



Review

# The Pathogenesis of Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor): An Overview

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**Abstract:** Giant condyloma acuminatum, also known as Buschke-Lowenstein tumor (BLT), is a rare disease of the anogenital region. BLT is considered a locally aggressive tumor of benign histological appearance, but with the potential for destructive growth and high recurrence rates. BLT development is strongly associated with infection with low-risk human papillomaviruses (HPVs), mostly HPV-6 and -11. Immunity to HPVs plays a crucial role in the natural control of various HPV-induced lesions. Large condyloma acuminata are frequently reported in patients with primary (e.g., DOCK8 or SPINK5 deficiencies) and secondary (e.g., AIDS, solid organ transplantation) immune defects. Individuals with extensive anogenital warts, including BLT in particular, should therefore be tested for inherited or acquired immunodeficiency. Research into the genetic basis of unexplained cases is warranted. An understanding of the etiology of BLT would lead to improvements in its management. This review focuses on the role of underlying HPV infections, and human genetic and immunological determinants of BLT.

**Keywords:** giant condyloma acuminatum; Buschke-Lowenstein tumor; human papillomavirus; immunodeficiency; genetics

## 1. Introduction

Papillomaviruses (PVs) are small circular double-stranded DNA viruses from the family Papillomaviridae. PVs are highly host-specific, and display preferential tropism for squamous stratified epithelia, including skin, and conjunctival, oral, and anogenital mucosae [1]. Human PVs (HPVs) are classified into five main genera ( $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\mu$ -, and  $\nu$ -HPVs) on the basis of their DNA sequences. To date, almost 450 HPV genotypes have been isolated and sequenced [2]. According to serological data, most humans have been exposed to HPVs, and HPV infection is one of the most common sexually transmitted diseases [3,4]. Epidemiological studies have shown the risk of anogenital HPV infections to be positively associated with number of sexual partners and inversely associated with age at first sexual intercourse [5,6]. Infection is usually asymptomatic or self-limiting. However, in some individuals, insufficient immune control of viral infection leads to persistent lesions, profuse warts, dysplasia, or cancer development [6,7].

The  $\alpha$ -HPVs include species with cutaneous (e.g., HPV-2, -27, and -57) and mucous membranes (e.g., HPV-6, -11, -16, and -18) tropism [1]. Based on their oncogenic potential they are further divided in low- and high-risk HPVs. Infection with low-risk HPV types usually remains asymptomatic or benign, and lesions regress spontaneously after a few weeks or months. Low-risk  $\alpha$ -HPVs can cause common warts but may also be responsible for tree man syndrome (TMS), as reported in several patients [8,9]. TMS is characterized by persistent giant cutaneous horns. Other low-risk  $\alpha$ -HPVs, such as HPV-6 and HPV-11, are associated with condylomas, but may contribute to the formation of giant condyloma acuminata with destructive local progression [10]. High-risk  $\alpha$ -HPVs are HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, and -70. Persistent infection with high-risk HPV types is the main risk factor of developing HPV-induced malignancies. In particular, HPV-16 is responsible for the majority of HPV-induced cervical cancer, oropharyngeal and anogenital squamous cell carcinoma (SCC) [11–13]. HPV types belonging to genus beta have a cutaneous tropism and typically cause asymptomatic infections in the general population. Patients with epidermodysplasia verruciformis (EV), a rare condition, present with profuse flat warts or scaly, reddish, brownish, or achromic plaques due to an isolated susceptibility to  $\beta$ -HPVs infection, and sometimes HPV-3 from the  $\alpha$  genus [14]. In these patients,  $\beta$ -HPVs with a high oncogenic potential, such as HPV-5, are co-factors of cutaneous SCC development [14–16]. Finally, the  $\gamma$ -,  $\mu$ -, and  $\nu$ -HPVs all present skin tropism and are associated with benign common warts (e.g., HPV-4, a  $\gamma$ -HPV) or plantar myrmecia (e.g., HPV-1, a  $\mu$ -HPV) [17].

