

# A novel H1 mutation in keratin 6a in an infant with pachyonychia congenita

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## ABSTRACT

Pachyonychia congenita (PC) is a rare genetic disorder which is inherited in an autosomal dominant pattern. We report a sporadic novel H1 mutation in the *KRT6A* gene (c. 428G>A/p. Ser143Asn) in a Chinese infant patient. The mutation is concurrent with a single-nucleotide polymorphism and resulted in a serine for asparagine substitution in H1 subdomain of *KRT6A* chain next to the rod domain. The infant showed the classic symptoms of pachyonychia congenita. Conclusion: The heterozygous missense mutation c. 428G > A/p.Ser143Asn in *KRT6A* exon 1 may cause severe disease.

**Key words:** Keratin 6A gene, keratin-6, mutation, pachyonychia congenita

## INTRODUCTION

Pachyonychia congenita (PC, OMIM 167200 and 167210) is a rare autosomal dominant genetic disease that mainly affects the nails, palmo-plantar skin and oral mucosa. The greatest impact on patients' life is widely considered to be due to severe plantar pain secondary to thick keratoderma.<sup>[1]</sup> Based on the causative mutations identified in *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17*, pachyonychia congenita is subdivided into five subtypes namely PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17 respectively.<sup>[1,2]</sup> The clinical phenotypes overlap substantially across PC-K6a, PC-K16, PC-K6b, and PC-K17; thick toenails and painful plantar keratoderma, are the major phenotypic features; other common clinical findings include thick fingernails, oral leukokeratosis, palmar keratoderma, follicular hyperkeratosis, cysts including

epidermal inclusion cysts and pilosebaceous cysts, hoarseness, and natal teeth.<sup>[2,3]</sup> Currently, information regarding clinical the phenotype of mutations in *KRT6C* is limited to a small number of reported cases. The individuals present with a milder phenotype than that caused by mutation in other genes, usually manifesting palmo-plantar keratoderma with only mild or no nail changes and plantar pain.<sup>[3-7]</sup> The age at onset and some phenotypic characteristics may help the clinician to suspect a specific subtype before genotyping is completed.<sup>[2,3]</sup> Herein, we report a novel H1 mutation in *KRT6A* in a Chinese infant.

## CASE REPORT

A 3½-month old female child presented with hoarseness, abnormal nails and oral mucosal plaques since birth. Nails appeared yellowish at birth and had gradually darkened and thickened subsequently [Figure 1a]. At one week of age she was noticed to have a whitish plaque on the palatal mucosa which was diagnosed as "thrush" with associated "onychomycosis". Laboratory tests however, could not demonstrate fungus and she did not respond to itraconazole treatment. On examination, follicular hyperkeratosis was detected on both ears which was

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seen to progress to involve her back, buttocks and thighs by 1 year of age. At around 1½ years of age, she was found to develop blisters on her soles after walking [Figure 1c]. A detailed family history did not reveal any family member affected by a similar illness.

After informed consent was obtained, genomic deoxyribonucleic acid (gDNA) was extracted from whole blood samples taken from the patient and 12 of her family members [Figure 2]. Polymerase chain reaction (PCR) and DNA sequence analysis of all exons in *KRT6A*, *KRT16*, *KRT6B* and *KRT17* were performed by using Platinum® Taq DNA polymerase (Life technologies Invitrogen, USA), ABI Gene Amp PCR System 9700 PCR instrument (Life technologies Applied Biosystems, USA), and ABI 3730XL type DNA sequencer (Life technologies Applied Biosystems, USA). In addition, gDNA from 105 unrelated healthy Chinese individuals was used as controls.

This study was approved by the Committee of Science and Ethics of the West China Second Hospital, Sichuan University.



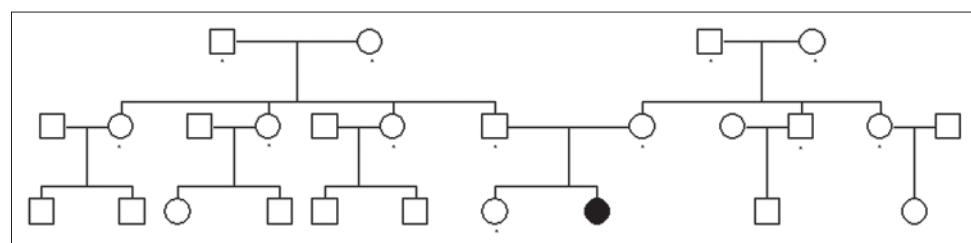
**Figure 1: Clinical features of the infant. (a) Hypertrophic nails at 3½ months of age (b) Oral leukokeratosis at the age of 6 months (c) Blisters on her feet at the age of 1½ years**

