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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.
A spectrum of mutations in keratins K6a, K16 and K17 causing pachyonychia congenita

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Received 30 March 2007; received in revised form 4 July 2007; accepted 10 July 2007

Summary

Background: Pachyonychia congenita (PC) is a rare autosomal dominant keratin disorder, subdivided into two major variants, PC-1 and PC-2. Predominant characteristics include hypertrophic nail dystrophy, focal palmoplantar keratoderma and oral leukokeratosis. Multiple steatocystomas that develop during puberty are a useful feature distinguishing PC-2 from PC-1. At the molecular level it has been shown that mutations in keratin K6a or K16 cause PC-1 whereas those in K6b or K17 lead to PC-2.

Objective: To identify mutations in 22 families presenting with clinical symptoms of either PC-1/focal non-epidermolytic palmoplantar keratoderma (FNEPPK) or PC-2.

Methods: Mutation analysis was performed on genomic DNA from PC patients by direct sequencing.

KEYWORDS
Keratoderma; Genodermatosis; Keratinizing disorder; Nail dystrophy; Bullous disease

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0923-1811/530.00 © 2007 Japanese Society for Investigative Dermatology. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jdermsci.2007.07.003
Introduction

Pachyonychia congenita, a rare autosomal dominant keratin disorder, can be divided into two main subtypes [1,2], PC-1 (OMIM #167200; Jadassohn-Lewandowski syndrome) and PC-2 (OMIM #167210; Jackson—Lawler syndrome). Characteristics common to both forms are hypertrophic nail dystrophy, focal palmoplantar keratoderma, follicular keratoses and oral leukokeratosis, as reviewed recently [3]. Hypertrophic nail dystrophy of the hands and feet, usually develops at or soon after birth and presents as very thickened nails that grow to full length or as nails that terminate prematurely (Fig. 1 a and b). Oral leukokeratosis is normally present soon after birth and can be one of the earliest clinical observations. This is generally more pronounced in PC-1 than PC-2 (Fig. 1c). Focal plantar keratoderma tends to develop later in life as children begin to walk, exerting pressure on the soles of the feet. In some cases, particularly in PC-1, this is very severe (Fig. 1 d) and is generally the most painful and debilitating aspect for the patients. Palmar keratoderma is generally less severe or absent. Follicular keratoses are often found in areas of friction such as the elbows and knees. Epidermal inclusion cysts can be found in both PC subtypes [3,4]. Pilosebaceous cysts such as sebaceous cysts and vellus hair cysts are PC-2 specific (Fig. 1e) and are the major clinical features distinguishing PC-2 from PC-1. These normally develop during puberty typically on the face and trunk. In addition, natal teeth and pili torti may be present in PC-2, however, these traits are not fully penetrant and, therefore, not always present in all members of the same family. Differential diagnosis based on clinical grounds, especially in young and/or not fully penetrant patients, can be difficult. Therefore, diagnosis at the molecular level is useful to differentiate these two conditions. For both PC subtypes, severity of the clinical phenotype can vary, not only between families but also within a family (clinical heterogeneity).

Keratins are the major structural proteins of the epidermis and its appendages and form the type I (K9—20) and type II (K1—8) groups of intermediate filaments. There are at least 54 functional keratin genes which are expressed in a tissue- and differentiation-specific manner [5,6]. Over the last decade, keratin mutations have been identified as the cause of a number of skin fragility disorders [7]. The specific expression pattern of the defective keratin determines which tissue(s) are affected. Four keratins are associated with PC, mutations in K6a or K16 cause PC-1 [8,9] and those in K6b or K17 lead to PC-2 [9,10]. In general, the mutations are either heterozygous missense mutations or small-in-frame deletion/insertion mutations. To date, the majority of those reported fall within the highly conserved helix boundary domains at either end of the keratin rod domain (Fig. 2). These regions are thought to be vital for end-to-end overlap interactions during the elongation phase of filament assembly [11]. A number of in vitro studies have demonstrated that keratin mutations cause disruption to filament assembly and network formation, the severity of which can vary with the position of, or the actual mutation. At the clinical level these mutations present as skin fragility disorders, for example PC, or epidermolysis bullosa simplex (EBS), depending on the expression patterns of the keratins involved [12].

