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# STATUS OF EPIDERMOLYSIS BULLOSA IN PAKISTANI POPULATION

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**Abstract**
*Epidermolysis bullosa is a group of uncommon genetically inherited illnesses that usually reveal itself in infancy or childhood. It has several characteristics, including blister production and significant skin and mucous membrane fragility. Since its introduction in the late 1880s, there have been numerous advancements in the classification of Epidermolysis Bullosa. Based on the location of the target proteins and the severity of blisters, we now define four basic kinds of Epidermolysis Bullosa: Epidermolysis Bullosa simplex, junctional Epidermolysis Bullosa, Dystrophic Epidermolysis Bullosa, and Kindler syndrome. This review covers different reported and published cases of the Pakistani population. In 20 different families a different type of EB is reported. In which we discuss clinical symptoms, types of mutation, novel mutation found in Pakistani families and consanguinity. In addition, the lack of advanced techniques of diagnosis is also discussed.*
**Keywords:** *Consanguinity, Dystrophic EB, Epidermolysis Bullosa (EB), EB Simplex, Junctional EB, Kindler Syndrome.*

## INTRODUCTION

Epidermolysis Bullosa (EB) is a set of rare genetic disorders, typically found in newborns (1). It is determined by different features including blistering, very fragile skin and mucosa. The trauma response in the formation of Vesiculobullous lesions (2). Scarring is common on the top surfaces of the limbs, hands, and feet; milia is common; and nails are frequently thickened and dystrophic or removed (3). The first author who used the term "epidermolysis bullosa" was Koebner to describe the condition in 1886 (4). In childhood the disease is also termed as "butterfly children" because the membrane of the skin is as brittle as butterfly wings (5, 6). Individuals affected with EB suffer intense pain throughout their lives (7). The pathogenic mutation in at least 18 different genes extends EB more than 30 clinical subtypes (8). Three typical forms of genetic EB are EBS (EB simplex), JEB (EB junctional) and DEB (dystrophic EB). These types are distinguished on the layer of vesicle separation and redivided by the arrangement of ancestral inheritance, mutation, form and structure and surface features of abrasions are involved. The fourth type added to the group was Kindler syndrome (KS) earlier known as photosensitive poikiloderma after the "Third International Consensus on Diagnosis and Classification of Inherited EB" (7, 9). The disorder takes place in all tribal groups and influences both genders equally (10). Globally 400,000-500,000 individuals are affected, and no definite therapy has yet been discovered (11). The NEBR ("National Epidermolysis Bullosa Registry") in the United States, predicted that in 1,000,000 newborn 50 cases of disorder occurs, in which EBS is 92%, DEB is 5%, JEB is 1% and 2% is miscellaneous (12).

We searched the keyword Epidermolysis bullosa in Pakistan in the PubMed search engine. PubMed searched a lot of articles, but we downloaded the related articles about EB in Pakistan and the review is written based on these articles.

The aim of the review is to collect and accumulate the published data from all over the country to check the prevalence of epidermolysis bullosa in Pakistan. The data is collected from published articles and the review is written based on available published data to check the prevalence of different types of EB in

Pakistan. Because the rate of consanguineous marriages is high in Pakistan, which increases the chances of autosomal recessive diseases. Due to lack of awareness, many people do not consult qualified physicians for congenital diseases. This may be a possible reason for unavailability of published data of epidermolysis bullosa from Pakistan.

## TYPES OF EB

There are four main forms of EB, namely, EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome, based on the distinctive ultrastructural position of skin separation (13).

