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Overview of genes involved in *Epidermodysplasia verruciformis*

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Abstract

Epidermodysplasia verruciformis also known as *EV* is a rare skin disorder caused by genetic mutations. These mutations can lead to susceptibility of beta human papilloma virus infection in which body having clinical manifestations of flat warts, macules and pityriasis versicolor-like lesions. Normal population is asymptomatic for HPV but genetically affected EV individuals may develop cutaneous malignancy especially squamous cell carcinoma in third or fourth decade of life. Cancer may be progressive towards UV rays and sun exposed regions of the body. Disease can be designated as typical or atypical type. Typical EV as keratinocyte intrinsic immunity defects leading to develop lesions by beta HPVs infection, atypical EV as T cells deficiency to cause immunosuppression. Most of typical EV cases involve alteration of transmembrane channel like genes family named as *EVER1* and *EVER2* genes. Another recently discovered *CIB1* mutation also performing crucial role in developing typical EV manifestations. Atypical EV cases involve different genes like *LCK, RHOH, STK4, DOCK8, COROIA, IL7, DCLRE1C, CARMIL2, ITK, RASGRP1, ANKRD26 and TPP2*. Most of atypical mutations can be loss of function mutation and patients are immunodeficient. This review comprises of role of these genes, their mutations and their role in leukocyte and keratinocyte immunity to develop EV disease.

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Introduction

Epidermodysplasia verruciformis also known as EV (MIM#226400) is a rare inherited skin disorder in which dispersed flat warts and pityriasis versicolor lesions appear on the body. These lesions are due to infection caused by β-genotype of human papillomavirus which occurs in response to defect in cell mediated immunity. Epidermodysplasia verruciformis was first described by a physician in 1922 named as Felix Lewandowsky and Wilhelm Lutz. Cockayne in 1933 hypothesized EV to be a congenital disease and transferred by recessive gene Pattern. (Kalińska-Bienias *et al.,* 2016). Pattern of inheritance can be X-linked recessive, autosomal dominant (Androphy *et al*., 1985; McDermott *et al.,* 2009). EV usually occurs during childhood or infancy and may occur sometimes in the middle age (Swati *et al.,* 2017). EV lesions can be associated with cutaneous malignancy (Lutzner *et al*., 1984), specifically squamous cell carcinoma affecting 30% to 70% of individuals. Cancer may progress to sun exposed areas of body, UV rays and this progress is reliant on the type of HPVs. More than 30 different types of EV-HPV have been reported (Zampetti *et al*.,2013). Among all HPVs 5,8,10 and 47 are cancer associated, 14,20,21 and 25 are benign warts or lesions of skin. Affected individuals are usually immune to other microbial and pathogenic infections even mucosal and cutaneous HPVs (De Jong *et al*., 2018a). The two types of lesions can be reported as Flat, warts or they can be verrucous. Flat warts lesions can be capped papules fluctuated as light pink to violet forming plaques of brown color having irregular shape and surface of scaly existence. EV is not racial and independent of gender (Przybyszewska *et al.*,2017). There are different risk factors for EV which cover consanguineous marriages, family history of disorder, individuals having organ transplantation due to use of drugs that are immunosuppressed and HIV infected individuals. Lesions appearance varies as they may disappear and body is affected with new appearance of lesions at different regions.

Epidermodysplasia verruciformis classification is based on clinical manifestations, pathogenesis, inherited and acquired factors. Genetically EV can be explained as classical and atypical inheritance. These cases include lesions caused by Human papillomavirus owed to impairment of cutaneous immunity while atypical EV presents characteristics of lesions along with other infections because of impaired T cell immunity (Youssefian *et al*.,2019a). Acquired EV is caused by impaired cell mediated immunity which can be seen in organ transplant individuals, warts, lymphedema, Hodgkin's disease anogenital dysplasia syndrome, cell leukemia and leproma leprosy and IgM deficiency. (Zampetti *et al*.,2013).

Epidermodysplasia verruciformis

Genetic basis of EV

Epidermodysplasia verruciformis typically includes transmembrane channel like protein coding genes *EVER1/TMC6* and *EVER2/TMC8* mutations while atypical EV includes mutations with the exception of *EVER* genes (Hung *et al*.,2018). The exact mechanism of typical EV is difficult to analyze and is considered as genetic disorder associated with *EVER1/2*mutations. Typical EV patients are not prone to other abnormalities of immunity as EV is initiated as a result of impairment of intrinsic immunity of keratinocytes when exposed to human papillomaviruses. Consequences of *EVER* genes mutation include proliferation and replication of human papillomaviruses in keratinocytes (lmahorn *et al.,2017).* With the advancement of technology and consistent research pattern new mutations have been found. Typical and atypical EV cases have been reported and this can be 500 for classical EV and 20 cases of Non classical EV (De Jong *et al*.,2018a).

