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Human genetic dissection of papillomavirus-driven diseases: New insight into their pathogenesis

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Abstract

Human papillomaviruses (HPVs) infect mucosal or cutaneous stratified epithelia. There are five genera and more than 200 types of HPV, each with a specific tropism and virulence. HPV infections are typically asymptomatic or result in benign tumors, which may be disseminated or persistent in rare cases, but a few oncogenic HPVs can cause cancers. This review deals with the human genetic and immunological basis of interindividual clinical variability in the course of HPV infections of the skin and mucosae. Typical epidermodysplasia verruciformis (EV) is characterized by β-HPV-driven flat wart-like and pityriasis-like cutaneous lesions and non-melanoma skin cancers in patients with inborn errors of EVER1-EVER2-CIB1-dependent skin-intrinsic immunity. Atypical EV is associated with other infectious diseases in patients with inborn errors of T cells. Severe cutaneous or anogenital warts, including anogenital cancers, are also driven by certain α-, γ-, μ or ν-HPVs in patients with inborn errors of T lymphocytes and antigen-presenting cells. The genetic basis of HPV diseases at other mucosal sites, such as oral multifocal epithelial hyperplasia or juvenile recurrent respiratory papillomatosis (JRRP), remains poorly understood. The human genetic dissection of HPV-driven lesions will clarify the molecular and cellular basis of protective immunity to HPVs, and should lead to novel diagnostic, preventive, and curative approaches in patients.

Introduction

Papillomaviruses (PVs) are small, non-enveloped viruses with double-stranded circular DNA genomes packaged into an icosahedral capsid. They are highly host-specific, and

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display strict tropism for cutaneous or mucosal stratifying epithelia (Doorbar et al. 2015). PVs target self-renewing stem cells in the infected epithelium. The virus life cycle is tropism-dependent and closely linked to host cell biology. PV infections are widespread, and usually asymptomatic or benign and self-healing, in individuals with intact intrinsic, innate, and adaptive immunity (Doorbar et al. 2015). Human PVs (HPVs) can be classified into five genera, and over 200 genotypes are recognized by the International Human Papillomavirus Reference Center (Papillomavirus Episteme (PaVE); https://pave.niaid.nih.gov/#home) (Van Doorslaer et al. 2013, 2017). HPVs are ubiquitous, with 60-95% of individuals in the adult population seropositive for at least one of the ~35 HPVs tested (Michael et al. 2008; Casabonne et al. 2009; Antonsson et al. 2010; Rahman et al. 2016).

α-HPVs display mucosal and cutaneous tropism. They are associated with cutaneous warts (e.g. HPV2), benign mucosal diseases (e.g. HPV6, HPV13) or genital and oropharyngeal carcinomas (e.g. HPV16, HPV18) (de Villiers et al. 2004; Schiffman et al. 2016). By contrast, β-, γ-, μ- and ν-HPVs display strict cutaneous tropism. The γ-, μ- and ν-HPVs cause benign cutaneous common and plantar warts, whereas β-HPVs generally cause asymptomatic infections, but are responsible for flat wart-like lesions in rare patients with epidermodysplasia verruciformis (EV) (Orth 2006). Persistent infections can lead to benign tumors and, in some cases, malignant transformation and progression to invasive cancer. γ- and ν-HPVs may, in rare cases, be found in skin cancer lesions. Both α- and β-HPVs contain genotypes associated with low and high risks of cancer: mostly mucosal cancers for α-HPVs and cutaneous cancers for β-HPVs. High-risk α-HPV genotypes cause cervical cancers in the general population, whereas high-risk β-HPV genotypes cause non-melanoma skin cancer (NMSC) in patients with EV. The α-HPVs of different subgroups encode distantly related E5 early viral proteins that may contribute to the severity of infection associated with some types of α-HPV (cutaneous types: E5β; low-risk types: E5γ, E5δ; high-risk types: E5α) (Bravo and Alonso 2004). Severe HPV infections are frequent in patients with acquired T-cell immunodeficiencies, whether due to HIV infection or immunosuppressive treatment, suggesting an important role for adaptive T-cell immunity in the control of HPV infection (Tschachler et al. 1996; Moerman et al. 2001; Gormley and Kovarik 2012; Wieland et al. 2014). Consistent with these findings, studies in human and animal models have shown that regressing warts are characterized by infiltrations of antigen-presenting cells (APCs) and lymphocytes, including $CD4^+$ T cells in particular, and, to a lesser extent, $CD8^+$ T cells (Iwatsuki et al. 1986; Okabayashi et al. 1991; Coleman et al. 1994; Selvakumar et al. 1997; Nicholls et al. 2001; Nakayama et al. 2011; Hibma 2012). We review here the inborn errors of immunity associated with susceptibility to HPV infection in patients without acquired immunodeficiency.

Typical and atypical epidermodysplasia verruciformis

The HPV disease best studied in terms of human genetics is unquestionably EV. EV was first described in 1922 (Lewandowsky and Lutz 1922) as a skin disease characterized by persistent disseminated flat wart-like and pityriasis versicolor-like lesions driven by β-HPVs. EV is a rare disease, with about 500 patients reported worldwide in 2017 (Imahorn et al. 2017; de Jong et al. 2018b), but seropositivity for β-HPVs has been reported in 20-65% of the population (Michael et al. 2008; Waterboer et al. 2009; Casabonne et al. 2009;

Antonsson et al. 2010; Iannacone et al. 2012; Rahman et al. 2016). Typical EV occurs in isolation, in the absence of other infections, and usually follows an autosomal recessive (AR) pattern of transmission. EV generally begins in infancy, with about 30-40% of EV patients developing non-melanoma skin cancer (NMSC) two to three decades later (Orth 2005). At least 25 different β-HPVs have been identified in EV lesions (Orth 2006, 2008). EV patients are typically infected with multiple HPV strains, but HPV-5 is the most prevalent in EV lesions. It is also the most frequently identified HPV in cases of NMSC in EV patients, reflecting its strong oncogenic potential (Orth 1986).

Since 2002, biallelic amorphic mutations of *TMC6*, *TMC8* and *CIB1*, encoding EVER1, EVER2, and CIB1, respectively, have been reported in 58 patients (26 kindreds) with typical EV (Table 1) (Ramoz et al. 2002; Crequer et al. 2013; Imahorn et al. 2017; de Jong et al. 2018a; Vahidnezhad et al. 2019). The EVER and CIB1 proteins have been shown to form a complex (de Jong et al. 2018a), but their function remains poorly understood. These genes are widely expressed throughout the body, including in leukocytes, but patients display no consistent abnormalities of circulating leukocytes (Lazarczyk et al. 2012; Crequer et al. 2013; de Jong et al. 2018a). Patients with typical EV have normal humoral immunity and antibody responses (Jabłońska et al. 1979), and normal NK cell activity (Majewski et al. 1986). The persistent and severe β-HPV infections observed in patients with typical EV, despite the largely intact immune system in these patients, suggest that these patients fail to mount an effective adaptive immune response to β-HPV. Intriguingly, EVER1 and EVER2 are tightly regulated following T-cell activation in mice and humans (Lazarczyk et al. 2012), and a role of the EVER1/EVER2/CIB1 complex in APCs, including Langerhans cells (LCs), has not been excluded. Regressing warts are infiltrated with LCs (Iwatsuki et al. 1986; Nakayama et al. 2011) and EV lesions contain far fewer LCs than healthy skin (Haftek et al. 1987; van Voorst Vader et al. 1987). This last observation may reflect the migration of LCs to lymph nodes, or a viral escape mechanism. To date, human Langerhans cell deficiency has been reported only in patients with reticular dysgenesis due to AK2 deficiency (Emile et al. 2000; Bigley et al. 2016). Unfortunately, reticular dysgenesis also results in multiple cytopenia and requires HSCT within the first few weeks of life, before exposure to HPV, making it difficult to draw any firm conclusions about the role LCs in anti-HPV immunity. We cannot, therefore, rule out the possibility that deficiencies of *TMC6*, *TMC8* or *CIB1* result in a subtle, as yet uncharacterized, T cell-intrinsic or APC-intrinsic deficiency. An isolated subtle impairment of T cells is unlikely to account for the typical EV phenotype. Indeed, clinical penetrance of the typical EV phenotype is complete at the age of 10 years in patients with EVER and CIB1 deficiencies, whereas most patients on iatrogenic immunosuppression or with congenital T-cell deficiencies do not develop EV, even in syndromic forms. It therefore seems more likely that EV patients are permissive to β-HPV infection and replication due to a keratinocyte-intrinsic or perhaps an APC-intrinsic defect resulting in an absence of appropriate adaptive T-cell responses.

