Dear Editor, Epidermolytic ichthyosis (EI; OMIM 113800), previously termed bullous congenital ichthyosiform erythroderma or epidermolytic hyperkeratosis, is a clinically heterogeneous disorder of keratinization. It is usually characterized by severe neonatal erythroderma, blistering and fragile skin, with the subsequent development of hyperkeratosis, predominantly in flexural areas. It is caused by mutations in either the KRT1 or KRT10 genes encoding the suprabasal keratins K1 and K10, respectively.1 Mutations are usually missense substitutions in the highly conserved alpha-helical rod domains of these keratins, which play a critical role in filament formation.2 We report a multigeneration kindred with EI due to a novel mutation in KRT10.

The proband was a 32-year-old woman from Shetland. She presented with widespread fine scale and erythema of her trunk and limbs, with a history of scaling and redness since birth but no blistering, erosions or collodion membrane reported. Clinical examination revealed widespread ichthyosis and erythema affecting the trunk and all four limbs, with more significant hyperkeratosis at the elbows, knees and ankles but relative sparing of palmoplantar skin (Fig. 1). Her father, uncle and grandmother were affected, and four further generations were reported to be affected. She had been maintained on oral isotretinoin 20–40 mg daily, thus modifying the clinical appearance, from the age of 13 years, but had recently developed lower back and hip pain. Radiographs of the lumbar spine and left hip demonstrated bridging osteophytes form T11 to L1, suggestive of diffuse idiopathic skeletal hyperostosis (DISH), and magnetic resonance imaging confirmed the presence of avascular necrosis of the left hip. This was successfully treated with core decompression of the left hip with improvement in the patient’s pain.

A biopsy of affected skin of the upper limb was obtained from the proband and processed for light microscopy by standard methods. Structural analysis demonstrated acanthosis, marked overlying hyperkeratosis and vacuolar change of the upper epidermal cells with prominent clumping of keratohyaline granules.

Following informed consent, genomic DNA samples were obtained from blood samples from the proband and her father. Mutation analysis of the coding regions and splice sites of the KRT1 and KRT10 genes was performed by standard polymerase chain reaction (PCR) and Sanger sequencing methods using specific primers. Sequence analysis of KRT10 revealed a previously unreported heterozygous deletion of 167 base pairs extending from intron 5 into exon 6 (c.1156–79_1243del), abolishing the intron 5 acceptor splice site (Fig. 2). This mutation was also present in the proband’s affected father.
RNA was obtained from the proband’s skin biopsy. Following reverse transcription by standard methods, reverse-transcriptase PCR was performed using primers flanking the deletion on exons 5 and 6 of KRT10. RNA analysis demonstrated that the KRT10 c.1156–79_1243del deletion activates a cryptic splice site 96 base pairs downstream from the consens. A small deletion on exons 5 and 6 of KRT10. RNA analysis demonstrated that the KRT10 c.1156–79_1243del deletion activates a cryptic splice site 96 base pairs downstream from the consens.

**Fig 2.** DNA sequencing of the KRT10 gene in the proband. Sequencing reveals a novel heterozygous deletion extending from intron 5 into exon 6 (K10 c.1156–79_1243del), abolishing the exon 6 acceptor splice site resulting in a shorter aberrant keratin 10 (K10) protein lacking a sequence motif critically important for keratin filament assembly. The mutation was present in the proband’s affected father but not in unaffected control samples.

To our knowledge, avascular necrosis of the femoral head occurs due to interruption of the microcirculation of the femoral head resulting in ischaemia, and may occur spontaneously or in relation to treatment with glucocorticoids, hypertension, sickle cell disease, trauma or other causes. Avascular necrosis of the hip has been reported with retinoids (all-trans-retinoic acid) used to treat haematological conditions; however, affected cases have often received concomitant glucocorticoids. The long-term effects of oral retinoids remain under debate; however, experience of exposure to isotretinoin at this dose and for this length of time has been reported in the literature only rarely in comparison with other retinoids. Previously reported skeletal abnormalities with retinoid therapy include periostal thickening, premature epiphyseal closure in children, osteoporosis, extraspinal tendon and ligament calcification, osteophytes and bony bridges between vertebrae as in the proband, in addition to DISH characterized by anterior spinal ligament calcification. However, there are few prospective studies on the skeletal effects of long-term systemic retinoids, and many of the bony changes reported are also prevalent in the general population. This finding adds to the evidence that KRT10 mutations are the principal cause of autosomal dominant EI with palmoplantar sparing. It also highlights the possible side-effects of long-term oral retinoid treatment in these inherited conditions.

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Table 1 Results of the efficacy of 311-nm ultraviolet (UV) B plus biologic combination therapy

| Biologic, ref./NCT no. | Number of patients treated in a study | Percentage PASI reduction |
|-----------------------|-------------------------------------|--------------------------|
|                       |                                     | Week 6                   | Week 12                  |
|                       |                                     | UV | No UV | UV | No UV |
| Etanercept1 | 5                                    | 85-0 | 55-2 | 90-7 | 81-0 |
| Adalimumab1, NCT00638469 | 6                                   | 83-5 | 46-1 | 67-7 | 51-2 |
| Golimumab | 2                                    | 82-9 | 69-3 | n.a. | n.a. |
| Ustekinumab4 | 9                                    | 81-6 | 54-1 | 84-6 | 78-9 |
| Alefacept1 | 14                                   | 72-6 | 31-5 | 82-7 | 63-7 |
| All biological agents | 36a                                  | 81-1 | 51-2a | 81-4 | 68-7a |

Data are mean values calculated from the results of 311-nm UVB half-side comparison studies, previously reported in refs 1–4 and two registered clinical trials. PASI, Psoriasis Area and Severity Index; n.a., not available. aCertain patients participated in more than one trial; therefore the total number for treatment with biological agents is higher than the total patient number (i.e., 28). ÆP = 0.001; ¶P = 0.0255 by two-tailed paired Student’s t-test comparing the UV-irradiated body halves vs. the nonirradiated body halves, based on intention to treat as in the first 6 weeks. Note that a portion of the patients (n = 6) were also treated between weeks 7 and 12 with total-body 311-nm UVB (including the previously nonirradiated body half).