Pachyonychia Congenita Project

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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.

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Mutations of *KRT6A* are more frequent than those of *KRT16* in pachyonychia congenita type **1**: report of a novel and a recently reported mutation in two unrelated Chinese families

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SIR, Keratins are structural proteins of epithelial tissue that consist of four helical segments named 1A, 1B, 2A and 2B.[1–3] Mutations at the beginning of helix 1A and the end of helix 2B can lead to different epithelial disorders.

Pachyonychia congenita (PC) is an autosomal dominant disorder characterized by hypertrophic nail dystrophy. In type 1 (MIM 167200), oral leucokeratosis, palmoplantar keratoderma and follicular keratosis may be observed. Type 2 (MIM 167210) has the useful distinguishing feature of sebaceous cysts which normally develop around puberty. As is known, keratin 6A (*KRT6A*) or keratin 16 (*KRT16*) defects cause PC-1, and mutations in keratin 6B (*KRT6B*) or keratin 17 (*KRT17*) cause PC-2.[1–3] Here, we report a novel mutation (Y465H) of *KRT6A* in a Chinese pedigree and a recently reported mutation (N171D) in a Chinese sporadic case of PC-1.

The Human Medical and Ethical Committee of Xi'an Jiaotong University approved the investigation presented here and all study subjects gave informed consent. We studied a Chinese pedigree of PC-1 (Fig. 1a) from Hebei province and a Chinese sporadic case from Shaanxi province.

Patient 1. All nails of the proband (female, aged 65 years) in this pedigree are characteristically thickened (Fig. 1b) and oral leucokeratosis has been present since birth. She has marked focal plantar keratoderma over pressure points with blistering of her feet during the summer months or after prolonged walking. The patient has had scattered follicular keratoses on the elbows, knees and buttocks since age 15 years. The other four affected family members had similar symptoms to the proband.

Patient 2. This sporadic patient (female, aged 24 years) has milder symptoms than members of the pedigree. All her fingernails and toenails have been characteristically thickened since birth. She also has follicular hyperkeratosis on the buttocks, but does not show any evidence of oral leucokeratosis. There are no hair anomalies, natal teeth or pilosebaceous cysts, which are diagnostic of PC-2 in all patients.

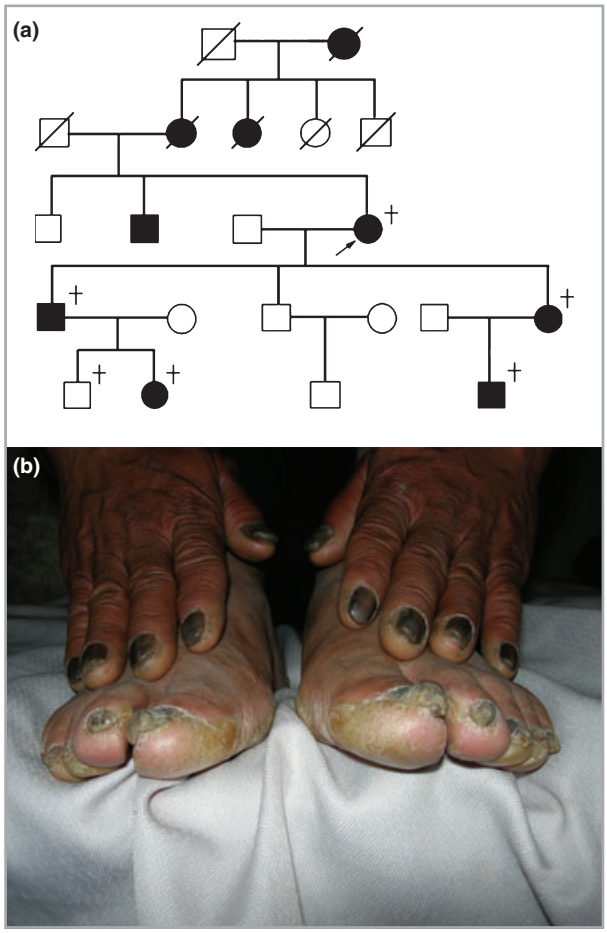

Fig 1. (a) Pedigree of the family showing autosomal dominant inheritance. Arrow, proband; +, members sequenced. (b) Hypertrophic dystrophy of the toenails and fingernails of the proband.