EVER-deficient keratinocytes display altered zinc homeostasis, due to an interaction with ZnT1, a zinc transporter, and enhanced proliferative activity (Lazarczyk et al. 2008). These features are not observed in CIB1-deficient patients, suggesting that the zinc homeostasis abnormalities induced by a deficiency of EVER1 or EVER2 are not responsible for EV (de Jong et al. 2018a). However, we cannot rule out the possibility that zinc homeostasis

abnormalities drive EV by impairing the function of EVER1 or EVER2. It has also been suggested that the EVER/CIB1 complex acts directly as a viral restriction factor for HP Vs. Unlike β-HPVs, α-, γ-, κ-, μ-HPVs all express E5 or E8, structurally similar viral hydrophobic transmembrane proteins with weak transforming activity *in vitro* (Nonnenmacher et al. 2006; Orth 2006). Mutant CRPV genomes lacking functional E8 genes do not cause lesions in rabbits. Thus, E5 and E8 are thought to be required for papilloma formation and for clinical manifestations of α-, γ- or μ-HPV infection in humans. Interestingly, E5 (from HPV-16) and E8 (from HPV-4 and CRPV) have been shown to target the EVER/CIB1 complex, and to inhibit the zinc regulatory function of EVER proteins (Lazarczyk et al. 2008; de Jong et al. 2018a). A lack of inhibition of the EVER/CIB1 complex, due to the absence of E5/E8, may explain the restriction of β-HPVs and the lack of papilloma formation in healthy individuals infected with these viruses, by contrast to individuals infected with α-, γ- or μ-HPVs. The precise mechanism by which the EVER/CIB1 complex restricts HPV replication remains unknown. CIB1 has also been shown to interact with E1 from HPV-5 (β-HPV) and E2 from HPV-16 (α-HPV). E1 and E2 are the two major early viral proteins required for HPV replication. It would be interesting to investigate whether the EVER/CIB1 complex restricts HPV replication in keratinocytes directly, through interactions with these proteins. Viral restriction by E1 inhibition early in the viral life cycle would be consistent with the general absence of EV lesion formation in the general population, despite a very high prevalence of β-HPVs.

EV can also occur as part of a syndrome, with other infections (de Jong et al. 2018b). This presentation, known as atypical EV, has been reported in patients with acquired immunodeficiency, on iatrogenic immunosuppression or suffering from primary immunodeficiencies due to profound T-cell defects. Atypical EV has been reported in 22 patients from 16 kindreds with biallelic mutations of *STK4* (Crequer et al. 2012a; Sharafian et al. 2019), *RHOH* (Crequer et al. 2012b), *CORO1A* (Stray-Pedersen et al. 2014), *TPP2* (Stepensky et al. 2015), *DCLRE1C* (Tahiat et al. 2017), *LCK* (Li et al. 2016), *PASGRP1* (Platt et al. 2017), *ITK* (Youssefian et al. 2019), *SMARCAL1* (Collins et al. 2018), IL7 (Horev et al. 2015) or *DOCK8* (Sanal et al. 2012; Liu et al. 2017) (Table 1). One patient with an X-linked (XL) hypomorphic mutation of *IKBKG* (R254G) was diagnosed with EV, whereas another had flat warts (E331del3) (Tobin et al. 2003; Hanson et al. 2008; Haverkamp et al. 2014). In addition to their role in immune cells, including T cells in particular, some of these genes are also expressed in the skin (table 2), and may play a role in skin-intrinsic HPV restriction. Studies of the genetic etiologies of typical and atypical EV have shown that the effective control of β-HPV infection requires skin-intrinsic viral restriction and a functional T-cell adaptive immune response.

Patients with severe combined immunodeficiency (SCID) and *IL2RG* or *JAK3* deficiency have about a 50% risk of developing severe cutaneous HPV infections, including EV (44% of the patients with HPV lesions), after successful hematopoietic stem cell transplantation (HSCT) (Table 1) (Laffort et al. 2004; Gaspar et al. 2004; Abd Hamid et al. 2017; Neven et al. 2009). Two transplanted patients with *IL7RA* deficiency were reported to have mild HPV infection (Neven et al. 2009). SCID patients undergoing transplantation for other deficiencies (e.g. *RAG1*, *RAG2*, *DCLRE1C*) are not at risk of developing severe warts. This strongly suggests that the patients with *IL2RG* or *JAK3* deficiency have a skin-intrinsic

defect, in addition to their T cell defect. A keratinocyte-intrinsic defect is one possibility, as suggested by reports of JAK3 and IL-2Rγ expression in keratinocytes (NISHIO et al. 2001; Nowak et al. 2017). One recent study suggested that IL2RG-deficient keratinocytes display abnormal chemokine secretion and an impaired ability to recruit immune cells (Nowak et al. 2017). However, according to the Human Protein Atlas (http://www.proteinatlas.org) (Uhlén et al. 2015), the mRNAs encoding IL2RG and JAK3 mRNA are barely detected, if at all, when total mRNA from skin or Hacat cells, a spontaneously transformed keratinocyte cell line, is sequenced (Table 2). Furthermore, IL2RG and JAK3 are not detected on western blots of primary keratinocytes (Dr. Emmanuelle Jouanguy, personal communication). However, it remains possible that HPV infection increases the levels of both these molecules in keratinocytes. Alternatively, skin and peripheral recipient APCs, which express IL-2Rγ and JAK3, may not achieve complete donor chimerism (Gaspar et al. 2004; Beilin et al. 2018). This may be the case for LCs, the differentiation of which is not affected by IL2RG or JAK3 deficiency (Asli et al. 2004; Rivas-Caicedo et al. 2009).

This hypothesis is plausible, as transplant recipients receive only weak conditioning, or no conditioning at all, before transplantation, due to the low risk of rejection in SCID. Consistent with this hypothesis, (i) despite the absence of an unequivocal demonstration that human LCs produce IL-2Rγ protein, DCs, macrophages and monocytes have been shown to express IL-2Rγ or respond to IL-2Rγ-dependent cytokines (Mohamadzadeh et al. 1996; Kitashima et al. 2018; Lin and Leonard 2018; Beilin et al. 2018) (Table 2); (ii) low-intensity conditioning does not result in a significant depletion of LCs (Collin et al. 2006); (iii) in most cases, all the myeloid cells of SCID patients who have undergone transplantation are either of recipient (59%) or of mixed recipient/donor (41%) origin (Laffort et al. 2004; Gaspar et al. 2004; Neven et al. 2009; Abd Hamid et al. 2017); (iv) LCs have the potential for self-renewal and the population present remains of donor origin after limb transplantation (Czernielewski and Demarchez 1987; Kanitakis et al. 2004); and (v) mouse LCs are not replaced after HSCT if they are not cleared by allogeneic T cells, despite the predominantly donor origin of peripheral myeloid cells (Merad et al. 2004). This last observation is important because it suggests that even full peripheral donor chimerism does not necessarily reflect full donor LC chimerism in the skin. One study in humans reported mixed LC chimerism in the long term in adult patients undergoing HSCT for leukemia (Hessel et al. 1996). Another study in adults reported full donor LC chimerism in all recipients one year after HSCT for a cancer, but full donor chimerism occurred later in patients receiving reduced-intensity conditioning than in those receiving full-intensity conditioning (Collin et al. 2006). In this last study, full donor chimerism of the myeloid compartment was achieved in 100% of patients one year post-HSCT, reflecting an important difference in conditioning procedures relative to SCID patients.

