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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	Spieces	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.

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7. References

- [1] Lewandowsky F, Lutz W. Ein Fall einer bisher nicht beschriebenen Hauterkrankung (Epidermodysplasia verruciformis). *Arch Dermatol Syphilol* 1922; 141 193-203.
- [2] Orth G. Epidermodysplasia verruciformis. In: Howley PM, Salzman NP, (ed.) *The papovaviridae*, vol 2. *The papillomaviruses*. New York: Plenum Press Inc.; 1987. p199-243.
- [3] Orth G, Jablonska S, Favre M, Croissant O, Jarzabek-Chorzelska M, Rzeska G. Characterization of two types of human papillomaviruses in lesions of epidermodysplasia verruciformis. *Proc Natl Acad Sci USA* 1978; 75 1537-41.
- [4] Majewski S, Jablonska S, Orth G. Epidermodysplasia verruciformis. Immunological and nonimmunological surveillance mechanisms: role in tumor progression. *Clin Dermatol* 1997; 15 321-334.
- [5] Jablonska S, Dabrowski J, Jakubowicz K. Epidermodysplasia verruciformis as a model in studies on the role of papovaviruses in oncogenesis. *Cancer Res* 1972; 32 583-589.
- [6] Majewski S, Jablonska S. Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancer of the skin. *Arch Dermatol* 1995; 131 1312-1318.
- [7] Lutzner MA. Epidermodysplasia verruciformis: An autosomal recessive disease characterized by viral warts and skin cancer. A model for viral oncogenesis. *Bull Cancer* 1978; 65 169-182.
- [8] Ramoz N, Taïeb A, Rueda LA, Montoya LS, Bouadjar B, Favre M, Orth G. Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21-p24 and 17q25. *J Invest Dermatol* 2000; 114 1148-1153.
- [9] Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. *Nat Genet* 2002; 32 579-581.
- [10] Kurima K, Yang Y, Sorber K, Griffith AJ. Characterization of the transmembrane channel-like (TMC) gene family: functional clues from hearing loss and epidermodysplasia verruciformis. *Genomics* 2003; 82 300-308.

- [11] Keresztes G, Mutai H, Heller S. *TMC* and *EVER* genes belong to a larger novel family, the *TMC* gene family encoding transmembrane proteins. *BMC Genomics* 2003; 4 24-35.
- [12] Cockayne EA. Inherited abnormalities of the skin and its appendages. London: Oxford University Press; 1933. p156.
- [13] Jacyk WK, Dreyer L, de Villiers EM. Seborrheic Keratoses of Black Patients with Epidermodysplasia Verruciformis Contain Human papillomavirus DNA. *Am J Dermatopathol* 1993; 15(1) 1-6.
- [14] Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M. *EVER* proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. *Microbiol Mol Biol Rev* 2009; 73(2) 348-370.
- [15] Glinski W, Jablonska S, Langner A, Obalek S, Haftek M, Proniewska M. Cell-mediated immunity in epidermodysplasia verruciformis. *Dermatologica* 1976; 153 218-227.
- [16] Prawer SE, Pass F, Vance JC, Greenberg LJ, Yunis EJ, Zelikson AS. Depressed immune function in epidermodysplasia verruciformis. *Arch Dermatol* 1977; 113 495-499.
- [17] Oliveira WRP, Carrasco S, Neto CF, Rady P, Tyring SK. Nonspecific cell-mediated immunity in patients with epidermodysplasia verruciformis. *J Dermatol* 2003; 30 203-209.
- [18] Glinski W, Obalek S, Jablonska S, Orth G. T-cell defect in patients with epidermodysplasia verruciformis due to human papillomavirus types 3 and 5. *Dermatologica* 1981; 162 141-147.
- [19] Majewski S, Skopinska-Rozewska E, Jabłonska S, Wasik M, Misiewicz J, Orth G. Partial defects of cell-mediated immunity in patients with epidermodysplasia verruciformis. *J Am Acad Dermatol* 1986; 15 966-973.
- [20] Majewski S, Jablonska S. Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancers: The role of local immunosurveillance. *Am J Med Sci* 1992; 304 174-179.
- [21] Berger TG, Sawchuk WS, Leonardi C, Langenberg A, Tappero J, Leboit PE. Epidermodysplasia verruciformis-associated papillomavirus infection complicating human immunodeficiency virus disease. *Br J Dermatol* 1991; 124(1) 79-83.
