Use of Articles in the Pachyonychia Congenita Bibliography

The articles in the PC Bibliography may be restricted by copyright laws. These have been made available to you by PC Project for the exclusive use in teaching, scholarship or research regarding Pachyonychia Congenita.

To the best of our understanding, in supplying this material to you we have followed the guidelines of Sec 107 regarding fair use of copyright materials. That section reads as follows:

Sec. 107. - Limitations on exclusive rights: Fair use
Notwithstanding the provisions of sections 106 and 106A, the fair use of a copyrighted work, including such use by reproduction in copies or phonorecords or by any other means specified by that section, for purposes such as criticism, comment, news reporting, teaching (including multiple copies for classroom use), scholarship, or research, is not an infringement of copyright. In determining whether the use made of a work in any particular case is a fair use the factors to be considered shall include - (1) the purpose and character of the use, including whether such use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the amount and substantiality of the portion used in relation to the copyrighted work as a whole; and (4) the effect of the use upon the potential market for or value of the copyrighted work. The fact that a work is unpublished shall not itself bar a finding of fair use if such finding is made upon consideration of all the above factors.

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.
ORIGINAL ARTICLE

Keratin 17 mutation in pachyonychia congenita type 2 patient with early onset steatocystoma multiplex and Hutchinson-like tooth deformity

Se-Woong OH, Moon Young KIM, Jeong Sun LEE, Soo-Chan KIM

Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine Seoul, Korea

ABSTRACT

Pachyonychia congenita type 2 (PC-2) is an autosomal dominant disorder characterized by hypertrophic nail dystrophy, focal keratoderma, multiple pilosebaceous cysts, and other features of ectodermal dysplasia. It has been demonstrated that PC-2 is caused by mutations in the keratin 17 and keratin 6b genes. In this report, we describe a missense mutation in the keratin 17 gene, M88T, in a Korean patient whose phenotype included early onset steatocystoma multiplex and Hutchinson-like tooth deformities along with other typical features of PC-2 such as hypertrophic nails, natal teeth and follicular hyperkeratosis.

Key words: Hutchinson teeth, keratin 17 mutation, pachyonychia congenita type 2.

INTRODUCTION

Pachyonychia congenita (PC) is a group of hereditary, autosomal dominant ectodermal dysplasias; the main feature is hypertrophic nail dystrophy. Two major clinical subtypes of PC are generally recognized, PC-1 (Jadassohn–Lewandowsky syndrome) and PC-2 (Jackson–Lawler syndrome). In PC-1, the pachyonychia is accompanied by oral leukokeratosis, palmo-plantar keratoderma, palmo-plantar hyperhidrosis and follicular keratosis. In PC-2, the pachyonychia is associated with focal keratoderma, follicular keratosis, multiple pilosebaceous cysts, natal teeth, hidradenitis suppurativa and hair abnormalities such as pili torti, bushy eyebrows or unruly hair. However, these features show variable expression.1,7 In classical PC-2, thickening of the nails usually begins within the first months of life. Natal teeth are sometimes present. However, the presence of pilosebaceous cysts is indispensable in the diagnosis of PC-2. Because the cysts usually appear around puberty, PC-2 is difficult to distinguish from PC-1 in childhood.4

Pachyonychia congenita has been linked to mutations in four differentiation-specific keratin genes. PC-1 is due to mutations in the keratin 16 (K16) gene or its expression partner, K6a. Meanwhile, PC-2 is due to mutations in the keratin 17 (K17) gene or the K6b gene.2 Mutations in K17 also cause steatocystoma multiplex, characterized by multiple pilosebaceous cysts with little or no nail involvement.3

Herein, we report a Korean patient presenting with the PC-2 phenotype. A mutation in the 1A domain of K17 underlies the affected patient’s phenotype.

SUBJECTS AND METHODS

We studied a Korean patient with PC-2. A 6-year-old Korean boy visited our department in March 2004. He had had natal teeth at birth and had developed hypertrophic nails 3 months later (Fig. 1a). At 1 year of age, he developed multiple skin-colored subcutaneous cysts (Fig. 1b). At 6 years of age, he had multiple, follicular, hyperkeratotic papules on his knees and elbows (Fig. 1c). He had no plantar hyperkeratosis.
or hair shaft abnormalities. His mouth and tongue were normal except for the teeth, which showed a Hutchinson-like central notch (Fig. 2). To rule out congenital syphilis, we performed Venereal Disease Research Laboratory (VDRL) and treponema pallidum hemagglutination (TPHA) tests, with negative results. None of his family members showed any features of PC-2.

