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# Genetics of Epidermodysplasia Verruciformis

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## 1. Introduction

Epidermodysplasia verruciformis (EV; MIM#226400) is a genodermatosis characterized by susceptibility to epidermodysplasia verruciformis-human papillomavirus (EV-HPV) infections which leads to early development of disseminated pityriasis versicolor-like and flat wart-like lesions [1]. The disease was first described by Lewandowski and Lutz in [1]. Approximately half of all patients with EV will develop cutaneous malignancies, predominately Bowen's type carcinoma in situ and invasive squamous cell carcinomas that occur mainly on sun-exposed areas in the fourth or fifth decade of life [2-4]. Thus, EV is in essence a genetic cancer of viral origin, and could also be regarded as a model of cutaneous HPV oncogenesis [5, 6]. In general, EV shows an autosomal recessive pattern of inheritance [7]. The EV loci were mapped to chromosome 2p21-p24 (EV2) and 17q25 (EV1) [8], respectively. In the EV1 interval, 2 adjacent related genes, EVER1 and EVER2, were identified in 2002 [9]. EVER proteins are members of transmembrane channel-like (TMC) family. They are encoded by 8 genes (TMC1-8). EVER1 and EVER2 correspond to TMC6 and TMC8, respectively [10, 11]. Therefore the recent literature has focused on the mutation finding the culpable gene. Clinical and histologic findings, EV-HPV, cutaneous oncogenesis, and genetics will be briefly reviewed.

## 2. Clinical and histologic findings

Classic EV begins during childhood with highly polymorphic cutaneous lesions, including pityriasis versicolor-like macules (Figure 1), flat wart-like papules (Figure 2), and lesions resembling seborrheic keratoses that can undergo malignant transformation [2, 4, 6, 12, 13]. Approximately half of all patients with EV will develop cutaneous malignancies, predominately Bowen's type carcinoma in situ and invasive squamous cell carcinomas (SCCs) that occur mainly on sun-exposed areas in the fourth or fifth decade of life [2, 4, 6, 12]. Development of malignant transformation is usually associated with HPV-5 and -8.

However, the mechanism of carcinogenesis induced by EV-related HPV types is not clear in contrast to the other oncogenic HPVs, these do not seem to need integration into the host's genome [14]. EV patients have impaired cell-mediated immunity (CMI) [15–20]. Decreased T-lymphocyte counts and CD4/CD8 ratios and a reduced T-cell responsiveness to mitogens were found in some patients.