Patients having similar clinical cutaneous lesions and other infections related to typical EV caused by other genetic alterations other than *EVER* genes can be denoted as atypical form of EV. The most important feature seen in these patients is impairment in EV-HPV hindrance caused by profound genetic T cell defects or genetic defects of unknown etiology. Patients of atypical EV may develop other infections and diseases. The common features are, development

of skin lesions at young age due to beta human papillomaviruses and consanguineous family inheritance. The clinical characters of atypical EV include growth retardation, autoimmune infections affecting other organs, bacterial infections of skin, ear and pneumonia, Gastrointestinal and respiratory infections, cutaneous infections of herpes viruses and non-beta HPV infections caused due to impaired immunity. Cancers like EBV and Burkitt lymphoma have been reported (De Jong *et al.*,2018a).

In general description of atypical EV, patient's predisposition to other infections is helpful in diagnosis of disease. However, when there is no evidence of other infectious manifestation then it becomes difficult to distinguish between classical and non-classical EV. In this circumstance molecular and cellular based investigation is helpful to suggest atypical EV condition. Thus these clinical symptoms and molecular data to analyze mutations put forwards typical EV as keratinocytes intrinsic defects and atypical EV triggered by adaptive T cell defect.

Involvement of genes with epidermodysplasia verruciformis

EVER1/EVER2 genes: *EVER1* and *EVER2* genes are identical to *TMC6* and *TMC8* genes which are trans membrane channel like genes family and consisting of total 8 genes that will encode for trans membrane proteins having 6 to 10 domains (keresztes *et al.*, 2003). These genes are present on chromosome number 17 having locus of *17q25.EVER1* gene contains 20 exons while *EVER2* gene contains 16 exons and number of introns carried by *EVER1/2*are 19 and 15 respectively. *EVER1* and *EVER2* genes encode for 4 and 1 transcripts. Out of four transcripts of *EVER1* gene in two of them all exons length is 2892 base pairs and 2789 base pairs. The third and fourth contain 2711 base pairs and 1838 base pairs having 19 and 12 exons respectively (Kalińska-Bienias *et al.*,2016). Mutation ratio expected to be 75% in *EVER1/2* genes in EV disease and 25% no mutation is due to heterogeneity of disease. These genes show significant part in immunity as they are expressed in skin tissues but most of transcription is seen in natural killer cells, B and T lymphocytes (Lazarczyk *et al.*, 2008). When these genes are expressed they give a complex of proteins along with ZnT1 in the membrane of endoplasmic reticulum involving Zn^{2+}stability of cell. EV patients are prone to HPVs skin infection due to impairment of Zn^{2+}balance while these HPVs are non-injurious to normal individuals. If these proteins have been mutated TMC/ZnT1 complex so that will cause replication of HPVs and resulting phenotype of EV (Lazarczyk *et al.*, 2012). The blocking mechanism of HPV infection by EVER1/EVER2 is still unknown. Ever genes mutation was initially identified by Ramoz and his coworkers (Ramoz *et al.*, 2002). Almost 17 genetic mutations in typical EV have been identified which were loss of function mutations. There are different cases which showed negative results of EVER1/2 genes mutations for that reason, to know true frequency of these alterations should be studied further. (Youssefian *et al.*,2019a).

CIB1-gene: *CIB1* gene known as calcium and integrin binding 1 (MIM#602293), is a protein coding gene having cytogenetic location *15q26.1*and 7coding exons. It encodes calcium and integrin protein 1 Which belongs to calcium binding EF hand domain (Helix loop helix structural motif/domain) family of proteins. EF hand motifs are found in all animal's proteins where they function divalent cations such as Ca^{+2} and Mg^{+2} coordination. This protein can interact with different proteins like platelet specific integrin alpha IIb beta 3p21 activated kinase, presenilin-2, DNA dependent protein kinase, focal adhesion kinase and protein kinase D. *CIB1* expression is predominant in contempt of small size and deficit enzymatic activity and it binds most of its cellular partners through hydrophobic cleft and performs variety of cellular processes. These may include cell division, cell differentiation, proliferation, migration, adhesion, survival and most important is calcium signaling. Dysregulation in these cellular processes can cause pathological conditions including cancer and cardiovascular disease. *CIB1* gene in these conditions is involved in cardiac hypertrophy, tumor growth and stress induced angiogenesis (Leisner *et*

al., 2016).

