The EVER genes – the genetic etiology of carcinogenesis in epidermodysplasia verruciformis and a possible role in non-epidermodysplasia verruciformis patients

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Abstract
In recent years, the two adjacent novel EVER1 and EVER2 genes have been identified, whose mutations are responsible for the development of epidermodysplasia verruciformis (EV). Epidermodysplasia verruciformis is a rare, autosomal recessive genodermatosis associated with increased risk of skin carcinoma. Up to now 7 mutations in the EVER1 gene and 5 mutations in the EVER2 gene have been identified only in EV. It was also determined that the EVER genes belong to a novel gene family, the transmembrane channel-like (TMC) family, and are responsible for properly functioning zinc homeostasis. These observations have given new insights into EV pathogenesis.

Key words: epidermodysplasia verruciformis, EVER genes and proteins, carcinogenesis.

Introduction
Epidermodysplasia verruciformis (EV), a rare disease characterized by verrucous cutaneous lesions and spots resembling pityriasis versicolor which may progress to squamous cell carcinomas due to abnormal susceptibility to a specific group of oncogenic EV human papillomavirus (HPV), was first described in 1922 by Lewandowsky and Lutz [1]. In 1933 Cockayne hypothesized that EV might be a congenital disease transmitted by a recessive gene [2]. Later, clinical observations of familial aggregations in 147 reported cases supported this type of inheritance, because 10% of EV families have more than one affected sibling, the proportion of siblings was 25%, and the male to female ratio was close to 1 : 1 [3]. However, there was one exception – one consanguineous family in which only males developed EV and therefore X-linked recessive inheritance was also suggested, which could point to a genetic heterogeneity of the disease [4]. In recent years two susceptibility loci for EV were mapped to chromosomal regions 17q25 (EV1) and 2p21-p24 (EV2) [5, 6], and this led to the identification of two novel genes, EVER1 and EVER2 in EV1, mutations in which play a role in development of EV [7]. The role of EVER proteins remains unclear. Studies conducted to date to determine the function of the EVER proteins have shown that they have an ability to participate in maintaining the zinc balance in cells [8].

The aim of this manuscript was to present the most important information and the results of the latest studies regarding EVER genes, their mutations and structures. The functions of EVER proteins and their role in HPV infections are also discussed.

EVER genes and their association with epidermodysplasia verruciformis
In 1999 Ramoz et al. identified the first susceptibility locus for EV (named EV1). In cited studies, genetic analysis included three consanguineous EV families (2 originated from Algeria marked as A1 and A2 pedigree and 1 originated from Columbia marked as C1 pedigree), in which 6 individuals were diagnosed with EV. All affected people were born from first cousin marriages. A genome-wide linkage analysis using 255 highly polymorphic microsatellite markers spanning 22 autosomes was performed. It was found that the susceptibility locus for EV is located on chromosome 17q25, at a distance of 1 cM.
between the D17S939 and D17S802 markers [5]. It needs to be stressed that the EV1 locus is situated in a larger region containing a locus for the susceptibility to psoriasis – PSORS2, which was previously reported [9]. It could explain the presence of EV HPV DNA in psoriatic papules in more than 90% of patients with psoriasis [10].

In 2000 the same authors mapped the second susceptibility locus for EV (EV2). Genetic analysis was carried out in two consanguineous EV families from Columbia (C2) and France (F1) comprising 7 EV patients and their families, inclusively 27 individuals. The EV2 locus was mapped to the chromosome region 2p21-p24 at an 8 cM interval between the D2S171 and D2S2347 markers [6]. The EV1 and EV2 loci included numerous genes encoding transcription factors, proteins involved in signal transduction and numerous expressed sequence tags [11, 12]. In 1999 Kuhlenbaumer et al. reported an integrated physical and partial transcript map of region 17q25 encompassing the EV1 locus [13]. Also for the EV2 locus a map of the 1 cM region telomeric to the D2S174 marker has been reported. It is known that this region includes 5 genes and among them is the gene encoding the centromere protein A [14]. Further studies allowed for the identification of the novel genes responsible for EV. The analysis included two previously described Algerian (A1 and A2) and two Colombian families (C1 and C2) and one additional Algerian family (A3). It was found that the EV1 region contains the following genes: thymidine kinase 1, synaptogyrin 2 and four novel genes named EV1Xa, EV1Xb, EV1Xc and EV1Xd [15]. In the next stage, by RT-PCR in lymphoblastoid cell lines only EV1Xc and EV1Xd transcripts were obtained and assigned the symbols EVER1 and EVER2 respectively. These two adjacent novel genes are in the opposite orientation from the first inframe ATG codon and are separated by 4732 bp. The presence of these mutations in both EVER1 and EVER2 genes is associated with EV [6].

