

REVIEW ARTICLE

Pleckstrin homology mutation in EVER genes may cause skin cancer

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Abstract

EVER genes belong to a completely unique gene family, the trans membrane channel-like (TMC) family, and are responsible for properly functioning zinc homeostasis. Mutations in two homologous genes, EVER1 and EVER2 increase the susceptibleness to infection with certain human papilloma viruses resulting in high risk of skin carcinoma and development of Epidermodysplasia Verruciformis (EV) is a rare, autosomal recessive genodermatosis.

Keywords: EVER genes; Human Papilloma Viruses; Epidermodysplasia Verruciformis; Skin Carcinoma

Introduction

Pleckstrin homology domains represent the eleventh most general domain in the human proteome [1]. Epidermodysplasia verruciformis (EV) 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; more commonly known as “Tree-man” disease, man with a massive growth of warts forming tree like arils, predominantly on hands and feet and less sporadically on neck and face [2].

EVER gene mutation

EVER genes belong to a completely unique gene family, the trans membrane channel-like (TMC) family, and are responsible for properly functioning zinc homeostasis. Mutations in two homologous genes, EVER1 and EVER2 increase the susceptibleness to infection with certain human papilloma viruses resulting in high risk of skin carcinoma and development of epidermodysplasia verruciformis (EV) is a rare, autosomal recessive genodermatosis. EV involves the mutation of EVER1 and EVER2 genes on chromosome 17 (17q25.3). The EVER1 and EVER2 are also known as trans membrane channel-like Protein 6 (TMC6) and TMC8 respectively. Both the genes act as zinc transporter which interacts with zinc transporter-1 protein [3]. Zinc-binding proteins are very important for maintaining virus life cycle, commonly adenovirus, retrovirus, herpes viruses etc. Zinc ion is required for the activation of AP-1 transcriptional activity, ultimately trigger virus protein production. Zinc also helps the virus by providing cellular immunity and antiviral responses. The EVER1 and EVER2 induce cellular defence against virus by limiting zinc ion availability [4].

Major Histocompatibility Complex class II (MHC II) is very important for cellular immunity and also associated with EV. DRB1, DQA10501, DQB10301 type of MHC II were very much common in the EV patients, which may associated to powerful susceptibility to EV [5].

EV is associated with the infection of non-enveloped, double stranded DNA (dsDNA) human papilloma virus (HPV). Basically HPV attacks the keratinocytes of skin or mucosal membranes with non-symptomatic infection, and then forming benign papillomas in form of warts or may cause malignancy [6]. About 120 types of HPV 5, 8, 10, 47 have high oncogenic potential and rest of this types has less oncogenic potential (HPV types 14, 20, 21, 25). These are mainly found in benign skin lesions [7]. HPV transforms keratinocytes, which changes its characteristics and suppresses p53 and pRb and stimulates pro-oncogenic HPV viral E6 and E7

proteins to amend cell cycle regulation and apoptosis [8].

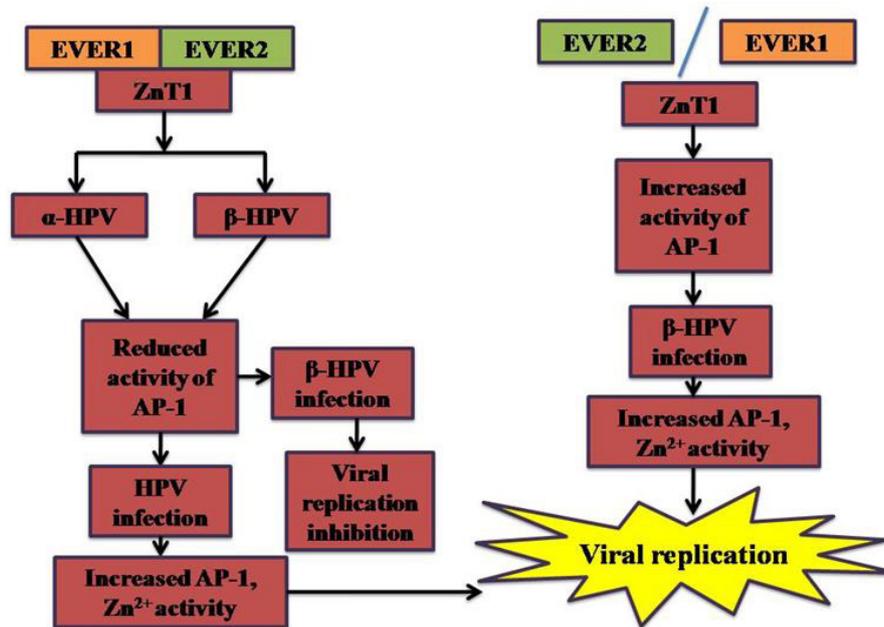


Figure 1: EVER1 and or EVER2 with ZnT1 associated with HPV infection and viral replication

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