A surprising finding of *CIB1* mutation related to typical EV rather than *EVER* genes opens a new door of research. A new homozygous null mutation for *CIB1* genes has been identified in consanguineous families which is a complete AR (Autosomal recessive) *CIB1* deficiency (de Jong *et al.*,2018b). It has been investigated typical EV in 24 patients from different locations including six different countries. As these patients suffered from typical EV so their mutational analysis was done for *TMC6* and *TMC8* genes in exons and specifically intron flanking regions. This investigation did not show mutation for these genes, despite of homogenous features of disseminated skin lesions, HPVs 5 and 8 presence and patients affected by cutaneous skin cell carcinoma in exposed body parts. These clinical and virological resemblance in features revealed typical EV disorder and could not be differentiated from patients who had *TMC6/TMC8*mutations. To analyze mutation genome wide linkage analysis and homozygosity mapping was performed on chromosome number 15 and it indicated a linkage peak at an interval of 2.4Mb showing genetic etiology of EV. This region was further reduced to an interval of about 1.74Mb to perform whole exome sequencing and finally this result was also confirmed by sanger sequencing method. All this experimental work elicited non synonymous mutation in *CIB1* that was a rare homozygous mutation in that specific interval as there were 33 and 9 other genes for protein coding and RNA respectively. On the other hand, this interval showed homozygous pattern having nonsynonymous mutation. Unaffected individuals of family did not carried mutation in this interval so results demonstrated *CIB1* null mutations including nonsense, splice site, frameshift insertion and deletion mutations. Accordingly, recessive pattern of linkage for *CIB1* allele showed AR etiology of *EV* caused by genetic defect. *CIB1* is responsible to form complex including *EVER1* and *EVER2* genes in keratinocytes additionally *CIB1* protein expression is not revealed in *EVER1/EVER2* deficient patients. Interesting feature to be observed is that T lymphocytes deficiency is not detected in patients therefore, *CIB1* can be correlated to typical sort of EV. This typical *EV* is inborn alteration of intrinsic immunity of cell prone to keratinocytes proliferation governed by beta HPVs. Deficiency of *CIB1* has no impact on homeostasis of zinc, activation of NF-kB, cell growth, adhesion and migration in keratinocytes. However, it is involved in restriction of HPVs thereby acting together with HPV*E8* and *E5*. Thus intrinsic immunity of keratinocytes dependent on this complex may be disrupted which provides a comfort zone for beta HPVs to develop *EV* (de Jong *et al.*,2018b).

Typical *EV* with *CIB1* alteration have been studied in another consanguineous family. The case was of an Iranian female of 42 years in a family of three siblings having cutaneous infection of flat warts and papules extended to trunk region. She had lesions started at puberty and severity increased to cause squamous and basal cell carcinoma. Two family members died, one in early age due to meningitis and other because of skin cancer. The genotyping of skin HPVs representing HPV 5 and 8, immunophenotyping and lesions analysis, all these finding can be suggested to be a typical form of *EV*. In order to analyze genetic cause of EV in this family whole exome sequencing and homozygosity mapping was performed. Family showed homozygous splice site mutation of *CIB1* and due to mutation alteration in splicing pattern of pre mRNA was confirmed that can further lead to mRNA decay. Identical to this another mutation has been found in a family (de Jong *et al.*, 2018b). These families' mutational relationship revealed founder effect that was analyzed by haplotype in which SNP markers were used (Vahidnezhad *et al.*, 2018).

Role of *CIB1* in development of EV along with *EVER1* and *EVER2* genes complex formation has been described. But mutation in *CIB1* gene and its function in *EV* is a new cause and unexpected. As deficiency of this gene in keratinocytes did not show defects of focal adhesion and migration of cell in vitro. There are various questions regarding *CIB1* gene alteration and involvement in restriction of HPVs as explained by de Jong *et al.*,2018. Several mechanisms of

restrictions in keratinocytes to regulator HPV infection such as interferon response, DNA damage, NF-KB, signaling mediated by c GAS/STING, TLR responses have been known so far. But CIB1 complex formation did not show all known mechanisms regulation. There is a need of further investigation to tackle *EVER1* and *EVER2* proteins expression and their collaboration with CIB1 complex formation (Notarangelo *et al.*,2018). Thus, *CIB1* mutation contributes novel finding linked to typical cases of EV that used to be associated only with *EVER1* and *EVER2* genes.