LCs were first described in 1868, but their exact role in immunity remains unclear (Merad et al. 2008; Deckers et al. 2018; Otsuka et al. 2018; West and Bennett 2018). Their strategic localization suggests a major role in skin antiviral immunity, and several studies have suggested that HPVs have developed mechanisms for evading LCs (Matthews et al. 2003; Fahey et al. 2009; Leong et al. 2010; Da Silva et al. 2014; Woodham et al. 2016). Little is known about the precise function of IL-2Rγ in LCs. The major roles of this molecule in myeloid cells have been reviewed elsewhere (Lin and Leonard 2018). In particular, IL-15, an

IL-2Rγ-dependent cytokine, promotes the differentiation of human monocytes into LC-like cells *in vitro* (Mohamadzadeh et al. 2001), and a recent study has suggested that IL-2Rγ expression is required for IL-15 transpresentation to $CD4^+$ T cells by DCs in mice (Beilin et al. 2018). Following their maturation, human LCs have been shown to upregulate IL-2Rα (CD25) and IL-2Rβ (Larregina et al. 1996), suggesting that these cells may respond to IL-2 stimulation in specific conditions. Additional studies of JAK3/IL2RG SCID patients with or without warts, after HSCT, may provide crucial insight into T cell-independent skin-intrinsic anti-HPV immunity.

Cutaneous warts

Cutaneous warts are skin lesions induced by HPVs, including common warts, flat warts and plantar myrmecia warts (Jablonska et al. 1985; Doorbar et al. 2015). The different types of cutaneous warts are characterized by distinctive clinical and histological features (Jablonska et al. 1985). Common, flat and plantar warts are generally associated with HPV-2, 3, 10, 27 and 57 from the α-genus, HPV-4, 60 and 65 from the γ-genus, and HPV-1 and 63 from the μ-genus. Lesions are usually benign and self-heal within two years, in the general population. Warts can appear at any age, but they are rare in early childhood, their prevalence increasing over time in school-aged children, with a peak at about 10-15 years of age (Kilkenny and Marks 1996). Cumulative exposure to cutaneous wart-causing HPVs is very high, with a seroprevalence in adults ranging from a few percent to >40% of the population, depending on the study considered (e.g. HPV1 = 5-45%; HPV2 = 5-10%; HPV3 = 5-20%; HPV4 = 20-45%) (Michael et al. 2008; Waterboer et al. 2009; Casabonne et al. 2009; Antonsson et al. 2010; Iannacone et al. 2012; Rahman et al. 2016). Some people develop disseminated common warts, often refractory to treatment (Leiding and Holland 2012). Like EV, disseminated common warts may be isolated or syndromic, occurring with many other infections.

Patients with syndromic common warts often have mutations of genes affecting the number or function of cells in multiple leukocyte compartments (Table 1). GATA2 haploinsufficiency causes susceptibility to recurrent warts (~50% of patients), mycobacterial and fungal infections, with a high risk of myelodysplastic syndrome, acute myeloid leukemia, lymphedema and pulmonary alveolar proteinosis (West et al. 2014; Hsu et al. 2015; Kuriyama et al. 2018). GATA2 is a transcription factor regulating numerous biological processes, including hematopoietic stem cell maintenance. The susceptibility to infection of patients with GATA2 deficiencies can be attributed to progressive multiple cytopenia, affecting monocytes, DCs, neutrophils, B cells, NK cells and $CD4^+$ T cells (Dickinson et al. 2014; Spinner et al. 2014; Hsu et al. 2015).

Patients with monoallelic *CXCR4* gain of function (GOF) mutations suffer from WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis). The vast majority of patients (~80%) develop common warts, mostly in their teens (McDermott and Murphy 2019). GOF *CXCR4* mutations lead to neutropenia due to the impaired egression of neutrophils from bone marrow. Patients also have low counts of dendritic cells, memory B cells and naïve $CD4^+$ and $CD8^+$ T cells, and an accumulation of effector memory $CD4^+$ and $CD8^+$ T cells associated with a restricted T-cell repertoire (Gulino et al. 2004; Tassone et al.

2010; McDermott et al. 2011). A major role for myeloid cells in the susceptibility to HPV of WHIM patients was suggested by the complete remission of warts observed in a patient who spontaneously lost the WHIM allele in the myeloid compartment (McDermott et al. 2015).

Ataxia telangiectasia (AT) is a multisystem disorder caused by biallelic mutations of *ATM*, and characterized by cerebellar degeneration, telangiectasia, immunodeficiency and susceptibility to cancer (Rothblum-Oviatt et al. 2016). ATM plays an important role in the repair of double-strand DNA breaks, such as those occurring during the V(D)J recombination of TCR and BCR (Bredemeyer et al. 2006). AT patients have a profound immunodeficiency, conferring susceptibility to bacterial and viral infections, and ~20% of patients develop common HPV warts (Nowak-Wegrzyn et al. 2004). AT patients have a normal myeloid compartment but low counts of B cells and naïve $CD4^+$ and $CD8^+$ T cells, and abnormal TCR and BCR repertoires (Staples et al. 2008; Driessen et al. 2013; Chopra et al. 2014; Kraus et al. 2014).

AR dedicator of cytokinesis 8 (DOCK8) deficiency is found in patients with severe allergy, chronic infections, and early-onset cancer (Aydin et al. 2015; Zhang et al. 2018). The spectrum of infections observed in these patients includes recurrent bacterial respiratory infections, mucocutaneous candidiasis, and chronic cutaneous viral infections, including common warts caused by HPV, which are observed in 40% of patients. DOCK8 is mostly expressed in hematopoietic cells, and the immunological phenotype of the patients includes high serum IgE levels, eosinophilia, and T- and NK-cell lymphopenia. The susceptibility of the patients to cutaneous viral infections can be explained by a defect of DC and T-cell migration (Harada et al. 2012; Zhang et al. 2014).

Other genes for which mutations have been reported to affect the immune system in a broad manner, with occasional reports of extensive warts, include *ITGB2* (n = 3; <1% of patients) (van de Vijver et al. 2012; Leiding and Holland 2012; Almarza Novoa et al. 2018), *WAS* (~4% of patients) (Stevens et al. 1975; Ormerod et al. 1983; Sullivan et al. 1994; Kim et al. 2010), *ADA2* (n = 5; 1-5% of patients) (Trotta et al. 2018; Arts et al. 2018), and *NFKBIA* (n=1; ~6% of patients) (Boisson et al. 2017; Sogkas et al. 2020). The rarity of HPV susceptibility in patients with WASP, ITGB2, ADA2 and NFKBIA deficiencies can be attributed to the residual activity of the protein in patients surviving early childhood without transplantation.

Complete loss-of-function mutations of SCID genes have never been associated with warts at disease onset. However, patients with hypomorphic mutations of SCID genes (e.g. *IL2RG*, *LIG4*, *ADA*, *JAK3*, *ZAP70*) have been shown to develop recurrent common and plantar warts, with or without other infections (Table 1) (Brooks et al. 1990; Shovlin et al. 1993; Schmalstieg et al. 1995; Frucht et al. 2001; O'Driscoll et al. 2001; Antony et al. 2002; Tamura et al. 2015; Chinn et al. 2017; Yamashita et al. 2019). Furthermore, as discussed in detail in the section on EV, SCID patients with deficiencies of IL-2Rγ and JAK3 frequently develop disseminated and recurrent common warts after HSCT (Gaspar et al. 2004; Laffort et al. 2004; Neven et al. 2009; Henrickson and Treat 2017; Abd Hamid et al. 2017). All of the patients developing recurrent warts (100%) had common warts, and 44% also had EV-like lesions. HPV2, HPV3 or HPV57 was identified in two thirds of the patients tested. The

presence of warts in these patients, who had undergone transplantation, suggests that their HPV susceptibility may be due to a skin-intrinsic defect, possibly affecting keratinocytes or LCs, rather than a primary T-cell defect, as discussed above.

