Dermatology Reports

https://www.pagepress.org/journals/index.php/dr/index

eISSN 2036-7406

Please cite this article as:

Diociaiuti A, Zingarelli RD, D'Urso DF, et al. Autosomal recessive epidermolysis bullosa simplex due to compound heterozygous mutations in *DST* gene: first Italian case and literature review. *Dermatol Rep 2025 [Epub Ahead of Print] doi: 10.4081/dr.2025.10206*

Submitted 01/12/24 - Accepted 18/02/25

Autosomal recessive epidermolysis bullosa simplex due to compound heterozygous mutations in *DST* gene: first Italian case and literature review

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Key words: autosomal recessive epidermolysis bullosa simplex; dystonin gene; bullous pemphigoid antigen 1; acral blistering; nail dystrophy.

Contributions: MEH, conceptualization; AD, RDZ, DFD, investigation; GZ, MEH, supervision; AD, RDZ, MEH, writing—original draft; AD, GZ, MEH, writing—review and editing. All authors have read and agreed to the final version of the manuscript.

Conflict of interest: the authors have no competing interests to declare.

Ethics approval and consent to participate: ethical review and approval were unnecessary for this case report study, as only diagnostic procedures were conducted, all preceded by the signing of Ethical Committee-approved, written informed consent forms.

Consent for publication: informed consent for genetic analysis, publication of the patient's details, and any accompanying images was secured from the patient's parents.

Availability of data and materials: data supporting this study's findings are available from the corresponding author upon reasonable request.

Acknowledgements: the study was supported by the "Progetto Ricerca Corrente" of the Italian Ministry of Health, Rome, Italy. We thank the patient's parents for agreeing to share pictures and data of their child and Gabriele Bacile for iconography preparation.

Abstract

Epidermolysis bullosa simplex (EBS), the most common type of EB, is characterized by skin fragility and blister formation within the basal epidermal layer. Most cases are due to autosomal dominant mutations in the keratin genes, *KRT5* and *KRT14*. However, mutations in different genes are responsible for other EBS subtypes. We describe the clinical and molecular features of the first Italian child with autosomal recessive localized EBS due to mutations in the *DST* gene encoding the BP230/BPAG1-e protein of hemidesmosomes. Molecular genetic analysis identified compound heterozygous *DST* nonsense variants, allowing the exclusion of a sporadic case of dominant EBS due to a *de novo KRT5/KRT14* mutation. A literature review retrieved members from 20 families from Middle Eastern and South Asian countries presenting with *DST*-mutated EBS. In addition to illustrating the clinical features of this EBS variant, our case shows the relevance of genetic diagnosis to distinguish EBS subtypes due to different inheritance modes, thereby providing families with appropriate genetic counseling.

Introduction

Inherited epidermolysis bullosa (EB) comprises a clinically and genetically heterogeneous group of disorders characterized by fragility and blistering of the skin and mucous membranes. Four main types of EB are identified based on the level of blister formation within the skin: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB).[1] EBS is characterized by blistering within the basal epidermal cell layer and is further classified into two major subtypes according to the inheritance mode, autosomal dominant and autosomal recessive EBS, each comprising several variants defined based on a combination of clinical, immunofluorescence, ultrastructural, and molecular features.[1,2] Clinical manifestations range from localized forms with acral skin blistering only to generalized variants that can present extracutaneous involvement such as cardiomyopathy or muscular dystrophy. Most EBS cases are inherited in an autosomal dominant manner and result from mutations in the *KRT5* or *KRT14* genes, which encode keratins 5 and 14 expressed in the basal layer of the epidermis (Figure 1).[1-3] However, mutations in non-keratin genes, including *PLEC*, *KLHL24*, *EXPH5*, *CD151*, and *DST,* are responsible for rare EBS subtypes (Figure 1).[1,2] In particular, homozygous pathogenic variants in the *DST* gene, which encodes the bullous pemphigoid antigen of 230 kDa (BP230), also known as BPAG1, have been described in a few cases of localized or intermediate recessive EBS characterized by predominant acral skin blistering.[1,4] BP230, a member of the plakin family of cytolinker proteins, is a cytoplasmic component of the hemidesmosomes of stratified and pseudostratified epithelia. It binds to epidermal keratins, specifically keratin 5 and 14, and, together with plectin, tethers them to the hemidesmosome, thus

ensuring epithelial adhesion through the keratin tonofilament-hemidesmosome-anchoring fibril complex (Figure 1).[4]

We report the first Italian case of autosomal recessive EBS due to compound heterozygous null mutations in the *DST* gene in a toddler with localized cutaneous blistering.