Five millilitres of peripheral blood was obtained from the proband, four affected family members, one unaffected member in the pedigree, the sporadic patient and 100 unrelated and unaffected people. Extraction of genomic DNA, polymerase chain reaction (PCR) primers and programs have been described previously.[4,5] Mutation detection was performed by direct sequencing of PCR products on an ABI 377 automated sequencer (Perkin-Elmer-Cetus Instruments, Norwalk, CT, U.S.A.).

Amplification and DNA sequencing of *KRT16* revealed no mutations, and consequently *KRT6A* was screened. Direct sequencing of the PCR products revealed a heterozygous 1393T>C mutation of in all five affected members of the pedigree (Fig. 2a), predicting the substitution of tyrosine by

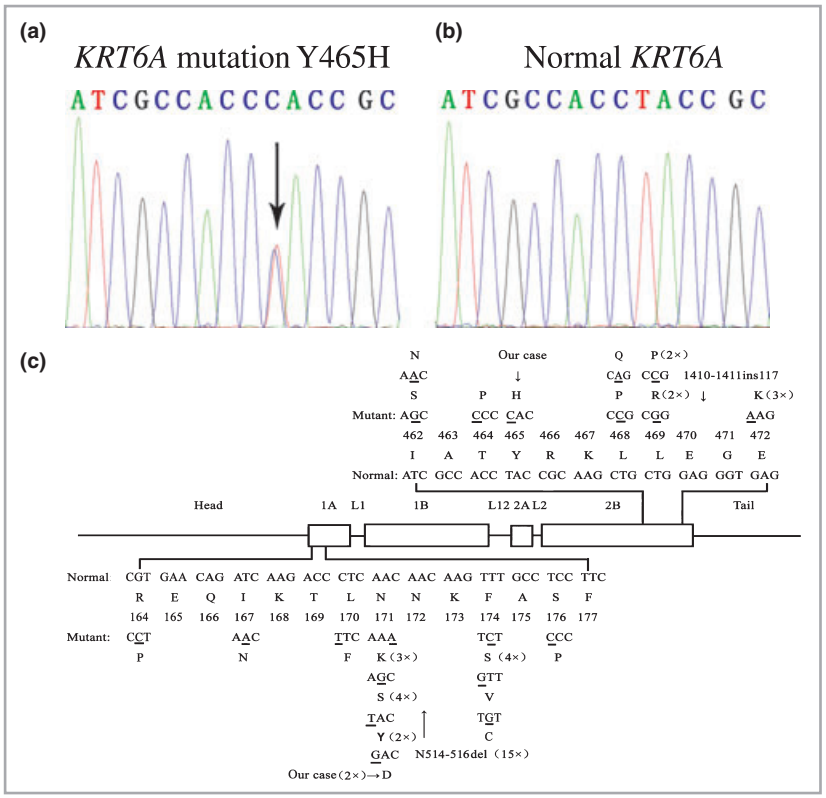

Fig 2. (a) Heterozygous missense mutation 1393T>C (arrow) of *KRT6A* exon 1 sequence (+ strand) corresponding to codons 462–466, predicting amino acid change Y465H in the pedigree. (b) Normal *KRT6A* exon 1 sequence (+ strand) corresponding to codons 462–466. (c) Schema of KRT6A protein structure and summary of reported *KRT6A* gene mutations in pachyonychia congenita type 1. Keratin has helix domains (1A, 1B, 2A, 2B) separated by linker domains (L1, L12, L2). The mutations reported here are at the beginning of the 1A domain and the end of the 2B domain, respectively. N171K (3 ×), N171S (4 ×), etc. indicate that these mutations have been independently reported more than once.

histidine in codon 465 (Y465H). In the sporadic patient, a 511A>G mutation was revealed, predicting the substitution of asparagine by aspartic acid in codon 171 (N171D). Mutation of Y465H is located at the end of the 2B domain and N171D at the beginning of 1A domain. No mutations were found in the unaffected members in the pedigree and 100 unrelated controls (Fig. 2b), which ruled out the polymorphism.

