TO THE EDITOR

Desmosomes are intercellular junctions that are important in cell adhesion and the maintenance of epithelial integrity (Samuelov and Sprecher, 2015). The three main desmosomal protein groups are the cadherin desmogleins 1–4 and desmocollins 1–3, the armadillo plakophilins 1–3 and plakoglobin, and the plakin family member desmoplakin (Gestios et al., 2004; Harmon and Green, 2013). Germline mutations in at least 11 desmosomal genes have been implicated in a range of pathologies involving skin, hair, and heart, or combinations thereof (Najor, 2018) (Supplementary Table S1 for summary).

In 2009, Ayub et al. identified a homozygous nonsense mutation (c.2129T>G; p.Leu710*) in DSC3 in four siblings from a consanguineous Afghani family who presented with a new genodermatosis affecting hair and skin (Ayub et al., 2009). Clinically, eyebrows and eyelashes were absent, and the scalp hair was sparse and fragile. In addition, generalized skin vesicles occurred that would burst periodically, releasing thin watery fluid. A histologic analysis of the scalp showed slight follicular plugging but no epithelial fragility. The disorder was proposed as a new skin fragility genodermatosis, but others suggested that the data, as presented, were more consistent with keratosis pilaris (Payne, 2010). Moreover, the lack of clear clinical illustrations of any vesicles or skin biopsy data meant that there was insufficient evidence to formally classify the loss of DSC3 as an inherited desmosomal skin fragility disorder (Fine et al., 2014).

Here, we report an unrelated individual with a different homozygous nonsense mutation in DSC3, who has unequivocal skin blistering and hypotrichosis. The proband is a 5-year-old boy born to consanguineous Egyptian parents (see Figure 1 for clinicopathologic features and Supplementary Figures S1 and S2). At birth, his skin appeared normal, but from 4 years of age, he started to develop blisters on his hands, feet, and knees, as well as at sites of trauma. There was no scalp hair at birth, and although hair grew during infancy, it was always sparse and easily pulled out. On examination, there were trauma-induced bullae and crusted erosions on the hands, knees, legs, and feet. No intracutaneous fragility was noted. His scalp hair and eyebrows were sparse and thin, and there was also follicular hyperkeratosis on the scalp, trunk, and extremities. His skin was dry, and he had cracked lips with angular cheilitis. His nails showed areas of leukonychia and thinning with breakage. No abnormalities were detected on cardiac examination, chest X-ray, or echocardiography. Additional features included slight thinning and irregularities of dental enamel, an inverted left nipple, and incomplete syndactyly of the second and third toes of both feet, and clinodactyly of the fourth toe of the right foot, although the partial syndactyly was also present in his sister (Supplementary Figure S3) and mother and thus may reflect a separate autosomal dominant gene abnormality (currently unknown) rather than a consequence of the recessive DSC3 pathology we report here.

A skin biopsy of rubbed normal skin revealed acanthosis and panepidermal widening of the spaces between keratinocytes. Ultrastructurally, the desmosomes had variable appearances: some showed near-normal morphology, but several were small with cell-cell detachment mostly occurring through the inner desmosomal plaques (Figure 1 and Supplementary Figures S4 and S5). Following ethics committee approval (St Thomas’ Hospital, London, United Kingdom) and written informed consent, whole-exome sequencing was performed using genomic DNA extracted from blood samples from the proband, his sister, and both parents, in accordance with the Declaration of Helsinki principles. Candidate mutations were prioritized by filtering for rare variants with a frequency < 0.01 in public repositories, such as the 1000 Genomes Project, Exome Aggregation Consortium, and an
We identified a homozygous loss-of-function mutation in DSC3 (c.2180T>G; p.Leu727*); both parents and the unaffected sister were heterozygous for this variant (Sanger sequencing confirmation shown in Figure 2a; see Supplementary Table S5 for primer details). This mutation is similar in nature to the previously reported DSC3 mutation, p.Leu710*, but whereas the latter is located within the transmembranous domain of DSC3, p.Leu727* sits within the intracellular region of the protein (Figure 2b).

