Single glycine deletion in \textit{COL7A1} acting as glycine substitution in dystrophic epidermolysis bullosa

\textbf{Editor,}

Dystrophic epidermolysis bullosa (DEB) is a genetic mechanobullous skin disorder caused by variants in the \textit{COL7A1}-gene encoding type VII collagen (\textit{C7}).\textsuperscript{1} \textit{C7} is the main constituent of anchoring fibrils, which plays a major role in the dermo-epidermal adhesion. We report a novel \textit{COL7A1} single glycine deletion exerting the same pathological effect as glycine substitutions in its triple-helical domain (THD).\textsuperscript{2,3}

The index patient was a 53-year-old Caucasian man with epidermolysis bullosa (EB), referred for diagnostics to the Groningen Centre for Blistering Diseases. Since birth, he suffered from fragile skin of predominantly the shins and feet, with friction-induced blistering, painful erosions and scarrring. He had lost all fingernails and most of his toenails by the age of 2 and had been diagnosed with EB at the age of 12, but the subtype had remained unknown. Clinical examination revealed tense bullae on shins and feet with atrophic scars, milia, absent fingernails and remnants of toenails (Fig. 1a,b). His teeth showed enamel hypoplasia and caries. The clinical diagnosis was a rather mild, localized phenotype of DEB with predominant pretibial involvement, which could be either dominant (DDEB) or recessive (RDEB). The family history revealed two heterozygous \textit{COL7A1} variants (NM_000094.4): a single glycine deletion p.(Gly1860del),\textsuperscript{4} as previously implicated in DDEB.\textsuperscript{6} As this variant concerns a conserved glycine residue in the THD,\textsuperscript{5} we hypothesized that this variant was DEB-causing, resulting in a diagnosis of RDEB-localized in the index patient. Co-segregation analysis revealed that the three family members with dystrophic nails carried the p.(Gly1860del) variant, but not p.(Arg2791Trp) (Fig 1a). The asymptomatic brother carried the p.(Arg2791Trp) variant, but not p.(Gly1860del) (Fig 1a). DNA from the asymptomatic mother was unfortunately not available for analysis and carriership could not be confirmed.

Although suggested to be a dominant \textit{COL7A1} variant in the initial report,\textsuperscript{4} the p.(Arg2791Trp) has only been reported in recessive DEB cases since (https://www.deb-central.org/). The conclusion that this variant is a recessive \textit{COL7A1} variant is further supported by the findings in the asymptomatic brother and mother (a likely carrier) in our family.

The novel in-frame glycine deletion p.(Gly1860del) is thought to be pathogenic for several reasons. The Gly1860 residue is located in a collagenous subdomain (i.e. the ninth) and part of the conserved, repetitive Gly-X-Y structure, \textit{C7} is the main constituent of anchoring fibrils (Fig. 2b). Whole-exome sequencing-based EB-gene panel analysis (Agilent SureSelect Human All Exome V6_S07604514, Santa Clara, CA, USA) revealed two homozygous \textit{COL7A1} variants (NM_000094.4): a pathogenic missense variant in exon 113, c.8371C>T, p.(Arg2791Trp), and a variant of unknown significance in exon 66, c.5579_5581delGAG, p.(Gly1860del). As this variant concerns a conserved glycine residue in the THD, we hypothesized that this variant was DEB-causing, resulting in a diagnosis of DDEB.

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**Figure 1**  Pedigree and clinical features of the affected family members with dystrophic epidermolysis bullosa. (a) Pedigree analysis: black square indicates the affected index with RDEB–localized (II-2); half-filled black squares (males) and circles (females) indicate the affected family members with DDEB–localized (I-1, III-1 and III-2); (−) indicates wild-type allele and (+) indicates mutated allele; N/D, not determined. (b) Clinical photographs: tense bullae, atrophic skin and scarring of the shins and feet with small remnants of toenails in the index patient (II-2). Dystrophic nails of the hands and feet in the 79-year-old father (I-1). Dystrophic toenails in the 23 (III-1)- and 20-year-old (III-2) daughters.

**Figure 2**  Transmission electron microscopy (TEM) and immunofluorescence antigen mapping (IFM) in the index patient. (a) Left panel: TEM of non blistered skin (inner upper arm) reveals a reduced number of hypoplastic anchoring fibrils (arrows). Bar 1.0 μm. Right panel: higher magnification of box area shows the hypoplastic anchoring fibrils in detail. Other structures of the dermal–epidermal junction are normal. Bar 0.25 μm. (b) Middle panel: IFM of non blistered skin (inner upper arm) shows reduced staining for type VII collagen (LH7.2) [2+ compared to 4+ in control (left panel)]. Bar 10 μm. Right panel: higher magnification of box area in middle panel at increased exposure demonstrates faint granular intracytoplasmatic deposits of type VII collagen within the basal keratinocytes (asterisks). Bar 2.5 μm.
Conflict of interest
None reported.

Ethical approval
The patients in this manuscript have given written informed consent to publication of their case details and images. They also consented to diagnostic testing.


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