Pachyonychia Congenita Project

15 March 2005

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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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necessarily mean there is only one candidate gene. We do not know whether SSH1, ARPC3, and SART3 are involved in the same pathway, but some papers suggest that SSH1 and ARPC3 may be involved in the actin cytoskeleton pathway (Welch *et al.*, 1997; Pollard *et al.*, 2000; Volkmann *et al.*, 2001; Niwa *et al.*, 2002; Pelham and Chang, 2002).

As to the heterozygous C/A-peak perhaps it is caused by the low-resolution online image referred to (Figure 1 which is reproduced here). We are not sure whether the S63N mutation is innocuous or not, but it should be confirmed by experiments.

We sincerely thank the authors for their attention to our research. The conclusions in our papers may be not perfect, but the data generated by the experiment are valid.

CONFLICT OF INTEREST

The author states no conflict of interest.

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Editor's Note

Journal of Investigative Dermatology (2007) **127,** 2060; doi:10.1038/sj.jid.5700955; published online 5 July 2007

TO THE EDITOR

An Associate Editor with expertise in the field reviewed the online publication in question, along with an independent observer, and agrees with Dr Zhang. In addition, the Editor reviewed all figures associated with this publication, including those submitted for review purposes and those published online and in print, and the Editor agrees with Dr Zhang. The Editor appreciates the concern over the validity of original data published in the *JID*, and considers this case closed.

Lowell A. Goldsmith

Editor

A Novel Mutation in K6b in Pachyonychia Congenita Type 2

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TO THE EDITOR

Pachyonychia congenita is a rare autosomal-dominant disorder of keratin that was first described in 1685 (Leachman *et al.*, 2005). Named by Jadassohn and Lewandowsky in 1906, this syndrome is characterized by hypertrophic nail dystrophy, focal palmoplantar keratoderma, follicular keratoses, and other ectodermal features varying by subtype. It is now well known that pachyonychia congenita type 1 (PC-1), also known as Jadassohn–Lewandowsky syndrome, is caused by mutations in either keratin 6a (K6a) or keratin 16 (K16), whereas pachyonychia congenita type 2 (PC-2), also known as Jackson–Lawler syndrome, is caused by mutations in keratin 6b (K6b) or its expression partner keratin 17 (K17) (Munro, 2001). Both subtypes have hypertrophic nail dystrophy and painful plantar keratoderma as the most significant clinical findings with features such as natal teeth, steatocysts, and hair abnormalities being more common in PC-2 and oral leukokeratosis more common in pachyonychia congenita type 1 (Leachman *et al.*, 2005).

The number of patients worldwide that are believed to have PC is between 1,000 and 10,000 (Kaspar, 2005). There have been more than 82 mutations published in the literature thus far with all established mutations consistent

Abbreviations: K6a, keratin 6a; K6b, keratin 6b; K16, keratin 16; K17, keratin 17; PC-1, pachyonychia congenita type 1; PC-2, pachyonychia congenita type 2

with an autosomal-dominant presentation or a spontaneous mutation (29–46% of patients have a negative family history) (Leachman *et al.*, 2005). Nearly all of the reported mutations occur at the beginning or end of the central keratin rod domain, within the helix initiation motif or helix termination motif (Smith *et al.*, 2005). These particular regions are integral in end-to-end association of protein subunits during keratin filament assembly (Smith *et al.*, 2005). In PC-2, mutations have been noted in the helix initiation and termination motifs of K17, but only in the helix termination motif of K6b (Smith *et al.*, 1998; Leachman *et al.*, 2005). We report a patient with typical clinical features of PC-2 and a novel mutation in the helix initiation motif of K6b, the first genetic defect identified in this portion of the gene.

A 14-year-old Caucasian female presented to our university clinic in January 2000. She reported history of thickened nails since she was 2 months old and thickening of her soles over the past several years. However, she was most bothered by the continued development of multiple cysts, clinically consistent with steatocystomas and milia. On physical exam, she had thick, hyperkeratotic toenails and yellowish, hyperkeratotic plaques on bilateral soles (Figure 1). She had multiple milia and steatocystomas scattered over her face and upper chest (Figure 2). She had no oral lesions, and her hair and teeth were normal. There was no definite family history, but her father reportedly had dystrophic toenails (evaluation and genetic testing of the parents were refused).

After obtaining informed consent, and in compliance with the Declaration of Helsinki Principles, genomic DNA was extracted from a buccal swab obtained from the patient by standard method. Direct sequencing of DNA from the patient revealed a heterozygous deletion of three base pairs in exon 1 of the *KRT6B* gene, in the helix initiation motif. The mutation is denoted p.Asn172del (N172del) on the protein level and c.516_518del3 on the cDNA level. No mutations were found in the keratin 6a, keratin 16, or K17 genes. The K6b mutation identified in this patient has not previously been reported. Interestingly, the analogous amino acid on keratin 6a has been found to contain deletions or missense mutations resulting in clinical features consistent with PC-1. Moreover, N172 (or N171 depending on the numbering convention used) on keratin 6a is the most common locus for mutation in PC-1 (Leachman *et al.*, 2005; Smith *et al.*, 2005).

Although other mutations in K6b have been reported, this is the first mutation to be found within the helix initiation motif of K6b. Other known mutations in PC-2 include a heterozygous missense mutation E472K, located in the helix termination motif of K6b, and a handful of mutation sites in the helix initiation and termination motifs of K17 (Covello *et al.*, 1998; Smith *et al.*, 1998; Hashiguchi *et al.*, 2002; Smith *et al.*, 2005; Oh *et al.*, 2006).

