A novel frameshift mutation of *COL7A1* in an Egyptian patient with autosomal recessive dystrophic epidermolysis bullosa

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Background
Dystrophic epidermolysis bullosa (DEB) is a rare inherited disorder characterized by extremely fragile skin and mucus membranes that blister following minor trauma with scarring and nail dystrophy. The three most common subtypes of epidermolysis bullosa are simplex, junctional, and dystrophic based on the level of tissue separation and site of blister formation. DEB is caused by mutations in *COL7A1* gene, which encodes collagen type VII and is transmitted either in dominant or recessive mode. The diagnosis of DEB is based on the characteristic clinical features confirmed histopathologically.

Patient and methods
The author report a new case of recessive DEB presenting with severe blistering studied through whole exome sequencing.

Results
Whole exome sequencing revealed a novel homozygous single-base deletion (R2024Gfs*182) in *COL7A1* gene. Both parents were confirmed heterozygotes for the mutation by Sanger sequencing.

Conclusion
Apart from adding a novel frameshift collagen VII deletion mutation to the repertoire of known mutations in the disease, to the best of our knowledge, this is the second report of genetically characterized patients of DEB from Egypt.

Keywords:
COL7A1, dystrophic epidermolysis bullosa, novel mutation

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Introduction

Epidermolysis bullosa (EB) is a rare inherited mechanobullous disorder that affects skin and mucous membranes. The disease is characterized by skin fragility with blistering and ulceration secondary to minor trauma. EB is classified according to its inheritance pattern into autosomal dominant (DDEB) or autosomal recessive (RDEB). EB is classified into 10 subtypes with three most common ones, namely, the simplex, the junctional, and the dystrophic types, based on the level of the epidermis or basement membrane zone in which blister is formed (Saeidian *et al.*, 2018).

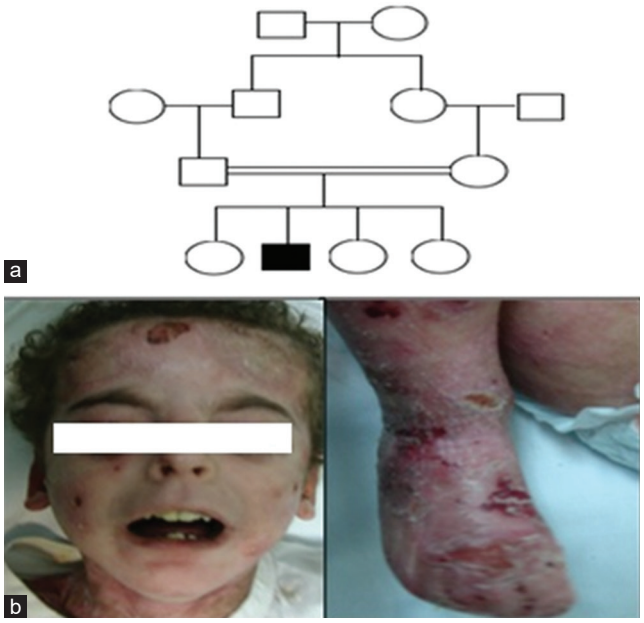
Dystrophic epidermolysis bullosa (DEB) (OMIM # 226600) is a rare subtype of the disease with subepidermal blistering. DEB is caused by mutations in *COL7A1*gene (Hovnanian *et al.*, 1992), located on chromosome 3p21, encoding type VII collagen, a major protein component of the anchoring fibrils (AFs) that play a critical role in securing the attachment of the dermal-epidermal basement membrane to the underlying dermis. *COL7A1* gene is a complex gene consisting of 118 exons, and mutational analysis of this gene remains difficult using the usual Sanger sequencing, and high throughput analysis is demanded for such a huge gene (Vahidnezhad *et al.*, 2017).

To date, more than 700 pathogenic mutations have been detected within *COL7A1* in different variants of DEB (Saeidian *et al.*, 2018). Herein, we report on the second novel mutation in exon 73 of the *COL7A1*gene.

Case report

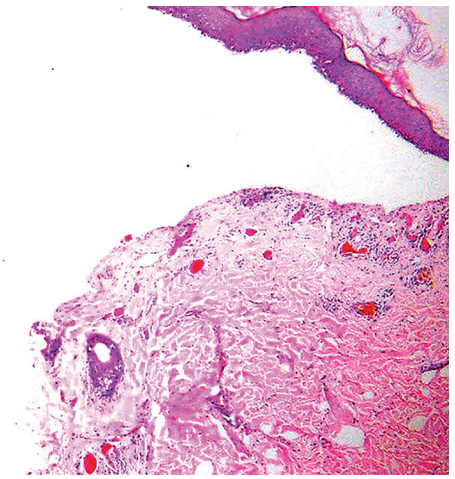
A 3-year-old boy was referred to the Genodermatoses Clinic, National Research Centre (NRC) Cairo, Egypt, with a history of progressive spontaneous bullae formation. The patient was subjected to thorough clinical evaluation following a specially designed clinical sheet with up to at least three-generation pedigree construction (Fig. 1a). He was born with low birth weight for a first-degree consanguineous couple with no family history of bullous disease. He had three unaffected sisters. Upon examination, the patient had extensive mutilating scarring of the skin involving his head, neck, abdomen, arms, and legs

Figure 1



(a) Pedigree analysis of studied RDEB family; (b) multiple blisters, scarring, and pseudosyndactyly.

Figure 2



Histopathology section showed subepidermal blister with preservation of the dermal papillae pattern, indicating a nonscarring bullous process. Scanty mononuclear dermal infiltrate confirming the noninflammatory nature of the blister.

with pseudosyndactyly in fingers and toes (Fig. 1b). Intraoral examination revealed multiple carious lesions with severe gingival inflammation. Histopathological examination of skin biopsy specimen showed absence of AFs and detachment of epidermis from dermis owing to subepidermal blister formation confirming the diagnosis of DEB (Fig. 2).