## EPIDERMOLYSIS BULLOSA SIMPLEX

It is described by an illness of keratinocytes, blisters within epidermis and some participation of systems. Mostly within epidermis the dermis cleavage happens in EBS, which is the consequence of genetic defects in the keratin 5 and 14 genes, encoding the type I and II and keratin production, expressed in the initial layer of the upper dermis and epithelial related complexes of keratinocytes (14, 15). The pattern of the disorder is mostly AD (autosomal dominant), but some cases of AR (autosomal recessive) have been reported. EB simplex is divided as follows: EBS-localized (formerly known as EBS, Weber-Cockayne), EBS-generalized (Köebner subtype), and EBS –DM (Dowling-Meara) usually presents with generalized herpetiform (9, 16).

## JUNCTIONAL EB

The pattern of the disorder is AR, but some AD forms have been documented recently (17). This disorder is defined by skin cleavage at the level of the lamina lucida. More than 50% of patients with JEB a mutation takes place in the LAMB3 gene, encoding laminin 5. Apart from that some other genes are also involved which encode collagen XVII and integrin $\alpha 6\beta 4$. JEB is classified in two types of JEB herlitz and JEB non-herlitz (14).

## DYSTROPHIC EPIDERMOLYSIS BULLOSA

Dystrophic EB (DEB) is a genetic disease which affects the dermis and other organs. It is characterized by anchoring fibrils affecting the skin and following breaking of the sub-basal lamina. The genetic defects occurred in the gene which encodes type VII collagen (14). The subtypes of DEB are DEB Recessive (RDEB) and DEB Dominant (DDEB) differing from one and other by pattern of inheritance. In general, DDEB presents with milder phenotypes while RDEB is among the most devastating forms of EB (12).

## KINDLER SYNDROME

Kindler syndrome is an autosomal recessive disorder due to a genetic defect in FERMT1 (KIND1) encoding the fermitin family homologue 1 (kindlin-1). The disorder was added to the classification of EB in 2008. It is characterized by general blisters at the beginning, with little quantity of marking. Horny skin (Keratoderma), atrophic skin, poikilodermatous pigmentation, sensitivity to light, and rarely delay growth of mind and bone disorders are observed. Hyperplasia of gums, inflammation of colon, inflammation of esophagus, and urethral squeezing has also been reported (9, 18, 19).

## TYPES OF EB IN PAKISTAN

According to our knowledge in 20 reported families which are affected with EB. In which 8 families are affected with kindler syndrome (20, 21), 5 with JEB (8, 22, 23), 2 families EB with pyloric atresia (24, 25), 2 with EBS (8, 21) ,1 DEB (21), 1 EBA (Epidermolysis Bullosa Acquisita) (26) and 1 was unclassified (27). There are 8 affected families with kindler syndrome, in which six were reported in 2004 (20), while 2 were reported in 2018 in which six individuals were affected (21), the six families affected with KS were Pakistani British families. Affected individuals were 8 in which six males and 2 females (20). In four of JEB families three are JEB Herlitz type and the R650X mutation in LAMA3 is considered a unique mutation, which has been reported in three families of Pakistani origin (22). The fourth case was of non Herlitz type of JEB and it is the

first published case, before this case it was considered that non Herlitz JEB is absent in Pakistan because of an unpublished report of this type. At the age of 3 years the child almost became normal, and symptoms disappeared. But after 6 months the symptoms appeared with great intensity (23). The fifth case is a recently identified form of JEB due to mutation in ITGA3 coding for the integrin alpha-3 subunit (8). There are two families of EB with pyloric atresia in which the first one is reported in 1990 (24) and the 2nd one that is the result of genetic defect in plectin gene was reported in 2005 (25). It is a very important case because EB with pyloric atresia is identified to be the result of modification in the hemidesmosomal genes ITGA6 and ITGB4, encoding the a6 and b4 integrin polypeptides, correspondingly. But in this case, it is caused by mutation in plectin gene (25). There were two families affected with EBS, the first family included three affected individuals. The affected individuals exhibited the features of epidermolysis bullosa simplex (21). The second case is the newly documented one of EBS, from Pakistan of AR-EBS caused by EXPH5 alteration have been reported (8). There is one family of DEB in which three children were diseased by RDEB, which includes two brothers and one sister (21). The next case was affected with Epidermolysis Bullosa Acquisita (EBA). A 46-year-old man exhibited the symptoms of EBA. Although there was no family history of any kind of EB (26). The last case was a newborn baby, three hours after the birth the baby developed the blisters and the dermatologists diagnosed it as Epidermolysis bullosa (27).