Nevertheless, consistent with the major role played by T cells in anti-HPV immunity, PIDs primarily affecting the number or function of T cells are associated with severe common warts due to HPV infection (Table 1). Five patients with AR IL-7 deficiency have been reported to suffer from common and flat warts, and two of these patients also had cryptococcal meningitis (Horev et al. 2015; Kosumi et al. 2020). IL-7 signals through a heterodimeric receptor consisting of IL-7Rα and IL-2Rγ, encoded by two genes associated with $T^{-}B^{+}$ SCID in humans (Noguchi et al. 1993; Puel et al. 1998). Four IL-7-deficient patients had profound CD4 lymphopenia, and three had CD8 lymphopenia. Unfortunately, no phenotypic characterization was performed for the remaining lymphocytes, including for the patient with normal $CD4^{+}$ T-cell counts. The T-cell lymphopenia observed in IL-7-deficient patients is less severe than that observed in patients with a deficiency of either of its individual coreceptors, suggesting that intact T-cell differentiation is crucial for immunity to common warts caused by HPV. The strong lymphopenia observed in IL-7-deficient patients suggests that the spectrum of infectious susceptibility in these patients may expand with the discovery of additional patients.

A single patient with AR complete CD4 deficiency was recently described. This patient, a 45-year-old woman, had isolated disfiguring warts on her hands and feet from the age of 10 years onward (Fernandes et al. 2019). CD4 is a T-cell surface coreceptor for human leukocyte antigen (HLA)-II. Upon binding, CD4 increases the likelihood of positive selection in the thymus and enhances the antigen response of $CD4^{+}$ T cells in mice (Marrack et al. 1983; Glaichenhaus et al. 1991; Strong et al. 2001). $CD4^{-}TCR\gamma\delta^{-}TCR\alpha\beta^{+}$ cells with a phenotype and number similar to those of normal $CD4^{+}$ T cells were observed in the CD4-deficient patient, demonstrating the redundancy of the CD4 protein for $CD4^{+}$ T-cell development in humans. CD4 is also expressed in myeloid cells, but its role in these cells remains unclear. This single case study suggests that $CD4^{+}$ T cells, and perhaps $CD4^{+}$ myeloid cells (monocytes, DCs, LCs), play a key role in the control of common skin warts.

STK4 deficiency is an AR disorder associated with recurrent bacterial and viral infections, including Epstein Barr virus (EBV)-induced lymphoproliferation and lymphoma (Crequer et al. 2012a; Abdollahpour et al. 2012; Halacli et al. 2015; Dang et al. 2016; Schipp et al. 2018; Sharafian et al. 2019; Al-Saud et al. 2019). STK4 deficiency results in $CD4^{+}$ T-cell, $CD8^{+}$ T-cell and B-cell lymphopenia. Four of the 16 patients with complete STK4 deficiency reported to date (25%) had disseminated common warts, and two had atypical EV (see the section on EV).

Complete magnesium transporter 1 (MAGT1) deficiency (also known as XMEN) is an X-linked combined immunodeficiency affecting hemizygous male carriers (Li et al. 2011b; Ravell et al. 2020). MAGT1 is involved in magnesium regulation and protein glycosylation. Patients are highly susceptible to EBV infection and EBV-driven cancers, recurrent infections of the ear and nose, and viral infections of the skin, including molluscum and skin warts (in 30% of patients). These patients also have low levels of NKG2D expression on the

surface of NK and $CD8^+$ T cells (100%), low IgG levels (~75%) and CD4 lymphopenia (~40%), potentially accounting for susceptibility to EBV infections, infections of the ear and nose and viral infections of the skin, respectively. Defective glycosylation probably contributes to the susceptibility to infection of these patients, by specifically impairing the cell surface expression of several immune receptors, including CD28 and CD70, on T lymphocytes (Ravell et al. 2020).

Patients with AR CARMIL2 deficiency have a broad clinical phenotype, including common skin warts (~30% of the patients) and molluscum contagiosum, bacterial and fungal infections, dermatitis, inflammatory bowel disease, esophageal eosinophilia and EBV-induced smooth muscle tumors (Wang et al. 2016; Sorte et al. 2016; Schober et al. 2017; Alazami et al. 2018; Marangi et al. 2020; Atschekzei et al. 2019; Magg et al. 2019; Maccari et al. 2019). CARMIL2 is broadly expressed in the immune system, in all lymphocytes and some myeloid cells. CARMIL2 deficiency impairs NF-κB activation downstream from CD28 and BCR in T and B cells, respectively (Wang et al. 2016). Patients with CARMIL2 deficiencies have normal numbers of T cells, but low counts of Treg cells, central memory CD4 and CD8 T cells, and memory B cells. Patients lacking B cells due to BTK deficiency are not specifically at risk of HPV infection (Winkelstein et al. 2006). This suggests that defective CD28 signaling in T cells is the primary driver of susceptibility to HPV warts in patients with CARMIL2 deficiency. Unfortunately, no CD28-deficient patients have yet been identified, so it is not currently possible to confirm or exclude this hypothesis. Furthermore, the possible intrinsic role of CARMIL2 in dendritic cells, which also express this molecule, remains to be explored (Wang et al. 2016).

Finally, other genes for which mutations mostly affecting lymphocytes, but with occasional cases of extensive warts, have been reported include *RHOH* (n=1; 50% of patients) (Crequer et al. 2012b), *PIK3CD* (n = 4; ~8% of patients) (Angulo et al. 2013; Coulter et al. 2017), *PIK3R1* (n = 1; ~3% of patients), (Elkaim et al. 2016), *ICOS* (n = 1; ~8% of patients) (Schepp et al. 2017), *CD40L* (n = 3; <1% of patients) (Yilmaz et al. 1995; Chang et al. 1998; Ho et al. 2018) and *CORO1A* (n =1; ~12% of patients) (Punwani et al. 2015; Yee et al. 2016).

Overall, studies of the genetic etiologies of recurrent common and plantar warts have suggested that $CD4^+$ T cells play a major role in the control of infection. It is therefore surprising that, with few reported exceptions, HLA-II deficiencies are not frequently associated with susceptibility to warts (Ouederni et al. 2011; Guirat-Dhouib et al. 2012). This may reflect the very short life expectancy of patients in the absence of bone marrow transplantation (Klein et al. 1993; Reith and Mach 2001). Cytotoxic lymphocytes might also be expected to be crucial for the clearance of infected cells, as shown by the $CD8^+$ T-cell infiltration observed in regressing warts (Coleman et al. 1994). However, the lack of inborn errors resulting in complete isolated CD8 T-cell or NK-cell deficiencies makes it impossible to draw firm conclusions about the exact contribution of these subsets to anti-HPV immunity. HLA-I and CD8A deficiencies, which specifically impair, but do not abolish CD8 and/or NK cell function, do not result in susceptibility to HPV (de la Calle-Martin et al. 2001; Zimmer et al. 2005; Hanalioglu et al. 2017). Similarly, MCM4 and GINS1 deficiencies, which lead to a large decrease in NK cell numbers, are not associated with

warts (Gineau et al. 2012; Orange 2013; Cottineau et al. 2017). Finally, a few warts were found in one of the two reported patients with biallelic IRF8 deficiency, who present a restricted dendritic cell deficiency, suggesting that these patients may be susceptible to severe HPV infection if they do not undergo transplantation at a young age (Hambleton et al. 2011; Bigley et al. 2018). The very high penetrance of HPV infection in patients with GATA2 and CXCR4 deficiencies is, therefore, probably due to a synergistic effect of combined APCs and T-cell deficiencies. GATA2, IRF8 and CXCR4 deficiencies are all associated with normal or slightly low levels of Langerhans cells, making it impossible to draw conclusions about this major subset of skin epidermis APCs either (Tassone et al. 2010; Bigley et al. 2011; Hambleton et al. 2011).

