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LETTER TO THE EDITOR

A novel large *FERMT1* (*KIND1*) gene deletion in Kindler syndrome

KEYWORDS
Blister; Kindlin-1; Kindler syndrome; Poikiloderma; Deletion

Dear Sir,

Kindler syndrome (KS; OMIM 173650) is a rare heritable skin disorder which begins with congenital skin blistering and photosensitivity, which improves with age, and continues with progressive generalized poikiloderma and extensive skin atrophy [1]. Additional clinical features include mucosal involvement, e.g. early and severe periodontitis, and/or esophageal, gastrointestinal and genital involvement [1,2]. The risk of mucocutaneous malignancy is increased [1]. KS results from recessive loss-of-function mutations of the *KIND1* gene (now called *FERMT1*) that encodes the protein kindlin-1, a component of focal adhesions in epithelial cells [3]. Here, we add new data to our previous results, which demonstrated that large deletions in the *FERMT1* gene and DNA rearrangements might account for a significant number of the KS cases in whom pathogenic mutations could not be detected using genomic PCR amplification [4].

Three patients from southern Bulgaria were investigated in this study. Patients 1 and 2 were siblings and unrelated to patient 3. No consanguinity was known; patient 3 had three unaffected brothers and two unaffected sons (described in [6]). Skin biopsy specimens were analyzed with transmission electron microscopy (EM), and with indirect immunofluorescence staining (IIF) as described before with primary antibodies to: kindlin-1 (to the amino acids 541—674; [5]), collagen XVII, laminin β3 chain, α6 integrin and collagen VII [5]. Genomic DNA extracted from peripheral lymphocytes was used for PCR amplification, sequencing and analysis of the entire coding region and exon—intron boundaries of the *FERMT1* gene, as described [4]. The study was conducted according to the Declaration of Helsinki principles, and the participants gave their written informed consent.

The clinical features of the patients are presented in Table 1 and Fig. 1a. EM on a skin specimen of patient 1 demonstrated three levels of separation in the dermal—epidermal junction zone (DEJZ) — within the basal keratinocytes, along the lamina lucida and under the lamina densa — and in the skin of patient 2, reduplication of the lamina densa was prominent (not shown). IIF revealed reduced kindlin-1 staining (Fig. 1b) and positive but interrupted staining pattern for collagen XVII. Antibodies to laminin 332 and collagen VII produced thickened and patchy staining, with interruptions or branching of the DEJZ in the skin of both patients 1 and 2 (not shown). Integrin α6 which is targeted to the ventral surface of basal keratinocytes in control skin was also found at the lateral and apical cell membranes in the patients' skin (not shown). Even if these morphological features were indicative of KS, no *FERMT1* mutations were disclosed using the DNA sequencing strategy successfully used in the past. The fact that no amplicons were obtained for exons 14 and 15 suggested the presence of a homozygous genomic deletion spanning the region. Therefore, we designed several primers located in intron 13 and downstream of the 3′UTR, which allowed us to circumscribe the deleted interval. With primers 13F2:5′-CTTGCACCAGCTACCCTCTC-3′ and 15R3:5′-GGCTGCCAATAATGTTGGTT-3′, an about 2 kb product was obtained with genomic DNA from all three patients, instead of the expected 9.988-kb amplicon (Fig. 1c and d). The 2-kb PCR products were

Abbreviations: KS, Kindler syndrome; EM, electron microscopy; IIF, indirect immunofluorescence; DEJZ, dermal—epidermal junction zone; UTR, untranslated region; FERM, four point one ezrin radixin and moesin; PH, pleckstrin homology.

