

Loss of desmoglein 1 associated with palmoplantar keratoderma, dermatitis and multiple allergies

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Summary

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Conflicts of interest

None declared.

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Monoallelic desmoglein 1 mutations have been known for many years to cause striate palmoplantar keratoderma, but only recently, biallelic loss-of-function mutations were associated with a new disorder, designated as SAM syndrome (comprising severe dermatitis, multiple allergies and metabolic wasting) in two consanguineous families. We report on a new case from a third independent family with the homozygous nonsense mutation, c.2659C>T, p.R887* in exon 15 of *DSG1* (desmoglein 1 gene). This mutation led to mRNA decay and loss of expression of desmoglein 1. The clinical phenotype consisted of severe palmoplantar keratoderma, dermatitis and multiple allergies. In contrast to the previous cases, malabsorption, hypoalbuminaemia, developmental delay, hypotrichosis or severe recurrent infections were not observed.

What's already known about this topic?

- Monoallelic mutations of the desmoglein 1 gene (*DSG1*) cause striate palmoplantar keratoderma, whereas recently biallelic mutations have been associated with the syndrome of severe dermatitis, multiple allergies and metabolic wasting (SAM).
- The SAM phenotype was defined based on the study of two consanguineous families comprising six affected children.

What does this study add?

- We identified a case with a new homozygous *DSG1* loss-of-function mutation.
- In the present case, the mutation led to *DSG1* mRNA decay and loss of desmoglein 1 in the skin and manifested with severe palmoplantar keratoderma and dermatitis, with recurrent episodes of aggravation.
- Compared with the previous description of the SAM phenotype, the present case displays common features, but had a milder course, without metabolic wasting, severe growth retardation or premature death.
- Remission of the dermatitis was achieved with topical calcineurin inhibitors.

The barrier function of the skin results from a dynamic balance between proliferation, regeneration, differentiation, adhesion and shedding of the epidermal keratinocytes.¹ The integrity of the epidermal barrier plays an essential role in cutaneous homeostasis and also in the pathogenesis of allergic skin disorders.² This concept is strongly supported by several Mendelian disorders of cornification associated with

severe atopy, in which the expression of essential components of epidermal barrier formation, e.g. filaggrin, corneodesmosin or LEKTI, is altered. Recently, Samuelov *et al.*³ uncovered a new syndrome comprising severe dermatitis, multiple allergies and metabolic wasting (SAM) caused by biallelic mutations of the desmoglein 1 gene (*DSG1*).³ Here we report the third family with a homozygous nonsense *DSG1*

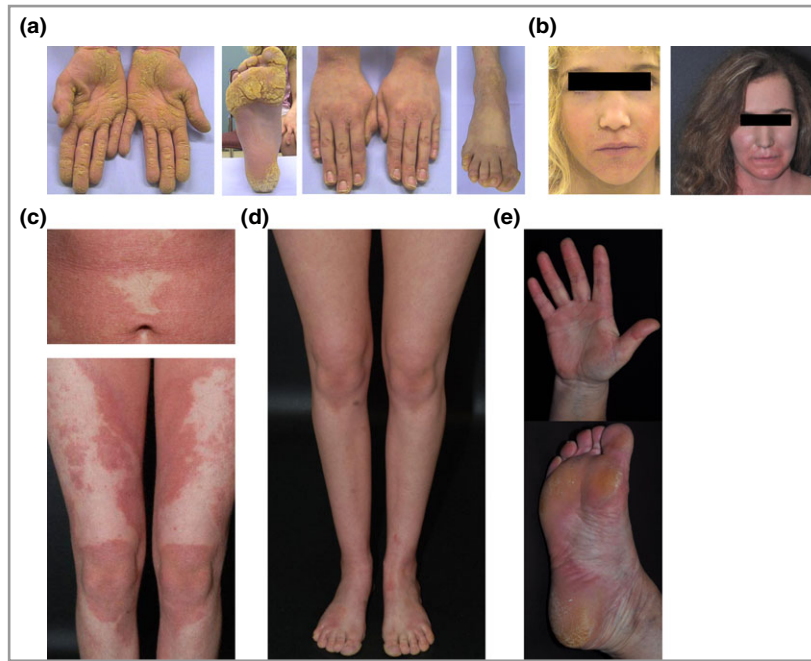


Fig 1. Clinical manifestations associated with *DSG1* mutations. (a) The panels show the palms, soles and the dorsal aspects of hands and feet of the index patient at the age of 8 years. Note massive palmoplantar keratoderma and erythematous lesions with fine scaling. (b) The patient had curly, but not sparse hair, as shown at the ages of 8 (left) and 17 (right) years. (c) Large, sharply demarcated erythematous plaques on the trunk and legs during an episode of aggravation at the age of 15 years. (d) Several weeks later, remission was achieved under treatment. (e) The palm and sole of the patient's mother, demonstrating keratosis on the pressure sites of the sole.

