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A Novel Heterozygous Missense Mutation in *COL7A1* Gene in Dystrophic Epidermolysis Bullosa

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ABSTRACT Hereditary Epidermolysis Bullosa is categorized by blister formation on the skin which includes Dystrophic Epidermolysis Bullosa as one of its types. It is characterized by blister formation on hands, feet, knees, and elbows. The severe condition leads to vision loss and blemishes. The objectives included the identification of *COL7A1* gene mutation for DEB susceptibility through sequence analysis of hot spot regions of 73, 74 and 75 exons. The experimental design included the enrolment of DEB-affected two families. The genetic analysis techniques included inorganic DNA extraction, Polymerase Chain Reaction and Sanger sequencing method. The study inferred the identification of novel missense mutation in exon 75 of *COL7A1* gene at (c. 6223 G>T) where the aspartic acid is converted into tyrosine in the heterozygous condition in affected families. The recognized novel missense mutation is silent (heterozygous) which becomes severe when homozygous. However, whole-exome sequencing strategy may identify the causative mutations.

INTRODUCTION

Epidermolysis Bullosa (EB) is commonly known as an inherited and heterogeneous inherited group of rare disorders characterized by blisters and mucocutaneous fragility (Bardhan et al. 2020). It also causes skin sensitivity and makes it exceptionally delicate and rankles easily. Skin and rankle disintegrations frame considering minor injury or blisters formation in response to mechanical trauma, for example, rubbing or scratching (Fine 2010). EB is a family of the bullous problems caused by a non-appearance of basement membrane components because of gene mutation. It is a highly heterogeneous group of skin fragility disorders with extensive phenotypic changeability because of mutation in more than 20 specific genes. The accurate early diagnosis of EB is effective in early prognostication of the severity of the disorder, timely decision-making option for the patient, genetic counselling for the affected family, long term surveillance for the complication, clinical trial inclusion and medicine precision (Has et al. 2020a). There is no solution for this overwhelming group of disorders; in any case, various preclinical improvements demonstrate guarantee, and a few methodologies have just achieved the phase of early clinical trials (Uitto et al. 2018). Disclosures of the molecular basis of epidermolysis bullosa have brought about the improvement of indicative tools, including pre-birth and pre-implantation testing. To have a better knowledge of the Basement Membrane Zone (BMZ) and the genes responsible for its parts, more current medications (for instance, gene or protein therapy) may give answers for the skin delicacy found in patients with EB. Furthermore, EB is characterized into four classifications: (a) EB simplex (intraepidermal skin separation), (b) Junctional EB (skin detachment in lamina Lucida or fo-

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cal BMZ), (c) Dystrophic EB (DEB) (sublamina densa BMZ division) and (d) Kindler disorder (very rare, rankling at any point) (Fine et al. 2008; McGrath and Mellerio 2006) Historically, EB subtypes have been characterized by skin morphology (Daisuke et al. 2010).

DEB is one of the significant types of EB. The severity of this disorder changes broadly between diseased persons. In gentle belongings, rankling may fundamentally influence the feet, knees, elbows and hands. It often causes chronic wounds and progressive soft tissue fibrosis on the skin (Mittapalli et al. 2020). Extreme instances of this problem include extensive rankling that can prompt vision misfortune, distortion, and other health complications. Specialists characterize DEB into three different groups. Though the sorts vary in seriousness, their highlights cover all together, and the main cause is a defect in the identical gene (Benedittis et al. 2004) Autosomal recessive DEB, Hallopeau-Siemens type (RDEB-HS) is the utmost thrilling. Affected new-born children are born with extreme rankling and areas of missing skin, that occurs due to injury in birth. Commonly, rankles exist over the whole body and influence mucous layers, for example, the digestive tract and moist covering of the mouth. Another category of autosomal recessive DEB is recognized as the non-Hallopeau-Siemens type (non-HS RDEB). This problem is less extreme to some extent than the exemplary kind and incorporates further subdivisions. Rankling is restricted to the feet, elbows, hands and knees in slight cases. Autosomal dominant type (DDEB) is the third important type of DEB The indications of this condition will, in general, be slighter than autosomal recessive types, by rankling regularly constrained to the knees, feet, hands and elbows (Dharma et al. 2001). Diagnostic testing and grouping in EB start employing Immunofluorescence Mapping (IFM) as well as Transmission Electron Microscopy (TEM), ideally on new blisters. Once the dimension of skin cleavage and the antigen staining profile have been resolved, the mutational investigation is suggested because this allows the most exact sub-classification. The exact analysis permits visualization, genetic counselling, and prenatal diagnosis (Bruckner 2010). No proper medications have been introduced for DEB, and diagnostic treatments are the pillar of clinical management (Denyer 2010). Therapies for DEB require the knowledge of mutant genes and particular gene mutations. For that purpose, the number of clinical trials are in practice that includes the clinical efficacy of genes for the drugs required to over DEB (Has 2020b). The prevention of new rankles and ulcers and wound consideration are the most vital parts of treatment. Severe cases with secondary symptoms in various organs require coordinated effort among paediatricians, dermatologists, internal medicine specialists, dermatologic specialists, dental practitioners, nutritionists, psychologists, therapists, and other specialists (Shinkuma 2015).

