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CASE REPORT

Pachyonychia congenita: report of two cases and mutation analysis

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ABSTRACT

Pachyonychia congenita (PC) comprises a group of rare autosomal dominant genetic disorders that involve ectodermal dysplasia. It is characterized by hypertrophic nail dystrophy, focal palmoplantar keratoderma, follicular keratoses, and oral leukokeratosis. Historically, PC has been subdivided into two subtypes, PC-1 or PC-2, on the basis of clinical presentation. However, differential diagnosis based on clinical grounds, especially in young and/or not fully penetrant patients, can be difficult. In addition, clinical analysis of the large case series has shown that there is considerable phenotypic overlap between these two subtypes recently. Based on the advent of molecular genetics and the identification of the genes causing PC, more specific nomenclature has been adopted. Therefore, diagnosis at the molecular level is useful and important to confirm the clinical impression. In this report, we describe two typical cases of PC with mutation analysis revealed a small deletion (514_516delACC, Asn172del) and a point mutation (487 G > A, GAG → AAG, Glu163Lys) in the KRT6A gene.

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Introduction

Pachyonychia congenita (PC), a rare autosomal-dominant ectodermal dysplasia caused by mutations in one of a number of keratin genes, is characterized by hypertrophic nail dystrophy, focal palmoplantar keratoderma and blistering, oral leukokeratosis, cyst formation, palmoplantar hyperhidrosis, and follicular keratoses on the trunk and extremities.

Historically, PC has been subdivided into two subtypes, PC-1 or PC-2, on the basis of clinical presentation.1 However, the causative mutations were identified in several PC patients currently and more specific molecular genetic nomenclature has been adopted by causative genes,2,3 which include KRT6A, KRT6B, KRT16 and KRT17.4,5

Genetic analysis of PC not only confirms the clinical diagnosis but also aids in genetic counseling. Only two cases of PC (one is PC1 and another is PC2) have been previously reported in Taiwan but without genetic analysis.6,7 In this report, we describe two typical cases of PC with mutation analysis and review of the literature.

Case reports

Case 1

A 36-year-old Taiwanese man presented with marked thickening of all 20 nails present since infancy and palmoplantar hyperkeratosis which had developed during childhood with painful bullae making walking and participation in sports difficult. It was not clear whether natal or neonatal teeth were present. The patient’s intelligence was normal. The patient’s father had similar abnormally thickened nails but declined clinical examination. He is unmarried and has no offspring.

Physical examination revealed marked thickening of all finger and toe nails (Figures 1A and B), callus-like focal plantar keratoderma on the palms and soles (Figure 1C), hyperhidrosis, and leukokeratosis of the tongue (Figure 1D). Potassium hydroxide mounts and fungal cultures of the finger and toenails showed negative results. In addition, there were numerous cysts and nodules of various sizes all over the patient’s body (Figure 1E). Excision biopsy of one cystic lesion from the chest showed steatocystoma. There was no evidence of ocular, hair, or dental lesions. Based on the characteristic clinical findings, a diagnosis of PC type 1 (PC1) was made.

Case 2

A 45-year-old Taiwanese man presented with marked thickening of all 20 nails present since birth with rough and discolored surface, and subungual hyperkeratosis was apparent (Figure 2). Nails ever
dislodged due to external force, but new growing nails had the same characteristics as the previous nails. Focal palmoplantar hyperkeratosis was mild without blistering and did not bring any discomfort to the patient. Only occasional cysts or nodules over the patient’s body were noted. It was not clear whether natal or neonatal teeth were present. No obvious other characterized clinical features of PC were noted. He is unmarried and has no offspring. He denied that any member of his family, including his parents and siblings, had the same presentation as himself. He also mentioned that a number of methods have been tried to solve the thickened nail problem but none had any obvious effect.

Figure 1 Clinical manifestations of pachyonychia congenita type 1. (A) Marked thickening of all finger; (B) toe nails; (C) callus-like plantar keratoderma on the heels; (D) leukokeratosis of the tongue; (E) numerous cysts and nodules of various sizes all over the patient’s body.

Polymerase chain reaction amplification and automated sequencing
Genomic DNA was extracted from peripheral blood from the patient with the informed consent. The DNA sample was then subjected to mutation screening by amplification of segments of KRT6A and KRT16 gene.

For polymerase chain reaction (PCR) amplification, approximately 200 ng of genomic DNA, 12.8 pmol/L of each primer, 10 μmole/L dNTP and 1.25 U of AmpliTaq Gold (Perkin Elmer, Roche Molecular Systems, Inc., Branchburg, NJ USA) were used in a total volume of 50 μL. The oligonucleotide primers designed to amplify the mutation in exon 1 of the KRT6A gene are: forward primer,

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\text{Forward Primer: 5'}-\text{TAGGATGAGGTTCTCATCAG-3'}
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5′−CTTCCCTCTCCTCCAGCC−3′; reverse primer 5′−CTCTTAGTCT CTCCTGGCAG−3′. The product size is a 683 base pair. The amplification conditions were 94°C for 5 minutes, followed by 35 cycles of 94°C for 45 seconds, annealing temperature (60°C) for 45 seconds and 72°C for 45 seconds, and extension at 72°C for 10 minutes. The PCR products were examined on 2% agarose gel. The PCR product was subjected to direct automated sequencing (377 ABI Advanced Biotechnologies, Columbia, MD USA).