- [22] Barr BB, Benton EC, McLaren K, Bunney MH, Smith IW, Blessing K, Hunter JA. Human papillomavirus infection and skin cancer in renal allograft recipients. *Lancet* 1989; 21(1) 124-129.
- [23] Gross G, Ellinger K, Roussaki A, Fuchs PG, Peter HH, Pfister H. Epidermodysplasia verruciformis in a patient with Hodgkin's disease: characterization of a new papillomavirus type and interferon treatment. *J Invest Dermatol* 1988; 91(1) 43-48.
- [24] Tanigaki T, Kanda R, Sato K. Epidermodysplasia verruciformis (L-L, 1922) in a patient with systemic lupus erythematosus. *Arch Dermatol Res* 1986; 278(3) 247-248.
- [25] Rogers HD, Macgregor JL, Nord KM, Tyring S, Rady P, Engler DE, Grossman ME. Acquired epidermodysplasia verruciformis. *J Am Acad Dermatol* 2009; 60(2) 315-320.
- [26] Kawase M, Honda M, Niimura M. Detection of human papillomavirus type 60 in plantar cysts and verruca plantaris by the in situ hybridization method using digoxigenin labeled probes. *J Dermatol* 1994; 21(10) 709-715.
- [27] Kawase M. Self-assembly of the major capsid L1 protein of human papillomavirus type 5 into virus-like particles in insect cells. *Tokyo Jikeikai Medical Journal* 1996; 111 75-83.
- [28] Majewski S, Jabłńska S. Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancer of the skin. *Arch Dermatol* 1995; 131(11) 1312-1318.

- [29] de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. *Virology* 2004; 324 17-27.
- [30] Schiffman M, Herrero R, Desalle R, Hildesheim A, Wacholder S, Rodriguez AC, Bratti MC, Sherman ME, Morales J, Guillen D, Alfaro M, Hutchinson M, Wright TC, Solomon D, Chen Z, Schussler J, Castle PE, Burk RD. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology* 2005; 337 76-84.
- [31] Bernard HU, Burk RD, Chen Z, van Doorslaer K, Hausen Hz, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* 2010; 401(1) 70-79.
- [32] Howley PM, Lowy DR. Papillomaviruses and their replication. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE., (ed.) *Fields Virology*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p2197-2330.
- [33] Fuchs PG, Pfister H. Papillomaviruses in epidermodysplasia verruciformis. In: Lacey C, (ed.) *Papillomavirus reviews: Current research on papillomaviruses*. Leeds: Leeds University Press; 1996. p253-261.
- [34] Deau MC, Favre M, Orth G. Genetic heterogeneity among human papillomaviruses (HPV) associated with epidermodysplasia verruciformis: evidence for multiple allelic forms of HPV5 and HPV8 E6 genes. *Virology* 1991; 184 492-503.
- [35] Kawase M, Orth G, Jablonska S, Blanchet-Bardon C, Rueda LA, Favre M. Variability and phylogeny of the L1 capsid protein gene of human papillomavirus type 5: contribution of clusters of nonsynonymous mutations and of a 30-nucleotide duplication. *Virology* 1996; 221(1) 189-198.
- [36] de Koning M, Quint W, Struijk L, Kleter B, Wanningen P, van Doorn LJ, Weissenborn SJ, Feltkamp M, ter Schegget J. Evaluation of a novel highly sensitive, broad-spectrum PCR-reverse hybridization assay for detection and identification of beta-papillomavirus DNA. *J Clin Microbiol* 2006; 44 1792-1800.
- [37] Orth G. Human papillomaviruses and the skin: More to be learned. *J Invest Dermatol* 2004; 123:XI-III.
- [38] Orth G. Human papillomaviruses associated with epidermodysplasia verruciformis in nonmelanoma skin cancers: Guilty or innocent? *J Invest Dermatol* 2005; 125:XII-II.
- [39] Boxman IL, Berkhout RJ, Mulder LH, Wolkers MC, Bouwes Bavinck JN, Vermeer BJ, ter Schegget J. Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers. *J Invest Dermatol* 1997; 108 712-715.