Through direct sequencing of the PCR products, we identified a novel mutation Y465H in the pedigree of PC-1. The codon Y465 is a new mutation site for PC-1; no mutation has previously been reported in this codon. The N171 codon of *KRT6A* is the most common codon for mutations in PC-1 (Fig. 2c) (http://www.interfil.org). The mutation of N171D that we found in the sporadic case has been reported recently.[6]

PC-1 is due to mutations of the *KRT16* gene or its expression partner *KRT6A*, whereas PC-2 is caused by mutations in the *KRT17* or *KRT6B* genes.[1–3] There are 48 reported mutations in the *KRT6A* gene in addition to the two mutations in our study, and 20 mutations in the *KRT16* gene (http://www.interfil.org). Concerning the domains involved, 35 mutations of *KRT6A* occur in domain 1A, and 13 in domain 2B. However, 27 mutations of *KRT17* have been reported, and only four of *KRT6B* until now.[1–3,6–9] Mutations of *KRT17* in PC-2 are seven times more frequent than those of *KRT6B*. Just like *KRT6A*, 26 mutations of *KRT17* are located in domain 1A, only one in domain 2B. It is concluded that mutations of *KRT6A* are more frequent than those of *KRT16* in PC-1, whereas mutations of *KRT17* in PC-2 are more frequent than those of *KRT6B*, and the 1A domain is a hot mutation 'domain'.

In conclusion, we report two heterozygous mutations Y465H and N171D in the *KRT6A* gene in a Chinese pedigree and a Chinese sporadic patient with PC-1. Because mutations of *KRT6A* are more common than those of *KRT16* in PC-1, in the future we may screen first for mutation in *KRT6A* in studies of PC-1. Further study is needed to determine why the *KRT6A* mutation is more involved.

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References

1 Irvine AD, McLean WHI. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation. *Br J Dermatol* 1999; **140**:815–28.

2 Irvine AD, McLean WHI. The molecular genetics of the genodermatoses: progress to date and future directions. *Br J Dermatol* 2003; **148**:1–13.

3 Leech SN, Moss C. A current and online genodermatosis database. *Br J Dermatol* 2007; **156**:1115–48.

4 Smith FJ, Del Monaco M, Steijlen PM *et al.* Novel proline substitution mutations in keratin 16 in two cases of pachyonychia congenita type 1. *Br J Dermatol* 1999; **141**:1010–16.

5 Smith FJ, McKenna KE, Irvine AD *et al.* A mutation detection strategy for the human keratin 6A gene and novel missense mutations in two cases of pachyonychia congenita type 1. *Exp Dermatol* 1999; **8**:109–14.

6 Liao H, Sayers JM, Wilson NJ *et al.* A spectrum of mutations in keratins K6a, K16 and K17 causing pachyonychia congenita. *J Dermatol Sci* 2007; **48**:199–205.

7 Feng YG, Xiao SX, Ren XR *et al.* Keratin 17 mutation in pachyonychia congenita type 2 with early onset sebaceous cysts. *Br J Dermatol* 2003; **148**:452–5.

8 Xiao SX, Feng YG, Ren XR *et al.* A novel mutation in the second half of the keratin 17 1A domain in a large pedigree with delayed-onset pachyonychia congenita type 2. *J Invest Dermatol* 2004; **122**:892–5.

9 Covello SP, Smith FJ, Sillevis Smitt JH *et al.* Keratin 17 mutations cause either steatocystoma multiplex or pachyonychia congenita type 2. *Br J Dermatol* 1998; **139**:475–80.

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Conflicts of interest: none declared.