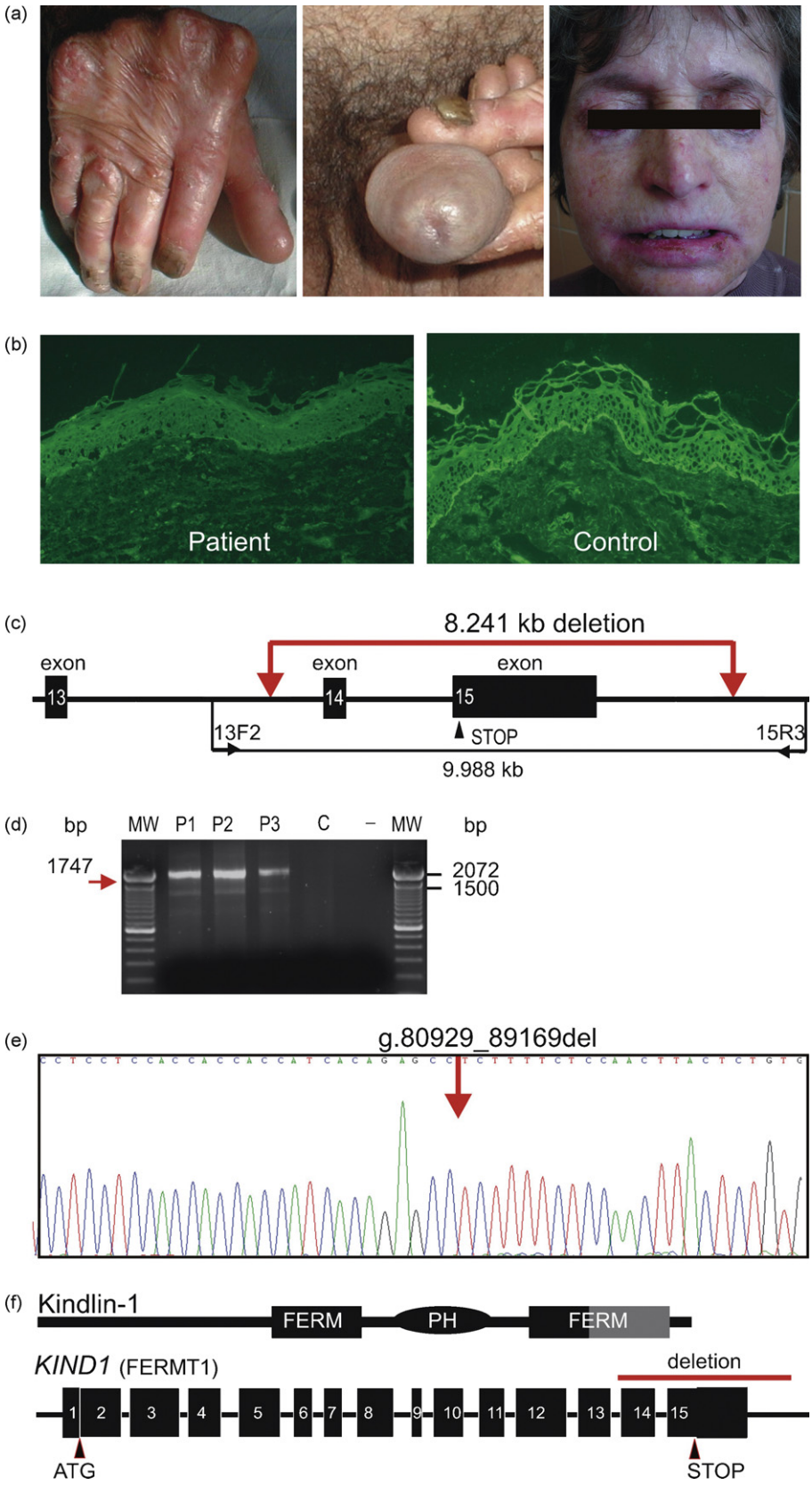

Figure 1 (a) Clinical presentation: the left and middle pictures show patient 1 with webbing and contractures of the hand, nail dystrophy, and stenosis of the urethral meatus. The right panel shows poikiloderma and erosions and crusts on the lower lip in patient 3. (b) Immunofluorescence staining of skin sections with antibodies to kindlin-1 revealed a reduced signal (green) in the patient's skin compared to the control skin. (c) The *FERMT1* genomic region spanning exons