Here, we report the molecular characterization of 22 new PC families and further expand the spectrum of causative mutations in the K6a, K16 and K17 genes.

Methods

2.1. Clinical material

Genomic DNA was extracted from peripheral blood lymphocytes using a standard procedure, with informed consent and appropriate ethical approval that complies with the Helsinki Accord.
Fig. 1  Cardinal clinical features of pachyonychia congenita. (a) Hypertrophic nail dystrophy showing premature tapering of the nails in family 2. (b) Nail dystrophy in the form of thickened nails in family 10. (c) Oral leukokeratosis is generally more pronounced in PC-1 than PC-2, (family 2). (d) Focal palmoplantar keratoderma in family 15. (e) Widespread distribution of steatocystomas in PC-2.

Fig. 2  Diagram showing the basic protein structure of a keratin filament and the position of novel mutations in K6a and K16. The α-helical rod domain is divided into four domains, the 1A, 1B, 2A, 2B, connected by linkers, L1, L12 and L2. At either end of the rod domain (shown in grey) are the highly conserved helix boundary domains, the helix initiation motif (amino terminus) and helix termination motif (carboxy terminus). H1 and H2 sub-domains are present in type II keratins. The “stutter” sequence is marked by S.
<table>
<thead>
<tr>
<th>Family</th>
<th>PC subtype</th>
<th>Occurrence</th>
<th>Nail changes</th>
<th>Plantar keratosis onset</th>
<th>Oral leukokeratosis</th>
<th>Follicular keratoses</th>
<th>Notes</th>
<th>Keratin</th>
<th>Novel/known</th>
<th>Protein change</th>
<th>Domain</th>
<th>DNA change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PC-1</td>
<td>Familial three generations</td>
<td>Sporadic</td>
<td>Birth</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters. Atypical, inflammatory distribution of plantar keratoderma onto the dorsal aspect of the feet</td>
<td>K6a</td>
<td>Novel</td>
<td>p.Arg164Pro</td>
<td>1A, HIM</td>
<td>c.491G&gt;A</td>
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<tr>
<td>2. PC-1</td>
<td>Sporadic</td>
<td>Day after birth</td>
<td>Birth</td>
<td>3—12 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Novel</td>
<td>p.Asn171Asp</td>
<td>1A, HIM</td>
<td>c.511A&gt;G</td>
</tr>
<tr>
<td>3. PC-1</td>
<td>Sporadic</td>
<td>Birth</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Novel</td>
<td>p.Asn171Tyr</td>
<td>1A, HIM</td>
<td>c.511A&gt;T</td>
<td></td>
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<td>4. PC-1</td>
<td>N/A</td>
<td>Birth</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Age 2: no nail dystrophy yet</td>
<td>K6a</td>
<td>Novel</td>
<td>p.Asn171Tyr</td>
<td>1A, HIM</td>
<td>c.511A&gt;T</td>
<td></td>
</tr>
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<td>5. PC-1</td>
<td>Sporadic</td>
<td>Birth</td>
<td>10 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Novel</td>
<td>p.Phe174Cys</td>
<td>1A, HIM</td>
<td>c.521T&gt;G</td>
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<tr>
<td>6. PC-1</td>
<td>Sporadic</td>
<td>Infancy</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Asn171Ser</td>
<td>1A, HIM</td>
<td>c.512A&gt;G</td>
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<tr>
<td>7. PC-1</td>
<td>Sporadic</td>
<td>Birth</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Asn171Ser</td>
<td>1A, HIM</td>
<td>c.512A&gt;G</td>
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<tr>
<td>8. PC-1</td>
<td>Familial</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Asn172del</td>
<td>1A, HIM</td>
<td>c.514_516delAAC</td>
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<tr>
<td>9. PC-1</td>
<td>Sporadic</td>
<td>Birth</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Asn172del</td>
<td>1A, HIM</td>
<td>c.514_516delAAC</td>
<td></td>
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<td>10. PC-1</td>
<td>Sporadic</td>
<td>Infancy</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Early tooth loss/decay, build up of ear wax</td>
<td>K6a</td>
<td>Known</td>
<td>p.Asn172del</td>
<td>1A, HIM</td>
<td>c.514_516delAAC</td>