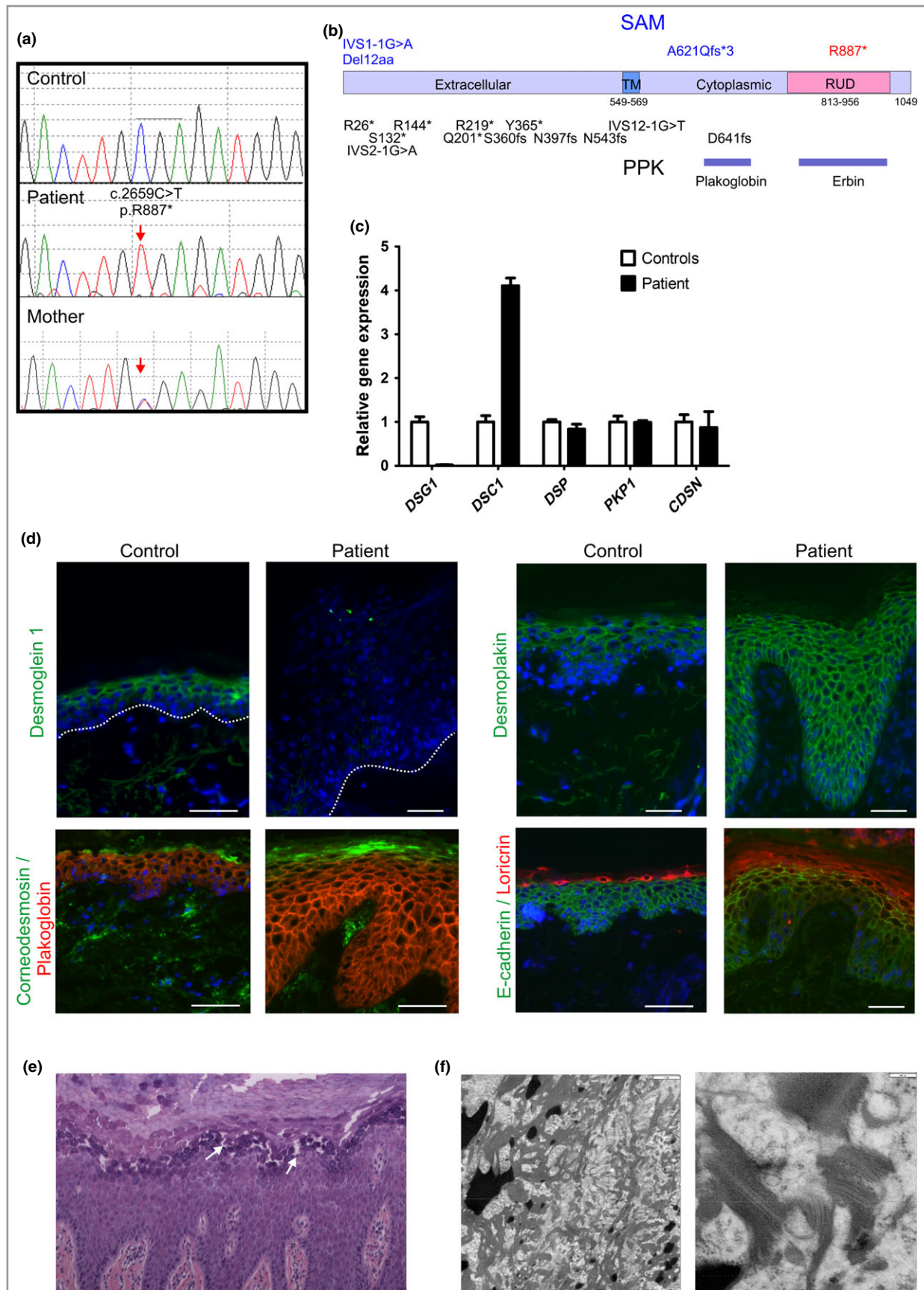
mutation, and show that the SAM syndrome covers a spectrum of phenotypic severity.