RHOH gene: *RHOH* termed as ras homolog gene family member H (MIM#602037) having cytogenetic location*4p14*. This is hematopoietic cell specific member of Roh GTPase family performing function as a signal transducer in cells. *RHOH* also termed as TTF (Translocation three four) on the basis of its role in non-Hodgkin lymphoma associated with translocation observed in B cell lines. The Size of *RHOH* gene is 35kb consisting of 2 exon having all coding region in second exon (Dallery-Prudhomme *et al.*,1995). Conical RhoGTpases act as intracellular Switches from which various membrane signals are transduced comprises of B and T cell receptors. *RHOH* including atypical Rho GTPases have absence of GTPase action and remains active (GTP – bound confirmation). *RHOH* two significant functional protein zones are located upstream from the sequence encoding Y38X which is precipitous termination codon; ITAM –like (immunoreceptor tyrosine-based activation motif–like) in any other Rho GTpases and CAAX box these motifs are not found, common lipid amendment site to all GTpases mediating location of protein in membranes. In all public databases RHOH contains no known frame shift or polymorphic alleles. Indifferent B cell cancers somatic mutation of RHOH has been found previously including Burkitt lymphoma. This B cell cancer and *RHOH* link recommended homozygosity for Y38X might promoted of Burkitt lymphoma expansion. In two young sibling's manifestation of infectious diseases and T cell inadequacy including infections of EV-HPV showed homozygosity for mutation which causes *RHOH* stop codon (Crequer *et al.*,2012a).

STK4/MST1

STK4 known as Serine /Threonine protein kinase 4 gene or mammalian sterile 20-like 1gene (MIM#604965) having cytogenetic location *20q13.12* and 11 exons encodes cytoplasmic kinase protein expressed ubiquitously. It has structure similarity with yeast Ste20. The amino acid sequence of serine threonine kinase *MST1* is highly conserved and consists of catalytic domain at N terminal, auto inhibitory segment and coiled SARAH domain at C terminal which is responsible to moderate hetero and homo dimerization. It is involved in different pathways which can control cell death processes. *STK4* acts as proapoptotic kinase. Cleavage of 36kDa protein by caspases as a result of apoptotic stimuli and translocation of 36kDa N-terminal fragment towards nucleus and phosphorylation of histones suggests *STK4* proapoptotic function (Abdollahpour *etal.*,2012 and Nehme *et al.*,2012). STK4 is important for transcription factors FOXO1 and FOXO3 (fork head box proteins) which are crucial for T cells homeostasis and cytotoxic T cells response in viral infections of chronic nature (Sharafian *et al.*,2019).

In human deficiency of *MST1*can be linked with lymphopenia of CD4+ T cells along with naïve CD4+ cells, CD8+ T cells, various mitogens, heart malformation, neutropenia, pulmonary infections candidiasis susceptibility and cutaneous warts. The most peculiar deficiency of *MST1* has been revealed in EV patients different from typical *MST1* deficient individuals which do not develop EV-HPV infections. It has been observed in a family having skin lesions caused by beta HPVs and it was histologically different from typical patients of EV. The homozygous non sense mutation of *MST1* gene in patient exhibited loss of expression to cause disease. All immunological and T cell abnormalities can be attributed to *MST1* deficiency in this case (Crequer *et al.*, 2012b).

STK4 deficiency can cause combine immunodeficiency that can be autosomal recessive. Another mutation of *STK4* gene have been found in 13 old patient manifesting respiratory infection,

juvenile idiopathic arthritis and Epidermodysplasia verruciformis. A dominant feature in these patient was recalcitrant and chronic lesions of EV in sun exposed regions. Persistent warts of non EV type and lymphoproliferative disorder induced by EBV in some individuals related to *STK4* deficiency. Patients showing lymphocytopenia of CD4 cell and increased IgM concentration. WES (Whole exome sequencing) specified a homozygous mutation that was a frame shift mutation and created a stop codon in coiled coil domain which was premature and resulted in diminished protein with 295 amino acids rather than 487 amino acid found in normal protein. In *STK4*deficiency patients developed autoimmunity and some patients had autoantibodies without development of autoimmune disease. Impaired T cells development and unrestricted activation of B cells can lead to autoimmunity in *STK4* deficient patients (Sharafian *et al.*,2019).