After obtaining informed consent, total genomic DNA was extracted from a sample of his peripheral blood lymphocytes using a DNA extraction kit (QIAamp DNA Blood Midi kit, Qiagen, Hilden, Germany), and the DNA was used as a template for polymerase chain reaction (PCR) amplification of the exonic sequences of the K17 and K6b genes. Because the K17 gene has two pseudogenes (ψK17B, ψK17C)\textsuperscript{11} which complicate the mutation analysis, we designed the primer to prevent pseudogene contamination. The primer was set at the site with the greatest difference between the true gene and the pseudogene (Fig. 3). Specifically, the following primers were used to amplify exon 1 of the K17 gene: forward primer 5′-ATG GAA ACA GAG GAG CA-3′, reverse primer 5′-GCT GAC TCA GAC TGC TGT-3′. Amplification was performed at 95°C for 1 min, followed by 35 cycles of 95°C for 40 s, 58°C for 40 s, and 72°C for 1 min. The final extension was at 72°C for 3 min. Sequence analyses were performed using Big Dye terminator technology (ABI 3100 Perkin-Elmer, Warrington, UK). Genomic DNA samples from 50 normal, healthy Koreans were used as controls.

The mutation was confirmed using a restriction endonuclease. The PCR products were digested with \textit{Nla} III at 37°C for 2 h and analyzed on a 2% agarose/TBE (Tris borate ethylene diamine tetra acetate [EDTA]; 100 mmol Tris-HCl, 83 mmol boric acid, 1 mmol EDTA; pH 8.3) minigel.
RESULTS

Direct sequencing of the PCR products revealed a T-to-C transition at nucleotide 411 (ATG → ACG) in exon 1 of the K17 gene (Fig. 4). This transition results in the replacement of methionine with threonine in codon 88 (M88T), located in the 1A domain of K17. This sequence alteration destroys a Nla III restriction site, and was used to confirm the mutation in the affected individual (Fig. 5). No such mutation was found in any of the 50 unrelated controls. No mutation in the K6b gene was detected in the patient.

DISCUSSION

Keratins are structural proteins present in all epithelial cells. They are divided into type I (K9–20) and type II (K1–8) and form heterodimeric 10-nm intermediate filaments that are expressed in specific epithelial tissues as specific type I/type II keratin pairs. Every keratin has a similar structure, possessing a 310-amino acid residue central α-helical rod domain. This rod domain consists of four helical segments called 1A, 1B, 2A and 2B, which are divided by linkers known as L1, L12 and L2. The sequences at either end of the rod domain, the helix boundary motifs, are highly conserved and are critical for the assembly of intermediate filaments. Most pathogenic mutations are in the highly conserved helix boundary motifs, and all of the previously reported mutations found in PC patients affect one of the highly conserved sequences at either end of this helical rod domain except for one mutation in the mid-region of the 2B helical domain of K16.

Keratin 17 is expressed in the outer root sheath of the hair follicle, sebaceous glands, nail beds and other appendages. To date, 14 mutations in K17 have been described in patients with either PC-2 or steatocystoma multiplex. All of them have been located in the helix initiation domain (1A). We have also identified a missense mutation, M88T, in this domain. This mutation was previously reported by Celebi et al.

The most interesting clinical manifestation of our patient is the Hutchinson-like tooth deformity, a characteristic finding of congenital syphilis. We ruled out congenital syphilis in our patient by the negative results of the VDRL and TPHA tests. Although the Hutchinson-like tooth deformity has not been previously reported in PC, we cannot completely exclude the possibility that it is a novel manifestation of PC-2. In classical PC-2, pilosebaceous cysts usually appear at puberty; however, our patient has had cystic nodules on the face since the age of 1 year and had a heterozygous missense mutation,
There is also a previous report regarding the M88T mutation in K17 in which a sebaceous cyst developed in the second decade of life.\textsuperscript{13} There are two reports regarding early onset of the cysts, developing at the age of 1 and 5 years.\textsuperscript{6,14} These patients had the heterozygous missense mutations N92S and V102M, respectively. N92S is the most commonly reported mutation in PC-2, but there is only this one case of early onset sebaceous cysts for that mutation. Therefore, it seems that there is no correlation between early onset pilosebaceous cysts and a specific mutation. It is known that steatocystoma multiplex occurs in adolescence and develops under the influence of androgens.\textsuperscript{15} Feng \textit{et al.}\textsuperscript{6} speculated that the androgenic stimulation of the sebaceous gland and environmental factors, in addition to the site and type of the keratin mutation, may influence the age of onset of sebaceous cysts. We do not know which factors influence the onset of sebaceous cysts. However, it seems that other modifying factors such as environmental factors or androgenic stimulation contribute to determining the age of onset for sebaceous cysts.

ACKNOWLEDGMENTS

We thank Dr Jong-Eun Lee in DNA Link for advice and technical assistance. This work was supported by the BK21 project for Medical Science, Yonsei University.

REFERENCES