Anogenital HPV lesions

HPVs also cause anogenital lesions. Low-risk HPV6 and HPV11 are the most common causes of anogenital condyloma, a very common sexually transmissible disease with a prevalence of 0.2% to 5.1% worldwide (Patel et al. 2013). In rare cases, extreme manifestations of condyloma, such as Buschke Lowenstein tumor (Gissmann et al. 1982; Boshart and Hausen 1986; Lévy and Lebbe 2006), may be observed. High-risk HPV16 and HPV18 are implicated in the vast majority of cervical and anogenital cancers (Clifford et al. 2003). Every year, HPVs cause more than 500,000 cases of cervical cancer and more than 30,000 cases of anal cancer (Schiffman et al. 2016; Arbyn et al. 2020). Cervical cancer was the fourth most common cancer in women worldwide in 2018 (Arbyn et al. 2020). In the adult population, 5-40% of individuals have been reported to be seropositive for HPV6, 2-20% for HPV11, 10-40% for HPV16, and 5-10% for HPV18 (Waterboer et al. 2009; Casabonne et al. 2009; Antonsson et al. 2010; Combes et al. 2014; Loenenbach et al. 2019). Several genes involved in the immune response, some of which are also associated with susceptibility to common warts, have occasionally or frequently been shown to be associated with anogenital HPV infections (Table 1).

Patients with CXCR4 or GATA2 deficiencies are particularly susceptible to anogenital warts and HPV-induced anogenital dysplasia (Tarzi et al. 2005; Kawai and Malech 2009; Spinner et al. 2014; Kuriyama et al. 2018; Toboni and Bevis 2018). Several case reports for rare primary immunodeficiencies and anogenital HPV manifestations have been published, concerning HPV-induced vulvar carcinoma in a patient with ICOS deficiency (a T-cell costimulatory molecule) (Schepp et al. 2017), extensive anogenital warts in two patients with ITGB2 deficiency (van de Vijver et al. 2012; Leiding and Holland 2012), extensive genital warts in an adult WAS patient (Mehta et al. 2008), genital lesions in a ZAP70-deficient patient (Chinn et al. 2017), extensive HPV-related anogenital disease in one patient with hypomorphic DCLRE1C deficiency (Woodbine et al. 2010), large perineal condyloma in MAGT1-deficient patients and recurrent condyloma in two CARMIL2-deficient patients (Sorte et al. 2016; Ravell et al. 2020). Several case reports have been published for SPINK5 deficiency and severe anogenital HPV infections, including one case of extensive anogenital papillomatosis ($HPV51^+$, an α-HPV) and two Buschke Lowenstein tumors (Li et al. 2011a; Ashton et al. 2017; Fölster-Holst et al. 1999). SPINK5 deficiency leads to congenital ichthyosis, trichorrexis invaginata (“bamboo hair”) and severe atopic manifestations (Chavanas et al. 2000). Recurrent skin infections occur in 75% of SPINK5-deficient patients

(Bitoun et al. 2002), but data on HPV infections in these patients are very limited and merit a dedicated study (Weber et al. 2001). Overall, the data available for these patients, like those for susceptibility to common warts caused by HPV, suggest a crucial role for T cells and, probably, APCs in the control of anogenital HPV lesions.

HPV lesions at other mucosal sites

Juvenile recurrent respiratory papillomatosis (JRRP)

Recurrent respiratory papillomatosis (RRP) is a rare disease with an estimated prevalence of ~1 to 4/100,000 children (Derkay 1995; Armstrong et al. 1999; Larson and Derkay 2010; Marsico et al. 2014). It is caused predominantly by HPV6 and HPV11 (Derkay and Wiatrak 2008; Venkatesan et al. 2012). These two closely related alpha-HPVs are generally associated with benign genital warts (see above). Patients with JRRP display no particular susceptibility to other types of infectious agents, including viruses, and are not more susceptible to HPV infections at other body sites. They have detectable antibodies against HPV, and only minor alterations to the immune system have been reported, including Th2 polarization, restricted Vβ TCR repertoires in CD4 and CD8 T cells, and natural killer cell dysfunction (Bonagura et al. 2010).

Biallelic GOF *NLRP1* mutations were recently identified in three patients with JRRP and mild skin abnormalities, including a few common warts (Table 1) (Grandemange et al. 2017; Drutman et al. 2019). NLRP1 is a protein present in most tissues that acts as a sensor for the innate immune complex known as the inflammasome (Martinon et al. 2002; Mitchell et al. 2019). Inflammasomes are protein oligomers that form part of the innate immune system. Autosomal dominant (AD) and AR *NLRP1-GOF* deficiencies in humans have been reported to cause three Mendelian diseases with overlapping, but different phenotypes, all of which include benign-to-cancerous hyperproliferative skin lesions (Mamaï et al. 2015; Zhong et al. 2016; Grandemange et al. 2017). The mechanism underlying JRRP in the three patients with *NLRP1-GOF* mutations remains unclear. Despite strong histological support for an infectious etiology (Drutman et al. 2019), the HPV strain driving the lesion was not identified, and the possibility of NLRP1-GOF mutations themselves causing hyperproliferative lesions in the upper airways has not yet been excluded. The discovery of JRRP in only 7% of patients (3/43) with *NLRP1* GOF mutations is consistent with the absence of HPV6/11 exposure at birth in most children, or with incomplete penetrance. However, further studies will be required to clarify the pathophysiological mechanisms underlying this disease.

Other mucosal lesions

HPVs can also induce lesions at other mucosal sites, such as the oral, oropharyngeal and ocular mucosae (Schiffman et al. 2016; Kobayashi et al. 2018; Betz 2019; Theotoka et al. 2019). HPVs, particularly the high-risk HPV16, were implicated in ~29,000 oropharyngeal and 9000 oral and laryngeal cancers worldwide in 2012 (Schiffman et al. 2016). The low-risk HPV6 and HPV11 are strongly associated with conjunctival papilloma, squamous papilloma, and condyloma of the oral cavity (McDonnell et al. 1987; Sjö et al. 2007; Betz 2019). HPV13 and HPV32 are responsible for multifocal epithelial hyperplasia (MEH;

Heck's disease), a generally benign disease usually presenting as multiple exophytic papules or nodules on the oral mucosa, gingiva, tongue, and lips (Betz 2019). MEH is rare, except in certain ethnic groups, such as Eskimos and Waimiri Atroari Indians, in which a prevalence of up to 40% and 21%, respectively, has been reported in children (Said et al. 2013; Betz 2019). Together with reports of familial cases (Premoli-De-Percoco et al. 1993; Hall et al. 2010; Akoğlu et al. 2015), this strongly suggests that MEH has a strong host-genetic component. In the Mexican Mestizo population, the human leukocyte antigen HLA-DR4 was found to be associated with a 3.9 time increase in the risk of developing MEH (Garcia-Corona et al. 2004). To date, only three patients with oral HPV lesions and an identified genetic etiology have, to my knowledge, been reported: RFXANK deficiency in two siblings with oral HPV6 infection (Guirat-Dhouib et al. 2012), and severe, recurrent oral HPV lesions in a ZAP70-deficient patient (Chinn et al. 2017). Together with the high susceptibility of patients with acquired immunodeficiency to head and neck HPV infection and cancer (D'Souza et al. 2014; Betz 2019), these case reports suggest that inborn errors of T-cell immunity can underlie susceptibility to severe HPV infection of the oral, oropharyngeal and ocular mucosae.