**Figure 1.** Pityriasis versicolor-like macules

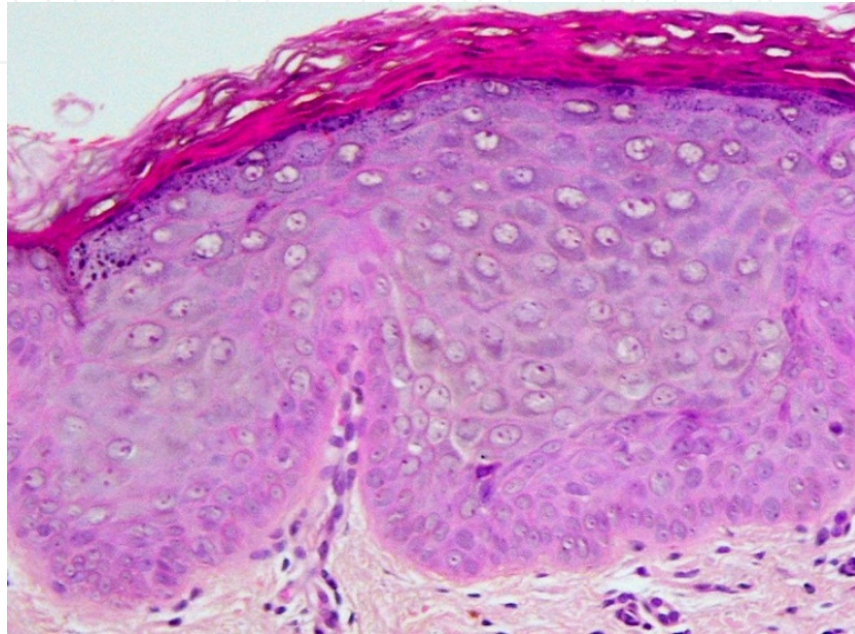


**Figure 2.** Flat wart-like papules

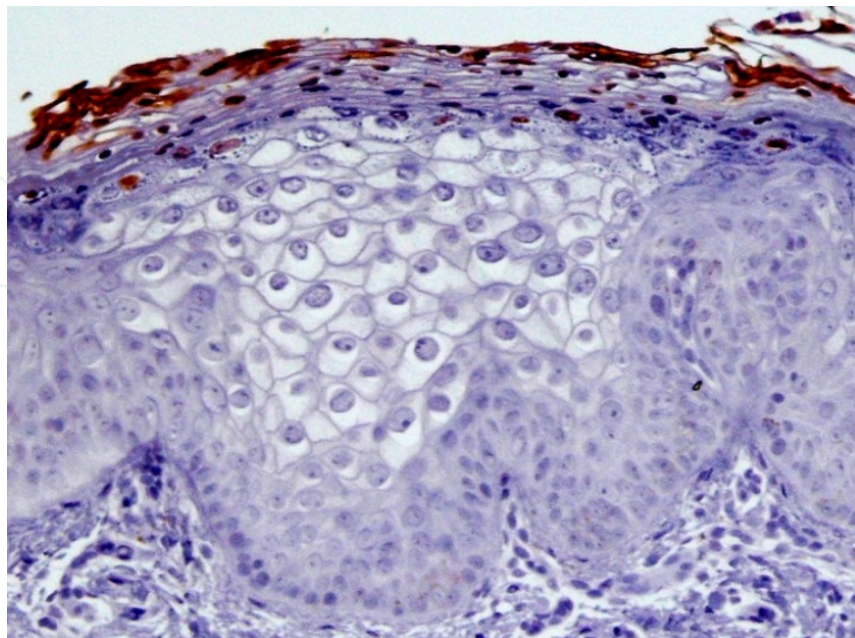


There is an indication of EV-like disease being a result of exogenous immunodeficiency in HIV infection and in the patients with immunodeficiency states (e.g. following renal transplantation, in systemic lupus erythematosus or Hodgkin's disease) [21-24]. This form has been named "acquired epidermodysplasia verruciformis" [25].

Histopathologically, lesions demonstrate stereotypical enlarged keratinocytes in upper epidermis with gray-blue cytoplasm, enlarged round nuclei with pale chromatin, and one or multiple nucleoli (Figure 3). The Immunohistochemistry findings showed the HPV antigens