MST1 deficiency can be a genetic cause to develop EV-HPVs infections. Both by affecting T cells or playing a similar role as *EVER* proteins. T cells are predominant in protecting immunity against HPVs to cause cutaneous infections. EVER proteins like role can be explained as *MST1* used to be identified as a Hippo tumor suppressor pathway member, plays negative role in cell proliferation and it can promote differentiation of cells by YAP inactivation that can influence keratinocytes proliferation in skin. Therefore, it may be predicted that *MST1* can regulate viral replication restriction in keratinocytes like EVER proteins to keep low rate of cell proliferation (Crequer *et al.*, 2012b). *STK4* can be part of the cause in class switching and hyper mutation by histone H2B phosphorylation. Mutation existing at coiled coil domain in class switching should be explored further. *STK4* gene mutation results in common immunodeficiency which includes broad range of similarity with other immunological and clinical characteristics of T lymphocytes genetic defects. Among these genetic defects *RHOH, DOCK8* deficiency and *GATA2* mutation are essential (Sharafian *et al.*,2019). Further research should be conducted to understand diagnostic studies of *MST1* deficiency and its susceptibility to HPVs infections.

CORO1A gene: *CORO1A* known as *CORONIN 1A*(MIM#60500) gene having cytogenetic location *16p11.2*, consisting of 10 coding exons. It encodes regulating protein expressed in hematopoietic cells (shiow *et al.*,2008). It can also be expressed in other sites like thymus, spleen lymph nodes, brain and less expressed in lungs. It is from coronin actin binding proteins family which are involved in cytokinesis, phagocytosis cell motility and vesicular transport. *Coronin -1A* is involved in development and cellular growth by regulating actin cytoskeleton and TGF-beta /SMAD3 signaling. The regulation of actin cytoskeleton is carried out through F-actin polymerization counter and calcium calcineurion signaling in T cells. *Coronin-1A* immmunophysiological role is to facilitate organisms like mycobacterial survival in macrophages by localization of phagosome contained by specific mycobacteria. It has been identified as basic autosomal recessive immunodeficiency due to heterozygous mutation of *CORO1A* with 11 exon variant in two affected siblings causing lymphocyte impairment together with naive T-cell lymphopenia open-handed severe combined immunodeficiency (SCID) and clinical infectious phenotypes. *Coronin 1A* deficiency in patients with mucocutaneous immunodeficiency syndrome embrace EV-HPV infection, HSV, molluscum Contagiosum and leprosy and there may be a possibility of evolving bronchiectasis and lymphomas aggravated by means of EBV (Stray-Pedersen *et al.*,2014).

LCK gene: *LCK* is lymphocyte specific protein tyrosine kinase (MIM#153390) having cytogenetic location *1p35.2*, Two transcript variants and 12 coding exons. LCK gene belongs to SRC family of oncogenes and encodes p56(LCK) which is a non-receptor protein tyrosine kinase (PTKs) performs function to transduce T cells receptor activation. The encoded protein is involved in signaling to select and mature T cells development as well as entire adaptive immune response. It is made up of four homology domains of

SRC that are conserved in different ways in SRC family members. The localization of protein is in the plasma membrane and binds to the different signaling molecules including CD4 and CD8 receptors and others (Germani *et al.*, 2003).

Unlike classical EV having *EVER1/2* mutations, patients of atypical cases not only associated with EV manifestation nevertheless represent T cell deficits, fungal, bacterial infections and different malignant cases. These atypical cases lack *EVER* genes mutation but are affected by mutations of genes which can influence immunity. Three patients of EV have been studied form a single Chinese Hui family having a consanguineous pattern of inheritance, pityriasis lesions on neck, face and forearms. The patients test was negative for HIV and HSV but they showed deficiency of CD4- T cells and its lowest levels among them. As there was absence of *EVER 1/2* mutation so, WES was performed to search novel mutation of gene liable for EV manifestations. Analysis showed homozygous splice site mutation in *LCK* gene which could be the consequence of deletion in exon 3 of *LCK* isoform responsible for frameshift mutation thus, mRNA decay. Bacterial infections, CD4+Tcell lymphopenia, infection of HPV and malignant phenotypes in patients recommended importance of *LCK* deficiency to develop atypical EV (Li *et al.*,2016).

These findings of EV patients as immunodeficiency proposed EV is not a defined genetic illness, however it is a clinical phenotype of numerous inherited disorders. The defects of T cells attributable to mutations of genes are responsible for malignancy and EV-HPV infections. Since expression of *EVER* proteins also occurs in T cells, so their insufficiency probably results in minor T cell aberrations. The immunity of T cell can be reduced in typical *EV* patients with EVER deficiency. Subsequently, it is a meaningful concept to elucidate part of these genetic alterations in T cell deficient individuals that will be helpful to know pathogenicity caused by HPV infections and their association in development of malignancy. (Li *et al.*,2016).