Extensive HPV lesions of all types are frequently observed in individuals on immunosuppressive therapy or with human immunodeficiency virus (HIV) infection, suggesting a crucial role of CD4<sup>+</sup> T cells in controlling HPVs [18]. Severe isolated or syndromic (associated with other infections) HPV lesions are also observed in individuals with inborn errors of immunity [18,19]. For instance, the isolated susceptibility of EV patients to  $\beta$ -HPVs results from inherited EVER1 (encoded by *TMC6*), EVER2 (encoded by *TMC8*), or calcium- and integrin-binding protein 1 (CIB1) deficiency [20,21]. Syndromic EV results from mutations in genes involved in T cell immunity (e.g., *STK4*, *RHOH*) [17]. Mutations of certain immune response-related genes, such as *GATA2*, *CXCR4*, and *DOCK8*, are associated with a greater predisposition to multiple types of HPV-induced lesions, including extensive anogenital warts [19]. Moreover, recent studies have shown that the defective CD28 signaling pathway can also decrease the anti- $\alpha$ - and  $\gamma$ -HPV responses, thereby increasing the risk of extensive warts and condylomas [8,22]. This review explores the roles of HPV infection, immunodeficiencies, and host genetics in the pathogenesis of anogenital HPV lesions, with particular focus on giant condyloma acuminatum.

## 2. Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor)—A Short Description of the Disease

### 2.1. Classification

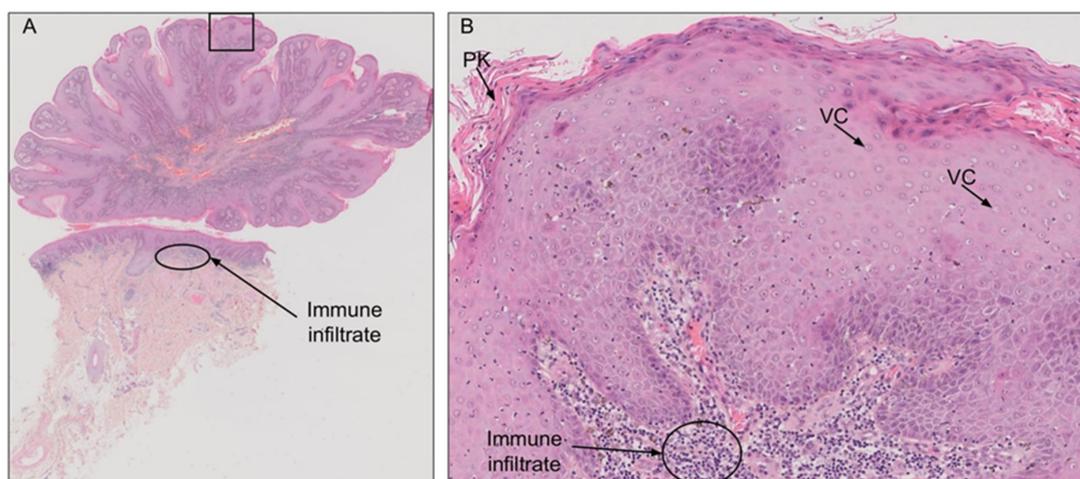
Giant condyloma acuminatum is also known as Buschke-Lowenstein tumor (BLT). BLT was first reported in 1896, in Neisser's *Sterokopischer Atlas*, by Abraham Buschke [23]. Subsequently, in 1925, Abraham Buschke and his assistant Ludwig Löwenstein described BLT as a penile lesion clinically resembling both common condylomas and SCC, but with a different histological appearance and biological behavior [24,25]. BLT is considered to be a locally aggressive tumor characterized by (i) benign histology, (ii) a potential for destructive growth, (iii) malignant transformation (estimated rate of 56%) without propensity for metastasis, and (iv) with a high rate of recurrence after excision (66%) and an overall mortality of approximately 20% [26]. Some authors consider BLT to be intermediate between condyloma acuminatum and SCC, whereas others classify it as an anogenital verrucous carcinoma (a well-differentiated type of SCC) [27,28]. According to recent studies, BLT and verrucous carcinoma should be recognized as two separate entities [29,30]. Indeed, BLTs are associated with low-risk HPV-6 or HPV-11 (see Section 3), whereas verrucous carcinomas are not usually HPV-driven [30,31].

