, immunological findings and molecular profile. J Clin Immunol. 2013;33(3):513–9. [PubMed: 23143406]

199. Ouederni M, Vincent B, Frange P, Touzot F, Scerra S, Bejaoui M, et al. Major histocompatibility complex class II expression deficiency caused by a RFXANK founder mutation: a survey of 35 patients. Blood. 2011;118(19):5108–18. [PubMed: 21908431]

200. Du X, Tang W, Chen X, Zeng T, Wang Y, Chen Z, et al. Clinical, genetic, and immunological characteristics of 40 Chinese patients with CD40 ligand deficiency. Scand J Immunol. 2019:e12798. [PubMed: 31179555]

201. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003;82(6):373–84. [PubMed: 14663287]

202. Alazami AM, Al-Helale M, Alhissi S, Al-Saud B, Alajlan H, Monies D, et al. Novel CARMIL2 Mutations in Patients with Variable Clinical Dermatitis, Infections, and Combined Immunodeficiency. Front Immunol. 2018;9:203. [PubMed: 29479355]

203. Sorte HS, Osnes LT, Fevang B, Aukrust P, Erichsen HC, Backe PH, et al. A potential founder variant in CARMIL2/RLTPR in three Norwegian families with warts, molluscum contagiosum, and T-cell dysfunction. Mol Genet Genomic Med. 2016;4(6):604–16. [PubMed: 27896283]

204. Li FY, Chaigne-Delalande B, Su H, Uzel G, Matthews H, Lenardo MJ. XMEN disease: a new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus. Blood. 2014;123(14):2148–52. [PubMed: 24550228]

205. Blommaert E, Peanne R, Cherepanova NA, Rymen D, Staels F, Jaeken J, et al. Mutations in MAGT1 lead to a glycosylation disorder with a variable phenotype. Proc Natl Acad Sci U S A.

2019;116(20):9865–70. [PubMed: 31036665] * Mutations in MAGT1 were previously linked to primary immunodeficiency characterized by chronic EBV infections attributed to a Mg2+ homeostasis defect (XMEN). This paper reports identification of two patients with defective serum transferrin glycosylation and mutations in MAGT1. These patients presented with a phenotype characterized by intellectual and developmental disability. The authors compared the clinical and cellular phenotype of the two patients with that of a previously identified XMEN patient, and showed that MAGT1 deficiency was associated with enhanced expression of TUSC3, the homolog of MAGT1, suggesting a compensatory mechanism. MAGT1 deficiency is, therefore, a disorder associated with two different clinical phenotypes caused by defects of glycosylation.

