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Ectodermal dysplasia–skin fragility syndrome: a novel mutation in the *PKP1* gene

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Summary

Ectodermal dysplasia–skin fragility syndrome (EDSFS) is an autosomal recessive genodermatosis characterized by skin fragility, palmoplantar hyperkeratosis, onychodystrophy, perioral fissuring and noncicatricial alopecia. It is caused by plakophilin-1 (PKP1) deficiency, which results in desmosomal abnormality and poor intercellular cohesion between the epidermal cells. We report a case with a novel *PKP1* mutation in intron 6.

Ectodermal dysplasia–skin fragility syndrome (EDSFS) is a rare genodermatosis currently included in the group of hereditary epidermolysis bullosa simplex disorders. It is caused by deficiency of the protein plakophilin-1 (PKP1) deficiency, which results in desmosomal abnormality and poor intercellular cohesion between the epidermal cells.[1] We report a case with a novel *PKP1* mutation in intron 6.

Report

A 15-year-old white boy presented with skin fragility, which had been present since early infancy. The boy had been fostered shortly after birth, and no information on his family background was available. According to his foster parents, the patient had displayed diffuse erythema and widespread erosions since the first weeks of life. When he was 2 years old, he started to develop thickening and fissuring of the palms and soles, abnormalities of the fingernails and toenails, and crusted erosions around the mouth and on the inguinal areas. His scalp hair, eyebrows and eyelashes had always been short and sparse, and pruritus was a continual and major problem. Investigations conducted in infancy showed that he had low plasma zinc levels, but oral therapy with zinc had proved ineffective. Mutational analysis of the *SLC39A4* gene had excluded acrodermatitis enteropathica.

On examination, a diffuse generalized noncicatricial alopecia was seen; the scalp hair was sparse, short and curly, and the eyelashes and eyebrows were almost absent. Irregular wide scars were present on the cheeks, but the patient denied having any previous erosive lesions on the area. Perioral fissuring was prominent (Fig. 1a). There was diffuse erythema, along with scattered crusting and erosions, over the whole body surface (Fig. 1b). The palms and soles displayed diffuse hyperkeratosis and deep fissures, and the fingernails and toenails were thickened and dystrophic (Fig. 1c). Maceration and deep fissuring was present in the perineal area and inguinal folds (Fig. 1d). Sweating was normal. Biopsies were taken for further investigations.

On histological examination, orthokeratosis, hypergranulosis and isolated dyskeratotic cells were seen within the upper and intermediate epidermal layers. The keratinocytes had wide intercellular spaces, with scattered foci of acantholysis (Fig. 2a). A striking perinuclear eosinophilic mass was seen within some

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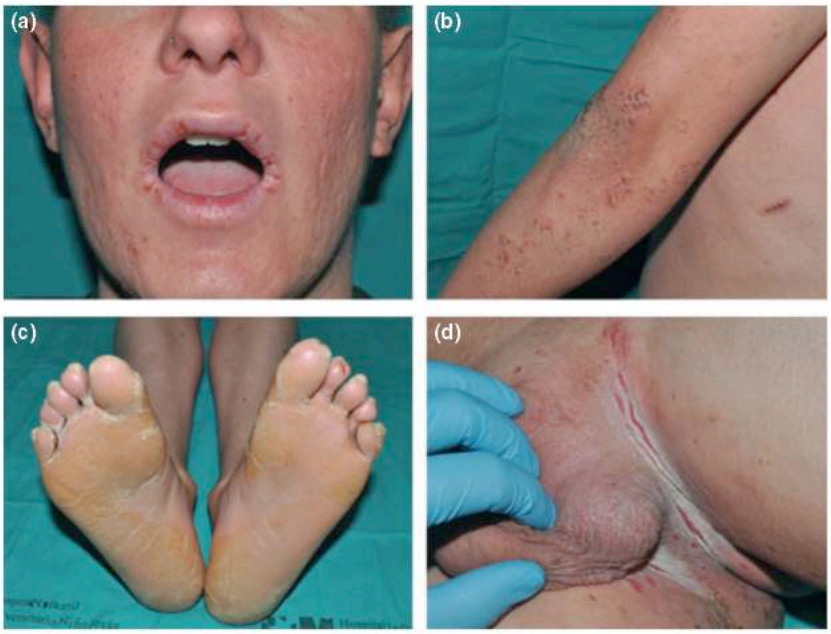

Figure 1 Dermatological abnormalities in a patient with plakophilin-1 (PKP1) gene mutation: (a) perioral fissuring and crusting; (b) diffuse erythema and scattered erosions and crusts on the arms and trunk; (c) diffuse plantar hyperkeratosis and fissures on the digits (note also the thickening of the toenails); and (d) hyperkeratotic and fissured perineal lesions.