In this case, recessive DEB inheritance pattern was assumed based on parental consanguinity and a characteristic severe phenotype. Methods: DNA was extracted from peripheral blood lymphocytes from patient and parents by standard methods after obtaining informed consents, following the Helsinki and NRC Review Board Guidelines. Whole exome sequencing using an Illumina HiSeq. 2000 revealed a novel homozygous mutation c. 6070delA (p.R2024Gfs*182) in exon 73of *COL7A1* gene (Figs. 3 and 4). The detected mutation resulted in frame shift and a downstream premature termination codon (PTC) in exon 73. The c. 6070delA was predicted to be deleterious according to SIFT (confidence score 0.858). Molecular analyses of the parents' DNA by Sanger sequencing revealed that both parents were heterozygotes for the detected mutation and hence obligate carriers.

Discussion

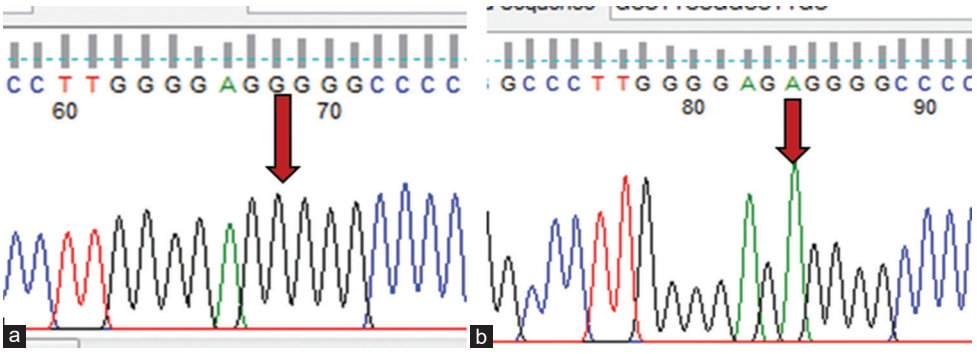
Distinct mutations in *COL7A1* have been reported in DDEB and RDEB, and each mutation has different effects on the resulting protein. DDEB is caused mainly by glycine substitutions within the triple helix of *COL7A1*. RDEB mutations include nonsense, splice site, deletions, or insertions that lead to loss-of-function mutations in *COL7A1*. RDEB is divided into two major subtypes: the severe generalized subtype, previously called Hallopeau-Siemens (RDEB-HS), and the generalized-other subtype (RDEB-O), previously called non-Hallopeau-Siemens (RDEB-nHS) (Saeidian *et al.*, 2018).

Severe RDEB-HS subtype is usually caused by null mutation on both alleles, which leads to complete absence of type VII collagen and AFs at the basement membrane zone as in our patient. The patients with milder RDEB-nHS phenotypes carry at least one mutation allowing some residual type VII collagen production. The severity of the disease depends on the type and location of the mutation (Van den Akker *et al.*, 2009). Nakamura *et al.* (2004) suggested that the heterogeneous phenotypes reported in DEB might be owing to modifying genes and epigenetic or environmental factors.

In Egypt, we do not have an exact estimate of the prevalence of DEB; however, the high consanguinity prevalence in a populous country such as Egypt might imply an expected high risk for inherited disorders especially the autosomal recessive traits. The current study is the second study in Egypt. Our team previously reported two homozygous missense mutations (p.G2055R and p.G2063W located in exons 73 and 74) in two unrelated consanguineous Egyptian families with siblings having DEB (Mansour *et al.*, 2017).

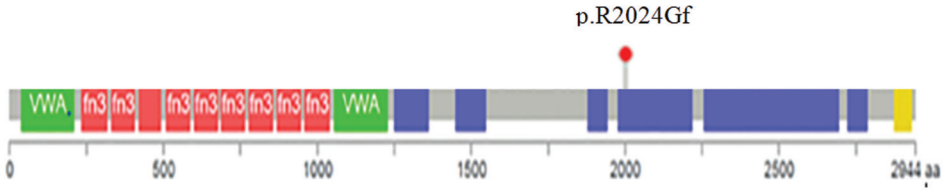
The clinical severity of the disease correlates with the position of the PTCs within *COL7A1*. Upstream PTCs of the triple helical region result in severe

Figure 3



(a) Direct sequencing of the patient's PCR product of exon 73 revealed deletion of A at position 6070; (b) direct sequencing of the normal control with wild-type sequence.

Figure 4



Domain structure of *COL7A1* protein showing Von Willebrand factor type A domain (VWA), Fibronectin type III domain (fn3), collagen triple helix domain (blue), and Kunitz domain (yellow). The red needle represents p.R2024Gfs (c.6070delA) variation.

clinical symptoms, whereas downstream PTCs are associated with mild symptoms (Khaniani *et al.*, 2015). In our study, we report the second novel mutation (c. 6070delA) in exon 73 of the *COL7A1* in a patient with a RDEB. The deleterious effect of this mutation results from its position in collagen triple helix domain, where the mutation resulted in PTCs with consequent truncated polypeptides that are unable to assemble into functional AFs. The c. 6070delA of the *COL7A1* gene has not been reported in the HGMD professional database.

To the best of our knowledge, our patient is the third Egyptian DEB to be confirmed by molecular analyses using whole exome sequencing and revealed a novel frameshift mutation in *COL7A1*, leading to truncated protein at the beginning of the ninth transmembrane domain with consequent severe phenotype.

Conflicts of interest

There are no conflicts of interest.

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