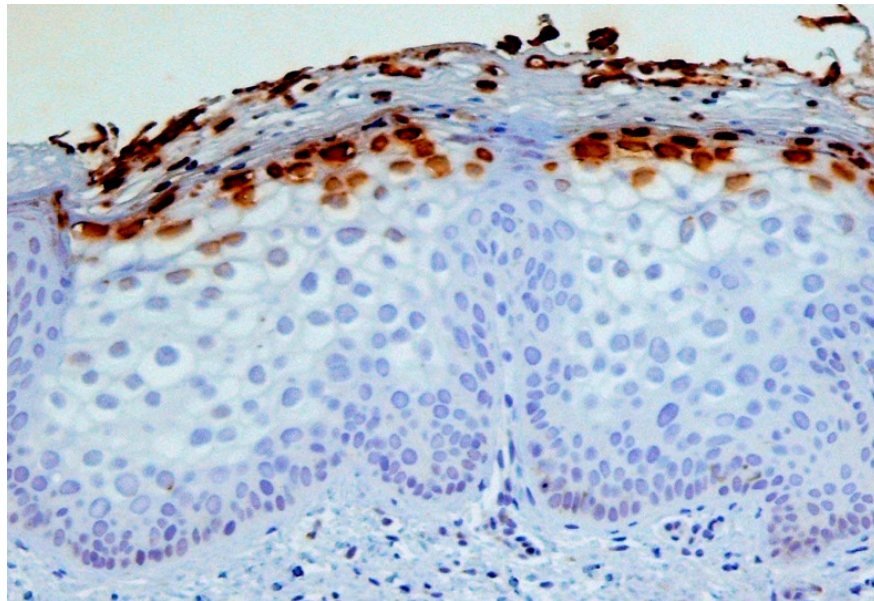


**Figure 3.** Enlarged keratinocytes in upper epidermis with gray-blue cytoplasm (haematoxylin and eosin)

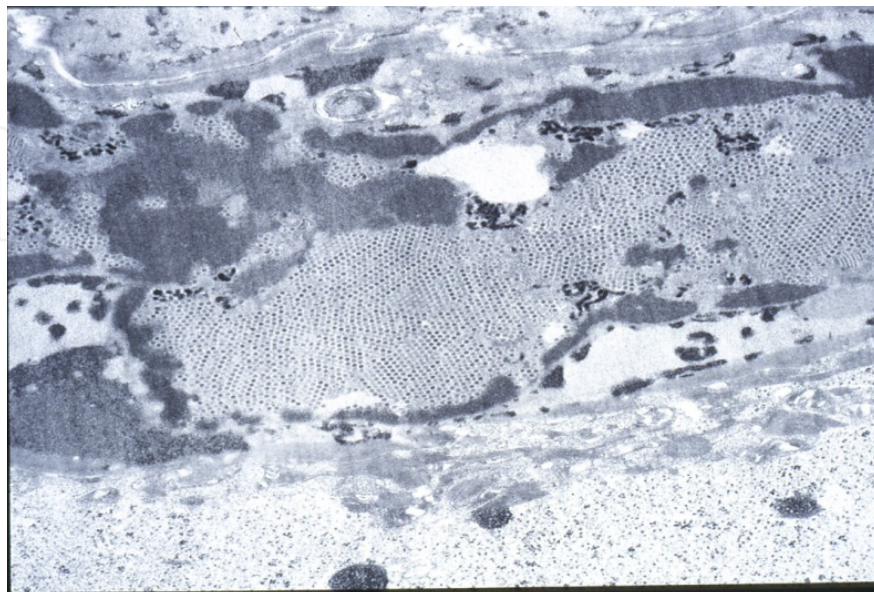


**Figure 4.** HPV antigens using anti-HPV monoclonal antibody are demonstrated

using anti-HPV monoclonal antibody (K1H8) were located in the cell nucleus of the third superior of the epithelium, observing the brownish-gold colored precipitins caused by cromogen in the nucleus of these cells (Figure 4). In *in situ* hybridization (ISH) EV HPV-5 DNA was detected in upper epidermis, abundant in parakeratotic cells (Figure 5) [26]. In electron microscopy, The nuclei are clarified with maeginated chromatin, and crystalline viral particles are present in nucleoplasm and in the prominent nucleoli (Figure 6). Under an electron microscope, HPV5 virions purified from pooled scales of EV patients and virus-like particles (VLP) assembled from a purified recombinant baculoviruses expressing the L1 major capsid protein of HPV5 were observed(Figure 7) [27].



**Figure 5.** HPV-5 DNA is demonstrated in the nuclei of spinous and granular cells (ISH)



**Figure 6.** Crystalline viral particles in electron microscopy



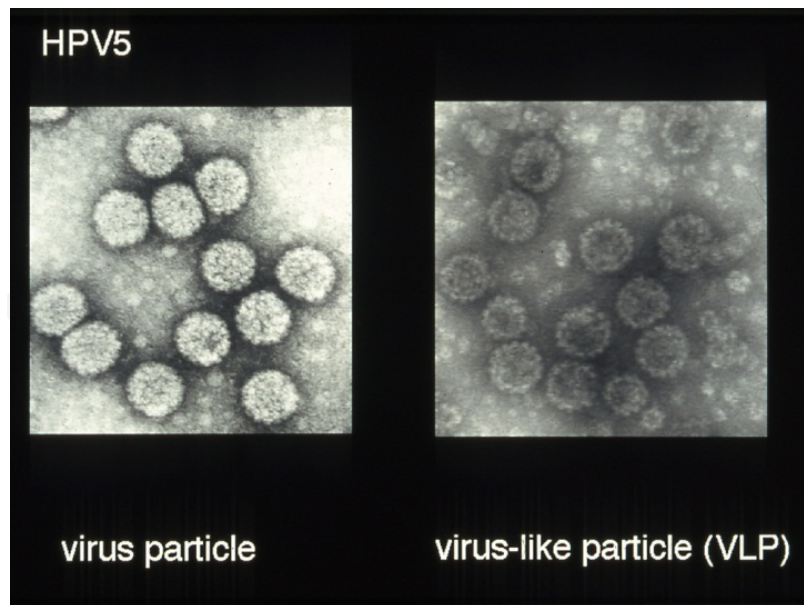


Figure 7.