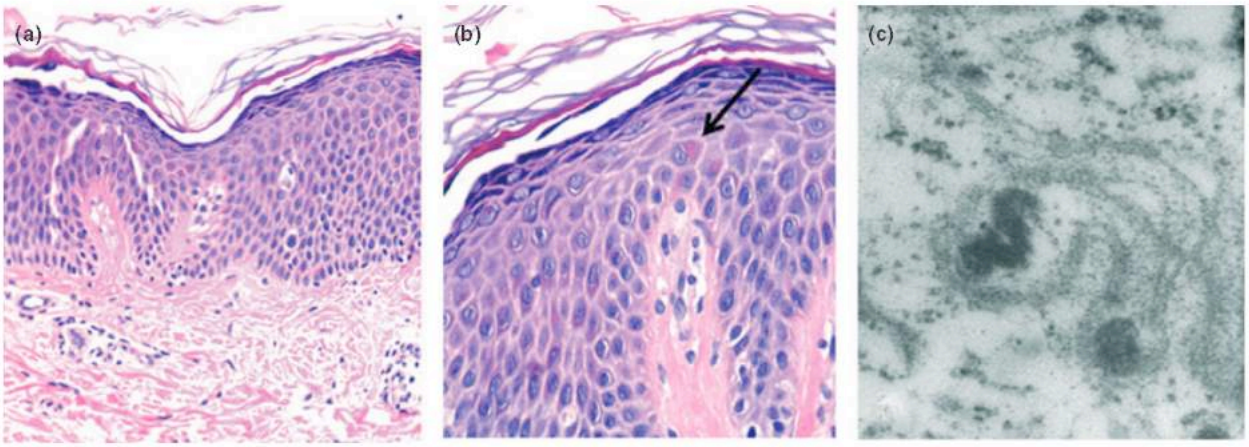

Figure 2 (a) Orthokeratosis, hypergranulosis and wide intercellular spaces between keratinocytes, with scattered foci of acantholysis. (b) Isolated dyskeratotic cells and a striking paranuclear eosinophilic mass were seen in some keratinocytes (arrow). Haematoxylin and eosin, original magnification (a) × 40; (b) × 80. (c) Ultrastructural study showing small poorly formed desmosomes and clumping of tonofilaments (scanning electron microscopy; original magnification × 80 000.

dyskeratotic keratinocytes (Fig. 2b). Transmission electron microscopy showed small, poorly formed desmosomes and perinuclear clumping of tonofilaments (Fig. 2c). Light microscopy examination of the hair shaft showed multiple foci of trichorrhexis. Scanning electron microscopy (Quanta 200; FEI Company, Hillsboro, OR, USA) and microanalysis (Genesis X-ray Microanalysis System; EDAX Inc., Mahwah, NJ, USA) of the hair confirmed ultrastructural abnormalities, including two different populations of hairs: one population of a lighter colour and approximately 33–35 μm in diameter, and the other of a darker hue and up to 65–70 μm in diameter.

After obtaining informed consent, we extracted DNA from peripheral blood samples taken from the patient. Individual exons of the *PKP1* gene (OMIM 601975) were amplified by PCR with primers located within flanking intronic sequences as previously reported.[2] The PCR products were directly sequenced. Mutation analysis of the *PKP1* gene showed a homozygous mutation in position 1233-2A>G (Fig. 3a). RNA was extracted from a skin biopsy using standard methods.