## 2.2. Clinical Presentation

BLT tends to occur in individuals in their forties. It has an estimated incidence of about 0.1% in the general population and a male-to-female ratio of 2.7:1 [28,32,33]. However, its precise incidence is unknown. It presents as a slow-growing cauliflower-like mass in the genital or anorectal area, with relatively slow infiltration into deeper tissues [26]. The disease starts from a long-standing condyloma acuminatum, which can grow to sizes of more than 10 cm in diameter. Progression from the first symptoms of condyloma to BLT development may take 2.8–9.6 years, or longer [26]. Tumor growth is usually slow, but may be rapid in immunocompromised individuals [34,35]. Non-sexual transmission via fomites is possible, but cases of condyloma acuminata and BLT in children should always raise the suspicion of sexual abuse, for which both medical and social evaluation is essential [36]. Unusual clinical presentations of BLT with rapid growth may suggest malignant transformation [28].

## 2.3. Diagnosis

BLT is diagnosed on the basis of patient history, clinical and histological presentation. Histologically, the tumor is characterized by papillomatosis, hyperkeratosis, parakeratosis, acanthosis, and koilocytosis (Figure 1) [34]. Careful histological examination is crucial to exclude transformation to SCC. Imaging studies, such as computed tomography and magnetic resonance imaging, are strongly recommended for assessment of the local and regional extension and to ensure that optimal therapy is prescribed [37].



**Figure 1.** Hematoxylin and eosin staining of a penile Buschke-Lowenstein tumor (BLT). (A) BLT presents with a typical cauliflower shape, without invasion of the dermis. (B) Magnification of the indicated area from A. The histological features are typical of HPV infection, with numerous vacuolated cells (VC; koilocytosis) and parakeratosis (PK). Large immune infiltrates are visible in the dermis downstream from the lesion.

## 2.4. Treatment

A wide radical excision, followed by reconstructive surgery, seems to be the optimal therapeutic strategy for BLT management [38]. However, for extensive tumors, preoperative chemotherapy or radiotherapy can be used to promote tumor shrinkage, rendering the debulking procedure safer [39]. Follow-up visits are necessary due to the high risk of recurrence (estimated at more than 60%) [26]. BLT-related mortality appears to be mostly associated with infectious complications [29]. The maintenance of good hygiene and the correct healing of postoperative wounds are, therefore, essential to reduce the risk of death. Immunomodulatory treatments have also been tested in clinical trials. Topical imiquimod, which induces interferon alpha (IFN)- $\alpha$  production upon binding to Toll-like receptor 7 (TLR7), has shown benefit in the treatment of BLT [40–43]. Interestingly, Geusau et al.

reported a regression of deeply infiltrating BLT following long-term intra-lesional IFN- $\alpha$ 2b therapy [44]. Unfortunately, less favorable outcomes were reported in other studies after imiquimod or IFN- $\alpha$  treatment [45–47]. IFN- $\alpha$  exerts antiviral activity by inducing the expression of protective genes with products that inhibit viral replication and reduce viral dissemination. However, patients with inherited IFNAR1, IFNAR2, IFNGR1, or IFNGR2 deficiencies are not susceptible to severe HPV infections, suggesting that type I and II interferons are not central to HPV-disease pathogenesis [48–50]. Similarly, epidermal growth factor receptor (EGFR) overexpression in benign condyloma acuminata may play a role in dysplastic cell proliferation. This led Bowman et al. to implement systemic chemotherapy including the EGFR inhibitor cetuximab in a patient with metastatic BLT, resulting in a partial response for eight months [51]. Finally, HPV quadrivalent and nonavalent vaccines (Gardasil vaccines) significantly decrease the incidence of genital warts [52]. Although no studies measured the impact of vaccination on BLT incidence, HPV vaccines are also likely to decrease the risk of BLT given that the two causal HPV types, HPV-6 and HPV-11, are included in these vaccines. In addition, some authors suggested their possible therapeutic properties and presented clinical cases of regression of giant condyloma acuminata after HPV vaccination [53,54]. These promising observations show that more studies are required to evaluate the therapeutic value of HPV vaccines and other immunomodulatory treatments against BLT. In summary, surgery is the only really effective treatment of BLT to date, but less invasive procedures may also be beneficial.

