Research letter

Striate palmoplantar keratoderma resulting from a missense mutation in *DSG1*

DOI: 10.1111/bjd.16320

Dear Editor, Palmoplantar keratodermas (PPKs; OMIM #144200) are a large phenotypically and genetically heterogeneous group of keratinization disorders characterized by marked hyperkeratosis on the surface of the palms and soles.[1]

Striate PPK (SPPK) features linear hyperkeratosis of the volar aspects of the fingers, extending onto the palms, as well as focal plantar keratoderma. The disease is most commonly caused by heterozygous mutations in *DSG1*, which encodes desmoglein 1 [DSG1 (SPPK1; OMIM #148700)],[2,3] but it can also arise from mutations in *DSP*, which encodes desmoplakin (SPPK2; OMIM #612908),[4] or *KRT1*, which encodes keratin 1 (SPPK3; OMIM #607654).[5] To date, > 25 mutations in *DSG1* have been identified in patients with SPPK1. These mutations have uniformly been found to result in a premature termination codon (PTC).[2,3]

We present, to our knowledge, the first case of SPPK caused by a missense mutation affecting a residue predicted to be of critical importance for DSG1-mediated adhesion.

The patient was a 27-year-old woman of Jewish origin. She reported thickening of the skin of her palms and soles since 1 year of age, resulting in pain while walking. She denied any additional systemic or dermatological manifestations apart from yellow discolouration of all toenails. Her father and her sister reportedly displayed similar clinical features. The patient exhibited foci of yellowish, fissured hyperkeratotic plantar skin involving weight-bearing areas, as well as subtle linear hyperkeratosis of the volar aspects of the fingers (Fig. 1a). Haematoxylin and eosin staining of a skin biopsy showed hypergranulosis, marked orthohyperkeratosis and widening of the intercellular spaces between keratinocytes (Fig. 1b).

To identify the causative mutation underlying the patient's SPPK, after obtaining ethical approval and informed consent, we used direct sequencing of genomic DNA to sequence fully all coding exons of *DSG1*, *KRT1*, *DSP* and *KRT16*. We discovered a heterozygous A to G transition at position 254 (c.254A>G) within exon 4 (Fig. 1c) of *DSG1* (reference sequence Ensembl accession number ENST00000257192·4), resulting in a p.Y85C substitution. The sequence variation was not detected in 629 healthy Jewish controls and was not found in the National Center for Biotechnology Information, University of California Santa Cruz; Human Gene Mutation Database; Exome Sequencing Project, Exome Aggregation Consortium; or the 1000 Genomes and Ensembl genomic databases, comprising > 58 000 individual sequences. The p.Y85C variation is predicted to be deleterious by two prediction tools [PolyPhen2 score 1 (range 0–1); SIFT (Sorting Intolerant From Tolerant) score 0 (range 1–0)] and was found to affect a highly conserved residue [Conseq score 9 (range 1–9)]. No mutations were identified in *KRT1*, *DSP* or *KRT16*.

To assess the consequences of the mutation, we modelled the wild type and mutant DSG1 proteins using three prediction tools (Fig. 1d): Swiss-Prot and LOMETS (https://zhanglab.ccmb.med.umich.edu/LOMETS/)[6] predictions were based on the crystal structure previously determined for the human DSG2 ectodomain [Protein Data Bank (PDB) code 5ERD, chain A, 36% identity], whereas Phyre2 was used based on the human DSG3 ectodomain (PDB code 5EQX, chain A, 55% identity).[7] Similarity between the model structures was assessed using PyMOL alignment (PyMOL Molecular Graphics System, Version 1·8; Schrödinger Inc., New York, NY, U.S.A.).

Like other members of the cadherin superfamily, desmosomal cadherins are thought to form transadhesive dimers, which rely on the interaction between the conserved tryptophan (W2) of one molecule and a specific hydrophobic pocket, serving as an acceptor site, on the interacting molecule from the opposing cell.[8,9] This was recently shown to depend predominantly on a heterotypic interaction between the donor site of a desmocollin molecule and the acceptor pocket of a DSG molecule,[10] which is lined by the side chains of specific conserved residues, including Y85 (numbered Y36 in the final DSG chain).[8–10]

Accordingly, we found that the affected amino acid, Y85, resides within the first extracellular domain of the protein (Fig. 1e), inside a hydrophobic, positively charged area (Fig. 1f). The p.Y85C mutation could affect the binding capability of the hydrophobic pocket in several ways. Firstly, while the hydroxyl side chain of Y85 was found to reach the inner part of this pocket, the C85 mutation lacks the length to do so (Fig. 1f). Secondly, the mutant C85 residue is predicted to interact aberrantly with C127, a part of the adhesive interface of the pocket,[9] and could potentially form a disulfide bond either through an intramolecular *cis*-interaction, due to proximity of the two amino acids, or through a *trans*-interaction with another bound desmosomal cadherin. When we used the same modelling tools to examine the effect of p.V83D and p.R86C, both very rare heterozygous nonpathogenic variants in close proximity to p.Y85C, we discovered that although residing close to the hydrophobic pocket, they are not

