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Compound heterozygosity for dominant and recessive *DSG1* mutations in a patient with atypical SAM syndrome (severe dermatitis, multiple allergies, metabolic wasting)

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Running head: Novel DSG 1 mutations in SAM syndrome

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To the Editor

SAM syndrome (OMIM 615508), comprising severe dermatitis, multiple allergies and metabolic wasting, was first described by Samuelov et al in 2013¹. Cutaneous findings consisted of congenital erythroderma, superficial skin erosions, fine scales and palmoplantar keratoderma and were accompanied by extracutaneous findings including perinatal

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hyponatremia, food allergies, elevated IgE levels, recurrent infections, metabolic wasting, malabsorption, esophageal reflux and eosinophilic esophagitis, cardiac defects, microcephaly and development delay^{2,3}. In the initial description, SAM syndrome was caused by biallelic loss-of-function mutations of the desmoglein 1 (*DSG1*) gene¹ and resulted in a severe lethal prognosis in 3 out of 6 cases. Hence, the clinical and genetic spectrum of SAM-syndrome is not fully defined, yet. Subsequent papers reported unique cases with milder course of the disease due to *DSG1* or desmoplakin-gene (*DSP*) mutations^{4, 5, 6}. Here we describe a new case with mild clinical manifestations, which were caused by two heterozygous *DSG1* mutations, with dominant and recessive inheritance, respectively.

A 2-year-old female presented to our department showing transient erythematous patches, covered by fine scales, extended on the face and the upper and lower limbs. She also exhibited linear palmar keratoderma and plantar keratoderma on the pressure areas, since she was 1 year old. The hair was very curly, but otherwise normal, as were the nails and teeth. (Fig 1 a-c) The general condition was good, without other health problems and normal growth parameters.

Laboratory tests revealed elevated total IgE (109,4 UI/ml, normal values: < 40 UI/ml), and positive prick testing showed immediate hypersensitivity to plants (ambrosia, artensia). The patient was not affected by any respiratory related allergy.

Clinical examination of her parents revealed linear palmar keratoderma and focal plantar keratoderma on the pressure areas in her father (Fig 1 d, e), but no skin lesions in her mother (Fig 1 f, g). Anamnestically, palmoplantar keratoderma was present in other paternal relatives, but in none of the maternal ones.

Following written informed consent, genomic DNA was extracted from EDTA-blood and mutation analysis of *DSG1* was performed⁴. The study 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 two heterozygous mutations, c.811_812delAC, p.Q271Vfs*20 in exon 7 and c.2100+4A>G, IVS14+4A>G, in intron 14 of *DSG1*. The frame shift mutation, c.811_812delAC was present in the father and c.2100+4A>G was found in the mother (Fig 2 a). To the best of our knowledge, these variants have not been reported before (HGMD Professional 2016.2, ExAC, 1000G). (Fig 2 b). Mutation Taster (www.mutationtaster.org/) classifies the variant c.2100+4A>G as “disease causing”, while NetGene2 (<http://www.cbs.dtu.dk/services/NetGene2/>) predicts a reduction of the confidence of the donor splice site of exon 14 from 0.63 to 0.47, supporting its pathogenic role.

In our case, the frameshift mutation c.811_812del causing desmoglein 1 haploinsufficiency acted in a dominant manner, being associated with palmoplantar keratoderma in the paternal family. In contrast, the splice site mutation, c.2100+4A>G was silent in a heterozygous state in the mother. Thus it can be considered as recessive or low penetrance mutation. It is conceivable that this intronic mutation generates a leaky, partially functional donor splice site, which allows expression of low levels of full-length desmoglein 1. Compared with cases in the initial description of the syndrome, the present case shows milder clinical manifestations, without metabolic wasting, hypotrichosis, or other health problems¹. Often the palmoplantar keratoderma is overlooked by the patients and doctors, or the manifestation is not properly investigated. Yet it is a crucial diagnostic clue for several syndromes, including the SAM syndrome.

Figures

Fig 1. Clinical manifestations of the patient (a-c): erythematous patches on the face, linear palmar keratoderma and plantar keratoderma on the pressure areas; The clinical manifestations of the father (d,e): linear palmar keratoderma and plantar keratoderma on the pressure areas; no skin lesions to the mother (f, g).

Fig 2. The *DSG1* mutations found in this study. (a) Partial sequence of exon 7 and 14 of *DSG1* in the index patient, her mother and father. The red arrows indicate the mutations. (b) Schematic representation of desmoglein 1 with the extracellular, transmembrane (TM) and cytoplasmic regions, and the repeat unit domains (RUD). Mutations described so far in the literature are depicted: in red are mutations causing severe dermatitis, multiple allergies and metabolic wasting (SAM syndrome), in black mutations causing palmoplantar keratoderma (PPK), the mutations identified here are in bold.

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