The main cause of these three forms of DEB is due to mutations in the *COL7A1* gene. DEB is triggered by changes in the *COL7A1* gene encoding type VII collagen. Dysfunction of type VII collagen prompts subepidermal rankling instantly underneath the lamina densa bringing about mucocutaneous delicacy and complications, for example, stubborn ulcers, broad scarring, malnourishment, and distortion (Ryyanen et al. 1991). This gene instructs to synthesize a protein that functions in the collection of type VII collagen. Collagens give assembly and solidarity to connective tissues, for example, ligaments, tendons and skin, all through the body. The main function of Type VII collagen is in reinforcing and balancing out the skin. This is the principal segment of assemblies called anchoring fibrils which synthesize the epidermis which is the finest layer of skin and is present above the dermis layer. A defect in *COL7A1* alters the structure or disturbs the activity of type VII collagen, which obstructs its capability to associate the epidermis to the dermis. At the point when a defect occurs in type VII collagen, any minor injury causes the isolation of the epidermis to the dermis. This detachment stimulates the creation of rankles, which are responsible for broad scarring as they recover. *COL7A1* has 120 exons and its location on a chromosome is at 3p21.31. The epidermal keratinocytes and dermal fibroblasts combine to produce Type VII collagen is a homotrimer composed of three proα1 (VII) chains which are encoded by the 32 kb *COL7A1* gene on chromosome 3p21 (Christiano et al. 1991a). The mRNA transcript of approximately 8.9 kb is translated into a procollagen α1 (VII) chain composed of 2,944 amino acids (Bauer et al. 1979).

Objectives

The present study aimed to identify the mutation in the hotspot exons (73, 74 and 75) of the

COL7A1 gene in patients affected with DEB from Quetta, Balochistan.

METHODOLOGY

Participants Enrolment

In the case study, two affected families of DEB were identified, by consulting dermatologist of Outpatient Department (OPD) of Combined Military Hospital (CMH, Quetta). History information was obtained from the family members and the Cyrillic program (v2.1) was used for drawing pedigree according to the information provided by the representative member of the families, at least 3 generations of family data was collected. After approval from the Institutional Research Board (IRB) of the Department of Biotechnology, (Ref # FLS&I/ BUITEMS, 4858) and informed consent from the patient and their healthy controls blood samples were drawn and collected in anticoagulant (EDTA) tubes.

DNA Extraction and Estimation

DNA extraction was performed using the established inorganic method in the molecular genetic laboratory of BUITEMS. The confirmation of genomic DNA extracted was done by 1.5 percent agarose gel electrophoresis (Bio Rad-USA) containing ethidium bromide (Sigma Aldrich, St-Louis, USA) and visualized on UV –transilluminator (Schimadzu, Japan). DNA quantification was performed using Nanodrop 2000C Spectrophotometer (Thermo Scientific, DE, and USA).