**EVER genes – their structure, localization and correlations with the transmembrane channel-like (TMC) gene family**

The EVER1 and EVER2 genes are located on chromosome 17q25. The EVER1 gene consists of 20 exons and 19 introns and encodes four transcripts. Two of the transcripts containing all exons have a length of 2891 bp and 2789 bp. The third contains 19 exons and is about 2711 bp in length. The last one contains 12 exons and is 1838 bp in length. The EVER2 gene consists of 16 exons and 15 introns and encodes only one transcript of the length of about 4419 bp (http://www.ensembl.org/Homo_sapiens/Transcript/). In 2003 Keresztes et al. and Kurima et al. reported that the two newly detected EVER1 and EVER2 genes were identical to the TMC6 and TMC8 genes, respectively, and belonged to a novel gene family, the transmembrane channel-like gene family (TMC) [16, 17]. All TMC gene families consist of 8 genes, which encode transmembrane proteins with 6 to 10 domains. They also showed that all TMC proteins contain a 120-amino acid sequence, the TMC domain [16, 17]. The exact role of all TMC genes and their mutations is unknown. Besides TMC6 and TMC8 genes it was found that dominant and recessive mutations in the TMC-1 gene and its murine ortholog-transmembrane cochlear expressed gene 1 (tmc-1), which is expressed in cochlear hair cells of the inner ear, cause hearing loss [18].

**Mutations and polymorphisms of EVER genes**

Mutations of the EVER1 and EVER2 genes were found in 31 (75.6%) of 41 EV patients in the course of a collaborative study [19]. The fact that no mutations were detected in 25% of the EV patients indicates the genetic heterogeneity of the disease and may suggest not yet identified genes responsible for the development of the disease in some cases. So far in the literature there have been reported seven in EVER1 and five in EVER2 mutations resulting from several mechanisms: nonsense mutations, single nucleotide mutations, splice site mutation, or deletion of exons (Table 1). In a group of Polish EV patients two mutations in the EVER2 gene and lack of any mutations in the EVER1 gene have been identified. The first mutation was transversion G>T at nucleotide position 150 within intron 4. It has been assumed that this mutation (named IVS4-1G>T; T150fsX3) is characteristic for the Polish population of patients with EV. The second mutation leads to the deletion of nucleotide T at position 705 within exon 8 (del705T, G235fsX47) (Majewski et al., data not shown). Besides mutations of EVER genes several polymorphisms have also been detected in EV. In the literature two polymorphisms of EVER genes registered in the dbSNP database in NCBI (rs7208422 and rs12452890) and one newly found (917 c. 457C→T) have been demonstrated [20–22].

**EVER proteins – their location and structure**

The full length transcripts of the EVER1 gene encode two polypeptide chains consisting of 805 amino acids. In alternative splice events there are synthesized two isoforms consisting of two smaller proteins of length 384 and 454 amino acids (www.ensembl.org/Homo_sapiens/Gene). EVER1 protein is an integral membrane protein with ten domains (www.cbs.dtu.dk/services/tmhmm-2.0), two leucine-zipper motifs and two putative glycosylation sites (www.emboss.sourceforge.net/). The terminal regions of EVER2 protein are located lumina! ally to the cell membrane (www.uniprot.org/help/uniprot). The EVER2 gene contains one transcript of length 4419 bp, which encodes one protein of 726 amino acids. The EVER2 protein is also an integral membrane protein, which contains eight domains, three leucine-zipper motifs and two pu-
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### The role of **EVER** proteins in the immune system

