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Diagnostic challenges in a family with dominant dystrophic epidermolysis bullosa and isolated hereditary nail disorder: paternal gonosomal mosaicism for *COL7A1* variant and maternal *RSPO4* variant

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Variants in the *COL7A1* gene lead to dystrophic epidermolysis bullosa (DEB), encompassing both dominant (DDEB) and recessive (RDEB) forms.[1] Conversely, variants in the *RSPO4* gene are responsible for isolated, nonsyndromic anonychia.[2] This case series explores the coexistence of *COL7A1* and *RSPO4* gene variants within a family, presenting challenges in determining the genetic inheritance pattern.

A 13-year-old female patient exhibited vesicles, bullae, erosions, milia and scar formation since birth, particularly in acral regions and trauma-prone areas (Figure 1a, b). Anonychia was observed in her toenails during the physical examination, with no abnormalities detected in teeth and hair. The patient's siblings, a brother and a sister, manifested nail deformities starting in infancy and similar cutaneous

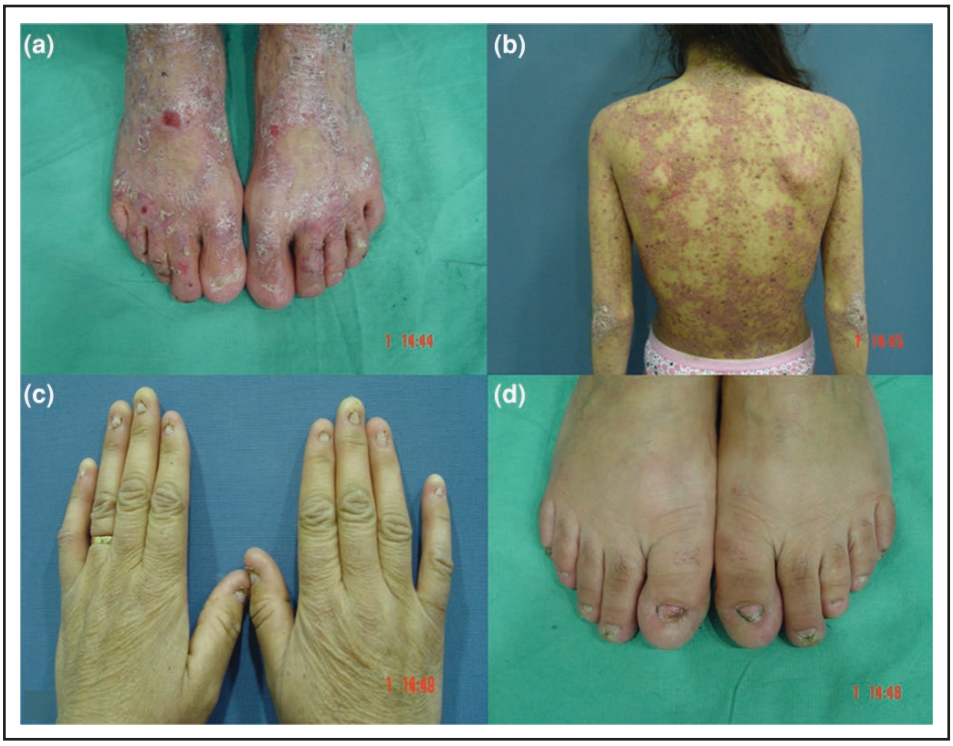


Figure 1 (a) Erosions, lichenified plaques and anonychia in the proband. (b) Crusts and erosions overlying an erythematous base on the back. (c, d) Close-up photos of the mother, showing complete absence of nails.

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findings, albeit milder and confined to more limited areas than the patient. The mother displayed deformities in 20 nails (Figure 1c, d), while the father's dermatological examination showed no pathology, such as signs of segmental features of DDEB or skin fragility.

Genomic DNA was isolated from peripheral blood samples of the patients. Sequence analysis was used to investigate variants in exon 73 of the *COL7A1* gene, a hotspot region for DDEB.[3] Sequencing was performed using a BigDye Terminator v3.1 Cycle Sequencing Kit on an ABI PRISM 3130 Genetic Analyzer (Thermo Fisher Scientific Inc., Waltham, MA, USA) according to the manufacturer's instructions.

The heterozygous c.6127G>A (p.Gly2043Arg) variant in the *COL7A1* gene (NM_000094.4) was identified in all three