206. Li FY, Chaigne-Delalande B, Kanellopoulou C, Davis JC, Matthews HF, Douek DC, et al. Second messenger role for Mg2+ revealed by human T-cell immunodeficiency. Nature. 2011;475(7357):471–6. [PubMed: 21796205]
207. Li FY, Chaigne-Delalande B, Rao VK, Zhang Y, Matthews H, Kuijpers TT, et al. Clinical utility gene card for: X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia (XMEN). Eur J Hum Genet. 2015;23(6).
208. Ravell J, Chaigne-Delalande B, Lenardo M. X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia disease: a combined immune deficiency with magnesium defect. Curr Opin Pediatr. 2014;26(6):713–9. [PubMed: 25313976]
209. Lacruz RS, Feske S. Diseases caused by mutations in ORAI1 and STIM1. Ann N Y Acad Sci. 2015;1356:45–79. [PubMed: 26469693]
210. Mendez-Echevarria A, Gonzalez-Granado LI, Allende LM, De Felipe B, Teresa DR, Calvo C, et al. Fatal Pneumocystis jirovecii and Cytomegalovirus Infections in an Infant With Normal TRECs Count: Pitfalls of Newborn Screening for Severe Combined Immunodeficiency. Pediatr Infect Dis J. 2019;38(2):157–60. [PubMed: 29613974]
211. Picard C, McCarl CA, Papolos A, Khalil S, Luthy K, Hivroz C, et al. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. N Engl J Med. 2009;360(19):1971–80. [PubMed: 19420366]
212. Fuchs S, Rensing-Ehl A, Speckmann C, Bengsch B, Schmitt-Graeff A, Bondzio I, et al. Antiviral and regulatory T cell immunity in a patient with stromal interaction molecule 1 deficiency. J Immunol. 2012;188(3):1523–33. [PubMed: 22190180]
213. Schaballie H, Rodriguez R, Martin E, Moens L, Frans G, Lenoir C, et al. A novel hypomorphic mutation in STIM1 results in a late-onset immunodeficiency. J Allergy Clin Immunol. 2015;136(3):816–9 e4. [PubMed: 25935105]
214. Rice L, Stockdale C, Berry I, O'Riordan S, Pysden K, Anwar R, et al. A Report of Novel STIM1 Deficiency and 6-Year Follow-Up of Two Previous Cases Associated with Mild Immunological Phenotype. J Clin Immunol. 2019;39(3):249–56. [PubMed: 30949876]
215. Dang TS, Willet JD, Griffin HR, Morgan NV, O'Boyle G, Arkwright PD, et al. Defective Leukocyte Adhesion and Chemotaxis Contributes to Combined Immunodeficiency in Humans with Autosomal Recessive MST1 Deficiency. J Clin Immunol. 2016;36(2):117–22. [PubMed: 26801501]
216. Nehme NT, Schmid JP, Debeurme F, Andre-Schmutz I, Lim A, Nitschke P, et al. MST1 mutations in autosomal recessive primary immunodeficiency characterized by defective naive T-cell survival. Blood. 2012;119(15):3458–68. [PubMed: 22174160]
217. Schipp C, Schlutermann D, Honscheid A, Nabhani S, Holl J, Oommen PT, et al. EBV Negative Lymphoma and Autoimmune Lymphoproliferative Syndrome Like Phenotype Extend the Clinical Spectrum of Primary Immunodeficiency Caused by STK4 Deficiency. Front Immunol. 2018;9:2400. [PubMed: 30386345]
218. Sherkat R, Sabri MR, Dehghan B, Bigdelian H, Reisi N, Afsharmoghadam N, et al. EBV lymphoproliferative-associated disease and primary cardiac T-cell lymphoma in a STK4 deficient patient: A case report. Medicine (Baltimore). 2017;96(48):e8852.
219. Balabanian K, Lagane B, Pablos JL, Laurent L, Planchenault T, Verola O, et al. WHIM syndromes with different genetic anomalies are accounted for by impaired CXCR4 desensitization to CXCL12. Blood. 2005;105(6):2449–57. [PubMed: 15536153]

220. Imashuku S, Miyagawa A, Chiyonobu T, Ishida H, Yoshihara T, Teramura T, et al. Epstein-Barr virus-associated T-lymphoproliferative disease with hemophagocytic syndrome, followed by fatal intestinal B lymphoma in a young adult female with WHIM syndrome. Warts, hypogammaglobulinemia, infections, and myelokathexis. Ann Hematol. 2002;81(8):470–3. [PubMed: 12224006]

221. Dorjbal B, Stinson JR, Ma CA, Weinreich MA, Miraghazadeh B, Hartberger JM, et al. Hypomorphic caspase activation and recruitment domain 11 (CARD11) mutations associated with diverse immunologic phenotypes with or without atopic disease. J Allergy Clin Immunol. 2019;143(4):1482–95. [PubMed: 30170123]

222. Marsh RA, Bleesing JJ, Chandrakasan S, Jordan MB, Davies SM, Filipovich AH. Reduced-intensity conditioning hematopoietic cell transplantation is an effective treatment for patients with SLAM-associated protein deficiency/X-linked lymphoproliferative disease type 1. Biol Blood Marrow Transplant. 2014;20(10):1641–5. [PubMed: 24923536]

223. Rosenzweig SD, Dorman SE, Uzel G, Shaw S, Scurlock A, Brown MR, et al. A novel mutation in IFN-gamma receptor 2 with dominant negative activity: biological consequences of homozygous and heterozygous states. J Immunol. 2004;173(6):4000–8. [PubMed: 15356149]

224. Chapgier A, Wynn RF, Jouanguy E, Filipe-Santos O, Zhang S, Feinberg J, 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):5078–83. [PubMed: 16585605]

225. Cui Y, Keles S, Charbonnier LM, Jule AM, Henderson L, Celik SC, et al. Combined immunodeficiency caused by a loss-of-function mutation in DNA polymerase delta 1. J Allergy Clin Immunol. 2019.