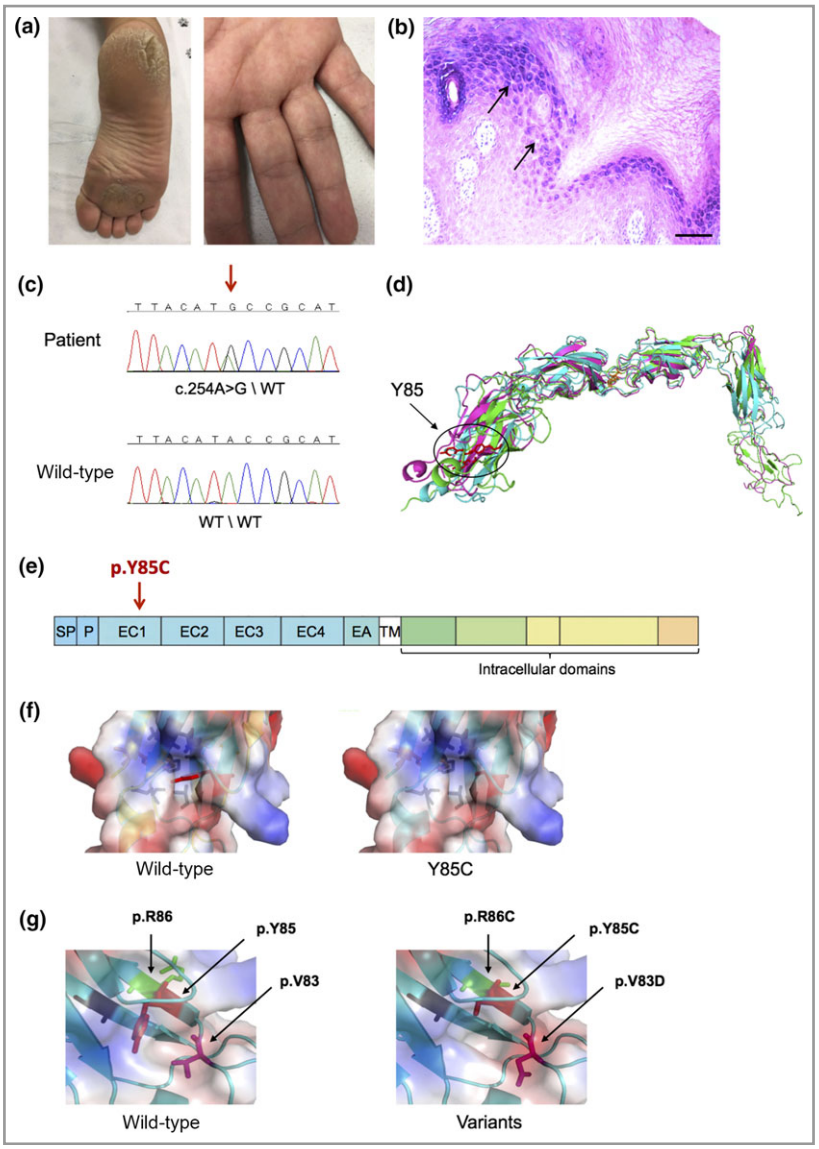

Fig 1. Clinical features, mutation analysis and protein modelling. (a) The patient presented with foci of plantar hyperkeratosis involving weight-bearing areas with multiple skin fissures (left panel). Linear hyperkeratosis of the volar aspects of the fingers was observed (right panel). (b) Haematoxylin and eosin staining of a skin biopsy obtained from the skin of the patient demonstrates hypergranulosis, marked orthohyperkeratosis and widening (arrows) of the intercellular spaces between keratinocytes, compatible with keratoderma (scale bar = 100 μm). (c) Direct sequencing of genomic DNA revealed an A > G transition at position c.254 within exon4 of *DSG1* (upper panel) compared with the wild-type (WT) sequence (lower panel). (d) Comparison between the molecular model of the human desmoglein 1 (DSG1) protein based on three prediction tools – LOMETS (green), Swiss-Prot (magenta) and Phyre2 (cyan) – shows that all the structures are similar (root mean square deviation < 4 with PyMOL alignment) and that the amino acid Y85 is located in the first domain (red, highlighted by black oval). (e) Schematic representation of the DSG1 molecule shows that the p.Y85C mutation is located inside the first extracellular domain (EC1) of the protein. EC, extracellular domain; EA, extracellular anchoring domain; P, propeptide region; SP, signal peptide; TM, transmembrane domain (protein scheme modified from Hershkovitz *et al.*)[3]. (f) Mutation modelling was performed based on the above-mentioned models. Protein molecules are overlaid with semi-transparent calculated electrostatic potential (blue = positive; red = negative) created using PyMOL. Y85 (in red) is located in a hydrophobic, positively charged pocket-shaped surface, predicted to serve as a pathway for DSG1 binding. While the hydroxyl group of the tyrosine lies within the inner part of the pocket (left panel), the mutant C85 substitution lacks the length to reach its inner rim (right panel). (g) Modelling of two rare heterozygous variants in close proximity to Y85 (red) was performed based on the above-mentioned models. The p.V83D variant (purple, right panel) resides further away from the hydrophobic pocket and will lead to a negatively charged glutamic acid that is not predicted to alter the negatively charged area of the wild-type p.V83 (purple, left panel); p.R86 (green, left panel) is located in proximity to the hydrophobic pocket and to p.C127 (in black) but faces the opposite direction. The p.R86C variant (green, right panel) is not predicted to affect the binding capability of the hydrophobic pocket or to form a disulfide bond with p.C127.