Keratins are structural proteins that form heterodimeric filaments, expressed in epithelial tissues as specific type I and type II keratin pairs (Smith *et al.*, 2005). In PC-2, the defective keratins are either K17 or K6b, which are constitutively expressed in the luminal cell layers of sebaceous glands, matrix and outer root sheath of hair follicles, and in the nail bed. Defects in these genes are thought to lead to keratinocyte fragility, leading to the clinical phenotype of PC-2 (Smith *et al.*, 2005). Significant overlap has been noted in patients with PC-2 and steatocystoma multiplex. The K17 mutation at R94C has been shown to cause steatocystoma multiplex without the nail changes in some families and the full PC-2 clinical phenotype in others, leading to the hypothesis that genetic or environmental modifiers

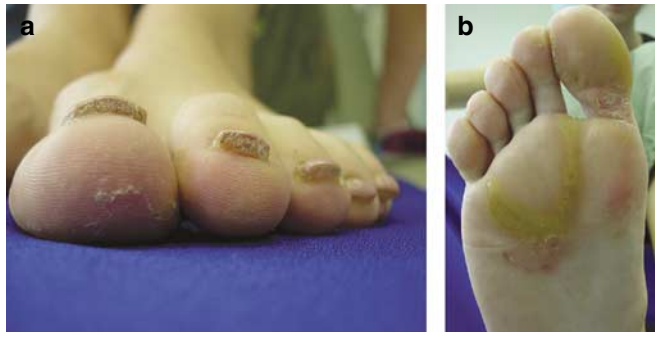

Figure 1. Clinical features of the patient with K6b mutation. (**a**) Photograph of the hyperkeratotic, dystrophic toenails. (**b**) Plantar keratoderma with fissuring and scale.

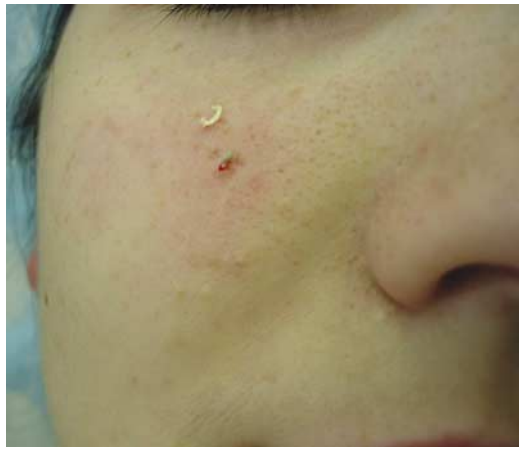

Figure 2. Facial steatocystomas. Note the multiple skin-colored papules on the patient's face with two papules extruding greasy contents consistent with steatocystomas.

influence the genotype–phenotype relationship (Covello *et al.*, 1998; Leachman *et al.*, 2005). No patients have been reported with K6b mutations and pure steatocystoma multiplex (McLean *et al.*, 2005), but our patient does have multiple flesh-colored papules which extrude greasy contents, consistent with steatocystomas.

Treatment for pachyonychia congenita is limited and fairly unsuccessful by current standards. The most debilitating feature as reported by patients is plantar pain, with the most promising treatments thus far consisting of activities to reduce friction and botulinum toxin to decrease sweating (Leachman *et al.*, 2005; Milstone *et al.*, 2005). Other features, such as hyperkeratosis of the nails, cysts, and mucous membrane lesions are managed by symptomatic treatment ranging from use of humectants and mechanical removal of keratin in thick nails to excision or incision and drainage of cysts. Fortunately, newer and better gene-based treatments are on the horizon. Exciting options being considered include triplex-forming oligonucleotides or zinc-finger nucleases to inactivate or induce correction of the mutant allele and most promising to date, the use of targeted small inhibitory RNAs to silence gene expression of the mutant allele (Lewin *et al.*, 2005; Hickerson *et al.*, 2006). Hopefully, with continued research into the genetics of pachyonychia congenita, the goal of gene-based therapy will become attainable.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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P75 Plays a Key Role in the Induction of the Sprouting of Sensory Nerve Fibers in Inflamed Skin

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TO THE EDITOR

In hyperkeratosis and acanthosis, peripheral branches of sensory nerves increase remarkably in number, particularly in the epidermis of inflamed skin (Mihm *et al.*, 1976; Pincelli *et al.*, 1990; Tobin *et al.*, 1992; Ostlere *et al.*, 1995). It has been supposed that nerve growth factor (NGF) secreted from keratinocytes in inflamed skin may induce the sprouting of the neurites of sensory fibers (Dou *et al.*, 2006) because of an increase in both NGF expression in the keratinocytes (Kinkelin *et al.*, 2000; Takano *et al.*, 2005; Tanaka and Matsuda, 2005) and cutaneous innervation in the epidermis in the inflamed skin (Horiuchi *et al.*, 2005). The NGF effect may occur via low-affinity receptors (p75) and high-affinity receptors (TrkA), although direct evidence for this is lacking. This study clearly demonstrates, by using p75 knockout mice, that sprouting of sensory fibers in the epidermis and hyperkeratosis and acanthosis of the inflamed skin are induced by an NGF–p75 pathway.

Abbreviations: NGF, nerve growth factor; PC, picryl chloride (2,4,6-trinitrochlorobenzene)