- [40] Astori G, Lavergne D, Benton C, Höckmayr B, Egawa K, Garbe C, de Villiers EM. Human papillomaviruses are commonly found in normal skin of immunocompetent hosts. *J Invest Dermatol* 1998; 110 752-755.
- [41] Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson BG. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensal nature of these viruses. *J Virol* 2000; 74 11636-11641.
- [42] Antonsson A, Karanfilovska S, Lindqvist PG, Hansson BG. General acquisition of human papillomavirus infections of skin occurs in early infancy. *J Clin Microbiol* 2003; 41 2509-2514.
- [43] Akgul B, Cooke JC, Storey A. HPV-associated skin disease. *J Pathol* 2006; 208 165-175.
- [44] Gewirtzman A, Bartlett B, Tyring S. Epidermodysplasia verruciformis and human papilloma virus. *Curr Opin Infect Dis* 2008; 21 141-146.

- [45] Pfister H. Chapter 8: Human papillomavirus and skin cancer. *J Natl Cancer Inst Monogr* 2003; 31 52-56.
- [46] Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. *Semin Immunol* 2006; 18 362-374.
- [47] Dell'Oste V, Azzimonti B, De Andrea M, Mondini M, Zavattaro E, Leigheb G, Weissenborn SJ, Pfister H, Michael KM, Waterboer T, Pawlita M, Amantea A, Landolfo S, Gariglio M. High beta-HPV DNA loads and strong seroreactivity are present in epidermodysplasia verruciformis. *J Invest Dermatol* 2009; 129:1026-1034.
- [48] Weissenborn SJ, Nindl I, Purdie K, Harwood C, Proby C, Breuer J, Majewski S, Pfister H, Wieland U. Human papillomavirus-DNA loads in actinic keratoses exceed those in non-melanoma skin cancers. *J Invest Dermatol* 2005; 125:93-97.
- [49] Yutsudo M, Hakura A. Human papillomavirus type 17 transcripts expressed in skin carcinoma tissue of a patient with epidermodysplasia verruciformis. *Int J Cancer* 1987; 39: 586-589.
- [50] Haller K, Stubenrauch F, Pfister H. Differentiation-dependent transcription of the epidermodysplasia verruciformis-associated human papillomavirus type 5 in benign lesions. *Virology* 1995; 214 245-255.
- [51] Purdie KJ, Suretheran T, Sterling JC, Bell L, McGregor JM, Proby CM, Harwood CA, Breuer J. Human papillomavirus gene expression in cutaneous squamous cell carcinomas from immunosuppressed and immunocompetent individuals. *J Invest Dermatol* 2005; 125 98-107.
- [52] Dang C, Koehler A, Forschner T, Sehr P, Michael K, Pawlita M, Stockfleth E, Nindl I. E6/E7 expression of human papillomavirus types in cutaneous squamous cell dysplasia and carcinoma in immunosuppressed organ transplant recipients. *Br J Dermatol* 2006; 155 129-136.
- [53] Cockayne EA. Inherited abnormalities of the skin and its appendages. London: Oxford University Press; 1933. p156.
- [54] Rajagopalan K, Bahru J, Loo DS, Tay CH, Chin KN, Tan KK. Familial epidermodysplasia verruciformis of Lewandowsky and Lutz. *Arch Dermatol* 1972; 105 73-78.
- [55] Sehgal VN, Luthra A, Bajaj P. Epidermodysplasia verruciformis: 14 members of a pedigree with an intriguing squamous cell carcinoma transformation. *Int J Dermatol* 2002; 41:500-503.
- [56] Androphy EJ, Dvoretzky I, Lowy DR. X-linked inheritance of epidermodysplasia verruciformis: Genetic and virologic studies of a kindred. *Arch Dermatol* 1985; 121 864-868.
- [57] Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. *Semin Immunol* 2006; 18 362-374.
- [58] Ramoz N, Rueda LA, Bouadjar B, Favre M, Orth G. A susceptibility locus for epidermodysplasia verruciformis, an abnormal predisposition to infection with the oncogenic human papillomavirus type 5, maps to chromosome 17qter in a region containing a psoriasis locus. *J Invest Dermatol* 1999; 112 259-263.