DCLRE1C gene: *DCLRE1C*known as DNA cross link repair 1C (MIM#605988) encodes ARTEMIS protein having cytogenetic location *10p13* and 14 exons. The encoded protein is essential in recombination of V(D)J and development of B and T cells. When ARTEMIS loses its activity it prompts seriously debilitated recombination of V(D)J to cause SCID, partial loss of gene function and hence protein impairment (Hypomorphic mutation). This can lead to mild cases of deficient immunity presenting wide range of clinical and immunological phenotypes. Hypomorphic mutation *DCLRE1C* genes which was homozygous also represented EV infection along with SCID in 21 years old individual from consanguineous family of Algeria. Patient presented flat warts and hypopigmented macules on different body regions. A homozygous miss sense mutation was detected in *DCLRE1C*gene by whole exome sequencing. The patient's clinical manifestation was considerable as survived from severe impaired function of T cells. This gene mutation and ARTEMIS impairment affecting T cell functions and development lead to another genetic etiology of EV other than typical EVER1/2 mutation. In an attempt to conclude that EV as a manifestation of T cell defects or related to immunodeficiency (Tahiat *et al.*,2017).

DOCK8 gene: *DOCK8*gene termed as dedicator of cytokinesis 8 (MIM#611432) having cytogenetic location *9p24.3* and 48 exons. This is a protein coding gene and belongs to family of *DOCK180* guanine nucleotide exchange factor. This factor along with RHO GTPases Interact to become essential components of intracellular signaling pathways. Deficiency of *DOCK8* can cause(HIES) hyperimmunoglobulinemia E syndrome which is AR combined immunodeficiency and underlie because of loss of function mutation of *DOCK8* gene.

Sanel and coworkers described seven children of Turkish family with DOCK8 deficiency and they were from four families of consanguineous inheritance pattern. Patients developed clinical manifestations of atopic dermatitis, otitis extrna, respiratory tract and GIT infections, HSV (herpes simplex virus) infections

including molluscum Contagiosum. The most important additional character was skin lesion which had resemblance with Epidermodysplasia verruciformis. These specific manifestations included hyperkeratosis papules, flat pinkish hypopigmented papules and macules extending from trunk to extremities. Lesions Histopathology demonstrated acanthosis and hyperkeratosis of EV appearance. This was a peculiar manifestation of human papillomavirus infection due to novel homozygous DOCK8 mutation (Sanel *et al.*,2012).

Another case was reported in Chinese patient having *DOCK8* mutation which caused EV and gross generalized molluscum Contagiosum(MC). A younger boy form a consanguineous family had multiple nodules and papules located on trunk and face regions of body. In *DOCK8* gene a homozygous point mutation c.5963G>C (p. Gly1988Ala) has been identified.

Assessment data suggested decreased IgM level but enlarged IgE, CD4 T cells lymphocytopenia and lower levels of IFN-αand TNF-αthan normal healthy individuals. Moreover, EV analysis using PCR for lesions and single nucleotide polymorphism suggested HPV5 type in lesions and *EVER1* gene was compound heterozygous and *EVER2*revealed silent mutation.

This data suggested *DOCK8* deficiency along with *EVER1* gene polymorphism can be attributed to cause of EV development or may be any other genetic etiology is possibility of Epidermodysplasia verruciformis (Liu *et al.*,2017). This research based study indicates that *DOCK8* mutations contribute to atypical EV which is due to immunodeficiency and not related to classical genetic mutation of *EVER1/2* genes.

CARMIL2 gene

CARMIL2 gene - Capping protein regulator and myosin 1 linker 2(MIM#610859) alternatively known as RLTPR (RGD Leucine rich repeat Tropomodulin domain and proline rich domain containing rich protein) having cytogenetic location *16q22.1* and 38 exons. This gene encodes *CARMIL* family of proteins. Protein is involved cell migration and negative regulation of protein capping in heterodimeric manner and it is associated to cause skin pathology. Mutation of gene is associated with T cell function impairment. Three families of Norwegian origin presented warts, dermatitis since their childhood, molluscum Contagiosum and other immunological features. Four family members showed a homozygous mutation and it was confirmed by sanger sequencing. Warts are common feature of HPV infection and to control these infections NK and T cells play an important role. The patient immunophenotyping showed reduce level of follicular T cells and CD4+ memory cells and in all four members (Sorte *et al.*,2016). Two mutation of*CARMIL2*gene have been acknowledged associated with atypical EV disease. (Youssefian *et al.*,2019a).

RASGRP1 gene: *RASGRP1* gene known *as RAS* guanyl nucleotide releasing protein 1 (MIM#603962) having cytogenetic location *15q14* and 17 coding exons. It is characterized as guanine nucleotide exchange factor (GEF) which functions in lymphocytes activation response by activating RAS through exchange of inactive GDP bound state by active GTP. It can activate MAP kinase cascade so as to involved in reorganization of cytoskeleton, transcription of molecules, regulation and development of T and B cells, differentiation and homeostasis.