### 3. The Role of Low-Risk HPVs in BLT Pathogenesis

Approximately 90% of genital warts are caused by HPV-6 or -11 [55], with HPV-6 predominating [56]. Low-risk HPVs have a low transformation capacity. Despite their high prevalence in genital warts, DNA from HPV-6 and HPV-11 were found only in 4% and 3% of anal cancers, respectively [57], and <1% of cervical cancers [58]. In contrast, HPV-6 and HPV-11 are found in most, if not all, BLT cases, demonstrating a key role for these viruses in tumor development [37,38,59–61]. An excellent review was previously dedicated to the pathogenicity and carcinogenicity of low-risk HPVs compared to high-risk HPVs [62]. It is believed that irrespective of high- or low-risk status, in the course of persistent infection, HPVs make common changes to the infected cells, and that there is convergence in the pathways that they affect [62]. Among a large number of biological activities, high-risk HPV E6 and E7 oncoproteins induce degradation of the tumor suppressor protein p53 and inhibit the retinoblastoma protein (pRb), respectively [62–65]. This leads to abnormal proliferation from the earliest layer of the epithelium, and oncogenic transformation of infected host cells. In contrast, low-risk  $\alpha$ -HPV do not induce cell proliferation in the basal and parabasal layer of the epithelium, contributing to their lower oncogenic potential [62]. This is probably explained by difference in biological activity of E6 and E7 proteins from low- and high-risk HPVs. The overexpression of E6 or E7 from low-risk HPV-6 or HPV-11 in various cellular models impact the expression of numerous host genes [66,67]. Unlike E6 from high-risk HPV-16, E6 from low-risk HPV-11 induces p53 degradation in a cell density-dependent manner [68]. E7 from low-risk HPVs targets pRb family members similarly to high-risk HPVs; however, they were shown to have a preference for p130 which regulates cell cycle entry in the upper epithelial layers [62,69].

While malignant cell transformation in response to high-risk HPV infection has been extensively studied and well characterized, little is known about the mechanisms involved in the progression of low-risk HPV-driven benign condyloma acuminatum to the BLT phenotype. To our knowledge, no studies investigated the viral protein expression patterns, in particular E6 and E7, in BLT compared to conventional condyloma. Nevertheless, the role of p53 in the malignant progression of BLT was highlighted by Pilotti et al., based on immunocytochemical and molecular data [70]. These authors studied five cases of vulvar verrucous carcinoma and two cases of BLT associated with invasive SCC. Neither p53 overexpression nor HPVs were detected in verrucous carcinoma samples, whereas both cases of BLT with invasive SCC tested positive for HPV-6 or -11 and presented p53

overexpression in nuclei. Interestingly, the malignant area of one of these BLT with SCC carried a pathogenic *TP53* missense mutation (Gly245Ser) in the DNA-binding domain of the p53 protein [70]. Altogether, while it has been known for a long time that HPV-6 or HPV-11 are required for BLT development, more studies are needed to understand the mechanisms underlying the transition between benign condyloma and BLT.

#### 4. Possible Impact of Viral Genome Rearrangements, Mutations, and Host Genome Integration on BLT Development

In normal conditions, HPVs exist as episomes in infected cells. During tumorigenesis, high-risk HPVs can integrate into the host genome, but they may sometimes remain episomal [71,72]. Integration disrupts the viral E2 gene and thus leads to dysregulation of viral E6 and E7 oncogene expression that promotes cell proliferation, abolishes cell-cycle checkpoints, and causes progressive genetic instability [71]. By contrast, probably reflecting their low oncogenic potential [73], low-risk HPVs, such as HPV-6 and HPV-11, do not usually integrate into host DNA, including in BLT [74,75], anal [76], cervical [58], and vulvar cancers [77]. To our knowledge, HPV-6 was never reported integrated in BLT, and only once in an anogenital cancer [78]. However, HPV-6 and HPV-11 integration was reported in some patients with head and neck cancers [79–81]. Altogether, the available data strongly suggest that HPV-6 or HPV-11 integration is not required for BLT development. This is reminiscent of episomal HPV-2 in a TMS case [8], another devastating benign cutaneous tumor driven by a low-risk HPV.

Instead of viral integration, mutations or rearrangement within the episomal virus may explain BLT development. Rearrangements within the upstream regulatory region (URR) of HPV-6 or HPV-11 from BLT were reported in multiple studies [75,82–85]. Duplications within the URR have also been detected in anogenital carcinomas associated with HPV-16 [86], laryngeal carcinomas containing HPV-11 [87], and one SCC of the lung [88] and two SCCs of the vulva related to HPV-6 infection [89,90]. It has been suggested that URR duplications may increase the otherwise low oncogenic potential of HPV-6 and HPV-11 by enhancing transcription of the transforming genes E6 and E7 [91,92]. However, Rübber et al. showed that host factors were probably more responsible for BLTs, with rearrangements of the URR of HPVs probably representing only secondary events in BLT development, as such rearrangements are also detected in benign genital warts [82]. In addition, to our knowledge, no nucleotide substitution identified in the HPV-6 or HPV-11 strains from BLT samples can explain tumorigenesis [75,82,83,93]. However, the full-length DNA sequence of the HPV strain within the BLT was not obtained for the overwhelming majority of reported cases. Further studies are required to determine whether mutations or viral genome rearrangements can influence the development of BLT and possible neoplastic transformation. This would require a systematic report of the full-length HPV sequence, as well as of the viral genome integration status in BLT.