DNA Amplification

Polymerase chain reaction for the hot spot exons that are 73, 74 and 75 was done by designing specific primers by retrieving a sequence of *COL7A1* from National Centre for Biotechnology Information (NCBI) and Primer 3. The sequence of *COL7A1* Exon 73, forward 5'GGGTGTAGCTGTACAGCCAC 3', Reverse 5'CCCTCTTCCCTCACTCTCCT 3', while for *COL7A1* Exon 74/75 Forward Primer 5'CCAGGAGAGTGAGGGAAGAG3' Reverse Primer 5'TAGGGTCAGAAATTCCAGGG 3'. Standard PCR was used following conditions to amplify the specific exons. Master mix was individually prepared for both exons that are 73 and 74, 75 Each reaction comprises of 5ul DNA, 1.5ul of each primer (20μM), 15 μl of Master mix (contain dNTPs, Taq polymerase, $MgCl_2$ and PCR Buffer) followed Initial denaturing at 95^0C for 6 minutes, 35 cycles each for 1 minute at 94^0C for denaturation, followed by 1.5 minutes at 58^0C for primer annealing and 2 minutes at 72^0C for an extension. The final extension for 10 min at 72^0C using a thermal cycler (BIO-RAD, USA). The amplified products were then analysed on 2.5 percent agarose gel and visualized on a UV transilluminator (Schimadzu, Japan).

DNA Sequencing

PCR products of exon 73, 74 and 75 of control and healthy individuals were further analysed by DNA sequencing to identify the mutations using Big dye terminator reagents (Applied Biosystem) in an AI Prison 310 Genetic Analyzer (Applera, Foster City, USA). The sequences were analysed using Bio edit (sequence alignment editor) and Seqman (version 12.3.1.48) by comparing sequences from NCBI.

RESULTS

Affected Family -1

This family was enrolled from Quetta, Balochistan. The disease was diagnosed by the Dermatologist of Combined Military Hospital (CMH) Quetta. From the collected data, pedigree was drawn for the four generations of the affected family depicted in Figure 1 that consist of 15 individuals. It was observed that both parents were phenotypically normal with progeny which have one deceased female (4.1) and one affected male (4.4). The mode of inheritance for the EB in this family was autosomal recessive. The affected individuals were present in four generations. Among the affected individuals one female with severe symptoms of EB died at the age of 3 years while the male was at age of 1.5 years. Whereas the observed symptoms in males were: Blisters on the left hand, fragile skin tissues and redness which can be observed in Figure 2. The blood samples were collected from healthy controls that were father, mother, and brother (3.3,3.4 and 4.3) and affected individual (4.4) as illustrated in Figure 1.

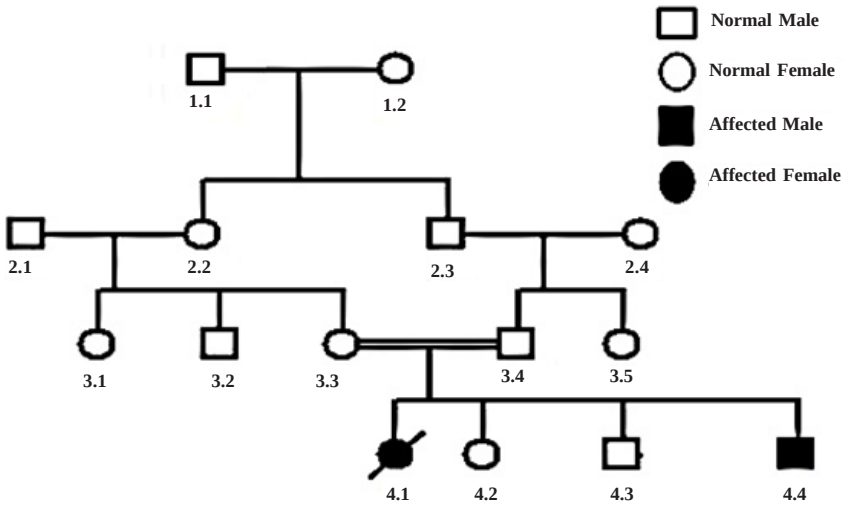

Fig. 1. Pedigree of family 1 DEB

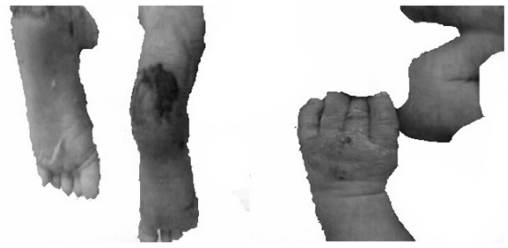

Fig. 2. Clinical features of patients (Family 1) showing blisters on ankles, heels and hands