predicted to disturb its binding capability or to have an effect on DSG1 dimerization (Fig. 1g).

We describe herein the first case, to our knowledge, of SPPK resulting from a heterozygous missense (as opposed to nonsense or frameshift) mutation in *DSG1*. Protein modelling predicts this mutation to abolish DSG1-mediated adhesive function, thus resulting in what could be manifested as functional haploinsufficiency. DSG1 has been shown to downregulate the Ras/mitogen-activated protein kinase pathway by interacting with Erbin; elevated Ras activity, resulting from DSG1 deficiency, is therefore thought to trigger cellular mechanisms leading to hyperkeratosis in SPPK.[11] Whether missense mutations in the extracellular domain affect this regulatory pathway remains to be determined. The putative mode of action of the mutation identified emphasizes the importance of the role of DSG1-mediated adhesive function in palmoplantar skin.

Acknowledgments

We thank the patient and her family for their collaboration. This work complies with the Committee on Publication Ethics (COPE) guidelines on good publication.

D. Vodo[1,2]
E.A. O'Toole[3]
N. Malchin[1]
A. Lahav[4]
N. Adir[4]
O. Sarig[1]
K.J. Green[5]
F.J.D. Smith[6]
E. Sprecher[1,2]

[1]*Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Centre for Cell Biology and Cutaneous Research, The Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, U.K.*
[4]*Schulich Faculty of Chemistry, Technion, Haifa, Israel*
[5]*Departments of Pathology and Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, U.S.A.*
[6]*Pachyonychia Congenita Project, School of Life Sciences, University of Dundee, Dundee, U.K.*

Correspondence: Eli Sprecher.
E-mail: elisp@tlvmc.gov.il

References

1 Itin PH, Fistarol SK. Palmoplantar keratodermas. *Clin Dermatol* 2005; **23**:15–22.
2 Lovgren ML, McAleer MA, Irvine AD *et al.* Mutations in desmoglein 1 cause diverse inherited palmoplantar keratoderma phenotypes: implications for genetic screening. *Br J Dermatol* 2017; **176**:1345–50.
3 Hershkovitz D, Lugassy J, Indelman M *et al.* Novel mutations in *DSG1* causing striate palmoplantar keratoderma. *Clin Exp Dermatol* 2009; **34**:224–8.
4 Armstrong DK, McKenna KE, Purkis PE *et al.* Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma. *Hum Mol Genet* 1999; **8**:143–8.
5 Whittock NV, Smith FJ, Wan H *et al.* Frameshift mutation in the V2 domain of human keratin 1 results in striate palmoplantar keratoderma. *J Invest Dermatol* 2002; **118**:838–44.
6 Boeckmann B, Bairoch A, Apweiler R *et al.* The SWISS-PROT protein knowledgebase and its supplement TrEMBL in 2003. *Nucleic Acids Res* 2003; **31**:365–70.
7 Kelley LA, Mezulis S, Yates CM *et al.* The Phyre2 web portal for protein modeling, prediction and analysis. *Nat Protoc* 2015; **10**:845–58.
8 Shapiro L, Fannon AM, Kwong PD *et al.* Structural basis of cell–cell adhesion by cadherins. *Nature* 1995; **374**:327–37.
9 Patel SD, Chen CP, Bahna F *et al.* Cadherin-mediated cell–cell adhesion: sticking together as a family. *Curr Opin Struct Biol* 2003; **13**:690–8.
10 Harrison OJ, Brasch J, Lasso G *et al.* Structural basis of adhesive binding by desmocollins and desmogleins. *Proc Natl Acad Sci U S A* 2016; **113**:7160–5.
11 Harmon RM, Simpson CL, Johnson JL *et al.* Desmoglein-1/Erbin interaction suppresses ERK activation to support epidermal differentiation. *J Clin Invest* 2013; **123**:1556–70.

Funding sources: this work was supported, in part, by the Pachyonychia Congenita Project.

Conflict of interests: none to declare.