## CLINICAL SYMPTOMS OF EB

### *EPIDERMOLYSIS BULLOSA SIMPLEX*

Epidermolysis bullosa simplex (EBS) is associated with a disease of keratinocytes, formation of blisters inside the epidermis and some systemic involvement. Dystrophic nails, loss of hair and lesions of mucous membrane may be observed if the disease is in severe form. Lesions do not result in atrophy or scarring. Blisters are more frequent in early childhood but gradually diminish with age. In the Weber-Cockaine subtype (EBS-WC) blister is categorized by low to high effect on the surface features and affected individuals may exhibit hyperhidrosis (9, 16). In its severe condition, surface features of the forelimbs and hindlimbs are also commonly involved, but the blistering occurs usually very quickly after the birth. The excess amount of keratin formation on the skin surface of the hands and the feet (Palmoplantar hyperkeratosis) and loss or falling of skin occur mostly in the generalized form. In the EBS-DM (herpetiformis) the mucus membrane of the oral cavity and the blisters of herpetiform are involved (16).

### *JUNCTIONAL EPIDERMOLYSIS BULLOSA (JEB)*

Junctional EB is associated with separation of the lamina lucida in the dermo-epidermal junction (14). The mucus membrane of the oral cavity, loss of hair and absence of the nails are frequently involved (28, 29). JEB Herlitz (lethal JEB) the skin of the lips, eyes and nose are eroded and normally a part of significance increases in function of the granulation tissue. In the disorder cornea and conjunctiva mucosa of the eye are involved. The respiratory, gastrointestinal and genitourinary mucosa are also involved. The respiratory symptoms are frequent and exuberant which includes hoarseness, coughing and other symptoms. Sepsis is the primary reason of mortality in Herlitz JEB, and the patient's lose their lives in infancy (30).

In the JEB mitis (non-herlitz) the patients express improvement in clinical symptoms with age after surviving initial stages. In comparison with Herlitz type the respiratory system is less affected in JEB mitis. Nevertheless, the scalp, teeth and nails are abnormal and mostly visible. Periorificial erosion and increase in function of the granulation tissue may be present. Mucosae are mostly eroded and followed by stricture. The blisters may present in intertriginous areas of some patients in this type of JEB (31, 32).

### *DYSTROPHIC EPIDERMOLYSIS BULLOSA (DEB)*

Dystrophic EB presents faulty adhesive fibrils and splitting of the sub-basal lamina (14). When the vesicles become healthy it would result in dystrophic calcification. Hair follicles become damaged resulting in the milia formation (33). In the dominant DEB subtype (DDEB) the generalized blisters appear after the birth or early childhood. Though, the blisters become more localized as the age increases (32, 33). The

mucosa of the oral cavity and teeth are also involved but blisters cover a large area and resembled with albopapuloid lesions (32).

The clinical symptoms of recessive DEB (RDEB) are from mild to severe. RDEB mitis is a mild/localized form in which toes, fingers and nails are involved. The clinical symptoms of this type resembled other inherited types of DEB (33). The "Hallopeau and Siemens" described the lethal form, typically expressing general blisters primarily on the surface of acral area which may result in the false fused digits of the hand ("boxing glove hands") and feet. Flexural deformities of the limbs are frequent and increase as time is increasing (32). Affected organs include nails and teeth are common, but obstruction of esophagus, stricture of urethra and anus, contraction of the foreskin and lesion of cornea are also observed. Anemia is caused by malabsorption of iron and shortfall in growth is caused by protein deficiency. In the recessive DEB the chances of SCC (squamous cell carcinoma) are very high (33).