Conclusion

In recent decades, the molecular characterization of primary immunodeficiencies in humans has provided new insight into specific immunity to HPV. The absence of overt HPV infections in patients with phagocytosis (e.g. *CYBA*, *NCF1* or *NCF4* deficiencies) or complement deficiency (e.g. C3 deficiency) indicates that these two important branches of immunity do not play an essential role in immunity to HPV (Rosenzweig and Holland 2004; Ram et al. 2010). Furthermore, severe HPV infection has rarely been reported in the many patients with profound immunoglobulin deficiencies (e.g. CD40L and BTK deficiencies), including those surviving to adulthood (Yilmaz et al. 1995; Chang et al. 1998; Notarangelo and Hayward 2000; Winkelstein et al. 2006; Ho et al. 2018). Thus, despite an obvious preventive effect of HPV vaccination (Schiller et al. 2012), and a case report showing wart regression under subcutaneous immunoglobulin treatment (Lin et al. 2009), B cells do not seem to play a key role in HPV susceptibility. A feature common to all primary immunodeficiencies frequently associated with atypical EV, common warts and anogenital HPVs is the impairment of T lymphocytes, sometimes together with APCs. The role of cytotoxic lymphocytes (CD8 T cells, NK cells) remains unclear, due to the absence of specific immunodeficiencies of these cells in humans. Consistent with the massive infiltration observed in regressing warts (Coleman et al. 1994), $CD4^+$ T cells clearly play a crucial role, as indicated by the high susceptibility to warts of patients with $CD4^+$ T-cell lymphopenia, whether inherited or acquired, and, more recently, in the first patient reported to lack CD4 expression (Fernandes et al. 2019). APC deficiency, probably in combination with a T-cell defect, also seems to play a major role in the extreme HPV susceptibility observed in GATA2 and CXCR4 deficiencies. Finally, the susceptibility to EV of patients with deficiencies of EVER1, EVER2 or CIB1 suggests a crucial role for keratinocyte-intrinsic immunity in the control of β-HPV infection. Many of the genes associated with HPV susceptibility are expressed not only by immune cells, but also in the skin (e.g. STK4; Table 2), and may therefore contribute to skin-intrinsic defects of immunity not only to β-

HPV, but also to other HPV types (α, γ, μ and ν). The recent discovery of *NLRP1* GOF mutations in patients with JRRP is consistent with this hypothesis.

In conclusion, despite the large amount of knowledge concerning HPV immunity gained from studies of human primary immunodeficiencies, many unanswered questions remain. First, the exact contribution of different lymphocyte and APC subsets to HPV-immunity in the skin and mucosae remains unclear. Second, the molecular mechanism at work during wart regression remains unknown. Finally, the mechanisms of keratinocyte-intrinsic immunity to β-HPVs, but also to α, γ, μ and ν HPVs, remain poorly understood. Ongoing and future genetic investigations of the cellular basis of cutaneous or mucosal susceptibility to HPV susceptibility will undoubtedly answer many of these questions. Such studies should improve our understanding of normal immunity to HPV, and will, we hope, provide new preventive, diagnostic and therapeutic tools much needed in the context of the current burden of HPV disease worldwide.

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Table 1:

Immunodeficiencies associated with susceptibility to HPV infection

Gene	Inheritance & mechanism	EV	Cutaneous warts	Anogenital lesions	Other mucosae	Clinical phenotype	Immunological phenotype	References HPV	References phenotype
ADA	AR Hypomorphic		+			Broad and severe susceptibility to infections. Hypomorphic mutations are associated with less severe infections.	The SCID form is associated with T-B-NK- phenotype. Hypomorphic forms are less severe, with low lymphocyte counts.	(Shovlin et al. 1993; Antony et al. 2002)	(Fischer et al. 2015)
ADA2	XLR		+			Autoinflammation, polyarteritis nodosa–type vasculitis, Blackfan-Diamond anemia, spastic paraplegia and immunodeficiency.	Variable leukopenia or lymphopenia.	(Trotta et al. 2018; Arts et al. 2018)	(Trotta et al. 2018; Arts et al. 2018)
ATM	AR		++			Neurological defects, recurrent bacterial sinopulmonary infections, common warts and opportunistic infections.	Broad lymphopenia affecting B cells, CD4 and CD8 T cells. Restricted TCR and BCR repertoires.	(Nowak-Wegrzyn et al. 2004)	(Staples et al. 2008; Driessen et al. 2013; Chopra et al. 2014; Kraus et al. 2014)
CAKMIL2	AR		++	+		Dermatitis, allergies, esophagitis, IBD and broad susceptibility to infections and warts.	Low memory $CD4^+$ and $CD8^+$ T cell and memory B cell levels. Impaired CD28 pathway in T cells.	(Sorte et al. 2016; Alazami et al. 2018; Atschekzei et al. 2019)	(Wang et al. 2016; Schober et al. 2017)
CD4	AR		+++			Isolated cutaneous warts	Normal T lymphocytes except for an absence of CD4 expression on CD8-TCR$\alpha\beta^+$ T cells (present in normal number)	(Fernandes et al. 2019)	(Fernandes et al. 2019)
CD40L	XLR		+			Bacterial sinopulmonary infections, cryptosporidiosis and opportunistic infections.	Undetectable levels of IgG and IgA, normal to high serum IgM levels Normal number and distribution of $CD4^+$ and $CD8^+$ subsets	(Yilmaz et al. 1995; Chang et al. 1998; Ho et al. 2018)	(Notarangelo and Hayward 2000)
CIB1	AR	+++ (T)				Isolated EV	No immunological abnormalities.	(de Jong et al. 2018a)	(de Jong et al. 2018a)
CORO1A	AR Hypomorphic	+ (A)	+			Broad and severe susceptibility to infections, particularly EBV. Hypomorphic mutations are associated with less severe infections.	$CD4^+$ T-cell lymphopenia. Very low frequency of naïve $CD4^+$ and $CD8^+$ T cells. Impaired NK function.	(Punwani et al. 2015; Yee et al. 2016)	(Moshous et al. 2013; Stray-Pedersen et al. 2014; Punwani et al. 2015; Yee et al. 2016)
CXCR4	AD GOF		+++	+++		Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome	Pancytopenia (neutrophils, monocytes, DCs, T cells, NK cells) Restricted TCR repertoire. Normal Langerhans cells	(Tarzi et al. 2005; Kawai and Malech 2009; McDermott and Murphy 2019)	(Gulino et al. 2004; Tassone et al. 2010; McDermott et al. 2011)
DCLRE1C	AR Hypomorphic	+ (A)		+		Broad and severe susceptibility to infections. Hypomorphic mutations are associated with less severe infections.	Low numbers of B cells, Hypogammaglobulinemia and Low levels/ absent $CD3^+$ T cells. Hypomorphic forms exist. Note: the case in Tahiat *et al* had low $CD4^+$ T- and B-cell counts and very low frequencies of naïve $CD4^+$ and $CD8^+$ T cells.	(Woodbine et al. 2010; Tahiat et al. 2017)	(Volk et al. 2015)
DOCK8	AR	+ (A)	+++			Eczema, recurrent respiratory tract infections, allergies, abscesses, viral infections and mucocutaneous candidiasis	High IgE levels, eosinophilia, Low CD4, CD8, NK and B-cell counts in 45%, 38%, 28% and 12% of the patients, respectively Impaired T- and dendritic-cell migration	(Sanal et al. 2012; Aydin et al. 2015; Liu et al. 2017)	(Zhang et al. 2014; Aydin et al. 2015)
EVER1	AR	+++ (T)				Isolated EV	Normal T-cell count, small proportion of naïve T cells.	(Ramoz et al. 2002; Crequer et al. 2013)	(Crequer et al. 2013)