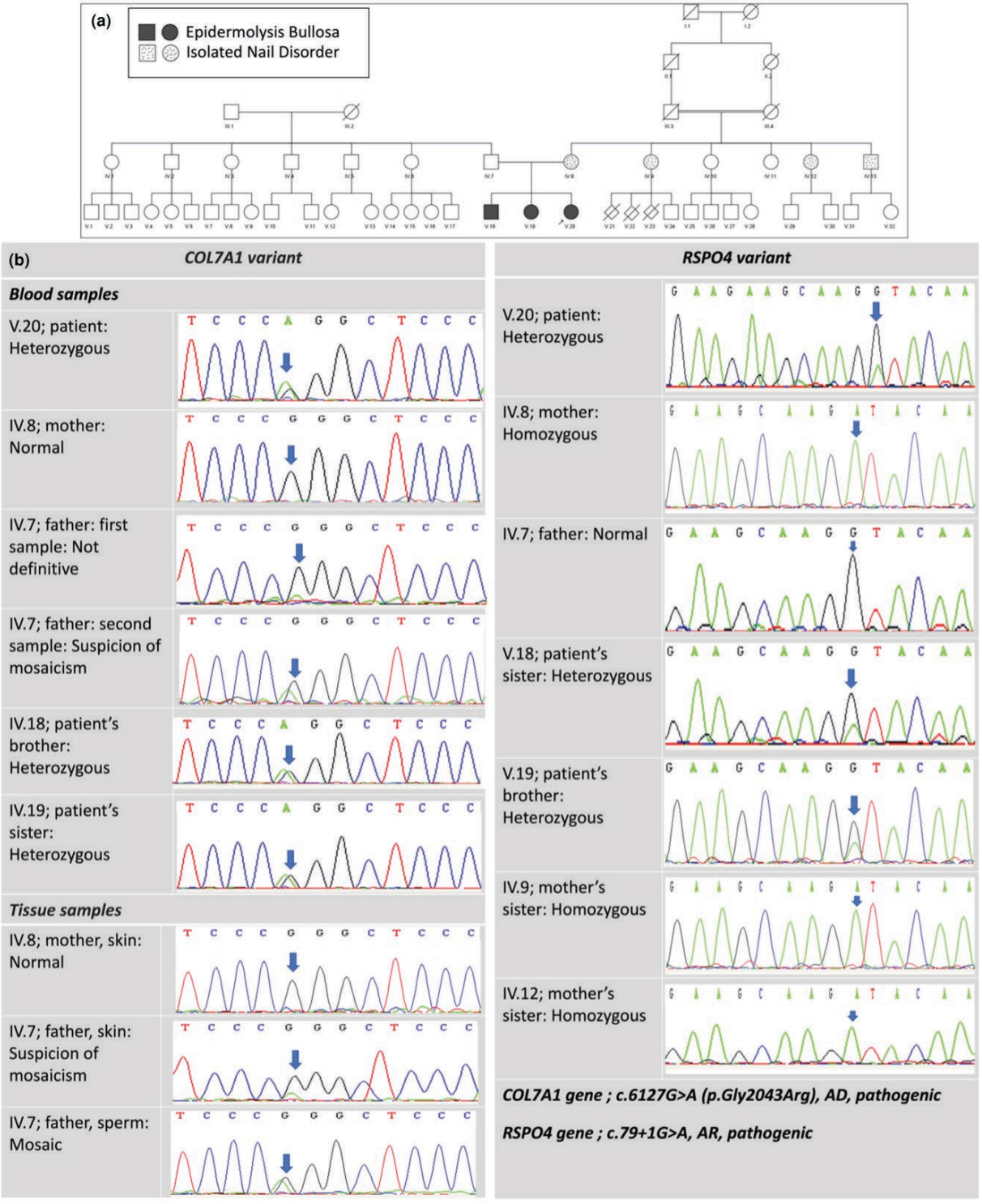


Figure 2 (a) Pedigree. (b) Sanger sequence of the *COL7A1* and *RSPO4* genes in the family. AD, autosomal dominant; AR, autosomal recessive.

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affected siblings. This variant has previously been associated with DDEB.[4] In the Sanger sequencing analysis performed on the peripheral blood of the mother and father, the mother was evaluated as having no mutation, but a clear evaluation could not be made in the different peripheral blood samples of the father that were studied, leading to suspicion of mosaicism. Later, variant analysis of DNA from parental skin biopsies showed that the mother still had no mutations, while mosaicism was suspected in the father. To study a third tissue, we planned to investigate the variant in the sperm DNA of the father. In this sample, the c.6127G>A (p.Gly2043Arg) alteration was detected as mosaic. These results show that the variant in the father is postzygotic (Figure 2).

To explain the isolated anonychia, all exons and exon–intron boundaries of the *RSPO4* gene (NM_001029871.4) were sequenced, and the homozygous c.79+1G>A variant, classified as pathological according to the American College of Medical Genetics 2015 criteria, was identified in the mother and her two affected siblings. The proband and her two siblings were found to have the same alteration in a heterozygous state (Figure 2).

In conclusion, paternal gonosomal mosaicism was identified as the mode of transmission for epidermolysis bullosa, while the maternal clinical status was associated with *RSPO4*-associated nonsyndromic isolated anonychia.

This study underscores the importance of analysing various tissues for variant analysis and emphasizes the rare possibility of different genetic diseases with common phenotypic findings in a single family. Although rarely reported, germline or gonosomal mosaicism should be considered when recurrent clinical findings are observed in the offspring, and different tissues should be studied in the parents.[5,6] In this family, the initial assessment based on the isolated anonychia in the mother and absence of DDEB findings in the father led to the assumption that the mother had a possible DDEB nail-only subtype. However, the DDEB phenotype observed in the proband and her two siblings appeared to be due to paternal gonosomal mosaicism.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data are available in a public repository at https://zenodo.org/records/12752704.

Ethics statement

Not applicable.

Patient consent

All patients were informed and provided consent for the study, and signed consent forms have been obtained.

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CPD questions

Learning objective

To recognize different modes of transmission for epidermolysis bullosa and isolated anonychia and to understand how they are identified in clinical practice.

Question 1

What genetic mutations are responsible for dystrophic epidermolysis bullosa and isolated anonychia, respectively?

(a) Mutations in the *COL7A1* gene and *RSPO4* gene.
(b) Mutations in the *KRT5* gene and *COL7A1* gene.
(c) Mutations in the *KRT14* gene and *RSPO4* gene.
(d) Mutations in the *LAMA3* gene and *RSPO4* gene.
(e) Mutations in the *RSPO4* gene and *COL17A1* gene.

Question 2

What was the mode of transmission identified for dystrophic epidermolysis bullosa in the case series presented?

(a) Autosomal recessive inheritance.
(b) Dominant due to paternal gonosomal mosaicism.
(c) Maternal inheritance.
(d) Somatic mosaicism.
(e) X-linked inheritance.

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