Case report

This 17-year-old female is the only offspring of apparently healthy parents, reported to be unrelated. She was diagnosed with atopic dermatitis as early as her first month of life. During infancy, she had severe generalized flares of dermatitis, and her weight was below the third percentile. The onset of palmoplantar keratoderma was before the age of 2 years. At the age of 8 years, she presented to our department with striate yellow keratoses on the hands and extremely thick focal keratoses on the pressure sites of the soles, which impaired her walking (Fig. 1a). Clinical examination revealed erythematous plaques with fine scaling on the face, scalp, folds and dorsal aspects of hands and feet (Fig. 1a,b). The hair was very curly, but otherwise normal (Fig. 1b), as were the nails and teeth. She was in a good general condition, with normal physical and mental development. A cardiology examination was

unremarkable. Laboratory work-up revealed no abnormalities, except of elevated total IgE (131 kU L^{-1}) and skin swabs positive for *Staphylococcus aureus*. Topical treatment with emollients and calcineurin inhibitors, combined with systemic antibiotics ameliorated the dermatitis, whereas sustained application of potent keratolytics and mechanical removal of the keratoses improved the condition of the palms and soles. At the age of 15 years, she presented because of the sudden onset of widespread, large, sharply demarcated erythematous plaques on her trunk and limbs (Fig. 1c). Clinical remission was achieved and maintained with careful skin care (daily bath, emollients) and topical calcineurin inhibitors (Fig. 1d), but erythematous plaques, sometimes with superficial erosions were constantly present in the skin folds. At the last visit at the age of 17 years, her weight and height were within the normal range, as was the laboratory work-up, including albumin, kidney and liver function. Total IgE was 1086 kU L^{-1} and moderate to high levels of specific IgE were detected for allergens from grass pollen (Phl p 2, 4, 5 and 6), birch pollen (Bet v1), birch pollen-associated foodstuffs like hazelnut and

Fig 2. The *DSG1* mutation and its consequences. (a) Partial sequence of exon 15 of *DSG1* in a control, the index patient and her mother. The red arrows indicate the mutation c.2659C>T, p.R887*. (b) Schematic representation of desmoglein 1 with the extracellular, transmembrane (TM) and cytoplasmic regions, and the repeat unit domains (RUD). The interaction sites with plakoglobin and erbin are indicated.⁷ The mutations described so far in the literature are depicted – blue text: mutations causing severe dermatitis, multiple allergies and metabolic wasting (SAM syndrome); black: mutations causing palmoplantar keratoderma (PPK); red: the mutation found in this study. (c) Quantitative reverse transcriptase-polymerase chain reaction analysis for gene expression of *DSG1*, *DSC1*, *PKP1*, *DSP* and *CDSN* was performed using cDNA derived from the epidermis of three controls and of the patient. Results represent the mean of three technical replicates and are provided as a percentage of expression relative to the gene expression of three controls, normalized to *GAPDH* mRNA levels. (d) Immunofluorescence staining of skin sections of a control and the patient (scapular region) with antibodies to desmoglein 1, desmoplakin, corneodesmosin, plakoglobin, E-cadherin and loricrin. Bars, 100 μm . (e) Haematoxylin and eosin staining of patient's skin biopsy from an erythematous lesion. The arrows indicate intragranular acantholysis. (f) The skin sections of the patient that were submitted to transmission electron microscopy did not reveal anomalies of intercellular adhesion. Note morphologically normal-appearing desmosomes in the granular layer.



soybean (Cor a1, Gly m4), housedust mites (DER p1, Der p2, Der f1 and Der f2) and cat dander (Fel d1) (ISAC-ImmunoCAP, ThermoScientific). Her personal history was negative for respiratory allergies. However, she reported symptoms of an oral allergy syndrome upon ingestion of hazelnuts and worsening of her skin condition on exposure to house dust and during the birch and grass pollen season, suggesting the clinical relevance of her sensitizations. Family history of respiratory allergies and atopic dermatitis was negative.

Following written informed consent, genomic DNA was extracted from ethylenediamine tetraacetic acid–blood and mutation analysis of *DSG1* was performed.⁴ The project was approved by the ethics committee of the University of Freiburg and was conducted according to the Declaration of Helsinki principles. In the index patient, we disclosed a homozygous nonsense mutation, c.2659C>T, p.R887* in exon 15 of *DSG1* (Fig. 2a,b). To the best of our knowledge, this variant has not been reported before (HGMD Professional 2014.1 professional, dbSNP, 1000 genome project, Exome Variant Server) and we excluded it from 200 population-matched control individuals. The mother was a heterozygous carrier of the mutation, and the father was not available for analysis. The mother had only moderate keratoses on the pressure sites of the feet, but no palmar keratoderma, despite having a manual occupation (Fig. 1e).

