Peeling skin syndromes (PSS) refer to a heterogeneous group of generalized and/or palmoplantar disorders. Inflammatory peeling skin disease (PSD) refers to PSS type B [MIM 270300] (1) and is an ichthyosiform erythroderma characterized by recurrent patchy peeling of the skin with accompanying pruritus. The disease persists throughout life, is accompanied by significant atopic manifestations, and can be reminiscent of Netherton syndrome (NTS) (1, 2). PSD is due to autosomal recessive loss-of-function mutations in the CDSN gene encoding corneodesmosin (CDSN) (3), as independently confirmed by several groups (4–7). Moreover, large deletions encompassing the CDSN gene have been identified as the molecular cause (8, 9).

CDSN is a basic phosphoprotein expressed in cornified epithelia and hair follicles (10). It is localized in the lamellar granules of the stratum granulosum and found in the corneodesmosomes of the stratum corneum. The protein has a high level of serine and glycine, with specific structure motifs rich in these amino acids at the N-terminal (aa 60–171) and C-terminal end (aa 375–450), designated as glycine loops. These structure motifs are suggested to mediate cell-cell cohesion. Progressive proteolytic degradation of CDSN by serine proteases (kallikrein 5 and 7) plays a key role in desquamation (11). Hence, PSD represents an impressive clinical example for the primary loss of function of CDSN.

This study investigated a new patient with a novel mutation of the CDSN gene and performed expression analysis to reveal information about the inflammatory component of the disorder.

METHODS AND RESULTS (for full details see Appendix S1)

The male patient had been treated for atopic dermatitis up to the age of 10 years until a clinical and histological diagnosis of PSD was first suggested. His parents were non-consanguine and healthy. Since the third week of life the patient suffered from peeling, scaling and eczema of the entire skin (Fig. 1a). The patient’s history showed sensitization and clinically relevant allergic reactions through contact with fish, peanut, house-dust mites or grass pollen. Moreover, he had palmoplantar hyperhidrosis. Routine laboratory parameters were normal, except for a highly elevated IgE level (3,204.0 kU/l, normal value < 26.3). Treatment was based on lipophilic ointment, antiseptics and antihistamines.

To generate three-dimensional (3D) skin equivalents, primary keratinocytes and fibroblasts were taken. After 24 h, skin equivalents of the patient showed a loss of CDSN expression (Fig. 1f). This lack of CDSN was further confirmed by Western blot analysis (Fig. 1e). This study investigated a new patient with a novel mutation of the CDSN gene and performed expression analysis to reveal information about the inflammatory component of the disorder.
DISCUSSION

Loss of corneodesmosin as a molecular cause of PSD was identified in 2010 by Oji et al. (3). Since then 6 different CDSN mutations, including large deletions of the CDSN locus on chromosome 6p21.3, have been published for PSD (4–9). The novel loss of function mutation c.1031delC investigated in this study is located directly before the C-terminal glycine loop of CDSN. The mutation predicts a protein with a long nonsense sequence (p.Ile345Ser*121) (Fig. S2). Quantitative RT-PCR experiments with primary keratinocytes of the patient showed decreased expression of CDSN mRNA (Fig. S1), suggesting nonsense-mediated mRNA decay as a possible reason. This is in contrast to the previously described stop codon mutation p.Gly142* residing within the first glycine loop, which showed an elevated (2-fold more) expression level of CDSN mRNA and a residual presence of the truncated protein (7).

Our immunohistological findings in skin biopsies and 3D skin equivalents revealed absent protein expression of CDSN, as confirmed by Western blot analysis (Fig. 1). The ultrastructural findings of this study confirm the pathological impact of CDSN deficiency on corneodesmosomal adherens, as shown previously (3, 9).

PSD and NTS, as well as the recently described SAM (severe dermatitis, multiple allergies and metabolic wasting) syndrome (12) share some characteristic clinical features, i.e., patients with these diseases often have pruritus and atopic manifestations (1, 2). Caspase-1 (CASP1) is activated by the inflammasome, a multiprotein complex, and promotes the secretion and processing of the proinflammatory cytokines like IL1β and IL18 (13). Dysregulation of epidermal CASP1 activity and elevated serum levels of IL18 have been observed in NTS (14); elevated IL18 levels have been shown in atopic dermatitis (15). To investigate whether the balance of CASP1 and IL18 is altered in PSD, we studied their relative expression levels. Interestingly, both CASP1 and IL18 expression levels were found to be up-regulated in the keratinocytes of the patient. These molecular findings correspond well with the clinical symptoms of PSD. Hence, this study supports the idea that peeling skin disease represents a novel monogenetic disease model for inflammatory and atopic skin diseases in general.

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