## RESULTS AND DISCUSSION

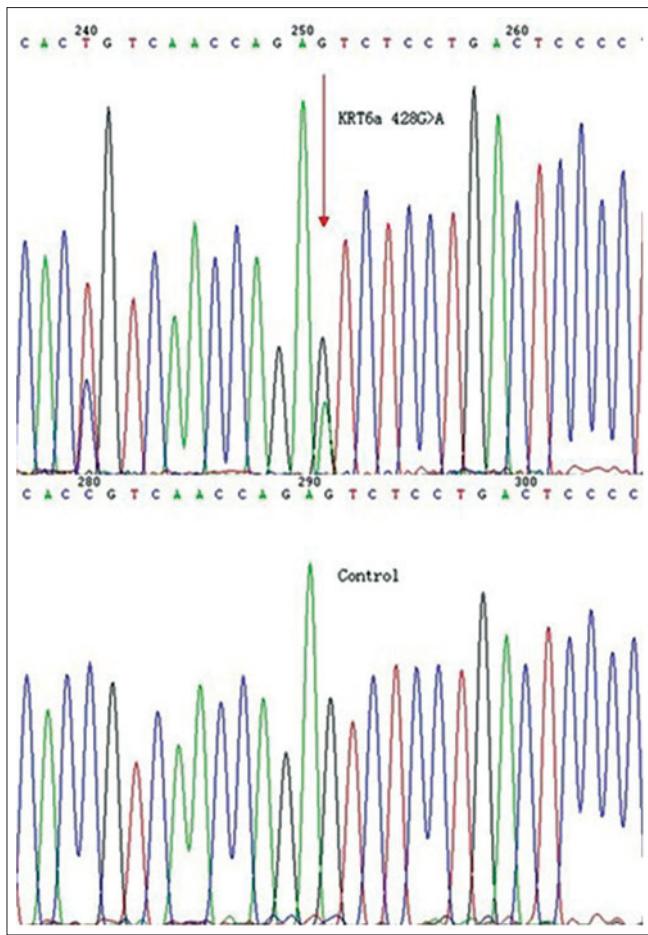
This 2-year-old patient had thickened toenails and fingernails, plantar keratoderma, oral leukokeratosis, hoarseness and follicular hyperkeratosis without natal teeth or steatocystoma multiplex. Both the thickened toenails and plantar keratoderma are major clinical features of pachyonychia congenita across all mutation subtypes.<sup>[2]</sup> We were unable to ascertain the occurrence of plantar pain because she was too young to express her pain clearly. Concurrent toenail and fingernail thickening since birth, oral leukokeratosis, hoarseness and follicular hyperkeratosis are findings that occur more frequently in the PC-K6a subtype than in other subtypes.<sup>[3]</sup>

Amplification and DNA sequencing did not reveal any mutation in all *KRT16*, *KRT6B*, and *KRT17* exons. However, one heterozygous missense mutation was found in *KRT6A* exon 1, c. 428G>A/p. Ser143Asn [Figure 3]. This mutation was not detected in any of the 105 controls and her family members including her father (for whom DNA fingerprinting analysis was done to establish paternity). This suggests a pathogenic mutation rather than a rare single-nucleotide polymorphism (SNP). This mutation occurred in the H1 subdomain of the K6A protein just before the rod domain. Early studies indicate that the H1 subdomain is important in the alignment of the nearest neighboring molecules in the keratin intermediate filament structure.<sup>[8,9]</sup> Mutations in the H1 domain do occur in other keratins, including *KRT16*; however, only two cases with mutation in H1 domain in *KRT6A* have been reported by Wilson *et al.*<sup>[1,7]</sup>

Our case in addition also demonstrated the nucleotide change c. 289G>A/p.Gly97Arg, which is a known single nucleotide polymorphism (SNP) in the dbSNP database (accession number: rs200254647). This nucleotide change was not detected in any of her family members.



**Figure 2: Pedigree chart of the family of proband: Dots in the pedigree indicate family members who were examined and were found not to carry the mutation c.289G>A/p.Gly97Arg**



**Figure 3: Mutation analysis of *KRT6A* showing a heterozygous missense mutation *KRT6A* c.428G>A/p.Ser143Asn and the sequence of a control individual**

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