<td></td>
</tr>
<tr>
<td>11. PC-1</td>
<td>Sporadic</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Asn172del</td>
<td>1A, HIM</td>
<td>c.514_516delAAC</td>
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<tr>
<td>12. PC-1</td>
<td>Familial three generations, five affected</td>
<td>Sporadic</td>
<td>Birth</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Leu469Arg</td>
<td>2B, HTM</td>
<td>c.1406T&gt;G</td>
</tr>
<tr>
<td>13. PC-1</td>
<td>Familial two generations, two affected</td>
<td>Birth</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Leu469Pro</td>
<td>2B, HTM</td>
<td>c.1406T&gt;C</td>
<td></td>
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<tr>
<td>14. PC-1</td>
<td>Sporadic</td>
<td>15 days</td>
<td>6 months</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Glu472Lys</td>
<td>2B, HTM</td>
<td>c.1414G&gt;A</td>
<td></td>
</tr>
<tr>
<td>15. PC-1</td>
<td>Familial three generations, 12 affected</td>
<td>Infancy</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K6a</td>
<td>Known</td>
<td>p.Glu472Lys</td>
<td>2B, HTM</td>
<td>c.1414G&gt;A</td>
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<tr>
<td>16. PC-1</td>
<td>Sporadic</td>
<td>None</td>
<td>18 months</td>
<td>No</td>
<td>N/A</td>
<td>Age 6: no nail dystrophy yet</td>
<td>K16</td>
<td>Novel</td>
<td>p.Asn125Ser</td>
<td>1A, HIM</td>
<td>c.374A&gt;G</td>
<td></td>
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<tr>
<td>17. PC-1</td>
<td>FNEPPK</td>
<td>Sporadic</td>
<td>8 yr</td>
<td>3—12 yr</td>
<td>No</td>
<td>No</td>
<td>Very mild nail changes</td>
<td>K16</td>
<td>Known</td>
<td>p.Asnn125Ser</td>
<td>1A, HIM</td>
<td>c.374A&gt;G</td>
</tr>
<tr>
<td>18. PC-1</td>
<td>FNEPPK</td>
<td>Familial six generations, eight affected</td>
<td>Familial three generations</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>No</td>
<td>Very mild nail changes</td>
<td>K16</td>
<td>Known</td>
<td>p.Asn125Ser</td>
<td>1A, HIM</td>
<td>c.374A&gt;G</td>
</tr>
<tr>
<td>19. PC-1</td>
<td>FNEPPK</td>
<td>N/A</td>
<td>13 months</td>
<td>No</td>
<td>N/A</td>
<td>Very mild nail changes</td>
<td>K16</td>
<td>Known</td>
<td>p.Asn125Ser</td>
<td>1A, HIM</td>
<td>c.374A&gt;G</td>
<td></td>
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<tr>
<td>20. PC-1</td>
<td>Sporadic</td>
<td>Few months</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>No</td>
<td>Originally diagnosed as EBS at birth due to skin blistering.</td>
<td>K16</td>
<td>Known</td>
<td>p.Arg127Pro</td>
<td>1A, HIM</td>
<td>c.380G&gt;C</td>
<td></td>
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<tr>
<td>21. PC-1</td>
<td>Sporadic</td>
<td>6 months</td>
<td>By 2 yr</td>
<td>Yes</td>
<td>No</td>
<td>Plantar blisters</td>
<td>K16</td>
<td>Known</td>
<td>p.Leu128Gln</td>
<td>1A, HIM</td>
<td>c.383T&gt;A</td>
<td></td>
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<tr>
<td>22. PC-1</td>
<td>Sporadic</td>
<td>10 yr</td>
<td>13—19 yr</td>
<td>No</td>
<td>No</td>
<td>Cysts on the face at birth.</td>
<td>K17</td>
<td>Known</td>
<td>p.Asn925Ser</td>
<td>1A, HIM</td>
<td>c.275A&gt;G</td>
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</tr>
<tr>
<td>23. PC-1</td>
<td>Sporadic</td>
<td>15 months</td>
<td>By 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K17</td>
<td>Known</td>
<td>p.Asn925Ser</td>
<td>1A, HIM</td>
<td>c.275A&gt;G</td>
<td></td>
</tr>
<tr>
<td>24. PC-1</td>
<td>Sporadic</td>
<td>2 years</td>
<td>1 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K17</td>
<td>Known</td>
<td>p.Asn925Ser</td>
<td>1A, HIM</td>
<td>c.275A&gt;G</td>
<td></td>
</tr>
<tr>
<td>25. PC-1</td>
<td>Sporadic</td>
<td>5 years</td>
<td>4 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K17</td>
<td>Known</td>
<td>p.Asn925Ser</td>
<td>1A, HIM</td>
<td>c.275A&gt;G</td>
<td></td>
</tr>
<tr>
<td>26. PC-1</td>
<td>Sporadic</td>
<td>10 years</td>
<td>10 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Plantar blisters</td>
<td>K17</td>
<td>Known</td>
<td>p.Asn925Ser</td>
<td>1A, HIM</td>
<td>c.275A&gt;G</td>
<td></td>
</tr>
</tbody>
</table>