#### 5. Secondary Immunodeficiencies in the Etiology of BLT

Cell-mediated immune response is crucial for control of HPV-induced lesions [94]. Indeed, patients on immunosuppressive drugs, and HIV-infected patients have a higher risk of severe HPV infections than the general population [95–97]. CD4<sup>+</sup> T cells as well as monocytes/macrophages prevail within regressing condylomas [44,98,99]. Akinboro et al. reported lower blood CD4<sup>+</sup> cell counts in HIV-positive patients with genital warts than those without such lesions (101 cells/ $\mu$ L vs. 294 cells/ $\mu$ L, respectively) [100]. They also found that the extent of the viral warts was correlated with CD4<sup>+</sup> T-cell count [100]. In this context, not surprisingly, BLT is more frequent in individuals with HIV infection [101–105] or on immunosuppressive drugs, such as patients with a history of stem cell or solid organ transplantation [106–109]. Risk of rapid progression of BLT into metastatic SCCs in HIV-infected patients is elevated [61,110]. Grodner et al. reported an improvement in voluminous pelvic BLT after highly active antiretroviral therapy alone in an HIV-infected patient [111]. Surgical excision of the BLT was initially planned but was postponed

when significant regression of the tumor was observed on antiretroviral therapy, together with CD4 immune recovery (gradual increase in CD4<sup>+</sup> T-cell count from 26 cells/ $\mu$ L to 229 cells/ $\text{mm}^3$  over a period of six months) and the suppression of HIV-1 replication (HIV RNA levels decreased from 5.21 log copies/mL to <20 copies/mL and remained undetectable thereafter). Given the absence of any other therapy in this patient, the authors concluded that cellular immune recovery after antiretroviral therapy alone was responsible for the regression of BLT. Thus, acquired immunodeficiencies should be considered in all cases of extensive HPV lesions, including BLT, to improve patient outcomes.

## 6. Leading Genetic Causes of Susceptibility to Extensive Anogenital HPV Lesions

Mutations in several immunity-related genes have been associated with extensive condyloma acuminata (Table 1).

**Table 1.** Primary immunodeficiencies associated with extensive condyloma acuminata.

Primary Immunodeficiency	Gene Mutated	Inheritance	Phenotype	References
CARMIL2 deficiency	<i>CARMIL2</i> ( <i>RLTPR</i> )	AR	Common warts, recurrent condylomas, broad susceptibility to infection, immune dysregulation, EBV-driven smooth muscle tumors	[17,22,112,113]
WHIM syndrome	<i>CXCR4</i>	AD	Common warts, condyloma acuminata, hypogammaglobulinemia (low IgG and IgA, normal IgM), infections, myelokathexis	[114–116]
DCLRE1C deficiency	<i>DCLRE1C</i>	AR (hypomorphic)	Extensive HPV-related anogenital lesions, atypical EV, low numbers of B cells, hypogammaglobulinemia	[117,118]
DOCK8 deficiency	<i>DOCK8</i>	AR	Common warts, condyloma acuminata, atypical EV, other viral cutaneous infections (VZV, HSV, molluscum contagiosum), eczema, food allergy, asthma, allergic rhinitis, bacterial pneumonia, candidiasis, abscesses, cancer, thrombocytosis, eosinophilia, lymphopenia	[119–121]
GATA2 deficiency [DCML, MDS, MonoMAC syndrome, WILD syndrome, Emberger syndrome]	<i>GATA2</i>	AD	Common warts, condyloma acuminata, VZV, HSV, fungal infections, lymphedema, myelodysplasia, leukemia, panniculitis, cancer, low B-cell levels	[19,122–125]
ICOSL deficiency	<i>ICOSLG</i>	AR	Common warts, extensive condyloma acuminata, orolabial HSV infections, angular cheilitis, mouth ulcers, hypogammaglobulinemia, neutropenia, lymphopenia	[126]
LAD-1	<i>ITGB2</i>	AR	Extensive common warts and condyloma acuminata, frequent systemic, skin, and soft tissue infections, inflammatory bowel disease, impaired wound healing, gingivitis, periodontitis	[19,127]
MAGT-1 deficiency XMEN syndrome	<i>MAGT-1</i>	XLR	Cutaneous warts, perineal condylomas, EBV infections, infections of the ear and nose, viral infections of the skin, cancers	[17,128]
Netherton syndrome	<i>SPINK5</i>	AR	Common warts, giant condyloma acuminata, ichthyosis, eczema, bamboo hair, asthma, food allergy, high IgE levels	[129,130]
WAS	<i>WAS</i>	XLR	Common warts, condyloma acuminata, thrombocytopenia, infections, eczema, cancers, autoimmune manifestations	[17,131]

