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LETTER TO THE EDITOR

Single glycine deletion in COL7A1 acting as glycine substitution in dystrophic epidermolysis bullosa

Editor,

Dystrophic epidermolysis bullosa (DEB) is a genetic mechanobullous skin disorder caused by variants in the *COL7A1*-gene encoding type VII collagen (C7).¹ C7 is the main constituent of anchoring fibrils, which plays a major role in the dermo-epidermal adhesion. We report a novel *COL7A1* single glycine deletion exerting the same pathological effect as glycine substitutions in its triple-helical domain (THD).^{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 scarring. 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 was negative for blistering diseases, but his 79-year-old father and two 20- and 23-year-old daughters suffered from dystrophic finger- and toenails (Fig. 1a,b), fitting a nails only type of DDEB-localized.¹

Transmission electron microscopy and immunofluorescence antigen mapping (IFM) showed reduced numbers of hypoplastic anchoring fibrils (Fig. 2a) and reduced C7 staining (2+ compared to 4+ in control) in the index's non-blistered skin (Fig. 2b), respectively. Granular intracytoplasmic deposits of C7 were noted in the basal keratinocytes (Fig. 2b). Whole-exome sequencing-based EB-gene panel analysis (Agilent SureSelect Human All Exome V6_S07604514, Santa Clara, CA, USA) revealed two heterozygous *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

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 *COL7A1* variant in the initial report,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 *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, 38 residues upstream from a non-collagenous imperfection.⁵ In-frame deletion of Gly1860 is absent in a large number of normal control genomes as are in-frame deletions of other single glycine residues in the THD (<https://gnomad.broadinstitute.org/gene/ENSG00000114270>). Substitution of the Gly1860 residue (p.(Gly1860Arg)) was previously implicated in DDEB.⁶ Additionally, one other single glycine deletion, p.(Gly2067del), has been reported to cause DDEB.⁷ The intracytoplasmic retention of C7, as seen for several glycine substitutions, indicates impaired stability of C7's THD.⁸

Altogether, p.(Gly1860del) is proposed a pathogenic *COL7A1* variant, causing mild DDEB in a heterozygous state and RDEB in a compound heterozygous state. According to the latest consensus classification, the combination of a dominant and recessive *COL7A1* mutation is supposed to cause a severe form of DEB.¹ The data from the family presented here demonstrate that such a genotype can also cause mild(er) DEB phenotypes, highlighting broader clinical variability of this type of DEB too. Furthermore, our data indicate that single glycine deletions in *COL7A1*'s THD may have the same molecular effect as glycine substitutions. Whether all single glycine deletions would exert a dominant negative effect or some would be recessive, as is the case with glycine substitutions,² needs to be seen. Finally, this study emphasizes the importance of careful examination of relatives and co-segregation analysis in case of unknown or unexpected clinical and molecular findings.

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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 intracytoplasmic 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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References

- Has C, Bauer JW, Bodemer C *et al.* Consensus re-classification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020; **183**: 614–627.
- Almaani N, Liu L, Dopping-Hepenstal PJC *et al.* Identical glycine substitution mutations in type VII collagen may underlie both dominant and recessive forms of dystrophic epidermolysis bullosa. *Acta Derm Venereol* 2011; **91**: 262–266.
- Dang N, Murrell DF. Mutation analysis and characterization of COL7A1 mutations in dystrophic epidermolysis bullosa. *Exp Dermatol* 2008; **17**: 553–568.
- Whitlock NV, Ashton GH, Mohammadi R *et al.* Comparative mutation detection screening of the type VII collagen gene (COL7A1) using the protein truncation test, fluorescent chemical cleavage of mismatch, and conformation sensitive gel electrophoresis. *J Invest Dermatol* 1999; **113**: 673–686.
- Christiano AM, Greenspan DS, Lee S, Uitto J. Cloning of Human type VII Collagen. Complete primary sequence of the alpha 1(VII) chain and identification of intragenic polymorphisms. *J Biol Chem* 1994; **269**: 20256–20262.
- Almaani N, Liu L, Harrison N *et al.* New glycine substitution mutations in type VII collagen underlying epidermolysis bullosa pruriginosa but the phenotype is not explained by a common polymorphism in the matrix metalloproteinase-1 gene promoter. *Acta Derm Venereol* 2009; **89**: 6–11.
- Lucky AW, Dagaonkar N, Lammers K, Husami A, Kissell D, Zhang K. A comprehensive next-generation sequencing assay for the diagnosis of epidermolysis bullosa. *Ped Dermatol* 2018; **35**: 188–197.
- Hammami-Hauasli N, Schumann H, Raghunath M *et al.* Some, but not all, glycine substitution mutations in COL7A1 result in intracellular accumulation of collagen VII, loss of anchoring fibrils, and skin blistering. *J Biol Chem* 1998; **273**: 19228–19234.

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