### 3. EV-HPV infection

The disease is a generalized HPV infection, resulting from a genetically determined susceptibility of the skin to infection with particular types of HPV [28]. Papillomaviruses (PVs) are small, non-enveloped, double-stranded DNA viruses, which can infect mucosal or cutaneous epithelia. At least 118 distinct papillomavirus (PVs) types, more than 100 of them isolated from humans, have been completely described. The human papillomavirus genotypes are distributed across 5 genera. The five genera encompassing human PV are called alpha (both mucosal and cutaneous types), beta, gamma, mu and nu (exclusively cutaneous types)[29]. Genera are divided into species and types on the basis of nucleotidic sequence comparisons. Members of species have similar biological or pathological properties (Table 1) [29-31]. EV HPV genotypes constitute the beta-papillomavirus genus and are distributed into five species [29, 31], mainly beta 1, comprising the potentially oncogenic types 5, 8, 14, 20, and 47 [2], and beta 2 (Table 1). Beta PV are ubiquitous in the general population and frequently establish themselves already during the first weeks of life. Hair follicles are regarded as natural reservoir. About 25% of beta PV detected in adults persist for at least 9 months. Due to very low virus production, seroconversion against beta PV starts sluggishly. Hyperproliferation of keratinocytes in psoriasis patients or after severe burn stimulates virus replication. Massive virus replication only occurs in EV patients, associated with the induction of disseminated skin lesions with a high risk of malignant conversion.

Papillomaviruses share the same genetic organization [32]. At least eight open reading frames (ORFs) are located on the same DNA strand, downstream of a noncoding, long regulatory region containing transcriptional and replication regulatory elements. The E1 and E2 ORFs encode proteins involved in the replication of the viral genome (E1, E2), the segregation of the viral genome in dividing cells (E2) and in the regulation of its transcription (E2). The E6 and E7 proteins interact with cell cycle regulatory proteins and are

required for promoting the S-phase and for inhibiting apoptosis in resting and in terminally differentiating keratinocytes. The E6 and E7 proteins of potentially oncogenic genotypes induce genetic and chromosomal instability. The E5 protein displays growth promoting properties. The L1 and L2 ORFs encode the major (L1) and minor (L2) capsid proteins [32]. The genomes of EV HPVs are characterized by a shorter size and a specific organization of the regulatory region, the lack of an E5 ORF [33], and a great intratype genetic heterogeneity [34, 35].

Genus	Species	Human papillomavirus(HPV)
β-papillomavirus	β- 1	HPV-5, -8, -14,-12, -19, -20, -21, -24, -25, -36, -47, -93, -98, -99, -105, -118, -124
	β- 2	HPV-9, -15, -17, -22, -23, -37, -38, -80, -100, -104, -107, -110, -111, -113, -120, -122, -151
	β- 3	HPV-49, -75, -76, -115
	β- 4	HPV-92
	β- 5	HPV-96, -150

**Table 1.** HPV-Type in 5 species of the genusβ-Papillomavirus

#### 4. Cutaneous oncogenesis –EV and non-EV

Highly sensitive PCR methods based on various sets of primers have been designed to detect a broad range of known EV HPVs or putative novel EV HPV-related genotypes [36]. This has brought a wealth of information about the epidemiology and biology of these viruses [37, 38]. EV HPVs were found to be highly prevalent in the normal skin of healthy adults [39–41] and shown to be acquired very early in infancy [42]. An impressive diversity of putative novel beta PV has been disclosed [41].

Nonmelanoma skin cancer (NMSC) is the most common form of malignancy in fair-skinned populations. The role of ultraviolet radiation as an environmental carcinogen, capable of inducing mutations in both genomic and mitochondrial DNA and thereby being a causative agent in the development of NMSC, is well established [43]. Although the importance of HPV in cervical SCC is well-documented, the role of HPV in cutaneous SCC is controversial [43, 44]. EV may offer a model for cutaneous SCC [28]. In both their benign and malignant lesions, a broad spectrum of predominantly beta PV were found with a combined prevalence of 90% for HPV 5 and 8 in SCC [2, 6]. In lesions of EV patients, the viral genome usually persists extrachromosomally and in high copy numbers (100–300 copies per cell equivalent) [45–47]. High viral loads have also been found in hair bulbs from plucked eyebrows of these patients [47]. In both immunocompetent and immunosuppressed non-EV patients these viruses are also frequently found; however, only very low copy numbers (usually below one copy per cell) were detected in actinic keratosis, SCC, basal cell carcinoma, and perilesional skin [48]. It has been shown that beta PV are transcriptionally active in benign and malignant lesions of EV patients [49, 50] and also in 3 of 4 actinic keratosis and 5 of 18 SCC of immunosuppressed non-EV patients [51, 52].