CARMIL2, capping protein regulator and myosin 1 linker 2; AR, autosomal recessive; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; CXCR4, CXC chemokine receptor 4; AD, autosomal dominant; DCLRE1C, DNA cross-link repair 1C; DOCK8, dedicator of cytokinesis 8; VZV, varicella zoster virus; HSV, herpes simplex virus; GATA2, GATA-binding protein 2; DCML, dendritic cell, monocyte, B and NK lymphoid deficiency; MDS, deafness, lymphedema, mononuclear cytopenia, infection, myelodysplasia; MonoMAC, monocytopenia and mycobacterial infection syndrome; WILD, warts, immunodeficiency, lymphedema, dysplasia; *ICOSLG*, inducible T-cell costimulator ligand; LAD-1, leukocyte adhesion deficiency type-1; *ITGB2*, integrin B2; *MAGT-1*, magnesium transporter 1; XMEN, X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia syndrome; XLR, X-linked recessive; EBV, Epstein-Barr virus; *SPINK5*, serine protease inhibitor Kazal-type 5; WAS, Wiskott Aldrich syndrome.

The genetic predispositions to common warts and anogenital HPV lesions overlap considerably [17]. Gain-of-function (GOF) mutations of the *CXCR4* gene encoding the receptor of the CXCL12 chemokine are responsible for WHIM syndrome (HPV-induced warts, hypogammaglobulinemia, recurrent bacterial infections, and myelokathexis) [114]. Patients with WHIM syndrome are particularly susceptible to extensive warts on the hands, feet, and trunk. They may also develop genital and anal condyloma acuminata, and female patients may develop vulval and cervical dysplasia [115,132]. Monoallelic missense and null mutations of *GATA2* lead to a deficiency in an important transcription factor for hematopoiesis and maintenance of the stem-cell compartment (*GATA2*) [19]. In addition to its role in myelodysplasia and leukemia, *GATA2* deficiency increases the risk of profuse and recurrent cutaneous or anogenital warts [124,125,133]. Difficulties in treatment of generalized unremitting warts are also observed in individuals with autosomal recessive dedicator of cytokinesis 8 (*DOCK8*) deficiency [119,120]. *DOCK8* is essential for the maintenance of T-cell integrity in collagen-dense tissues, and this translates into poor defense against pathogens in the absence of *DOCK8* [134]. *DOCK8* is also important for dendritic cell migration to lymph nodes [135]. Venegas-Montoya et al. reported a six-year-old *DOCK8*-deficient patient with disseminated flat warts, who also presented an extensive condyloma acuminata around the scrotum and groin folds [121]. Overall, mutations of *CXCR4*, *GATA2*, and *DOCK8* result in low numbers of both antigen-presenting cells and T cells. Thus, inborn errors of immunity simultaneously impairing these two arms of immunity underlie extreme penetrance of cutaneous and anogenital HPV infections.