Case Report

A 20-month-old male, from Apulia, was referred to our Center for Rare Skin Diseases due to suspected EB. The child had developed a few blisters on the knees, hands, and feet after starting to crawl. Physical examination revealed a single tense serous blister on the fourth left toe without milia and mucosal involvement (Figure 2a). He was otherwise in good general health. Due to the patient's age, it was decided to avoid skin biopsy requiring deep sedation[5] and to directly perform molecular genetic testing on blood genomic DNA from the proband and his parents, following informed consent. The NGS panel for genodermatoses (Nextera Rapid Capture Custom Enrichment Kit, Illumina) identified two compound heterozygous nonsense sequence variants in the *DST* gene (NM_001723.7), each inherited from one parent. The paternal variant, c.3460 A>T (p.Lys1154*), has not been previously described, is not annotated in the gnomAD database of human variations, and was considered likely pathogenic, according to the American College of Medical Genetics guidelines.[6] The maternal variant, c.3370 C>T (p.Gln1124*), has been reported in autosomal recessive EBS.[4] Based on molecular genetic findings, the diagnosis of autosomal recessive EBS due to *DST* compound heterozygous mutations was established. The patient is now 4 years old. He continues to present occasional trauma-induced acral blisters and focal plantar skin peeling and has developed mild toenail dystrophy (Figure 2 b,c).

Discussion

Twenty families with members affected by autosomal recessive EBS caused by mutations in the *DST* gene have been reported to date (Table 1).[4,7-16] The disease is characterized by mild to moderate skin fragility, usually manifesting in infancy with acral blisters. Cutaneous lesions frequently heal with dyspigmentation, and several patients develop plantar keratoderma or calluses and nail dystrophies over time. Hair and mucosae are never affected. Clinical features in our patient were mild and in line with literature findings. However, our patient was diagnosed in early infancy, while most reported cases received a diagnosis during adolescence to adulthood. In addition, most *DST*-mutated EBS cases have been described in consanguineous families from Middle Eastern and South Asian countries and carry homozygous mutations in the *DST* gene, while the disease in our proband, born to non-consanguineous parents, is due to compound heterozygous mutations.

The *DST* gene encodes for multiple isoforms of BPAG1/BP230 characterized by different tissue expression patterns. The three major isoforms are the neural, muscle, and epithelial one, named BPAG1-a, -b, and -e, respectively.[17] Similar to the majority of previous cases, mutations identified in our patient occur in the *DST* exon 23 (Table 1), which encodes for the coiled-coil rod domain expressed in the epithelial BPAG1-e isoform. In contrast, mutations in the neural-specific BPAG1-a isoform have been reported in patients with hereditary neuropathies.[17-19] In addition, a single case of a young woman presenting both skin and neurologic manifestations was described.[11] The patient carried compound heterozygous *DST* mutations, one expressed only in the neural BPAG1-a form and one involving both the neural and the epithelial isoforms of BPAG1.[11]

Most patients presenting with a localized EBS phenotype carry monoallelic dominant mutations in the keratin *KRT5* and *KRT14* genes, and a significant proportion of them (>30%) do not have a disease family history and are sporadic cases due to *de novo* mutations.[1,3] Autosomal dominant localized EBS due to *KRT5* or *KRT14* mutations is characterized by acral blistering, development of focal palmoplantar keratoderma, and nail dystrophy over time, in the absence of hair and mucosal involvement. A similar phenotype in our patient born to non-consanguineous healthy parents was due to autosomal recessive compound heterozygous mutations in the *DST* gene. Moreover, other localized EBS sporadic cases can be due to recessive mutations in the *EXPH5* gene.[20] Thus, in sporadic cases presenting with localized skin blistering, differentiation between a dominant EBS variant and a recessive one cannot be based on clinical features only and requires molecular genetic analysis that allows the identification of the causative gene, and establishes a correct diagnosis and the inheritance mode. Importantly, genetic diagnosis is required for appropriate genetic counseling, as the recurrence risk for the parents in recessively inherited EBS forms is 25% compared to ≤1% of sporadic EBS cases due to *de novo* heterozygous mutations in *KRT5* and *KRT14* genes.