It has been reported as deficiency of RASGRP1 has shown development of EV due to homozygous nonsense mutation in catalytic protein domain. This deficiency suggested intrinsic T cell deficiency. Clinical manifestations along with EV included CD4+ T lymphopenia, reduced function of natural killer cells, EBV lymphoma, impaired T cell multiplication towards antigens and mitogens. RAS deficiency showed humoral response dysregulation and that can increase susceptibility of viral infection like HPV to cause flat warts in this rare case of dermatosis which is known as epidermodysplasia verruciformis. (Platt *et al.*,2017).

ITK gene: *ITK* gene known as *IL2*inducible T cell kinase (MIM# 186973) belongs to five membered Tec kinase family of mammals. These proteins as non-receptor protein tyrosine kinase activity are involved in signaling and development of lymphocytes. The size of *ITK* gene is 112kb having 17 axons and cytogenetic location is*5q33.3*. This responsible to encode 620 amino acids and to form 71kDa protein. As other Tec family member BTK (Bruton agammaglobulinemia tyrosine kinase) *ITK* is composed of different domains including pleckstrin homology (PH) present at N terminus, Tec homology (TH), SH2(Src homology 2), SH3 (Src homology 3) and at C terminus a catalytic kinase domain. *ITK* is involved in differentiation and proliferation of T cells. *ITK* deficient patients have rapidly loss CD4+ T cells and hypogammaglobinemia growing advanced manner indicating common immunological characteristics (Ghosh *et al*.,2014).

EBV (Epstein Barr virus lymphoproliferative) disease caused by primary immunodeficiency of T cells is one of the important disorder related to Biallelic *ITK* gene mutation. *ITK* mutation can be associated with Beta Human papillomavirus causing epidermodysplasia verruciformis. T cell response to oncogenes can be affected by homozygous mutation of *ITK* gene causing loss of function (Youssefian *et al*., 2019b). EV has been examined in 9 consanguineous families using sanger sequencing which suggested *TMC8* mutation in two families. To identify other mutations homozygosity mapping analysis is performed which showed homozygous frame shift deletion mutation of *ITK* gene in two patients (Youssefian *et al*.,2017). Another evidence has been collected as homozygous deleterious missense mutation of ITK gene in an adult patient having T cell lymphoma also developed EV (Fouéré *et al*., 2018). A member from consanguineous family having scattered pattern of flat warts on herb body, found to be positive for HPV5 and 8 types, viral typing showing EBV, her sibling having Hodgkin lymphoma with clinical finding of EV, both suggested EBV and uncontrolled Beta HPV infection causing atypical EV. WES data suggested homozygous variation in three genes out of which *ITK* is associated with immunity and further confirmed by homozygosity mapping. Cutaneous infection of HPV is primarily caused by *ITK* loss rather than secondary to impaired immunity in EBV –LPDs (Lymphoproliferative disorders) (Youssefian *et al.,* 2019b). These findings demonstrated that EV-HPVs infections and malignancy can be attributed to primary immunodeficiency syndromes. Consequently, *ITK* gene showed a close association with EV phenotype and HPV infection that used to be related with EBV.

*IL7*gene: Interleukin 7 also called *IL7* (MIM#146660) having cytogenetic location *8q21.13*,one transcript variant and 6 coding exons. This gene encodes a protein that is essential in development of T cells, survival and homeostasis. Signaling is achieved by *IL-7* receptor having two chains *1L-7R* alpha (CD127) and gamma (γc) chains (Horev *et al*., 2015). A heterodimer is formed by hepatocyte growth factor and this cytokine which acts as B cell growth stimulating factor. T cell early development involves beta T cell receptors and its arrangement is supported by this cytokine as a cofactor. It is also important in lymphocytes of intestinal mucosa where it acts as a regulatory factor and proliferation of B cells acting as Hematopoietic growth factor. Severe combined immunodeficiency with B lymphocytes that includes T- B+ and NK+ results due to mutation in *IL-7* gene having *IL-7R* alpha deficiency. Disease associated by *IL-7* is Epidermodysplasia verruciformis. It is combined immunodeficiency due to *IL-7* mutation having CD4+ T cell lymphopenia, HPV infection causing verrucosis and may induce squamous cell carcinoma to sun exposed areas.

