LETTER TO THE EDITOR

Early severe pachyonychia congenita subtype PC-K6a with a novel mutation in the *KRT6A* gene

Editor

Pachyonychia congenita (PC) comprises a group of rare, almost exclusively autosomal dominant disorders of keratinization characterized by palmoplantar keratoderma and nail dystrophy.[1,2] PC is caused by heterozygous mutations in one of the five keratin genes: *KRT6A* (OMIM 148041), *KRT6B* (OMIM 148042), *KRT6C* (OMIM 612315), *KRT16* (OMIM 148067) and *KRT17* (OMIM 148069), which alter keratins 6a, 6b, 6c, 16 and 17, and divide PC into subtypes PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17 respectively.[2,3]

With regard to pathogenesis, the mutant keratins destabilize the intermediate cell filament network within epithelial cells;[4,5] thus, leading to cell fragility, cytoskeleton disruption, impairment of appropriate protein/protein interactions, cytolysis and skin disorders.[1,4] The mutational spectrum covers all types, the majority being missense or small insertion/deletion.[1,5]

We describe a young Venezuelan boy presenting from early childhood with features highly suggestive of PC, namely hypertrophic nail dystrophy, leukokeratosis and follicular keratosis. The child has been followed up from 7 to 11 years. He was the second child of non-consanguineous healthy parents. Family history was negative and not contributory to the diagnosis (Fig. 1a). The patient showed thickening and discoloration of all the nails (Fig. 2a–b), oral leukokeratosis mainly on the tongue (Fig. 2c), follicular keratoses in areas of friction (Fig. 2d), palmar hyperhidrosis and focal palmoplantar keratoderma with painful blisters.

Genomic DNA from the patient and all available members of the family was extracted from saliva after obtaining a written informed consent. The *KRT6A*, *KRT6B*, *KRT16* and *KRT17* genes were analysed through polymerase chain reaction followed by direct sequencing. The analysis revealed a novel heterozygous deletion/insertion mutation c.1406_1410delTGGAGinsGGTA (p.Leu469ArgfsX1) in the *KRT6A* gene in the proband (Fig. 1b). DNA sequencing was extended to all reachable members of the family (II:4, II:5, III:4, III:6) and no mutations were detected.

This is a frameshift mutation starting with codon 469, which is changed from leucine to an arginine residue, and ending with a premature stop codon at position 1 of the new sequence which results in the truncation of the protein motif TYRKLLEGE (residues 464–472) at the C-terminus of the coil 2B domain, a highly conserved region among the intermediate filament family,[6] and the loss of the entire tail region (Fig. 1c). The TYRKLLEGE motif is necessary for the lateral association of filaments, while the tail enhances the stability of filaments as demonstrated in studies with keratins K5 and K14.[7]

Spaunhurst *et al.*[8] in a large series of 157 patients with *KRT6A* (89 pts) or *KRT16* (68 pts) mutations from the International Pachyonychia Congenita Research Registry who were 12 years or older, found that patients with mutations in *KRT6A* had more extensive disease compared with patients who had mutations in *KRT16*.

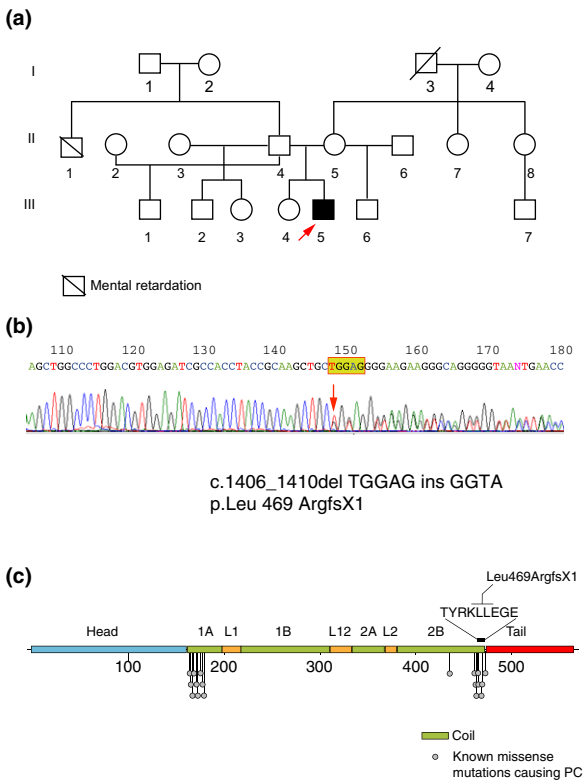

Figure 1 (a) Pedigree of the family, arrow indicates the proband (III:5), the only affected in the family with PC. (b) Heterozygous mutation (c.1406_1410delTGGAGinsGGTA, p.Leu469ArgfsX1) in the *KRT6A* gene. (c) This mutation causes the destruction of the highly conserved protein motif TYRKLLEGE (residues 464–472, small black rectangle) at the C-terminus of the coil 2B region and the loss of the entire tail region. Known missense mutations causing PC are indicated by the grey circles.