## 5. Genetics

As early as 1933, Cockayne postulated that EV was probably transmitted by a recessive gene [53] and an autosomal recessive mode of transmission was first proposed in 1972 [54].

Inspections of EV patient pedigrees have revealed that a large portion (approximately 10% in a review of 147 case reports [7]) are born to consanguineous parents. Additionally, because the proportion of EV siblings in families has approached 30% [55], the mode of EV transmission has been thought to be autosomal recessive. An X-linked recessive inheritance has also been reported [56], however, pointing to a possible genetic heterogeneity of the disease [57]. Recent studies have advanced our understanding of the genetic defects carried by EV patients. A genome-wide linkage study was performed recently on consanguineous EV families (first-cousin marriages), using the homozygosity mapping approach that represents a simple and efficient strategy to map rare human recessive traits [8, 58]. The two susceptibility loci EV1 and EV2 were first mapped to chromosomes 17q25 from the study of families from Algeria and Colombia and 2p21-p24 from French family, respectively, in 2000 [8]. Since those initial findings were reported, specific mutations in the genes EVER1 and EVER2, both located within the EV1 locus, have been discovered. Ramoz et al. [9] first described two highly conserved nonsense mutations in the EVER1 and EVER2 genes of all affected individuals in two Algerian and two Colombian consanguineous families. Subsequently, novel mutations in these genes were identified in patients of multiple races and nationalities [59-68,9]. In all, 15 truncating, loss-of-function mutations caused by several mechanisms (nonsense mutation, single nucleotide deletion, splice site mutation, and exon deletion) have been identified, eight in EVER1 and seven in EVER2. The TMC (transmembrane channel-like) gene family comprises eight genes (TMC1 to8) [10, 11]. EVER1 and EVER2 are identical to the TMC6 and TMC8 genes, respectively. Although the proteins encoded by the EVER genes have been shown to localize in the endoplasmic reticulum with features of integral membrane proteins, the exact function in development of persistent HPV infections has not yet been revealed [9,59]. It has been hypothesized that these proteins act as restriction factors for EV specific HPVs in keratinocytes, and that EV represents a primary deficiency of intrinsic immunity against certain papillomaviruses[57]. Although most EV patients studied (75.6%, according to collaborative efforts reported in the review by [57]) have been found to have homozygous mutations in EVER1 or EVER2, this still leaves a significant number of EV patients with unexplained inheritance patterns. Three cases have reported genetic analysis of EV patients in whom EVER1 or EVER2 mutations were lacking [69-71]. In a recent case-control study, EVER2 polymorphisms were associated with SCC development [66]. The exact function of TMC proteins still unclear, but it is assumed that they belong to a new group of channels or iron transporters and could be involved in signal transduction [10, 11]. EVER1/TMC6 and EVER2/TMC8 proteins are located in the endoplasmic reticulum of keratinocytes, where they form a complex with zinc transporter-1 (ZnT-1). EVER1/TMC6 and EVER2/TMC8 act as modifiers of zinc transporter ZnT-1. Potentially, EVER proteins mediate the protection against oncogenic HPV via regulation of cellular zinc balance [72, 73]. A mutation in the EVER1 or EVER2 gene might block the formation of the EVER/ZnT-1 complex, which would allow the expression of transcription factors (e.g.AP-1), thus promoting viral replication [14].



## 6. Conclusion

In EV patients there is a strong association between beta HPV infection and NMSC. This predisposition is genetically determined by mutations of the 2 genes EVER1/TMC6 and EVER2/TMC8. However, only in 75% of EV patients, an EVER mutation has been found. This suggests other genes are involved. A second EV susceptibility locus (EV2) on chromosome 2p21-p24 by autosomal recessive inheritance is assumed [8]. X-linked recessive inheritance [56] and autosomal dominant transmission have been reported [71]. Identification of additional genes associated with EV should provide more clues for the understanding of host defences against papillomaviruses.

## Author details

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