### *KINDLER SYNDROME*

Kindler syndrome is associated with generalized vesicles on newborn but poikiloderma and sensitivity to light may develop later. Scarring atrophy and dystrophic nails are included in the skin findings, sometimes completely copying symptoms of JEB-NH. Pseudo syndactyly, inflammation of colon, inflammation of esophagus, and urethral squeezing has also been reported (9). Teeth are not involved but hyperplasia of gingiva may be created. The two patients at least have been reported who had squamous cell carcinomas (30).

## CLINICAL SYMPTOMS OF EB IN PAKISTAN

In 8 affected families 2,3,4 and 5 were brothers and sisters. The patients' ages ranged from 3 months to 30 years, and all exhibited similar topographies of blistering caused by trauma, specifically on the feet and hands, since infancy. In infancy light sensitivity also started and caused redness of skin within minutes of solar exposure. The important clinical factor after blistering ended during teenage is loss of function with light to dark pigmentation on the skin. Loose eyelids and dysphagia are additional characteristics in maturity (20). Six patients in the other two families exhibited characteristics of low cutaneous vesicles mainly over junctions, photosensitivity, skin degeneration, irregular light and dark pigmentation and dark red blotches all over the physique. Disease severities were different amongst patients in the identical family. The skin degeneration, random pigmentation and dark red blotches were advancing quickly in each of the two families. As the family individuals were growing the blisters were decreasing (21). A 5-year-old baby affected with non Herlitz JEB presented blistering of the skin on feet, leg and hands since birth. Within one hour the shedding started from the face of the child and after 2-3 hours the shedding involved parts of legs and hands. Interestingly at the age of 3 years the child became normal. But 6 months later the symptoms started again and abnormalities of the fingernails and toenails and pseudosyndactyly appeared. The blistering of skin of the child on extremities increased severely at the age of 5 years. From some part of the skin such as hands, feet and legs the skin was absent. Tooth decay was in progress (23). The fifth case of JEB is a neonate patient who established temperature and hypoxia (high level of CO2 in blood) after 60 days of birth, protein was detected in urine after 150 days and vesicles on the front part of the legs were growing after 120 days. The baby had died at the age of 2 year and 5 months due to failure of multiple parts of the body. The clinical presentation of the kidneys, lungs and skin showed that the gene was expressed in the following organs of the body (8). A newborn baby having symptoms of vomiting, respiratory distress and bullous lesion on the upper lip with an obstructed gastric outlet was diagnosed EB with pyloric atresia. Furthermore, after operation the fresh blisters emerge on the surface of the extremities, lower back, sacral region and on regions where sticking tape was applied. The blisters became worse and followed by septic infection caused by bacteria and fungi. Malnourishment was also associated with it because of eating problems and plasma loss from the wounds. At the age of 2 months the patient had expired from developing sepsis and disseminated intravascular coagulation (DIC) (24). Three children affected with recessive dystrophic epidermolysis bullosa (RDEB). The affected brothers showed thin to missing head hair, cutaneous vesicles limited to the head skin and small abnormal nails of the finger or toes. The female patient in this family had cutaneous vesicles on the limbs but the head skin and nails were not affected (21). In this

family three individuals are affected with epidermolysis bullosa simplex. All patients of the family showed big vesicles, bullae, pus bubbles and eroded skin were more dominant on the dorsal side of the extremities and minor on the limbs, chest and palmoplantar skin. The vesicles were raised after mild mechanical stress and cured with light marking. The nails were loose and separated from the fingers and the toes. Hyperkeratosis on the palms and soles was not observed. The healthy family members including children have not shown any clinical presentation of skin or nails (21). In a second family of AR-EBS caused by a genetic defect in the EXPH5, two children were affected and had dispersed blisters and vesicles from childbirth. The wounds healed and left hypopigmentation after inflammation in 10 to 15 days. The blisters were decreasing and almost vanished with age (8). A 46 years old individual is affected with epidermolysis bullosa acquisita (EBA). He had a history of 3 months of blisters on the tongue, neck, scalp, upper trunk, knees and elbows. On these sites scaring and milia were also observed. On the lateral aspect of the tongue a tense hemorrhagic blister was also noticed (26). A newborn baby was affected with EB, after three hours of birth the baby developed blisters on the neck, ear, ankle and lips. The blisters containing straw colored fluid and small friction on the skin resulted in blister formation. Systematic examination was normal as were nails and hairs (27).

