Novel mutations in desmoglein 1: focal palmoplantar keratoderma in milder phenotypes

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DEAR EDITOR, Striate palmoplantar keratoderma (SPPK) (OMIM 148700) is an autosomal dominant genodermatosis characterized by linear hyperkeratosis of the volar aspects of the fingers extending onto the palm, associated with focal to diffuse hyperkeratosis of the soles.1 It is caused by heterozygous mutations in four different genes: desmoglein 1 (DSG1), desmoplakin (DSP), keratin 1 (KRT1) and keratin 16 (KRT16).1–4 We report three families, one Scottish, one English and one American, with autosomal dominant PPK as a result of three previously unreported DSG1 mutations, where the presence of a striate pattern appears linked to the severity of the phenotype.

Family 1 presented to their local dermatology services. Families 2 and 3 were identified through the International Pachyonychia Congenita Research Registry. All reported having PPK since early childhood, with a positive family history in all pedigrees. No affected individuals had any history of skin fragility, blistering, nail, hair or cardiac abnormalities. Plantar pain was not a significant reported feature other than for the proband in family 2, whose palmar disease was severe, associated with his work as a manual labourer.

In family 1, all affected members had mild focal keratoderma of the palms and soles except for the proband’s brother, with the most severe case in the family, who had striate keratoderma of the digits and palms bilaterally with the most severe focal pattern of the soles (Fig. 1, an additional figure illustrating clinical features in the three families is available on request from the authors). In family 2, the proband, a 34-year-old man, had a striate pattern of severe hyperkeratosis affecting both palms with painful, multiple deep fissures over the distal palm and fingers, a diffuse hyperkeratosis of the soles affecting the weightbearing surfaces and a dominant family history. In family 3, the proband had a focal pattern of hyperkeratosis affecting the palms and soles. A skin biopsy for histological assessment was declined by all patients.

Following written informed consent and ethical approval by a Western Institutional Review Board that complies with the Declaration of Helsinki, genomic DNA was extracted from peripheral blood leukocytes or from saliva collected in an Oragene DNA sample collection kit (DNA Genotek, Ontario, Canada). Family 1 was initially screened for focal pattern PPK/pachyonychia congenita mutations by polymerase chain reaction (PCR) and direct DNA Sanger sequencing of the keratin genes KRT6A, KRT6B, KRT6C, KRT16 and KRT17, before proceeding to DSG1 gene screening.5 The coding region and intron/exon boundaries of DSG1 were amplified using primers specific to DSG1 (details available on request from the authors). Purified PCR products were

![Fig 1. Pedigree of family 1 showing an autosomal dominant history of palmoplantar keratoderma. The arrow indicates the proband.](image-url)
sequenced on an ABI 3730 Automated DNA sequencing machine (Applied Biosystems, Foster City, CA, U.S.A.). Families 2 and 3 were screened using a 9-gene panel, designed using Agilent SureSelect (at myGenomics, Alpharetta, U.S.A.) that included these five keratin genes and DSG1, TRPV3, GJB6 and AAGAB, with pathogenic variants confirmed by Sanger sequencing. Variants were confirmed as pathogenic through sequencing unaffected and affected family members, and by reference to the in silico prediction tool, Mutation Taster. None of the variants were present on the database of Single Nucleotide Polymorphisms, 1000 Genome Project, NHLBI Exome Variant Server, Exome Aggregation Consortium or the Genome Aggregation Database.

A previously unreported 1 base pair heterozygous deletion mutation in DSG1, c.376_376delT, leading to a frameshift and premature stop codon, p.Tyr126Thrfs*5 was identified in the proband of family 1 and in three additional affected family members; two unaffected family members were wild-type. The proband of family 2 had a previously unreported nonsense mutation c.909G>A(p.Trp303*). The mutation was present in his affected mother but not in his unaffected father. Another previously unreported nonsense mutation was identified in the proband of family 3, c.1010T>G (p.Leu337*); no other family members were available for screening.

It is postulated that DSG1 mutations (frameshift or nonsense) causing SPPK result in haploinsufficiency through nonsense mediated mRNA decay because of premature termination codons. Multiple mutations in DSG1, frameshift and nonsense, and very recently a missense mutation have been described causing inherited PPK with variations in the clinical patterns of keratoderma noted. Although initially the majority of reported DSG1 mutations were associated with a striate pattern of hyperkeratosis, there is increasing evidence of nonstriate phenotypes caused by a recurrent nonsense mutation in DSG1. Arch Dermatol 2005; 141:625–8. This series raises the possibility that only the more severe DSG1 phenotypes are associated with a striate pattern and that DSG1 screening should be considered routinely in focal PPK, particularly those with no plantar pain.

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References


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Conflicts of interest: none to declare.