Conclusions

We describe the first Italian patient affected with autosomal recessive EBS due to *DST* compound heterozygous variants diagnosed in early childhood. In addition to extending the spectrum of *DST* mutations, our case further illustrates the crucial role of molecular genetic analysis in establishing an accurate diagnosis and recurrence risk in families.

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Figure 1. Schematic representation of the tonofilament-hemidesmosome-anchoring fibril adhesion complex in basal keratinocytes and its protein components altered in different epidermolysis bullosa (EB) types. Proteins altered (KRT5 and 14, BPAG1-e, KLHL24, exophilin-5, plectin, and CD151) in EB simplex are boxed.

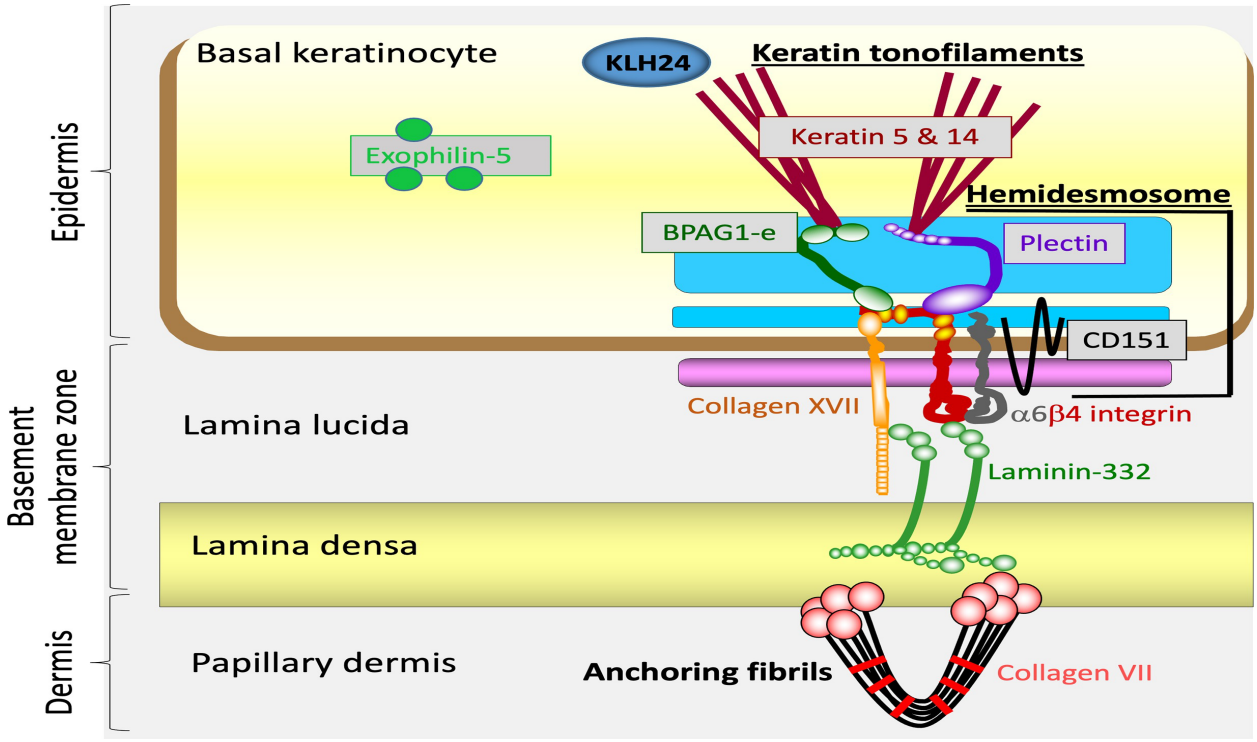

Figure 2. Patient clinical features. Tense serous blister involving the entire fourth left toe at 20 months of age (**a**). Metatarsal large tense blister, erosions, skin peeling on the right plantar surface (**b**), and mild toenail dystrophy (**c**) at age 4.