The characteristic phenomenon in EV is impaired cell-mediated immunity leading to the presence of established EV HPV infections and the malignant transformation of some of the lesions [24]. In several studies a decreased T-cell count, defective T-cell proliferation in response to phytohemagglutinin (PHA) and cutaneous anergy to a variety of antigens have been reported. It is known that patients with EV overproduce tumor necrosis factor α (TNF-α) in lesions and have a defect in AP-1 signaling in keratinocytes which are controlled by TNF receptor 1 (TNFR-1) [25]. The burning question is what might be the specific role of **EVER** genes in creating immune responses and the consequence of the mutations in **EVER** genes for the function of lymphocytes. It has been observed that **EVER** genes are transcribed not only in the human skin but also in CD4+ and CD8+ T lymphocytes, B lymphocytes and NK cells at high levels. The expression in immune system cells could point to their involvement in the immune response [24]. It is also speculated that the deficiency of **EVER** proteins in T-cells may contribute to susceptibility to HPV infections due to impairment of the immune response. Indeed, the recent study carried out on circulating lymphocyte populations in three adult EV patients sharing the same **EVER2** mutation (T150fsX3) showed mild T-cell abnormalities. The researchers observed a significant increase of memory CD4+ and effector memory CD8+ T cells, a bias of the TCR Vαβ and Vγδ repertoires and an increase of skin-homing CD4+ T-cell subsets. The count of CD4+ and CD8+ T cells and the proliferative capacity in response to anti-CD3 stimulation were normal [25]. Another study showed that activated CD4+ and CD8+ lymphocytes (via the TCR receptor) decreased expression of **EVER** proteins with accompanying accumulation of zinc ions in the cytoplasm [24].

### The role of **EVER** proteins in keratinocytes

The role of proteins encoded by **EVER** genes was unknown until the demonstrations carried out by Lazarczyk et al., who reported that **EVER** proteins might be responsible for the regulation of cellular zinc balance [8]. It is known that zinc is an important ion crucial for the proper functions of numerous proteins such as enzymes [26–28], signal transduction proteins and transcription factors. The authors found that **EVER** proteins interact with ZnT-1 and form the complex ZnT-1/EVER, which is associated with transferring the zinc from the cytoplasm into the endoplasmic reticulum (ER) lumen, decreasing the total amount of zinc in the cytoplasm and indirectly in the nucleus. The precise role of **EVER** proteins within the ZnT-1/EVER complex has not been determined yet. It is hypothesized that **EVER** proteins may act by: (i) modulating the activity of ZnT-1 or (ii) serving as zinc transporters themselves. It has been determined that a mutation in one of the **EVER** genes (regardless of

### Table 1. Mutations of **EVER1** and **EVER2** genes

| Mutation of **EVER1** gene | Position (cDNA) | Exon | Intron | Reference |
|---------------------------|----------------|------|--------|-----------|
| 1. Nonsense                | 220 C>T        | 4    | –      | Aochi et al., 2007 [41] |
| 2. Nonsense                | 280 C>T        | 5    | –      | Ramoz et al., 2002 [15] |
| 3. Nonsense                | 744 C>A        | 8    | –      | Tate et al., 2004 [42] |
| 4. Splice-site             | IVS8-2 A>T     | –    | 8      | Tate et al., 2004 [42] |
| 5. Nonsense                | 916 ins CATGT   | 9    | –      | Zuo et al., 2006 [22] |
| 6. Frameshift              | 968 delT       | 9    | –      | Gober et al., 2008 [43] |
| 7. Nonsense                | 1726 G>T       | 14   | –      | Ramoz et al., 2002 [15] |

| Mutation of **EVER2** gene | Position (cDNA) | Exon | Intron | Reference |
|---------------------------|----------------|------|--------|-----------|
| 1. Nonsense                | 188 G>A        | 3    | –      | Rady et al., 2007 [44] |
| 2. Frameshift              | 561_583del     | 6    | –      | Berthelot et al., 2007 [45] |
| 3. Nonsense                | 568 C>T        | 6    | –      | Sun et al., 2005 [46] |
| 4. Frameshift              | 754 delT       | 8    | –      | Ramoz et al., 2002 [15] |
| 5. Nonsense                | 1084 G>T       | 9    | –      | Ramoz et al., 2002 [15] |
whether EVER1 or EVER2) interrupts the function of the whole ZnT-1/EVER complex and leads to a flux in the reverse direction from ER to the cytoplasm and the nucleus [8]. The discovery of the molecular mechanism of EVER proteins in maintaining zinc homeostasis suggests that the ZnT-1/EVER complex participates in the regulation of the activity of many transcription factors. Indeed, upon further investigation it was found that the ZnT-1/EVER complex suppressed the activity of the AP-1 complex, which allows viral replication in the general population, B – lack of synthesis of E5 protein by EV-HPV protects against infections in the general population, C – in epidermodysplasia verruciformis mutations of EVER genes lead to impairment of the ZnT-1/EVER complex, allowing EV HPV infections.

**Figure 1.** Mechanism of action of EVER proteins in keratinocytes: A – infection of keratinocytes by genital HPV (HPV16) leads to synthesis of E5 protein and inhibition of the ZnT-1/EVER complex, which allows viral replication in the general population; B – lack of synthesis of E5 protein by EV-HPV protects against infections in the general population; C – in epidermodysplasia verruciformis mutations of EVER genes lead to impairment of the ZnT-1/EVER complex, allowing EV HPV infections.