## MUTATION IN PAKISTANI FAMILIES

EB is a genetic disease caused by the genetic defects in different structural proteins present in the cutaneous membrane (9). In the genetic defect at least 18 numerous genes spreads EB to more than 30 clinical subtypes (8). The mutation is reflected by clinical presentation, such as EBS is caused by genetic defect either in K5 or K14. Mostly three genes are involved in encoding laminin-332 and few other genes which encode collagen XVII and integrin $\alpha 6\beta 4$ cause JEB. JEB-NH have genetic defects similar but with lesser severity (30). Genetic defects in (COL7A1) gene are resulted in DEB (9). Kindler syndrome is caused by modification in the kinlin-1 gene (30).

Different mutations are also reported in Pakistani patients as shown in (table.1). In two families, a new disease-causing out of frame and a formerly reported difference in FERMT1 respectively identified, encoding the kindlin-1 protein. In FERMT1 identical alterations in both alleles cause KS (21). A new mutation is identified in the six Pakistani families affected with KS. It was discovered in sequencing that identical inclusion of cytosine at position 676 in exon 5 of KIND1, known as 676insC. In six families, five families had modification 676insC on the identical alleles. In one case (patient 1), however, the altered allele presented a different haplotype with six out of nine intragenic polymorphisms being different (20). Another alteration of R650X in LAMA3 is considered a unique mutation, which has been reported in three families of Pakistani origin (22). In JEB a homozygous mutation has been found in ITGA3 gene, which had an identical point mutation that happened inside the extracellular domain of $\alpha 3$ integrin, which may also compromise exon splicing (8). In EBS families, in a first family a known homozygous out of frame mutation was identified in K14. The similar mutation was already found in another family with EBS whose parents were relatives (21). In the second family of EBS, the new case was reported from Pakistan who has an identical form of gene. The locus of the pathologic mutation was within exon 6 and exophilin-5 were thoroughly absent (8). In family EB-PA the mutation was frameshift deletion, estimating an early termination codon 30 bp following from the location of omission within exon 15 (25). In the RDEB family, an already recognized missense variant was identified in the COL7A1 gene, which encodes for collagen VII alpha. Inactivated mutations in COL7A1 result in DEB (21).

## NOVEL MUTATION IN PAKISTAN

A new mutation is identified in the six Pakistani families affected with KS in. It was discovered in sequencing that identical inclusion of cytosine at position 676 in exon 5 of KIND1, known as 676insC. In six families, five families had modification 676insC on the identical alleles. In one case (patient 1), however, the altered allele presented a different haplotype with six out of nine intragenic polymorphisms being different (20). Another new pathogenic out of frame mutation is identified in a consanguineous family affected with KS (21). Another alteration of R650X in LAMA3 is considered a unique mutation, which has been reported in three families of Pakistani origin (22). The new case was reported from Pakistan who has an identical

form of gene. The locus of the pathologic mutation was within exon 6 and exophilin-5 was thoroughly absent (8).