It has been studied in an Arab family of consanguineous inheritance having verrucous lesions of skin and one of them suffering SCCs. Skin lesions revealed positive result for HPV-3 and T cell lymphopenia in all patients. WES showed non sense mutation of *IL-7* resulting in stop codon. This analyzed *IL-7* role in HPV infection and how its mutation affects immunity so as to cause EV disease (Horev *et al*., 2015).

TPP2 gene: *TPP2* gene also known as tripeptidyl peptidase II (MIM#90470) having cytogenetic location *13q33.1*, consisting of 29 exons and one transcript variant. This gene is responsible to code peptidase which performs the role of tripeptides removal from N terminus site of extended peptides that takes place in an environment of neutral pH. *TPP2* is involved in class I MHC antigen presentation, Cellular proteolysis and adaptive immune system. This protein is serine exopeptidase having higher molecular mass, active site has similarity to class of subtilisin instead of trypsin class (UCSC Genome browser). *TPP2* used to be linked with immunosenescence. *TPP2* contributes its role in survival, proliferation of cell and as antiapoptotic protease in stress conditions. It has been documented that *TPP2* deficiency can be associated with immunodeficiency and autoimmunity. This can be seen in premature senescence of *TPP2* deficiency which can further affect CD8+ T cells, fibroblasts along with B cells. Loss of function mutation in *TPP2* gene causes lymphoproliferation, Evan syndrome and vulnerability to mild infectious problems**.** A new finding for *TPP2* deficiency having minor infections along with cutaneous infections of HPV have been found. Patient showed flat warts which were hypopigmented, HPV-15 presence confirmed by PCR, increased level of IgM and IgG, normal lymphocytes amount, and reduction in CD4 T cells and B cells with mild leukopenia. Widespread and Recalcitrant infections of HPV was infrequent. These infections are uncommon in healthy individuals and have virulent features resembling Epidermodysplasia verruciformis which can be allied to T cell immunity. Consequently, *TPP2* alteration can represents T cell deficiency which can cause specific HPVs infection protruding to appearances of EV (Stepensky *et al.*,2015).

ANKRD26 gene: *ANKRD26* gene (MIM#601855) also known as Ankyrin repeat domain containing protein 26, having cytogenetic location *10p12.1* is responsible to code protein that covers N- terminal repeats of ankyrin involved in protein interaction. It consists of 34 exons and different transcript variants. It belongs to primate specific POTE family (Hahn *et al.*,2006). This gene is involved in signaling protein interaction inside the cell membrane. Expression has been shown in brain, lymphocytes, pituitary gland and various tissues. Mutation impact has been found in 5/ UTR region that is associated with inherited disorders like thrombocytopenia and myeloid malignancy. Up till now, no skin mutations have been reported linked to *ANKRD26* gene. A new case has been identified in which a 10 years old female with severe condition of EV showed mutation of *ANKRD26*.No *EVER* genes mutation have been identified but a rare non sense mutation in *ANKRD26* at exon number 11 with 40% allelic frequency. This alteration is responsible to influence downstream transcription of 22 exons. In skin conditions role of *ANKRD26* along with *EVER* genes can be explained due to few similarities. Such as, they all show their expression in lymphocytes rather than in skin therefore, involved in HPV cell proliferation mediated by immunity impairment.

There can be possibility of these genes action in skin by reason of participation in cell signaling. Protein expression showed similar pattern for these three genes and are mostly expressed in B cells, CD8 and CD4 cells. It can be suggested that most of *EV* cases are because of *EVER* genes mutations and remaining are of unidentified etiology may be associated with mutation of *ANKRD26* gene. Nevertheless, this desires further research to recognize exact alterations of *EVER* genes linked with *ANKRD26*(Uddin *et al.*,2018).

Conclusion

Genetic mutations can lead to hereditary disorders including cutaneous abnormalities like epidermodysplasia verruciformis. EV used to be designated as endogenous or exogenous disease having different mutations specially related to transmembrane channel like genes family and immunosuppression therefore mutated individuals will be prone to beta HPVs infection. However, new discovered mutations having manifestations of EV brought understanding for vulnerability of HPV so as

to reveal heterogeneity of EV. It includes T cells and keratinocytes immunity contribution but still there is a need of broad range of interpretation to evaluate typical or atypical cases by using molecular or cellular based analysis of EV.

There is limited acknowledgment regarding acquired cases as small number of patient's research have been carried out. Consanguinity plays a significant part to alter gene so as to involve EV defining phenotype caused by either leukocytes or keratinocytes immunity.Various typical and atypical genes with known mutations involved in development of EV menifestations have been identified but this knowledge is limited and needs to conduct further research to explore exact alteration approaches associated with susceptibility to EV-HPV infections.

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