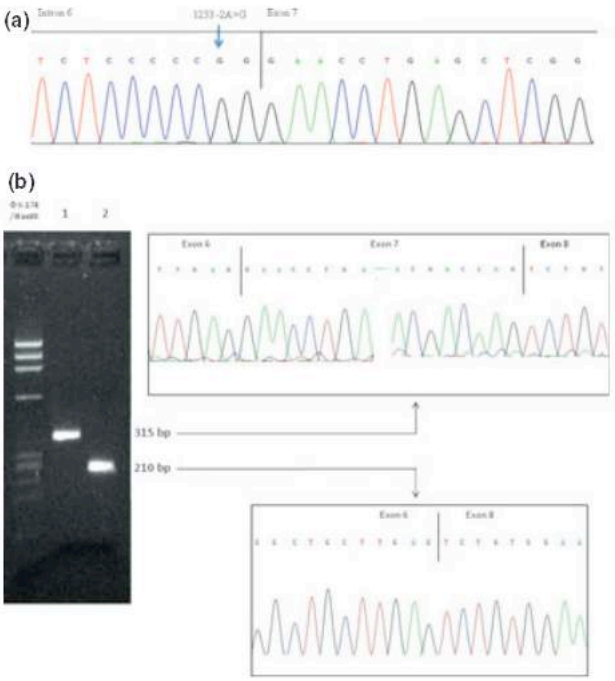

Figure 3 (a) Sequence of the intron 6/exon 7 junction showing the A>G mutation at position 1233; (b) reverse transcriptase PCR of RNA obtained from normal skin (1) and from the skin of the patient (2) showing the differences in size of the fragments obtained using primers from exon 6 and 8 and the sequences of the exon exon junctions.

Table 1 Primers used for PCR.

Exon	Sequence 5′→3′
6	GAACCTGTCTTTCCACTGA
8	CGTTATACTCCAGCTGGCGG

Reverse transcriptase PCR was performed at an annealing temperature of 63 °C, using primers designed from the coding sequences of exons 6 and 8 (Table 1), which revealed a transcript that lacked exon 7 and generated a frameshift, leading to a premature stop codon and a truncated protein (p.R411SfsX51; Fig. 3b).

EDSFS, first described by McGrath in 1999,[1] is an autosomal recessive genodermatosis characterized by skin fragility, palmoplantar hyperkeratosis, onichodystrophy, perioral fissuring and abnormal hair.[3] PKP1 is expressed in the upper layers of the epidermis, the nails and the hair follicles; its abnormality accounts for the pathological findings found in our case, which have also been extensively described elsewhere.[4] Most patients have scanty, curly and short scalp hair, and a variable degree of alopecia of the eyelashes and eyebrows. Previous histological studies have shown a mild decrease in the number of terminal scalp hairs without an increase in the amount of vellus hair.[4] Interestingly, we found two hair populations of very different diameters, 35 and 61 μm, respectively. As PKP1 is expressed in the suprabasal cell layers of the outer root sheath, it is probably involved in hair differentiation, thus its mutation produces morphogenetic disturbances. However, we cannot further explain the dissimilarity in the diameter of the hairs.

The *PKP1* gene has been mapped to chromosome 1q32, and several mutations have been reported to date.[1 3,5 10] Although there are subtle clinical differences between patients, no phenotype–genotype correlation has been fully established. In this study, we characterized a novel mutation in intron 6 (1233-2A>G), which affects the consensus acceptor splice site, and leads to a truncated protein. The mutation is located in the same position as that previously reported by Whittock *et al.*,[2] but the mutated nucleotide is G instead of T. The recurrence of two different mutations in the same nucleotide suggests that it might be a 'hot spot'. Our case further reinforces the observation that splice-site mutations in the *PKP1* gene are more common than expected. Splicing mutations account for 15% of most inherited diseases, but in EDSFS they have been detected in > 50% of cases, suggesting either a specific pattern of mutation or a bias in the location of the *PKP1* gene mutations described to date.

In conclusion, we present a further case of EDSFS syndrome with a novel mutation in intron 6, and we show that the mutation generates a transcript that lacks exon 7 and generates a truncated protein at codon 500; to our knowledge, this is the first report of this mutation.

Learning points

- EDSFS is an autosomal recessive genodermatosis, characterized by skin fragility, palmoplantar hyperkeratosis, onichodystrophy, perioral fissuring and abnormal hair.
- Hypohidrosis and pruritus are inconsistent but common features.
- EDSFS is due to plakophilin 1 deficiency, a desmosomal component.
- Desmosomal abnormality results in poor intercellular cohesion within the epidermis and fragility of the skin.

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