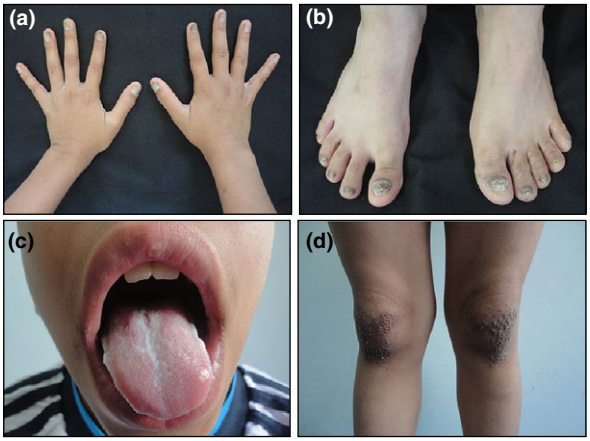

Figure 2 (a and b) Thickened and dark nails. (c) Tongue leukokeratosis. (d) Extensive follicular keratoses on knees.

Other large study series[3] or individual case reports[9] have highlighted the severity of the classical symptoms, their earlier onset in patients with *KRT6A* gene mutations, while milder forms were associated with other mutations such as *KRT6C*.[10]

In conclusion, we have reported on a novel mutation in *KRT6A* gene arising *de novo* and causing a severe form of PC with an early childhood presentation, highlighting functional impact of the novel p.Leu469ArgfsX1 mutation. The severity of the phenotype is due to the truncation of the TYRKLLEGE sequence motif and to the loss of the entire tail regions, which are essential for the cytokeratin filament polymerization and stability. The novel mutation in the *KRT6A* observed in our case confirms the role of this gene in causing early severe forms of PC and support the adoption of a classification system based upon the mutant gene for a disease which may span from mild localized (focal) to extensive mucocutaneous manifestations.

F. Cammarata-Scalisi,[1,*] K. Natsuga,[2] E. Toyonaga,[2] W. Nishie,[2] H. Shimizu,[2] A. Avendaño,[1] D. Araque,[1] G. Da Silva,[1] E. Bellacchio,[3] M. Callea[4]

[1]Unit of Medical Genetics, Department of Pediatrics, Faculty of Medicine, University of The Andes, Mérida, Venezuela, [2]Department of Dermatology, School of Medicine, Hokkaido University, Sapporo, Japan, [3]Bambino Gesù Children's Hospital IRCCS, Research Laboratory, Rome, Italy, [4]Department of Dentistry, Bambino Gesù Children's Hospital - IRCCS, Viale S. Paolo 15, 00147 Rome, Italy
*Correspondence: F. Cammarata-Scalisi.
E-mail: francocammarata19@gmail.com

References

1 Goldberg I, Fruchter D, Meilick A *et al.* Best treatment practices for pachyonychia congenita. *J Eur Acad Dermatol Venereol* 2014; **28**: 279–285.
2 Shah S, Boen M, Kenner-Bell B *et al.* Pachyonychia congenita in pediatric patients: natural history, features, and impact. *JAMA Dermatol* 2014; **150**: 146–153.
3 Eliason MJ, Leachman SA, Feng BJ *et al.* A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. *J Am Acad Dermatol* 2012; **67**: 680–686.
4 Knöbel M, O'Toole EA, Smith FJ. Keratins and skin disease. *Cell Tissue Res* 2015; **360**: 583–589.
5 Cao YA, Hickerson RP, Seegmiller BL *et al.* Gene expression profiling in pachyonychia congenita skin. *J Dermatol Sci* 2015; **77**: 156–165.
6 Lee CH, Kim MS, Chung BM *et al.* Structural basis for heteromeric assembly and perinuclear organization of keratin filaments. *Nat Struct Mol Biol* 2012; **19**: 707–715.
7 Wilson AK, Coulombe PA, Fuchs E. The roles of K5 and K14 head, tail, and R/K L L E G E domains in keratin filament assembly *in vitro*. *J Cell Biol* 1992; **119**: 401–414.
8 Spaunhurst KM, Hogendorf AM, Smith FJ *et al.* Pachyonychia congenita patients with mutations in KRT6A have more extensive disease compared with patients who have mutations in KRT16. *Br J Dermatol* 2012; **166**: 875–878.
9 Luo S, Luo Q, Zhang H *et al.* A novel H1 mutation in keratin 6a in an infant with pachyonychia congenita. *Indian J Dermatol Venereol Leprol* 2015; **81**: 385–387.
10 Wee JS, Smith FJ, Wilson NJ, O'Toole EA. Focal PPK secondary to a novel KRT6C mutation (Pachyonychia congenita-K6c). *J Eur Acad Dermatol Venereol* 2015; doi: 10.1111/jdv.13259. [Epub ahead of print] No abstract available. PMID: 26301947.

DOI: 10.1111/jdv.13800