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Table 1.

Primary immunodeficiencies associated with human herpes viruses infection

PID	Defective cells	HHV infection						References
		HSV1/HSV2	VZV	EBV	CMV	HHV6 HHV7	HHV8	
Inborn errors of adaptive humoral and cellular immunity								
SCID genes[1]	All lymphocytes	Recurrent skin infection; Meningitis	Disseminated infection	Viremia Meningitis	Viremia; Pneumonia; Retinitis; Meningitis	Hemophagocytic syndrome		(63, 111, 139, 168)
GATA2 (10–20%)	B, NK cells, DCs and monocytes	Disseminated skin infection; HLH[2]; Meningitis	Pneumonitis	Lympho-proliferation after HSCT	Disseminated infection			(45–49)
DOCK8	T, NK and B cells	Recurrent skin infection; Keratitis; Pneumonia; Conjunctivitis	Disseminated skin infection; CNS vasculopathy	Pneumonia	Viremia; Pneumonia; Meningitis; Retinitis			(41–43, 95, 192, 193)
DOCK2	T and NK cells		Disseminated infection due to vaccine strain VZV; Encephalitis		Viremia			(100, 145, 146)
CORO1A	All lymphocytes		Pneumonia; Meningitis; Disseminated infection	Lympho-proliferation				(96, 194)
WAS	T, B, cells, DCs, monocytes, macrophages, granulocytes, thrombocytes	Recurrent keratitis	Severe recurrent zoster	Lympho-proliferation; B-cell lymphoma	Viremia; Hemophagocytosis; Encephalitis; Hepatitis; Pneumonia		KS	(51, 52, 186, 195, 196, 197)
MHC class-II deficiency[3]	Impaired $CD4^+$ T cell activation	Recurrent gingivostomatitis; Meningitis	Varicella		Viremia; Pneumonia; Meningitis; Retinitis			(151, 195, 198, 199)
CD40L	Impaired $CD4^+$ T cell activation, B cells	Stomatitis; Pneumonia			Pneumonia; Encephalitis; Disseminated infection			(200, 201)
CARMIL2	T and B cells	Skin infection	Recurrent varicella	Viremia; Disseminated infection	Viremia			(114, 144, 202, 203)
IL2RB	T cells			Viremia	Viremia with hepatitis; Pneumonia; Disseminated infection			(142, 143)
MAGT1	T and NK cells	Recurrent skin infection	Severe varicella; recurrent zoster	Lympho-proliferation; B-cell lymphoma				(204–208)