HIM, helix initiation motif; HTM, helix termination motif; yr, year.
2.2. Mutation detection and confirmation

K6a, K16 and K17 were amplified by PCR using specific primers to avoid amplification of additional K6 genes or K16/K17 pseudogenes as previously described [13]. PCR products were purified using the QIA quick PCR purification kit (Qiagen) and sequenced on an ABI 3100 or 3730 automated sequencing machine according to the manufacturer’s instructions. The K16 deletion mutation c.1052_1059+16del24 was confirmed by cloning the PCR fragment into pCR2.1 vector (Invitrogen) and sequencing several independent clones. All mutations were excluded from 50 normal control DNA samples by sequencing or restriction enzyme digests (data not shown).

3. Results

3.1. Clinical details

Of the 21 families presenting with PC-1/FNEPPK, 7 showed autosomal dominant inheritance, while 13 were sporadic cases, and in one case, the family history could not be ascertained (Table 1). Families 1—15, 20 and 21 presented with the typical clinical hallmarks of PC-1 [3], as shown in Fig. 1a—d. The age of onset of the most common features are listed in Table 1. A number of more unusual symptoms have been reported in a few cases of PC [3] and in some cases in this study (Table 1). Interestingly, family 16 (K16 c.1052_1059+16del24) and three unrelated families (families 17—19) carrying mutation K16 p.Asn125Ser had a slightly different clinical presentation. Specifically, individuals in these families either had normal nails or very subtle nail changes, such as splinter haemorrhages, that developed later than in most classical cases of PC-1. There was also a lack of oral leukokeratosis and, therefore, these families could be classed as focal non-epidermolytic palmoplantar keratoderma (FNEPPK), a recognised allelic variant of PC-1 (OMIM #600962), in which K16 defects have been reported previously [14,15]. In family 22, PC-2 has been inherited through several generations and interestingly, the nail dystrophy and plantar keratoderma developed later in the proband of this kindred than in many cases of PC-1. In this individual, as with many other cases of PC-2, the plantar keratoderma is not as clinically problematic as the widespread distribution of steatocystomas which can require frequent surgical removal.