The role of EVER proteins in HPV infections

The role of the “EVER barrier” in EV HPV infections in EV and the general population also remains a mystery. It is hypothesized that properly functioning zinc homeostasis might constitute a natural protective barrier, which limits the access of zinc ions and prevents viral replication [29]. In EV, mutations of EVER genes lead to the synthesis of impaired EVER proteins and disrupt the ZnT-1/EVER complex, leading to an increased zinc level in the cytoplasm, allowing replication of EV HPV (Figure 1A) and unusual sensitivity to infections by EV HPV [29]. The intriguing question is in what way does the lack of properly functioning EVER proteins in EV lead to EV and skin cancers? It has been proposed that excess of zinc ions may induce c-Jun related pathways and the transcriptional activity of AP-1. It has been proved that the AP-1 factor is crucial for expression of the viral genome [33].

The next intriguing question is why in healthy people without mutations in EVER genes and with properly functioning EVER proteins the genital HPV viruses have the ability to induce various anogenital lesions, even such as cervical cancer. The answer can be proposed by two hypotheses. According to the first one, the EVER-based barrier might be highly selective and concern EV HPV, not genital HPV; and according to the second, the EVER-based barrier is equal for both EV HPV and genital types, but genital HPV probably develop a mechanism that facilitates their elusion of this barrier. Currently the second hypothesis seems to be more likely. The breakthrough was found in the role of the viral protein E5. Interestingly, the E5 protein is expressed only by genital HPV and not by EV HPV [34]. This protein is assumed to contribute to the development of a lesion by stimulating cell division [35]. ZnT-1/EVER was found to bind the E5 protein, leading to an increased zinc level in the cytoplasm, leading to an increased zinc level in the cytoplasm, and to an increase in concentration of free zinc in keratinocytes and allowing for the replication of genital HPV (Figure 1B). In non-EV patients the lack of E5 protects against EV HPV infections (Figure 1C) [29].
The role of polymorphism of EVER genes in carcinogenesis

So far in the literature there have not been any reported mutations of the EVER genes in any disorders other than EV. It needs to be stressed that there is an available report showing a link between polymorphism in the EVER genes and carcinogenesis. Patel et al. [36] showed a link between the genetic variation in the EVER2 gene and an elevated risk of squamous cell carcinoma (SCC). This study was based on the hypothesis that EVER genes, mutations of which play a key role in skin cancers in EV, may also be impaired in carcinogenesis in non-EV patients. It is also known that EV HPV DNA is detected in a high percentage of actinic keratosis (AK) (85%) and SCC (45%) cases [37]. It needs to be stressed that only 30–40% of EV patients develop non-carcinoma skin cancers. The clinical phenotype of EV is dependent on viral and immunological features that characterize EV patients. It could also point to the possible genetic heterogeneity of the disease [7]. Patel et al. showed that genotype TT of polymorphism rs72084422 (c.917A→T, p.N306l) in EVER2 is related to a 70% increase in the risk of SCC compared to the controls (OR = 1.7; 95% CI = 1.1–2.7; p = 0.01). It has also been associated with seropositivity for b-HPV5 and -8, and SCC [36]. In our latest studies we also found a possible association between AK and rs72084422 (c.917A→T, p.N306l) of the EVER2 gene in AK [38, article in press]. The exact mechanism of this polymorphism in carcinogenesis remains unknown, but in a recent study Gaud et al. demonstrated that the skin cancer-associated EVER2 306l protein coded by T alleles results in impaired TRADD–EVER2 interaction with lower levels of TNF-α apoptosis [31]. The concept of the role of polymorphisms of the EVER genes in carcinogenesis was also analyzed in cervical cancer, in which experimental and epidemiological studies have demonstrated, similarly to EV, the role of oncogenic HPV in its development. Up to now there are two publications available which assess polymorphisms of the EVER genes in this disease. Wang et al. found that some regions of the EVER genes are significantly correlated with the presence of cervical intraepithelial neoplasia III [39]. Studies carried out by Castro et al. showed a strong association between rs2290907 and rs16970849 in EVER genes and cervical cancers [40].

Summary

The discovery of the role of the EVER1 and EVER2 genes has led to better understanding of processes of skin carcinogenesis. Therefore, further research evaluating the relationships between the EVER genes, the mechanism of action of EVER protein and HPV is required to fully elucidate skin carcinogenesis.

Conflict of interest

The authors declare no conflict of interest.

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