Affected Family- 2

The second affected family was selected from Quetta, Balochistan. The family was identified and diagnosed by the Dermatologists of Combined Military Hospital (CMH), Quetta. The pedigree was drawn for the enrolled family which consists of 12 individuals. From Figure 3, it is observed that parents (3.2 and 3.3) were phenotypically healthy with one healthy (4.1) and one affected daughter (4.2). The mode of inheritance in this family was also autosomal recessive. In the fourth generation affected individual was identified. Clinical symptoms of an affected female (6 years old) were fused fingers, loss of nails, scars on palms, blisters on hands, feet, ankles, and knees as observed in Figure 4. The blood samples were collected from healthy control Parents (3.2 and 3.3) and affected daughter (4.2) as given in Figure 4.

Genetic Analysis

From the examination of genetic testing, the amplified product of exon 73 was 286bp while 368bp for exons 74 and 75 as shown in Figure 5. The Sanger sequencing indicated none of the mutations in exon 73 and 74 whereas the exon 75 of both the enrolled families shown heterozygous mutation at c.6223 G>T which was also compared with the healthy individual as shown in Figure 6. The heterozygous mutation results in conversion of GAT (Aspartic Acid) to TAT (Tyrosine) at position 2075 of the *COL7A1* gene. This alteration is involved in the novel missense mutation. This deletion is a novel mutation in the human *COL7A1* gene based on comparisons with the ExAC and Genome aggregated Database. The electrochromatogram in Figure 7 depicts the mutation that is found in the affected members of the enrolled families.

DISCUSSION

Epidermolysis Bullosa comprises a group of heritable skin disorders characterized by blister formation in response to minor trauma (Christiano et al. 1994b). The four major varieties-recessive

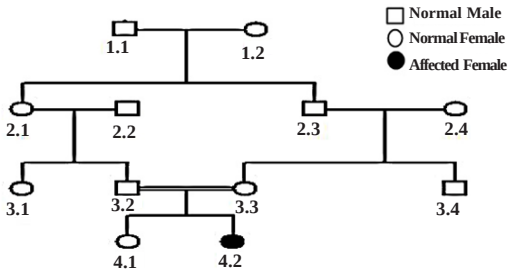

Fig. 3. Pedigree of family 2 DEB

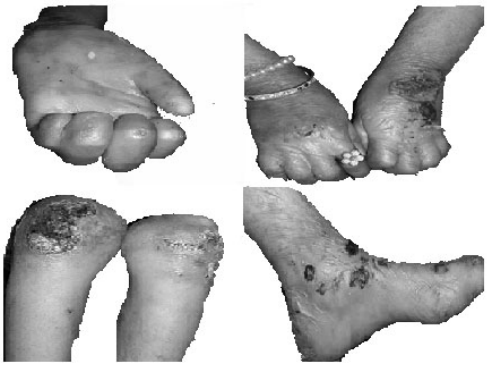

Fig. 4. Clinical features of DEB patient showing fused fingers and blister formation on hand, foot, and knees