### 7. Significance of the CD28 Axis in the Development of HPV-Related Anogenital Lesions

Individuals with autosomal recessive *CARMIL2* deficiency present a wide spectrum of clinical phenotypes, with bacterial, fungal, and viral infections, including anogenital condylomas in some patients [22,113]. *CARMIL2* is a protein involved in the CD28 cosignaling of T cells, and in cytoskeletal organization and cell migration [112]. The discovery of severe cutaneous HPV infections in patients with CD28 deficiency suggested that defective CD28 signaling in T cells was the main driver of HPV susceptibility in individuals with *CARMIL2* mutations [8]. However, in accordance with the incomplete penetrance of HPV infection in *CARMIL2*-deficient patients, the three reported CD28-deficient patients developed no anogenital lesions, despite one patient being seropositive for HPV-6 and HPV-11 [8]. Consistent with the hypothesis that the CD28 axis plays a crucial role in the anti-HPV response, mutations of the caspase activation and recruitment domain 11 (*CARD11*) and magnesium transporter 1 (*MAGT1*) genes also increase the risk of severe HPV infections [128,136]. *CARD11* is a scaffolding protein required for antigen receptor-induced NF- $\kappa$ B activation, notably downstream from CD28. *MAGT1* deficiency is a congenital disorder of glycosylation. *MAGT1* is crucial for the glycosylation and cell-surface expression of major immune receptors, including CD28. It has been reported that 27% of patients carrying dominant-negative mutations of *CARD11* suffer from unspecified skin warts [136], whereas, in individuals with *MAGT1* deficiency, flat warts, predominantly affecting the palms and soles, are observed in 30% of cases, and some patients develop extensive perineal condyloma acuminata [128]. Thus, the CD28 pathway probably contributes to anogenital HPV control, and the early pathogenesis of BLT.

### 8. Other Genes in the Pathogenesis of Anogenital HPV-Induced Lesions

There are few reports concerning other genes involved in predisposition to anogenital HPV infection. Individuals with Netherton syndrome, an autosomal recessive ichthyosis caused by mutations of *SPINK5*, are prone to the development of giant warts [129,130]. Ashton et al. published a pediatric case of BLT in the natal cleft in a patient with Netherton syndrome [130]. Extensive vulvovaginal and perianal warts, including BLT, have been reported in patients with integrin B2 (*ITGB2*) or DNA cross-link repair 1C gene (*DCLRE1C*) deficiencies [17,19]. Similarly, patients with autosomal recessive deficiency of the zeta chain-associated protein of 70 kDa (*ZAP70*) may present severe HPV infections. Chinn

et al. published a case report concerning a ZAP70-deficient woman with recurrent oral and cutaneous warts and HPV-induced cervical dysplasia [137]. Severe anogenital manifestations of HPV infection have also been observed in individuals with autosomal recessive inducible costimulator (ICOS) pathway deficiency. Schepp et al. reported HPV-induced vulvar carcinoma in one ICOS-deficient patient [138], whereas Roussel et al. recently reported the case of a male patient with an autosomal recessive mutation of the inducible T-cell costimulator ligand gene (*ICOSLG*) [126]. This last patient was 16 years old, and subsequently developed recurrent genital warts that spread, over the years, to involve the scrotum, perineum, perianal, and inguinal regions [126]. To our knowledge, there are no published case reports of familial BLT (multiple cases in the same family). Nevertheless, there is strong evidence that inborn errors of immunity can underlie severe anogenital HPV infections, including BLT.

The Table 2 summarizes all discussed genes and the function of encoded proteins.

**Table 2.** Summary of the discussed genes.

Gene (Official Symbol)	Gene (Official Full Name)	Function of Encoded Protein
<i>CARD11</i>	caspase activation and recruitment domain 11	a member of the membrane-associated guanylate kinase (MAGUK) family; plays a key role in adaptive immune response by transducing the activation of NF-kappa-B downstream of T-cell receptor and B-cell receptor engagement
<i>CARMIL2</i>	capping protein regulator and myosin 1 linker 2	a member of CARMIL family of proteins; involved in the CD28 cosignaling of T cells, and in cytoskeletal organization and cell migration
<i>CIB1</i>	calcium and integrin binding 1	regulator of diverse cellular processes including migration, adhesion, proliferation, and cell death/survival. CIB1 deficiency is associated with epidermodyplasia verruciformis
<i>CXCR4</i>	C-X-C chemokine receptor type 4	a receptor of the CXCL12 chemokine; is involved in multiple signaling pathways that orchestrate cell migration, hematopoiesis and cell homing, and retention in the bone marrow
<i>DCLRE1C</i>	DNA cross-link repair 1C	a nuclear protein; regulation of the cell cycle in response to DNA damage, and TCR and BCR recombination
<i>DOCK8</i>	dedicator of cytokinesis 8	a member of the DOCK180 family of guanine nucleotide exchange factors; critical role in cell migration and survival of several types of immune system cells
<i>GATA2</i>	GATA-binding protein 2	a member of the GATA family of zinc-finger transcription factors; plays a critical role in maintaining the pool of early hematopoietic cells
<i>ICOS</i>	inducible T cell costimulator	protein belonging to the CD28 and CTLA-4 cell-surface receptor family; T cell co-activating receptor, involved in T cell immune responses
<i>ICOSLG</i>	inducible T cell costimulator ligand	ligand of ICOS, involved in T cell immune responses
<i>IFNAR1</i>	interferon alpha and beta receptor subunit 1	forms one of the two chains of a receptor for IFN- $\alpha$ and IFN- $\beta$ ; involved in immune response; functions as an antiviral factor
<i>IFNAR2</i>	interferon alpha and beta receptor subunit 2	forms one of the two chains of a receptor for IFN- $\alpha$ and IFN- $\beta$ ; involved in immune response; functions as an antiviral factor
<i>IFNGR1</i>	interferon gamma receptor 1	the ligand-binding chain (alpha) of the gamma interferon receptor; non-redundant roles against intra-cellular pathogens (in particular mycobacteria)

