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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Identification of two recurrent mutations in keratin genes in three cases with pachyonychia congenita

Editor

Pachyonychia congenita (PC) is a group of autosomal-dominant ectodermal dysplasias containing two main clinical subtypes: PC-1 and PC-2. PC-1 is caused by mutations in either K16 or K6α, and PC-2 is caused by mutations in K17 or K6β. Here, we reported two mutations: 380G > C resulting in a substitution of Argine for Proline (R127P) in K16 in a sporadic case with PC-1 and 296T > C causing substitution of Leucine for Proline (L99P) in K17 in a family presenting with PC-2.

Patient 1 was a 16-year-old boy with PC-1 who showed thickened nails and hyperkeratotic lesions on the palms and soles (fig. 1a) since birth. Patients 2 and 3 were individuals with PC-2 in two generations (a 15-year-old son and his mother). They showed pilosebaceous cysts at puberty associated with pachyonychia and palmar hyperkeratosis beginning within the first month of life (fig. 1b).

Genomic DNA samples were extracted from the patients, unaffected numbers and 50 unrelated individuals. Fragments containing all exons of the K16 and exon 1 of K17 were amplified. Polymerase chain reaction products were sequenced and compared with the unaffected, unrelated control samples. Mutation 380G > C leading to R127P in K16 (fig. 2a) and 296T > C predicting L99P in K17 (fig. 2b) were detected in the three cases.

fig. 1  (a) Palmar hyperkeratosis and pachyonychia in patient 1. (b) Pachyonychia and steatocystoma multiplex presenting in patient 2 and 3 (his mother).
Here, two mutations in PC were identified: R127P in K16 and L99P in K17. Interestingly, the three cases all presented with the mutations of proline substitution. K16 mutations may cause PC-1 or focal non-epidermolytic palmoplantar keratoderma (FNEPPK), and K17 mutations may cause PC-2 or steatocystoma multiplex (SM) phenotypes. According to previous literatures, Arg127Cys in K16 resulted in FNEPPK, whereas Arg127Pro led to PC-1. It implied the importance of substitution for proline in the genotype-phenotype relationship. It had been speculated that proline mutations in K16 are more likely to result in the PC-1 rather than FNEPPK. To our knowledge, never had the proline substitution producing SM been reported. Similarly, we can make the prediction that proline mutations in K17 are more likely to cause PC-2 compared with SM. The identification of the two mutations here is consistent with the speculations above. It would be due to the chemical structure of proline being strongly detrimental to the helical tertiary structures compared with other amino acid substitutions. The mutagenesis experiments in vitro showed that proline substitutions occurring in the helix boundary motif sequences are particularly disruptive to the assembly and function of intermediate filaments with being greatly condensed. Therefore, it might be predicted to lead to severe phenotypes as PC-1 or PC-2 rather than FNEPPK or SM. More study about the mutations in K16 or K17 are needed to confirm the speculation about the correlations between the genotype and phenotype.

Acknowledgement

This project is supported by the grant from National Natural Science foundation of China.

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**fig. 2.** (a) Heterozygous missense mutation 380G > C in K16 in the patient 1 (a1). Normal DNA sequence of K16 exon 1 (a2). (b) Heterozygous missense mutation 296T > C in exon 1 of K17 in patient 2 (b1). Heterozygous missense mutation 296T > C in exon 1 of K17 in patient 3 (b2). Normal DNA sequence of K17 exon 1 (b3).
References


DOI: 10.1111/j.1468-3083.2008.02752.x