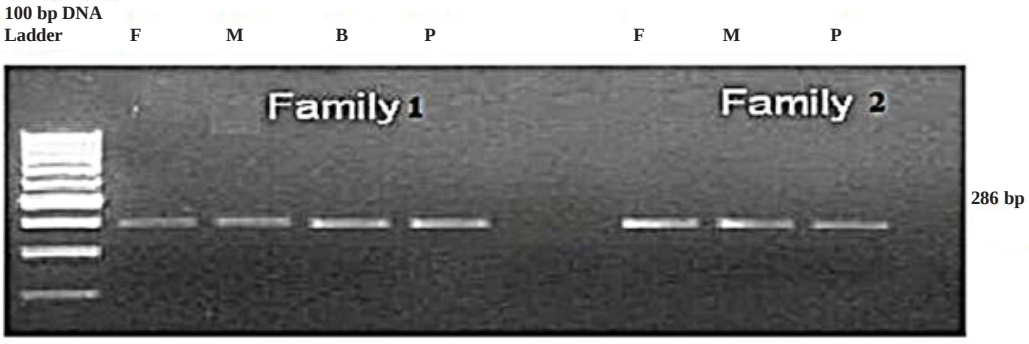

Fig. 5. PCR product of exon 73, family 1 and family 2

able and present a variable expression ranging from mild blistering of the hands and feet to severe generalized involvement. There are many genes reported as risk factors for the susceptibility of EB. A study conducted on the Chinese population identified all the types of EB. Among the genes involved in all the types of EB, the novel mutation P.E475k was identified along with the *KRT5* mutation and one recurrent mutation P.G2034R mosaic mutation. The identified mutations were analyzed by the next generation sequencing (NGS) which depicted that NGS can aid in identifying the cause of EB (Chen et al. 2020).

Up to the present time, over 600 mutations have been documented in (Human Gene Mutation Database) (Dang and Murrell 2008). Mutations causing DEB includes missense, nonsense, splice site and insertion/deletion. Reported genome rearrangements of *COL7A1* are merely 10 in number Mutations such as splice-site nonsense and frameshift because of premature termination codon (PTC) on both alleles of *COL7A1* gene results generally in severe recessive DEB Most often the milder RDEB is been caused by multifarious heterozygous mutations that involve one missense mutation, one PTC mutation so that the synthesis of full-length type VII collagen polypeptides takes place, but these newly synthesized polypeptides affect the stabilization of AF via di-sulfide bonds or few structural changes that change the conformation.

dystrophic EB (RDEB), recessive junctional EB, dominant dystrophic EB, and dominant EB simplex-are clinically and histologically distinguish-

Nearly 324 mutations that are pathogenic within *COL7A1* DEB variants have been identified that involves 127 missense, 9 insertions/deletions, 43

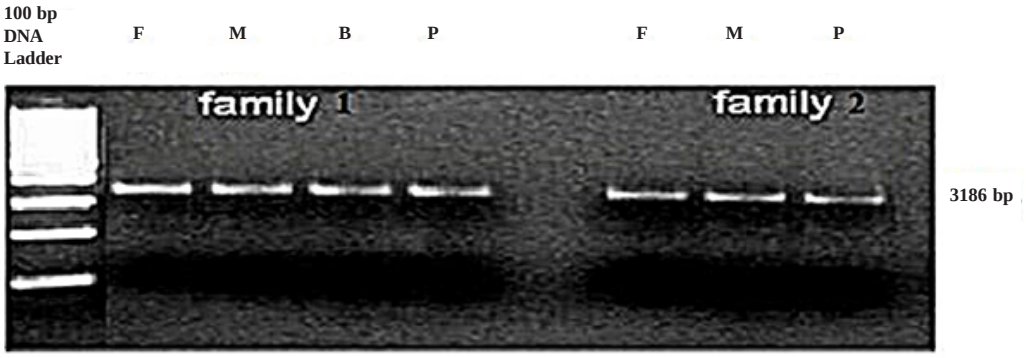

Fig. 6. PCR product of exon 74 and 75, family 1 and family 2

c.6223 G>T

GAT-TAT (Heterozygons)