**Table I.** Epidermolysis bullosa types, subtypes, genes and mutation in Pakistani population.

| Type of Eb | Subtypes of EB | Gene involved | Protein involved | Mutation | Mutation in Pakistan | Reference |
|---|---|---|---|---|---|---|
| EBS | Suprabasal | PKP1 | Plakophilin 1 | AR | | |
| | | DSP | Desmoplakin | AR | --- | --- |
| | Basal | KRT5 | Keratin-5 (K5) | AD | | |
| | | KRT14 | Keratin-14 (K14) | AD | Homozygous | (21) |
| | | PLEC1 | Plectin | AD | frameshift in | |
| | | ITGA6, ITGB4 | α6β4 integrin | AR | KRT14(c.92delT) | |
| | | DST | Dystonin; epithelial isoform of bullous pemphigoid antigen 1 (BPAG1-e) | AR | | |
| | | EXPH5 | Exophilin-5, also known as Slac2-b | AR | **Homozygosity for c.3650T> A (p. Leu1217*). *** | (8) |
| JEB | H-JEB | LAMA3, LAMB3, LAMC2 | Laminin-332 | AR | **R650X mutation*** | (22) |
| | Other JEB | LAMA3, LAMB3, LAMC2 | Laminin-332 | AR | --- | --- |
| | | COL17A1 | Collagen type VII | | | |
| | | ITGA6, ITGB4 | α6β4 integrin | | | |
| | | ITGA3 | α3 integrin | | **homozygous missense mutation.c.1883G>C (p. Arg628Pro) *** | (8) |
| DEB | Dominant DEB | COL7A1 | Collagen type XVII | AD | --- | --- |
| | Recessive DEB | COL7A1 | Collagen type VII | AR | Missense mutation | (21) |
| Kindler – Syndrome | | FERMT1 (KIND1) | Fermitin family homologue 1 (kindlin-1) | AR | **1.Frameshift (c.27delT; p. Phe9Leufs*23) *** 2.FERMT1 homozygous mutations(c.1718+2A>G) | (21) |
| | | | | | **3.homozygous insertion 676insC*** | (20) |

---: Not reported. *: Novel mutation. AR: Autosomal recessive. AD: Autosomal dominant. EBS: Epidermolysis bullosa simplex. JEB: Junctional Epidermolysis bullosa. DEB: Dystrophic Epidermolysis bullosa. EB-PA: Epidermolysis bullosa with Pyloric Atresia.

## CONSANGUINITY IN PAKISTAN

The rate of consanguineous marriages is very high in the Pakistani population. Beside this, 80% of these marriages are between first cousins (34). This high consanguinity along with large family size greatly enhanced prevalence of genetically inherited diseases (35). In the present study the rate of consanguineous marriages is very high. In sixteen families out of twenty, consanguinities are present. In which eight families of KS (20, 21), one family of EBS (21), all five families of JEB (8, 23, 36), one family of RDEB (21) and one family of EB-PA (25). In one family the parents were not relatives but the maternal grandfather and paternal

grandmother were first cousins (24). In the remaining four families, the consanguinity was not mentioned in the articles, but there is possibility that they may also have consanguineous marriages.

## CONCLUSION

This review evaluates all the aspects of EB in Pakistan such as different types of EB in Pakistan, the role of consanguineous marriages in EB in Pakistan, lack of facilities for diagnosis and treatment of EB. The rate of consanguineous marriages is very high in Pakistan which greatly enhances the chances of EB, like in this review the consanguinity was found in 16 families out of 20 families, which is 80%. So, counseling should be done in affected families to refrain from consanguineous marriages. Not enough facilities are there for the diagnosis, like one of the most recent cases of EBS was diagnosed based on clinical features. The diagnostic lab should be established in each district of Pakistan. No data is available which proves that prenatal diagnosis is possible in Pakistan. Patients must be facilitated with prenatal diagnosis if not on district level at least on province level. The treatment is the main issue not only in Pakistan but all over the world. Currently there is no cure for the EB and treatment which is currently employed is palliative rather than curative which is ineffective in treating life-threatening severe forms of the disease. All the scientific community should find a permanent treatment of the EB to give some relief to the patients.

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