Gene	Inheritance & mechanism	EV	Cutaneous warts	Anogenital lesions	Other mucosae	Clinical phenotype	Immunological phenotype	References HPV	References phenotype
EVER2	AR	+++ (T)				Isolated EV	Normal T-cell count, small proportion of naïve T cells.	(Ramoz et al. 2002; Crequer et al. 2013)	(Crequer et al. 2013)
GATA2	AD Haplo-insufficiency		+++	+++		Hematologic cancers, severe infections (viral, bacterial and fungal) and multiple non-infectious phenotypes	Pancytopenia (neutrophils, monocytes, DCs, T cells, NK cells). Only modest impact on Langerhans cells	(West et al. 2014; Spinner et al. 2014; Hsu et al. 2015; Kuriyama et al. 2018; Toboni and Bevis 2018)	(Bigley et al. 2011; Dickinson et al. 2014; Spinner et al. 2014)
ICOS	AR			+		CVID-like disease. Susceptibility to viral and opportunistic infections, as well as cancer.	Low B-cell count, hypogammaglobulinemia. Normal T-cell count. Low levels of T-follicular helper cells. Note: P6 with verrucosis in Schepp et al. had lymphopenia ($CD4^+$ and $CD8^+$ T cells, and B cells)	(Schepp et al. 2017)	(Schepp et al. 2017)
IKBKG	XLR	+ (A)				Infections, particularly disseminated mycobacterial infections +/− ectodermal dysplasia and anhidrosis	Normal immunological phenotype Note: P3 (R254G) with EV from Haverkamp et al. had $CD4^+$ T-cell lymphopenia. P1 (E315A) with flat warts from the same paper had a normal lymphocyte count, including $CD4^+$ T cells.	(Tobin et al. 2003; Hanson et al. 2008; Haverkamp et al. 2014)	(Filipe-Santos et al. 2006)
IL2RG	XLR Hypomorphic		+			Broad and severe susceptibility to pathogens. Hypomorphic mutations are associated with less severe infections.	The SCID form is associated with a T^- B^+NK^- phenotype. Hypomorphic forms are less severe, with low NK and T-cell counts.	(Brooks et al. 1990; Schmalstieg et al. 1995; Yamashita et al. 2019)	(Fischer et al. 2015; Yamashita et al. 2019)
IL2RG Post HSCT	XLR	+	+++			Severe cutaneous warts.	CD4 lymphopenia is frequent but not correlated with warts and IL2RG/JAK3/IL7R-deficient patients post HSCT have more naïve $CD4^+$ T cells than RAG1/RAG2/DCLRE1C-deficient patients post HSCT	(Gaspar et al. 2004; Laffort et al. 2004; Neven et al. 2009)	(Laffort et al. 2004; Neven et al. 2009)
IL7	AR	+ (A)	+++			Cutaneous warts *Cryptococcus neoformans* meningitis.	$CD4^+$ T-cell lymphopenia (except one patient)	(Horev et al. 2015; Kosumi et al. 2020)	(Horev et al. 2015; Kosumi et al. 2020)
IL7R Post HSCT	AR	+? (A)	+			Mild cutaneous warts.	CD4 lymphopenia is frequent but not correlated with warts and IL2RG/JAK3/IL7R-deficient patients post HSCT have more naïve $CD4^+$ T cells than RAG1/RAG2/DCLRE1C-deficient patients post HSCT	(Neven et al. 2009)	(Neven et al. 2009)
ITGB2	AR		+	+		Recurrent skin and mucosal bacterial infections.	Impaired adhesion to the vascular wall and migration to sites of infection and inflammation.	(van de Vijver et al. 2012; Leiding and Holland 2012)	(Etzioni 2010)
ITK	AR	+ (A)				Extreme susceptibility to EBV. Opportunistic infections.	Progressive hypogammaglobulinemia. Global lymphopenia with a progressive loss of $CD4^+$ T cells.	(Youssefian et al. 2019)	(Ghosh et al. 2014)
JAK3	AR Hypomorphic		+			Broad and severe susceptibility to infections. Hypomorphic mutations are associated with less severe infections.	The SCID form is associated with a T^- B^+NK^- phenotype. Hypomorphic forms are less severe, with low $CD4^+$, $CD8^+$ T and NK cell counts.	(Frucht et al. 2001)	(Frucht et al. 2001; Cattaneo et al. 2013)
JAK3 Post HSCT	AR	+ (A)	+++			Severe cutaneous warts.	CD4 lymphopenia is frequent but not correlated with warts and IL2RG/JAK3/IL7R-deficient patients post HSCT have more naïve	(Gaspar et al. 2004; Laffort et al. 2004; Neven et al. 2009)	(Laffort et al. 2004; Neven et al. 2009)

Gene	Inheritance & mechanism	EV	Cutaneous warts	Anogenital lesions	Other mucosae	Clinical phenotype	Immunological phenotype	References HPV	References phenotype
							$CD4^+$ T cells than RAG1/RAG2/DCLRE1C-deficient patients post HSCT		
LCK	AR Hypomorphic?	+ (A)				Broad susceptibility to infections. Early-onset inflammatory and autoimmune manifestations.	Impaired TCR signaling. $CD4^+$ T-cell lymphopenia	(Li et al. 2016)	(Hauck et al. 2012)
LIG4	AR Hypomorphic		+			Broad and severe susceptibility to infections. Developmental delays, and radiosensitivity.	Pancytopenia	(O'Driscoll et al. 2001; Tamura et al. 2015)	(O'Driscoll et al. 2001; Tamura et al. 2015)
MAGT1	XLR		++	+		X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (XMEN) disease.	$CD4^+$ T-cell lymphopenia. Hypogammaglobulinemia. Low NKG2D and CD28 expression on lymphocytes.	(Ravell et al. 2020)	(Ravell et al. 2020)
NFKBIA	AD GOF		+			Anhidrotic ectodermal dysplasia. Various pyogenic, mycobacterial, fungal, and severe viral infections.	Normal leukocyte counts. Impaired NF-κB-mediated responses in fibroblasts and leukocytes. Note: the patient described in Sogkas et al. had "severe CD4 lymphopenia"	(Sogkas et al. 2020)	(Boisson et al. 2017)
NLRP1	AD GOF		+ ?		+ ?	Multiple self-healing palmoplantar carcinoma (MSPC). Familial keratosis lichenoides chronica (FKLC). Autoinflammation with arthritis and dyskeratosis (AIADK)	Normal immunological phenotype Exaggerated activation of the NLRP1 inflammasome in respiratory epithelial keratinocytes.	(Grandemange et al. 2017; Drutman et al. 2019)	(Drutman et al. 2019)
PIK3CD	AD GOF		+			Sinopulmonary infections, herpesvirus infections, autoinflammatory disease, and lymphoma.	Frequent CD4 T-cell (84%) and B-cell (67) lymphopenia, and IgG deficiency.	(Angulo et al. 2013; Coulter et al. 2017)	(Coulter et al. 2017)
PIK3R1	AD GOF		+			Sinopulmonary infections, failure to thrive, neurodevelopmental delay, malignancy, autoimmunity and chronic diarrhea. Persistent CMV/EBV viremia.	B-cell lymphopenia (88%), low numbers of naïve $CD4^+$ (71%) and $CD8^+$ (100%) T cells, low serum IgG and IgA levels (87%).	(Elkaim et al. 2016)	(Elkaim et al. 2016)
RASGRP1	AR	+ (A)				Broad susceptibility to infections. Extreme susceptibility to EBV.	$CD4^+$ T-cell and B-cell lymphopenia.	(Platt et al. 2017)	(Salzer et al. 2016; Winter et al. 2018)
RFXANK	AR				+	Bare lymphocyte syndrome type II. Recurrent severe infections. Failure to thrive, diarrhea, liver/biliary tract disease. Autoimmune cytopenias.	Normal total T-cell count. Low $CD4^+$ Hypogammaglobulinemia or agammaglobulinemia	(Guirat-Dhouib et al. 2012)	(Hanna and Etzioni 2014)
RHOH	AR	+++ (A)	+			EV, common warts, Burkitt lymphoma, molluscum, suspected lung infection, gingivostomatitis.	Very low naïve $CD4^+$ and $CD8^+$ T-cell frequencies	(Crequer et al. 2012b)	(Crequer et al. 2012b)
SMARCAL1	AR	+ (A)				Spondyloepiphyseal dysplasia, focal segmental glomerulosclerosis and opportunistic infections.	Lymphopenia	(Collins et al. 2018)	(Boerkoel et al. 2002; Clewing et al. 2007)
SPINK5	AR			+		Comèl-Netherton syndrome (congenital ichthyosis, bamboo hair, and atopic diathesis).	Normal immunological phenotype. Mild immunological abnormalities.	(Li et al. 2011a; Ashton et al. 2017; Fölster-Holst et al. 1999)	(Renner et al. 2009)
STK4	AR	+ (A)	++			Recurrent pulmonary infections and superficial bacterial/viral infections.	$CD4^+$ T-cell lymphopenia. Frequent $CD8^+$ T-cell and B-cell lymphopenia	(Abdollahpour et al. 2012; Crequer et al.	(Abdollahpour et al. 2012; Crequer et al.