Direct genome sequencing of case 1 revealed a small deletion mutation (514_516delACC, Asn172del) (Figures 3A and B) in the exon 1 of KRT6A and Case 2 revealed a point mutation (487 G > A, GAG → AAG, Glu163Lys) of KRT6A, respectively (Figures 3C and D).

Discussion

PC is a rare autosomal dominant genodermatosis and has been linked to mutations in four keratin genes that are expressed in the epithelia, KRT6A, KRT6B, KRT16, and KRT17. Historically, PC was first described by Muller in the early twentieth century and has been subdivided into two subtypes, PC-1 (Jadassohn–Lewandowski type) or PC-2 (Jackson–Lawler type), under the classification proposed by Schonfeld on the basis of the clinical presentation.

Jadassohn–Lewandowsky type PC (PC1) is characterized by onychogryphosis, focal palmoplantar keratoderma, follicular hyperkeratosis, and leukoplakia of the oral mucosa. It is associated with mutations in the keratin 16 gene, or its expression partner keratin 6A. In addition to the features seen in type 1, Jackson-Lawler type PC (PC2) is characterized by bullae, palmoplantar hyperhidrosis, and cysts arising from the hair follicle infundibulum and sebaceous duct (eruptive vellus hair cysts and steatocystomas). Other findings in PC2 include natal teeth, hair abnormalities (pili torti), and hidradenitis suppurativa. However, a considerable phenotypic overlap between these two subtypes was found and case reports with misdiagnosis or cases with coincidental findings unrelated to PC is possible. It was not until the early 1990s with the emergence of molecular genetics technology that the causative gene was mapped to one of the keratin gene clusters. Shortly thereafter, the causative mutations were identified on several PC patients. Therefore, a combination of factors have led to the suggestion that PC should be reclassified including identification of the causative genes of PC can provide a rational means of classifying patients and the considerable phenotypic overlap between the two PC-1 and PC-2 was found by large case series analysis. Recently, more specific molecular genetic nomenclature has been adopted by the International Pachyonychia Congenita Consortium. In this system, PC-6a, PC-6b, PC-16, and PC-17 refer to cases with mutation identified in the genes KRT6A, KRT6B, KRT16, and KRT17, respectively. PC-U designates cases of suspected PC, where either a mutation has not been found or not been investigated.

To date, the majority of those reported mutations fall within the highly conserved helix boundary motifs of each keratin gene. These regions are thought to be vital for end-to-end overlap interactions during the elongation phase of filament assembly.

A large mutational study in PC was performed and shows approximately one-half of the kindreds had mutations in KRT6A (52%), 28% had mutations in KRT16, 17% in KRT17, and 3% of families had mutations in KRT6B. This mutation analysis study also identifies mutation hotspot codons of PC. The most common PC mutation is the p.Asn172del mutation that, to date, has been found in 32 out of 221 PC families (14%) with known mutations.

In Taiwan, there are only two previous case reports describing PC but with no genetic analysis. Our case report of these two patients is the first report of PC in Taiwan with mutation analysis (514_516delACC, Asn172del in the exon 1 of KRT6A) and (487 G > A, GAG → AAG, Glu163Lys of KRT6A), which is on the mutation hot-spot of PC.

In PC, there can also be variation in clinical severity between mutations in the same gene and even between individuals with the
same mutation. Polymorphisms, copy number variation, environmental factors, lifestyle, and patient care may account for some of this clinical variation.2 These factors may explain the variation in severity and clinical appearance between our two patients who have the same mutation gene (KRT6A). Therefore, an important conclusion is that PC can really be considered as a spectrum of phenotypes ranging from very mild to more severe.

In 2003, a patient advocacy group—Pachyonychia Congenita Project—was established to support those affected by PC and to both encourage and fund research into a cure for the condition. To achieve this goal, the International PC Consortium was founded in early 2004. This is a group of clinicians and scientists actively researching the causes of PC and, more importantly, the development of new treatments for PC.3 Various forms of treatment have been proposed for the skin and nail problems associated with PC, including keratolytic agents and lubricants, oral retinoids,1,7,17 high doses of vitamin A,18 vitamin E, X-ray therapy, protective footwear, topical aluminum chloride,19 and Botulinum toxin.20 None of these measures have produced any permanent solution to the distressing morbidity primarily related to the painful hyperkeratosis and blistering of the soles. Although it is a rare condition, PC is at the forefront of genetic research due to its broad clinical variation.2 These factors may explain the variation in genetic features of pachyonychia congenita.

Figure 3 (A) Automated DNA sequencing of KRT6A revealed a heterozygous 514_516delACC (Asn172del) mutation in Case 1; (B) normal sequence from control; (C) Case 2 shows point mutation (487 G > A, GAG → AAG, Glu163Lys) of KRT6A; (D) normal sequence from control.

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