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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.
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.

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...
histidine in codon 465 (Y465H). In the sporadic patient, a
S11A>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 previ-
ously 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 expres-
sion 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. How-
ever, 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 muta-
tions 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 stud-
ies of PC-1. Further study is needed to determine why the
KRT6A mutation is more involved.

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References


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Conflicts of interest: none declared.