p.2075 Aspartic Acid—Tyrosine

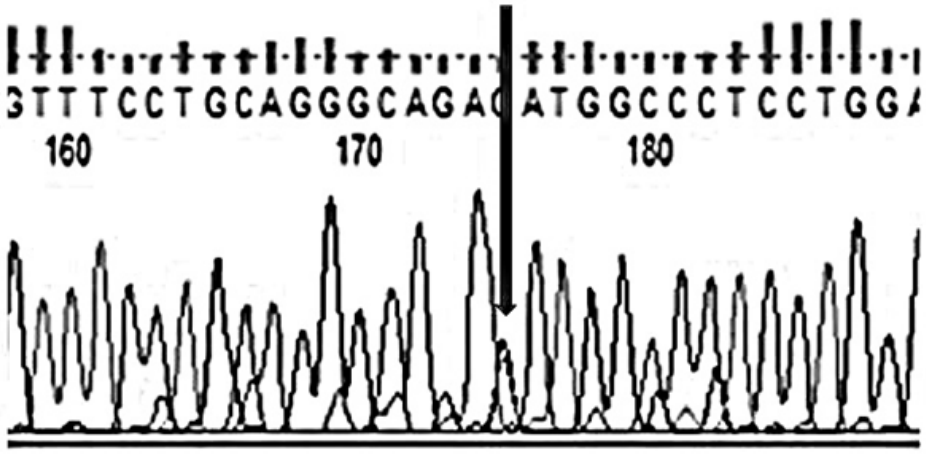

Fig. 7. Chromatogram of exon 75

non-sense, 65 deletions, 51 splice-site, 28 insertions and 1 regulatory mutation. The numerous mutations that are been assembled in exon 73 (10.74%) that involves (15 recessive and 20 dominant) which advocates that exon 73 represents a region of mutation in which functioning of the anchoring fibers has been affected (Hammami et al. 1998). The present study identified the mutations for the exon 73, 74 and 75 of the *COL7A1* gene being the most significant risk factors for the DEB progression. Among the selected exons, the novel mutation was identified in exon 75. Whereas another novel missense mutation has been identified in the exon 86 of the *COL7A1* gene that is known to be responsible of EB. The novel reported mutation c. 6797G>T was identified from the affected individual of Somalia (Venti 2020).

Various studies on *COL7A1* gene have identified glycine substitution but all are not dominant. However, glycine substitution may have the re-

cessive mode of inheritance, such substitutions do not depict any clinical phenotype in heterozygous condition, but clinical values can range from mild to moderate to severe RDEB when *COL7A1* gene has been coupled with other mutations such as splice-site, nonsense and insertion or deletion mutation (Mellerio et al. 1997; Denyer 2010). The present study identified the novel missense mutation in the DEB-affected individuals of the selected families. The missense mutation replaces the GAT (Aspartic acid) with TAT (Tyrosine) which perturbs the signaling pathway and proliferate the early signs of DEB.

Nearly 32 mutations in *COL7A1*are clinically glycine 'Silent' mutations that are been reported but it is not been clear that why few of these substitutions are dominant whereas others have no clinical phenotype in heterozygous condition (Mallerio 1997; Uitto et al. 2000). One of the possible reasons for such clinical states is the position of the mutations that may be in the collagenous domain of the *COL7A1* gene that results in abnormal folding. Furthermost glycine substitutions that are found close to N or C terminal ends of the triple helix or in the middle of the long unremitting segments of Gly repeats do not result in clinical phenotype. Though mostly mutations in *COL7A1* gene are specific to the relevant families that have no "hotspot" mutations however few persistent mutations have been identified in patients with a similar allelic background via haplotype analysis Six persistent mutations in Italy has been found that involves 4738G-A, 497insA, 7344G-A, 425A-C, 8441-14del21 and G1664A (Gardella et al. 2002; Ninging et al. 2008). However, the present study identified the hot spot regions of the *COL7A1* gene in exon 75 which is more susceptible in DEB as compared to other exons.

CONCLUSION

The present study identified a novel heterozygous missense mutation in exon 75 at position (c 6223 G>T) in affected individuals of both families as a result aspartic acid is changed into Tyrosine at position (p2075 GAT-TAT) but in heterozygous condition. The novel missense mutation of the present study is silent because of heterozygous condition, and it may lead to a severe form of DEB when homozygous.

RECOMMENDATIONS

The study focused on the hot spot regions of three exons of the *COL7A1* gene involved in the progression of DEB. Further studies can be conducted on the other exons of the *COL7A1* gene which may be responsible for the cause of DEB. Moreover, further genes can be identified as responsible for the DEB vulnerability.

LIST OF ABBREVIATIONS

BMZ Basement Membrane Zone
CMH Combined Military Hospital
DDEB Dominant Dystrophic Epidermolysis Bullosa
DEB Dystrophic Epidermolysis Bullosa
DNA Deoxyribonucleic Acid
EB Epidermolysis Bullosa
IRB Institutional Research Board
$MgCl_2$ Magnesium Chloride
NCBI National Centre for Biotechnology Information
NGS Next generation sequencing
Non-HS RDEB Non-Hallopeau-Siemens type
OPD Outpatient Department
PCR Polymerase Chain Reaction
RDEB Recessive dystrophic EB
RDEB-HS Autosomal recessive DEB, Hallopeau-Siemens type
TEM Transmission Electron Microscopy

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