Gene	Inheritance & mechanism	EV	Cutaneous warts	Anogenital lesions	Other mucosae	Clinical phenotype	Immunological phenotype	References HPV	References phenotype
								2013; Sharafian et al. 2019)	2013; Halacli et al. 2015, p. 4; Sharafian et al. 2019)
TPP2	AR	+ (A)				Evans syndrome and viral infection susceptibility.	Very low naïve $CD4^+$ and $CD8^+$ T-cell frequencies. Low B-cell count.	(Stepensky et al. 2015)	(Stepensky et al. 2015)
WAS	XLR		+	+		Thrombocytopenia, infections, eczema, cancers and autoimmune manifestations.	Progressive decrease in lymphocyte counts, resulting in variable degrees of lymphopenia. Impaired myeloid and lymphoid function. Note: data available show lymphopenia in patients with warts.	(Stevens et al. 1975; Ormerod et al. 1983; Sullivan et al. 1994; Mehta et al. 2008; Kim et al. 2010)	(Ochs et al. 2009)
ZAP70	AR Hypomorphic?		+	+	+	Broad and severe susceptibility to pathogens. Hypomorphic mutations are associated with less severe infections.	$CD8^+$ T-cell lymphopenia, absence of $CD4^+$ T-cell proliferation in response to mitogens Note: Patient from Chinn et al. also had $CD4^+$ T-cell lymphopenia	(Chinn et al. 2017)	(Wang et al. 2010; Chinn et al. 2017)

+, ++ and +++ correspond to the relative penetrance of the HPV disease in each genetic defect. +: low; ++: intermediate; +++: high or complete. Of note, some genetic disorders have very few reported cases, and the observed penetrance may vary in the future with the discovery of new patients. AR: autosomal recessive. AD: autosomal dominant. XLR: X-linked recessive. GOF: gain of function. (A) atypical EV. (T) typical EV. IBD: inflammatory bowel disease. NLRP1 is labeled with a “?” because HPV DNA was not formally identified in the lesions.

Table 2:

mRNA levels for HPV-associated genes in various primary and tumor tissues or cells

		Peripheral blood mononuclear cells					Epidermoid cell lines		Myeloid cell lines			Lymphoid cell lines	
	Skin	Monocytes	T cells	B cells	NK cells	DCs	A431	Hacat	HL-60	THP-1	U937	MOLT4	REH
ADA	2.8	64	10.3	1.3	16.9	41.6	1.4	0.2	0.6	1.9	3.3	197.1	10.6
ADA2	2.5	46.4	7.9	6.1	9.5	29.8	0	0.3	0.2	5.8	20.7	20.5	0.4
ATM	8.4	12.5	18.5	13.7	7.6	6.1	2.6	4	10.2	5.8	11.3	7	5.5
CARMIL2	0.4	0	2.7	1.5	1.7	1.1	0	0	2.4	0.6	0	21.6	36.4
CD4	3.5	42.5	29.1	0.1	0.3	46.7	0	0	13.5	38.1	35.9	4.8	0
CD40L	1.1	0	29.2	0	0.2	0	0	0	0.1	0	0	22.4	0
CIB1	10	45.4	55.2	87.9	35.9	43	24.5	25.5	31.9	19.3	36.5	24	13.6
CORO1A	3.4	67.5	66.4	41.6	39.1	67.7	0.2	0.4	59.6	34.7	75.5	57.6	31.3
CXCR4	2.3	7.2	32	47.3	4	16.8	0.1	0	10.4	20.5	17.2	68.5	36.3
DCLRE1C	7.8	14.5	12.2	23.5	8	17.2	11.8	9.9	7.4	13.6	7.9	10.8	12.3
DOCK8	3.3	21.5	5.5	7.3	6.6	15.4	0	0	16.8	50.6	10.6	15.7	19.8
EVER1	6.5	26.7	27.2	13.5	15.6	8.3	5.4	9.7	11.7	17.8	19	5.7	2.6
EVER2	1.7	6.6	13.1	5	6.7	2.1	0.1	1.1	20.4	4.2	17.3	7	0.4
GATA2	4.1	0	0	0	0	0	4.6	4.9	6.9	2.8	0.4	0	0
ICOS	0.6	0	18.4	0	0.3	0	0	0	0	0	0	15.3	0
IKBKG	11.4	21.8	17.9	11.3	13.8	13.7	15.9	15	10.3	11.5	18.7	10.6	11.7
IL2RG	2.7	19.7	115.3	51.9	94.6	30.6	0.1	0.1	8.9	0.3	37	31.9	7.3
IL7	9.6	0.8	7.5	10.9	0.5	2.4	0.2	3.3	0.1	0	0	0	0
IL7R	1.8	0.2	70.3	0.4	19.1	0.3	0.1	3.5	0.1	0	2	0.5	84.6
ITGB2	4.1	122.9	57.4	9.5	41	76	0.2	0	15	114.8	85.3	17	0.2
ITK	1	0.6	28	0	9.2	0	0	0	0	0	0	21.7	0
JAK3	1.3	9.6	15	7.4	8.4	4.5	0.1	0.1	0	1.3	13.7	3.6	4.6
LCK	1	0.3	112.2	6.1	42.8	0.5	0	0	0	0	0	98.9	3.8
LIG4	6.6	10.7	2.7	3.3	2.7	2.1	9.4	3.9	10.2	15.7	5.9	16.8	15.5
MAGT1	14.1	21.3	20.8	14.3	18.5	23.6	22.7	21.3	22.8	12.2	21.3	13.4	16.4
NFKBIA	48.2	58.3	37.3	45.3	33.2	55	12.9	17.1	6.1	13.1	4.6	8	18.3
NLRP1	35.2	7.5	7	5.3	3.8	4.6	6.2	2.8	0	0.2	0.2	0	2.4
PIK3CD	2	15	13.7	8.4	14.5	14.5	2.6	0.8	18.4	22	26.3	1.7	22.7
PIK3R1	19.1	4.1	14.8	2.2	8.2	2.1	1	2.6	6.7	4.8	8.5	26.4	15.4
RASGRP1	7.3	0	10.4	1.2	2.4	0	0	0.1	0.2	0	0	27.2	7.6
RFXANK	18.7	18.2	23.3	25.1	18.3	31.7	18.4	13.8	20.6	42.2	25.7	26.8	22.8
RHOH	1.2	0.2	54.8	41.2	12.3	4.7	0	0	5.8	0.1	1.2	49.6	5.3
SMARCAL1	15.2	14	12.8	8.9	16.6	15.9	9.6	7.3	6.8	11	9.2	12.6	14.4
SPINK5	48.6	0	0	0	0	0	0	12.1	0.2	0	0.2	0	0
STK4	11.4	13.3	14.5	10.8	10.3	6.9	11.6	12.4	26.7	16.9	12.8	19.9	12.9

		Peripheral blood mononuclear cells					Epidermoid cell lines		Myeloid cell lines			Lymphoid cell lines	
TPP2	14.1	6.1	12.1	6	10.9	5.8	15.9	15.7	37.6	42.2	27.2	17.3	19.2
WAS	2.2	5.3	3.2	2.1	2.1	3.5	0.2	0.7	9.6	19.2	24.4	19.4	16.9
ZAP70	1	0.2	37.4	0.4	26.4	0.2	0	0	0	0	0	61.5	2.4

All values were extracted from the Human Protein Atlas (https://www.proteinatlas.org/) (Uhlén et al. 2015). Gene names in bold typeface correspond to genes with intermediate or higher penetrance for HPV susceptibility. The values are the normalized values extracted from the Human Protein Atlas database. DCs: dendritic cells. A431: skin squamous cell carcinoma. Hacat: spontaneously immortalized keratinocytes. HL-60: acute myeloid leukemia. THP-1: promonocytic leukemia. U937: histiocytic lymphoma. MOLT4: acute lymphoblastic leukemia (T). REH: acute lymphocytic leukemia (Non-T; Non-B). Color code: white = 0; red = maximum value. The maximum value of each gene was set independently for the primary and tumor cell lines.