To evaluate the consequences of the mutation, biopsies were obtained and processed for morphological studies and RNA isolation. RNA was isolated from the epidermis, microdissected from 10-µm skin sections (Qiagen tissue isolation kit, Qiagen, Hilden, Germany), and quantitative polymerase chain reaction was performed as described.⁴ *DSG1* mRNA was strongly reduced in the patient, compared with the control skin, suggesting mRNA decay. The mRNA levels of DSP (desmoplakin gene), PKP1 (plakophilin 1 gene) and CDSN (cornodesmosin gene) were comparable with the control skin samples, whereas DSC1 (desmocollin 1 gene) mRNA upregulation was probably compensatory (Fig. 2c). Immunofluorescence staining was performed as described (Table S1, see Supporting Information).⁴ Consistent with the mRNA findings, staining for desmoglein 1 was largely negative in the patient's skin, whereas the staining for desmoplakin, plakoglobin, cornodesmosin and E-cadherin was comparable with the control. The differentiation markers loricrin (Fig. 2d) and filaggrin (not shown) were broadly distributed in the granular layer of the patient's skin. As a consequence of the absence of desmoglein 1, acantholysis was observed within the granular layer in the haematoxylin and eosin staining (Fig. 2e). In the sections submitted to electron microscopy, no abnormalities of intercellular adhesion were noted (Fig. 2f).⁵

Discussion

Desmoglein 1, a member of the cadherin family of calcium-dependent cell adhesion molecules is expressed in the epidermis as keratinocytes transit out of the basal layer.⁶ It is a key player in various human pathologies, i.e. pemphigus foliaceus,

staphylococcal scaled skin syndrome and genetic disorders.⁷ Desmoglein 1 haploinsufficiency has been known for many years to cause autosomal dominant striate palmoplantar keratoderma.^{8–14} In the mother of our patient, the heterozygous mutation p.R887* led only to minor focal keratoses of the soles. Recently, homozygous loss-of-function mutations were associated with a new disorder with severe dermatitis, multiple allergies and metabolic wasting in two families (Fig. 2b).³ Compared with these patients, the present case displays phenotypic similarities, but also differences (Table S2, see Supporting Information). The mutation p.R887* led to *DSG1* mRNA decay and loss of desmoglein 1 in the skin and manifested with severe palmoplantar keratoderma and dermatitis with episodes of aggravation. We did not find evidence for malabsorption, hypoalbuminaemia, developmental delay, hypotrichosis or severe recurrent infections. In the skin, absence of desmoglein 1 led to loss of intercellular adhesion and skin cleavage within the granular layer,⁵ resulting in a compromised epidermal barrier. This was associated with high IgE levels and sensitization to multiple environmental allergens. Desmoglein 1 was shown to be required not only for maintaining epidermal integrity in the superficial layers, but also to support keratinocyte differentiation by cooperating with *erbin* to repress MAPK signalling.^{6,15} This mechanism may hold true for the palmoplantar skin, which displays excessive hyperkeratosis. However, in our case the nonpalmoplantar skin appeared mainly clinically normal and expression of epidermal differentiation markers was not reduced. Of note, flexural areas exposed to mechanical friction and humidity were constantly affected, supporting a role of the epidermal fragility in the pathogenesis of this disorder. The mechanisms underlying the episodes of aggravation remain elusive. They could represent an excessive inflammatory response of the skin to common environmental insults exceeding a certain threshold, and are amendable by topical calcineurin inhibitors. The trigger factors are unclear. It is conceivable that mechanical traumatization and a warm, humid environment favour epidermal barrier disruption, bacterial colonization and penetration of allergens, which launch a cytokine response.

Taken together, we show here that loss of desmoglein 1 may result in a mild SAM syndrome, lacking main features like metabolic wasting, severe growth retardation or hypotrichosis. Additional studies are required to unravel the full phenotypic complexity and the pathomechanisms of this disorder. It is likely that multiple environmental factors and presumably genetic modifiers may account for the phenotypic variability in cases with *DSG1* mutations.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Primers and antibodies used in this study.

Table S2. Clinical characteristics of the patients with homozygous DSG1 loss-of-function mutations.