PID	Defective cells	HHV infection						References
		HSV1/HSV2	VZV	EBV	CMV	HHV6 HHV7	HHV8	
ORAI1	T cells			B-cell lymphoma	Pneumonia			(209, 210)
STIM1	T cells	Recurrent stomatitis	Severe varicella; Cellulitis	Chronic viremia	Chronic viremia		KS	(187, 211–214)
ICOS	T and B cells	Recurrent labialitis; Keratitis			Colitis; Vulvovaginitis; Disseminated infection	Colitis; Hepatitis		(147, 169)
STK4 (MST1)	T and B cells	Recurrent oral infection	Recurrent zoster	Viremia; Lympho-proliferation; B-cell lymphoma				(44, 215–218)
CXCR4	B and T cells neutrophils	Recurrent oral, genital infection	Recurrent zoster	Lympho-proliferation; B-cell lymphoma				(50, 219, 220)
OX40	$CD4^+$ T cells						KS	(188)
CARD11 GOF	T, B, NK, NKT cells			Viremia; B-cell lymphoproliferation				(117, 118)
CARD11 LOF	T and B cells	Skin infection	Persistent skin infection		Disseminated infection			(141, 221)
SH2D1A (SAP)	$CD8^+$ T and NK cells			Chronic active infection; HLH		Hemophagocytic syndrome		(120–122, 222)
ITK	$CD4^+$ T, $CD8^+$ T and iNKT cells			Lympho-proliferation; HLH, HL; B-cell lymphoma				(124)
CD27	$CD8^+$ T cells			Lympho-proliferation; B-cell lymphoma				(124)
CD70	$CD8^+$ T cells		Severe varicella	B-cell lymphoma				(129, 130)
CTPS1	T cells		Recurrent pneumonia; gastritis	Viremia; Severe mononucleosis; Lympho-proliferation (CNS)				(127)
TNFRSF9 (4–1BB)	$CD8^+$ T cells			Lympho-proliferation; B-cell lymphoma				(123, 125)
Inborn errors of adaptive and innate immunity								
STAT5B	$CD4^+$, $CD8^+$ T cells, NK cells		Hemorrhagic varicella; recurrent zoster; keratitis	EBV-T cell lymphoma				(97, 98, 195)
IFNGR1	All cells	Gingivo-stomatitis; Esophagitis; Recurrent skin infection	Varicella; Pneumonia; CNS infection		Disseminated infection		KS[4]	(53, 55, 184)

PID	Defective cells	HHV infection						References
		HSV1/HSV2	VZV	EBV	CMV	HHV6 HHV7	HHV8	
IFNGR2	All cells				Disseminated infection			(223)
IL12RB	T cells			Viremia	Colitis; Lymphoid hyperplasia of the esophagus			(143)
TYK2	All cells	Recurrent skin, mucosal infection	Recurrent skin infection					(56)
NEMO	All cells	Recurrent skin infection; HSE						(57, 62)
STAT1 GOF	All cells	Recurrent skin infection						(58–60)
STAT1 AR LOF	All cells	Recurrent skin infection; HSE	Disseminated varicella	Fulminant EBV infection (during HSCT)	Pneumonia			(61, 224)
POL III^{5}	Leukocytes?		CNS infection; Pneumonia					(103)
POL D1	Leukocytes	Recurrent labial and skin infections	Severe and recurrent chickenpox Encepahlitis					(225)
XIAP	Lack of NKT cells			Chronic active infection; HLH				(119)
Inborn errors of innate and tissue-intrinsic immunity								
MCM4	Decrease in NK cells	Recurrent skin infection	Severe varicella	Lympho-proliferation				(38, 39)
GINS1	Decrease in NK cells	Recurrent skin infection	Severe varicella		Pneumonia			(40, 158)
IRF8	Decrease and impaired function in NK cells, decrease in dendritic cells			Severe mononucleosis				(115)
UNC-93B	CNS neurons and oligodendrocytes	Forebrain HSE						(68)
TLR3	CNS neurons and oligodendrocytes	Forebrain HSE	Recurrent zoster ophthalmicus					(69, 73, 74, 102)
TRAF3	CNS neurons and oligodendrocytes	Forebrain HSE						(71)
TRIF	CNS neurons and oligodendrocytes	Forebrain HSE						(72)
TBK1	CNS neurons and oligodendrocytes	Forebrain HSE						(70)

PID	Defective cells	HHV infection						References
		HSV1/HSV2	VZV	EBV	CMV	HHV6 HHV7	HHV8	
IRF3	CNS neurons and oligodendrocytes	Forebrain HSE						(77)
snoRNA31	CNS neurons	Forebrain HSE						(83)
DBR1	Brainstem cells?	Brainstem HSE						(84)

1. SCID genes: *IL2RG, RAG1, RAG2, ADA, JAK3, IL7R*

2. HLH: hemophagocytic lymphohistiocytosis

3. MCH class II genes: *CIITA, RFXANK, RFX5, RFXAP*

4. CD4 lymphopenia at the time of KS

5. POL III genes: *POLR3A, POLR3C*

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