Punctate palmoplantar keratoderma: an unusual mutation causing an unusual phenotype

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Dear Editor,

Palmoplantar keratodermas (PPKs, OMIM #144200) refers to a large phenotypically and genetically heterogeneous group of keratinization disorders characterized by marked hyperkeratosis on the surface of palms and soles\textsuperscript{1}.

Punctate PPK (PPKP) features multiple hyperkeratotic papules that develop in early adolescence or later and are irregularly distributed on the palms and soles\textsuperscript{2}. The disease is clinically classified into three autosomal dominant subtypes: PPKP1 (OMIM #148600, 614936) characterized by multiple tiny punctate keratoses and caused by mutations in the \textit{AAGAB} or \textit{COL14A1} genes\textsuperscript{2,3}; PPKP2 (OMIM #175860) which features tiny hyperkeratotic spinous papules\textsuperscript{4} and PPKP3 or acrokeratoelastoidosis (AKE, OMIM # 101850) which manifests with small hyperkeratotic papules located over the peripheral margins of the palms and soles and is typically associated with degeneration of elastic fibers on histology\textsuperscript{5}. The molecular etiology of PPKP2 and AKE remains unknown.

In this study, we identified a recessive mutation in \textit{SLURP1}, encoding the secreted mammalian Ly-6/urokinase plasminogen activator receptor-related protein-1 (SLURP1), causing a phenotype indistinguishable from typical AKE.

The patient was a 17-year-old female, born to consanguineous parents of Arab Moslem origin. She reported tiny lesions over the skin of her palms and soles since the age of 7, with some improvement in the summer. She denied additional systemic or dermatologic manifestations as well as similar clinical symptoms among her family members, including two healthy parents and a brother.

On examination, the patient exhibited multiple circumscribed, hyperkeratotic and hyperpigmented papules on the dorsal and lateral aspect of the hands and digits, and along the lateral margins of both soles (Fig. 1a). Haematoxylin and eosin staining of a skin biopsy showed orthohyperkeratosis and Verhoeff’s elastic stain revealed a decreased number of
dermal elastic fibers which were markedly fragmented (Fig. 1b). Based on the clinical and histopathological findings, the patient was diagnosed with AKE.

Because of the high percentage of PPKP cases occurring due to mutations in AAGAB\(^1\), after obtaining ethical approval and informed consent, the genomic DNA of the patient was subjected to Sanger sequencing for AAGAB mutations, but no pathogenic variant was identified. Therefore, whole-exome sequencing was performed by Macrogen Ltd (Seoul, Korea) using in-solution hybridization with SureSelect Human All Exon V5 kit (Agilent, Santa Clara, CA, USA) followed by massively parallel sequencing (Illumina HiSeq4000) with 100-bp paired-end reads. Reads were aligned to the Genome Reference Consortium Human Build 37 (GRCh37/hg19) using Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net/).

The patient was found to carry a rare homozygous transition (rs62636565) at position 310 of the SLURP1 gene predicted to abolish the gene stop codon (c.310T>C, p.*104Argext*16; reference sequence Ensembl accession number ENST00000246515.1). The mutation was later confirmed using direct sequencing of all coding exons of SLURP1, including exon-intron boundaries (Fig 1c).

The mutation was found to co-segregate with the disease phenotype in the family supporting an autosomal recessive mode of inheritance (Fig. 1c). The sequence variation has been rarely reported (MAF = 0.0005) and has been so far identified in a heterozygous state exclusively (http://gnomad.broadinstitute.org).

The mutation results in the substitution of an arginine residue for the native gene stop codon and is predicted to result in an open reading frame containing an additional 15 amino acids at the C-terminus, resulting in an elongated mutant protein (Fig. 1d). Of note, the existence of an alternative stop codon in the immediate vicinity (0-49 nucleotides downstream) of the native stop codon, suggest that the mutant SLURP1 mRNA is not subjected to nonstop mediated mRNA decay but is instead translated into a protein of abnormal length\(^6\).
Mutations in SLURP1 are known to cause Mal de Meleda (MDM), an autosomal recessive diffuse and severe type of palmoplantar keratoderma, beginning soon after birth and worsening with age. SLURP-1 affects nuclear factor-κB (NF-κB)-mediated signalling through binding to the α7-nicotinic acetylcholine receptor7.

Apart from being inherited in an autosomal recessive fashion, the phenotype of the patient differs considerably from MDM, which usually features apart from PPK, nail anomalies, hyperhidrosis, recurrent infections and pseudoainhum8. A recent study showed that while most MDM-causing SLURP1 mutations result in protein multimerization, interfering with the secretion of SLURP-1 as a monomer, a mutation causing mildly reduced amounts of the secreted monomeric protein only, resulted in a milder phenotype9. It is possible that the unique mutation identified in the present study, has a less severe effect on the secretion or function of SLURP-1, resulting in an unusual phenotype. At this regard, it is of interest to note that PPKP1 has been associated with increased EGFR signaling10 but a recent study ruled out a possible interaction between EGFR signaling and SLURP-1 function11.

To conclude, we describe here the first non-stop mutation in SLURP1, resulting in a highly atypical phenotype, indistinguishable from AEK. These data need confirmation in additional cases.

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References


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Legends to figure

Figure 1. Clinical features and mutation analysis. (a) The patient presented with multiple circumscribed, hyperkeratotic and hyperpigmented small papules on the lateral marginal borders of both soles. (b) Hematoxylin and eosin staining of a skin biopsy obtained from the skin of the patient demonstrated marked orthohyperkeratosis (upper panel). Verhoeff’s stain showed sparse and fragmented elastic fibers in the dermis (middle panel) as compared to control (lower panel). (c) Direct sequencing of the gDNA of the patient revealed a T>C homozygous transition at position c.310 within exon 3 of SLURP1 (lower panel). The wild-type sequence is given for comparison (upper panel). The healthy parents of the patient were found to carry the mutation in a heterozygous state (middle panels). (d) A schematic diagram depicts the SLURP1 gene structure. Boxes represent exons (white: 5'UTR and 3'UTR; grey: coding sequence). The non-stop mutation reported in the present study is predicted to result in the addition of 45 nucleotides (15 additional amino acids) beyond the position of the native stop codon to lead to a mutant protein with 118 amino acids (red box).
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