Immunofluorescence microscopy in our patient’s skin revealed a complete absence of DSC3 labeling, consistent with nonsense-mediated RNA decay. To assess the impact of the loss of DSC3 in the patient’s skin, we also undertook quantitative real-time PCR for other desmosomal components. We observed 2–5-fold increases for DSC1, DSG1, DSG3, PKP1, DSP, JUP and keratins (KRT1, KRT10, KRT5, and KRT14), with only DSC2 and DSG2 not showing much difference from the controls (Figure 2c). At a protein level, however, immunostaining for these proteins (apart from DSC3) showed no major differences between the patient and control, although the intensity of PKP1 labeling was slightly reduced in patient skin (see Supplementary Table S6 for the list of antibodies assessed).

Figure 1. Clinicopathologic features of the 5-year-old boy with this desmosomal genodermatosis. (a, b) Scalp hypotrichosis. (c) Follicular papules on occiput. (d) Dermatoscopy reveals empty follicles, white dots, and a predominance of single follicle hair units. (e) Tense blister on the middle finger and leukonychia; (f) Inflammatory blisters on the medial aspect of the ankle. (g) Erosions and crusts on the heels. Additional clinical images are presented in Supplementary Figures S1 and S2. (h) Light microscopy shows acanthosis and pan-epidermal widening of spaces between keratinocytes (Richardson’s stain; Bar = 50 µm). (i) Transmission electron microscopy shows desmosome detachment between keratinocytes (Bar = 5 µm). (j) Desmosome numbers are reduced in some areas with intermediate filaments retracted from the keratinocyte cell peripheries (Bar = 2 µm). (k) Desmosomes are present between some cells although many are small and lack mid-line dense plates (Bar = 500 nm). Additional transmission electron microscopy images are available in Supplementary Figures S4 and S5. (l) DSC3 labeling in normal control skin epidermis showing pan-epidermal cell membrane staining (Bar = 50 µm). (m) In patient skin, there is a complete absence of DSC3 immunoreactivity (Bar = 50 µm). (n) PKP1 labeling in normal control skin showing keratinocyte cell membrane staining from the suprabasal layer upwards (Bar = 50 µm). (o) In patient skin, PKP1 staining is slightly reduced in intensity but the distribution is similar (Bar = 50 µm). (p) DSP labeling in normal control skin showing pan-epidermal cell membrane staining (Bar = 50 µm). (q) DSP staining in patient skin is similar to control (Bar = 50 µm).
One of the key phenotypic distinctions between our patient and the pedigree report by Ayub et al. (2009) is the blistering. Our patient clearly shows widespread trauma-induced blisters, which is more congruent with the findings in the conditional knockout mouse model (Chen et al., 2008). Regarding desmosomes and skin or mucosal fragility syndromes, pathogenic autosomal recessive mutations have now been demonstrated in DSG1, DSG3, DSC3, DSP, JUP, PKP1, and CDSN (see Supplementary Table S1). In addition, autosomal dominant mutations in DSG1 can occasionally cause blisters (Lovgren et al., 2017). Interestingly, the heterozygous sister of our patient also reported occasional trauma-induced blisters and erosions (Supplementary Figure S6), although neither (heterozygous) parent has any skin blistering.
The hypotrichosis and follicular papules in our patient are very similar to the cases described by Ayub et al. (2009). Hair shedding was also noted in the conditional Dsc3 knockout mouse, in which acantholysis occurred in the keratinocytes around the telogen club hairs (Chen et al., 2008). Autosomal recessive mutations in DSC2, DSC3, DSG4, DSP, JUP, and PKP1 have been shown to result in human hair abnormalities, as have autosomal dominant mutations in DSP and CDSN (see Supplementary Table S1).

The presence of follicular papules in association with recessive loss-of-function DSC3 mutations appears to be a notable finding (Ayub et al., 2009). Although a precise explanation for the papules is currently lacking, altered epidermal differentiation is likely. Our quantitative real-time PCR data provide some support for this possibility, although DSC3 is also known to interact with p53 and to have tumor suppressor gene function in inhibiting EGFR and extracellular signal–regulated kinase pathways (Cui et al., 2012). Whether or how DSC3 anomalies might be implicated in more common forms of keratosis pilaris warrants further exploration.

In summary, we present definitive clinopathologic and molecular evidence that the loss of DSC3 causes both skin fragility and hypotrichosis in humans and thereby expands the genotype-phenotype correlation for desmosomal genodermatoses.

Data availability statement
Datasets related to this article can be found at https://www.ncbi.nlm.nih.gov/bioproject/PRJNA561129, hosted at Sequence Read Archive (SRA) under the collection ID PRJNA561129.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL
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