A Recurrent Nonsense Mutation Occurring as a de novo Event in a Patient with Recessive Dystrophic Epidermolysis Bullosa


Basic Research Department, Epithelial Biomedicine Division, Regenerative Medicine Unit, Department of Genetics, Fundación Jiménez Díaz, Department of Dermatology, La Paz University Hospital, HLA Laboratory, Regional Transfusion Center, Centro de Investigaciones Biomédicas en Red en Enfermedades Raras (CIBERER), U704 and U714, Madrid, and Department of Bioengineering, Universidad Carlos III (UC3M), Leganés, Spain; The University of Texas M.D. Anderson Cancer Center, Science Park Research Division, Smithville, Tex., USA; Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell’Immacolata, IDI-IRCCS, Rome, Italy

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- De novo mutation
- Dystrophic epidermolysis bullosa
- Genetic counseling
- Skin disease

Dystrophic epidermolysis bullosa (DEB) is a rare genodermatosis characterized by persistent blister development on the skin and mucous membranes in response to minor trauma. Both autosomal-dominant (MIM 131750, 131800) and autosomal-recessive (MIM 226600) forms of DEB are caused by mutations in the COL7A1 gene (MIM 120120), encoding type VII collagen, a protein that assembles into anchoring fibrils [1]. To date, more than 550 mutations, most of which are family-specific, have been described in the COL7A1 gene (Human Gene Mutation Database; www.hgmd.cf.ac.uk). Herein, we report a COL7A1 deletion mutation in compound heterozygosity with the recurrent nonsense p.R1763X mutation [2] in a Spanish patient affected with severe generalized RDEB. Of note, mutation R1763X occurred as a de novo event in our proband.

The patient is a 38-year-old woman born to non-consanguineous parents and with no family history of skin diseases. The generalized cutaneous blistering with scarring from birth and the presence of pseudosyndactyly on the hands and feet since early infancy supported a clinical diagnosis of severe generalized RDEB (fig. 1a–d). Oral screening revealed ulcerations, ankylo-
Finally, the presence of p.R1763X mutation in the patient’s lymphocyte DNA, together with the generalized clinical presentation, argues against somatic mosaicism and in favour of a de novo mutation event in a single gamete or a germline mosaicism of the father. De novo mutations are infrequent in RDEB and, to our knowledge, only two have been reported to date \[6, 7\]. This case emphasizes the importance of mutation verification in the family as a part of the molecular diagnostic procedure so that de novo mutations can be identified and accurate genetic counseling provided to couples at risk of recurrence. The risk of de novo mutations in DEB, although small, should be considered when planning prenatal diagnosis.

**Disclosure Statement**

The authors declare no conflict of interest.
Fig. 2. Molecular characterization of the proband. a C→G transversion at nucleotide position 5287 leading to the missense mutation (p.R1763X) falls in exon 60 of the COL7A1 gene. The c.6266CCCC deletion (c.6266_6269del) in exon 75 leads to a premature termination codon in exon 82. b Pedigree with haplotype assignment of HLA typing results of the family. The proband inherited one HLA haplotype from each parent. c Haplotyping assay based on intragenic SNP selection shows that the haplotype 7 (H7) cosegregated with the deletion mutation inherited from her mother. The haplotype 1 (H1) was inherited from the father who does not carry the R1763X mutation.

References


Marcela Del Río
Universidad Carlos III de Madrid
Avda. de la Universidad, 30
ES–28911 Campus de Leganés
Madrid (Spain)
Tel. +34 91 624 9123, E-Mail mrnechae@ing.uc3m.es