- [59] Aochi S, Nakanishi G, Suzuki N, Setsu N, Suzuki D, Aya K, Iwatsuki K. A novel homozygous mutation of the EVER1/TMC6 gene in a Japanese patient with epidermodysplasia verruciformis. *Br J Dermatol* 2007; 157 1265-1266.

- [60] Gober MD, Rady PL, He Q, Tucker SB, Tying SK, Gaspari AA. Novel homozygous frameshift mutation of EVER1 gene in an epidermodysplasia verruciformis patient. *J Invest Dermatol* 2007; 127 817-820.
- [61] Rady PL, De Oliveira WR, He Q, Festa C, Rivitti EA, Tucker SB, Tying SK. Novel homozygous nonsense TMC8 mutation detected in patients with epidermodysplasia verruciformis from a Brazilian family. *Br J Dermatol* 2007; 157 831-833.
- [62] Sun XK, Chen JF, Xu AE. A homozygous nonsense mutation in the EVER2 gene leads to epidermodysplasia verruciformis. *Clin Exp Dermatol* 2005; 30 573-574.
- [63] Tate G, Suzuki T, Kishimoto K, Mitsuya T. Novel mutations of EVER1/TMC6 gene in a Japanese patient with epidermodysplasia verruciformis. *J Hum Genet* 2004; 49(4) 223-225.
- [64] Zuo YG, Ma D, Zhang Y, Qiao J, Wang B. Identification of a novel mutation and a genetic polymorphism of EVER1 gene in two families with epidermodysplasia verruciformis. *J Dermatol Sci* 2006 44(3) 153-159.
- [65] Arnold AW, Burger B, Kump E, Ruffle A, Tying SK, Kempf W, Häusermann P, Itin PH. Homozygosity for the c.917A→T (p.N306I) polymorphism in the EVER2/TMC8 gene of two sisters with epidermodysplasia verruciformis Lewandowsky-Lutz originally described by Wilhelm Lutz. *Dermatology* 2011; 222(1) 81-86.
- [66] Patel AS, Karagas MR, Pawlita M, Waterboer T, Nelson HH. Cutaneous human papillomavirus infection, the EVER2 gene and incidence of squamous cell carcinoma: a case-control study. *Int J Cancer* 2008; 122(10) 2377-2379.
- [67] Berthelot C, Dickerson MC, Rady P, He Q, Niroomand F, Tying SK, Pandya AG. Treatment of a patient with epidermodysplasia verruciformis carrying a novel EVER2 mutation with imiquimod. *J Am Acad Dermatol* 2007; 56(5) 882-886.
- [68] Landini MM, Zavattaro E, Borgogna C, Azzimonti B, De Andrea M, Colombo E, Marengo F, Amantea A, Landolfo S, Gariglio M. Lack of EVER2 protein in two epidermodysplasia verruciformis patients with skin cancer presenting previously unreported homozygous genetic deletions in the EVER2 gene. *J Invest Dermatol* 2012; 132(4) 1305-1308.
- [69] Akgül B, Köse O, Safali M, Purdie K, Cerio R, Proby C, Storey A. A distinct variant of Epidermodysplasia verruciformis in a Turkish family lacking EVER1 and EVER2 mutations. *J Dermatol Sci* 2007; 46(3) 214-216.
- [70] Zavattaro E, Azzimonti B, Mondini M, De Andrea M, Borgogna C, Dell'Oste V, Ferretti M, Nicola S, Cappellano G, Carando A, Leigh G, Landolfo S, Dianzani U, Gariglio M. Identification of defective Fas function and variation of the perforin gene in an epidermodysplasia verruciformis patient lacking EVER1 and EVER2 mutations. *J Invest Dermatol* 2008; 128(3) 732-735.
- [71] McDermott DF, Gammon B, Snijders PJ, Mbata I, Phifer B, Howland Hartley A, Lee CC, Murphy PM, Hwang ST. Autosomal dominant epidermodysplasia verruciformis lacking a known EVER1 or EVER2 mutation. *Pediatr Dermatol* 2009; 26(3) 306-310.
- [72] Lazarczyk M, Favre M. Role of Zn²⁺ ions in host-virus interactions. *J Virol* 2008; 82(23) 11486-11494.
- [73] Lazarczyk M, Pons C, Mendoza JA, Cassonnet P, Jacob Y, Favre M. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. *J Exp Med* 2008; 205(1) 35-42.