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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, due to 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 2-3 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, 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. 1a & Supplementary File,

S1, available from the author on direct request). In family 2, the proband, a 34 year-old male, 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 weight bearing surfaces and a dominant family history (S1). In family 3, the proband had a focal pattern of hyperkeratosis affecting the palms and soles (S1). 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.[1] The coding region and intron/exon boundaries of *DSG1* were amplified using primers specific to *DSG1* (available on request). Purified PCR products were sequenced on an ABI 3730 Automated DNA sequencing machine (Foster City, CA). Families 2 and 3 were screened using a 9-gene panel, designed using Agilent SureSelect (at myGenomics, Alpharetta, USA), which included these 5 keratin genes, and *DSG1*, *TRPV3*, *GJB6* and *AAGAB*, with pathogenic variants confirmed by Sanger sequencing. Variants were confirmed as pathogenic through sequencing unaffected and unaffected 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 (dbSNP), 1000 Genome Project, NHLBI Exome Variant Server, Exome Aggregation Consortium (ExAC) or the Genome Aggregation Database (gnomAD).

A previously unreported 1 bp 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 wildtype. The proband of family 2 had a previously unreported nonsense mutation, p.Trp303*; c.909G>A. 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, p.Leu337*; c.1010T>G; 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 due to premature termination codons.[5] 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.[6,7] Although initially the majority of reported *DSG1* mutations were associated with a striate pattern of hyperkeratosis, there is increasing evidence of non-striate patterns of keratoderma being present.[6,8] 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.

Acknowledgements

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Figure Legends:

Figure 1. (a) Pedigree of family 1 showing an autosomal dominant history of palmoplantar keratoderma. The arrow indicates the proband.

(Fig.1) Family1
DSG1 p.Tyr126Thrfs*5