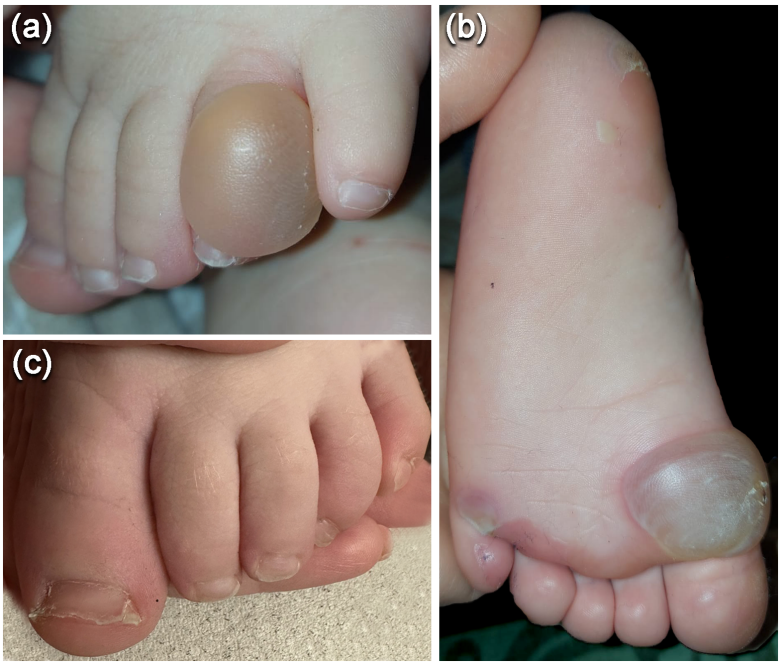

Table 1. Reported cases of autosomal recessive epidermolysis bullosa simplex due to *DST* mutations

Reference	**Pt. n.**	**Origin**	**Age**[#]	**Clinics**	***DST* Mutation(s)** (NM_001723.7)	**Exon**	**Zygosity**
Growes *et al.*[4]	1	Kuwait	38 y	Ankle & foot blisters, skin peeling, dyschromia, toenail dystrophy	c.3478C4T (p.Gln1124*)	23	Homozygous
Liu *et al.*[7]	4 (1 f)	Iran	34 y	Foot & friction-induced blisters	c.3853A>T (p.Arg1249*)	23	Homozygous
Takeichi *et al.*[8]	7 (4 f)	Kuwait	NR	Acral blisters, hyperpigmentation	c.3370C>T (p.Gln1124*)	23	Homozygous
He *et al.*[9]	1	Turkey	19 y	Acral blisters, plantar keratoderma	c.2618_2620delAAG (p.Glu873del); c.3805C>T (p.Gln1269*)^	17; 23	Homozygous
Turcan *et al.*[10]	1	Syria	39 y	Acral & trunk blisters, prurigo, hyperpigmentation	c.6559C>T (p.Gln2187*)	24	Homozygous
Cappuccio *et al.*[11]	1	Caucasian	17 y	Acral blisters, skin peeling, hyperpigmentation & atrophic scars	c.806C>T (p.His269Arg)/ c.3886A>G (p.Arg1296*)[§]	7/29	Heterozygous
Nanda *et al.*[12]	12 (5 f)	Kuwait	NR	Acral blisters	c.3370C>T (p.Gln1124*)	23	Homozygous
Ganani *et al.*[13]	2 (1 f)	Iraq	48 y, 49 y	Acral blisters, plantar keratoderma, hypopigmentation	c.3370C>T (p.Gln1124*)	23	Homozygous

Ganani *et al.*[4]	2 (1 f)	India	58 y & 70 y	Foot blistering, toenail dystrophy, calluses, hypopigmentation	c.7097dupA (p.Tyr2366*)/c.7429 delC (p.Leu2477Serfs*13)	24/24	Heterozygous
Ganani *et al.*[13]	1	India	8 y	Foot blisters, hypopigmentation	c.7097dupA (p.Tyr2366*)	24	Homozygous
Wen *et al.*[14]	1	Pakistan	17 y	Foot blisters	c.5469_5470delTC (p.Asn1823Lysfs*9)	23	Homozygous
Khalesi *et al.*[15]	1	Iran	15 y	Limb & trunk blisters, plantar keratoderma, hyperpigmentation	c.3370C>T (p.Gln1124*)	23	Homozygous
Al Towijry *et al.*[16]	1	Saudi Arabia	3 y	Acral blisters, hyperpigmentation	c.3370C>T p.(Gln1124*)	23	Homozygous
Present case	1	Italy	20 m	Acral blisters, toenail dystrophy	c.3460 A>T (p.Lys1154*)/c.3370 C>T (p.Gln1124*)	23/23	Heterozygous

Pt. n, number of patient(s) reported; NR, not reported; f, family/ies; y, years; m, months; [#]age of the index case at diagnosis; ^two homozygous sequence variants were identified in this patient; [§]NM_001144769.