Table 2. Cont.

Gene (Official Symbol)	Gene (Official Full Name)	Function of Encoded Protein
<i>IFNGR2</i>	interferon gamma receptor 2	the non-ligand-binding beta chain of the gamma interferon receptor. non-redundant roles against intra-cellular pathogens (in particular mycobacteria)
<i>ITGB2</i>	integrin subunit beta 2	an integrin beta chain; participate in cell adhesion as well as cell-surface mediated signaling
<i>MAGT1</i>	magnesium transporter 1	a ubiquitously expressed magnesium cation transporter protein; crucial for the glycosylation and cell-surface expression of major immune receptors, including CD28
<i>SPINK5</i>	serine peptidase inhibitor Kazal type 5	lympho-epithelial Kazal-type related inhibitor (LEKT1); plays a role in skin and hair morphogenesis, as well as anti-inflammatory and antimicrobial protection of mucous epithelia
<i>TMC6</i> ( <i>EVER1</i> )	transmembrane channel like 6	integral membrane protein located in the endoplasmic reticulum; predicted to form transmembrane channels; TMC6 deficiency is associated with epidermodysplasia verruciformis
<i>TMC8</i> ( <i>EVER2</i> )	transmembrane channel like 8	integral membrane protein located in the endoplasmic reticulum; predicted to form transmembrane channels; TMC8 deficiency is associated with epidermodysplasia verruciformis
<i>ZAP70</i>	zeta chain of T cell receptor associated protein kinase 70	an enzyme belonging to the protein tyrosine kinase family; plays a role in T-cell development and lymphocyte activation; essential for thymocyte development

## 9. Conclusions

The prognosis of BLT probably depends on tumor size, SCC transformation, local recurrence, secondary infections, and associated immunodeficiencies. Early diagnosis and appropriate aggressive therapy may reduce both medical and surgical morbidity, and overall mortality. Primary or secondary immunodeficiencies should be suspected in individuals with BLT. In the absence of acquired immunodeficiency, genetic investigations should be envisaged. Recent studies have shown that inborn errors of immunity conferring a predisposition to common warts and anogenital HPV lesions largely overlap, and that they impair host cellular immunity, including that mediated by CD4<sup>+</sup> T cells, in particular. The smaller number of reports of severe anogenital warts than of cutaneous warts in patients with primary immunodeficiencies probably reflects the epidemiology of the disease, with a peak incidence in childhood for cutaneous warts, and during the third decade of life for anogenital warts [139,140]. Inborn errors of immunity conferring predisposition to various infections, including those caused by HPVs, probably manifest before exposure to sexually transmissible HPVs. As a result, prophylactic measures or a severe course of immunodeficiency (e.g., early death, transplantation) probably reduce the incidence of anogenital HPV lesions in such patients. Despite the large body of knowledge available regarding HPV infections, further immunological and genetic investigations into susceptibility to severe and persistent HPV lesions of the anogenital region are required. The study of patients with isolated severe anogenital HPV infections is of particular interest, and may unravel important molecular pathways, as recently exemplified by the discovery of CD28 deficiency in patients with tree man syndrome [8]. Such efforts should lead to improvements in the clinical management of patients.

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