3.2. Mutation analysis

Mutations were identified in 22 new cases of PC from Ireland, Italy, Netherlands, Spain, UK and USA as.
detailed in Table 1. Mutation analysis was performed on one member of each family (with the exception of family 13 where DNA was available from 2 members). Four novel mutations were identified in 5 families for the K6a gene; K6a p.Arg164Pro, p.Asn171Asp, p.Asn171Tyr x2, p.Phe174Cys (Fig. 3). Five previously identified mutations were found in K6a (p.Asn171Ser x3, p.Asn172del x3, p.Leu469Pro, p.Leu469Arg and p.Glu472Lys x2) [13,16]. Note that according to the recently revised mutation nomenclature K6a p.Asn172del is the correct numbering for the mutation that was previously denoted K6aAsn171del in several earlier publications. In a further six cases of PC-1, we found mutations in K16. In one case, an unusual mutation resulting in deletion of 24 bp was identified, c.1052_1059+16del24, as shown in Fig. 3. This mutation spans the exon 5/intron 5 junction, deleting the last 8 bp of exon 5 (cDNA bases 1052—1059 inclusive) and the first 16 bp of intron 5. In protein terms, it is impossible to say with absolute certainty what this genomic mutation does without analysis of mRNA from the patient, which was not available for this study. However, it is likely to lead to skipping of exon 5, which is an in-frame exon. This is predicted to lead to a deletion of 42 amino acids from the 2B domain of the K16 protein which would be consistent with the diagnosis of dominant PC-1 or a related FNEPPK phenotype. Known mutations found in K16 were p.Asn125Ser, p.Arg127Pro and p.Leu128Gln [13,16,17]. The single PC-2 family analysed had the most commonly reported mutation in K17, p.Asn92Ser [13]. The position of the new mutations identified in K6a and K16 within the keratin protein domain structure are shown in Fig. 2.

4. Discussion

PC was first shown to be a keratin disorder at the molecular level in the mid 1990s when mutations were identified in K6a, K16 and K17 [8,9], shortly followed by mutations in K6b [10]. Including the cases analysed here, the total number of mutations reported in these 4 genes associated with PC is 108 (www.interfil.org; and [18]). The majority of these fall within the highly conserved helix boundary domains at either end of the α-helical rod domain. This is similar to that seen for many other keratin disorders and these findings provide further evidence to support the importance of these domains and their role in keratin filament assembly. For PC there is not such a clear genotype/phenotype correlation as there is for EBS, another keratin disorder caused by mutations in either K5 or K14 [19]. In EBS a number of mutations have been found in the rod domain, internal to the helix boundary domains; in general mutations in these regions lead to a milder phenotype than those within the helix boundary domains. Of the 22 mutations reported here, only one was found centrally within the rod domain (Fig. 2). This was an unusual novel mutation in K16 which results in deletion of 24 bp, c.1052_1059+16del24 across the exon 5/intron 5 junction. This sporadic case (family 16) presented with focal keratoderma at the age of 18 months. The patient, now aged 6, has not yet developed nail dystrophy or other features. We predict that the mutation would result in skipping of exon 5 leading to a deletion of 42 amino acids from the 2B domain of the K16 protein which, from previous cases, may result in a predominantly FNEPPK phenotype rather than a more severe PC-1 presentation. It will be interesting to follow this case in future years.

Of interest here, unrelated families 17—19, who all carry the K16 mutation p.Asn125Ser presented with only mild nail changes but with mild—severe focal plantar keratoderma. These findings are consistent with two out of three other reported cases of this same mutation [13,14]. The numbers are still too small to determine whether the K16 p.Asn125Ser/FNEPPK is a truly distinct genotype:phenotype correlation. A case with a mutation at the same codon resulting in a different amino acid substitution, K16 p.Asn125Asp [13] had more typical PC-1 with earlier onset, severe nail dystrophy and plantar keratoderma. In this instance, the actual amino acid change may play a role in determining the clinical phenotype along with the position of the amino acid within the keratin molecule. In addition, genetic modifiers and environmental factors are likely to be involved in the severity of the clinical phenotype [20].

Currently there are no specific therapies for PC, or the most painful and disabling feature of the disorder, plantar keratoderma. One treatment that has been used successfully in a small number of PC patients to relieve pain from plantar keratoderma is botulinum toxin [21]. This promising pain-relief therapy requires further testing in a double blind randomised trial. However, there are now several research programs focussing on the development of more specific therapeutics for PC. Due to the dominant-negative nature of the mutations, the effect of the mutant allele has to be overcome or ablated. One approach currently being investigated is to target the specific mutation by siRNA to down-regulate the mutant protein [22]. It is predicted that even partial reduction of the mutant protein would result in an improvement in clinical phenotype. Since there are in total at least 55 different causative mutations (www.interfil.org; [18]; and those in this report) for PC, the
identification of novel or recurrent mutations in new cases of PC is not only important for confirming the clinical diagnosis but will continue to be necessary for the development of potential gene-specific or mutation-specific treatments.

Conflicts of interest

The authors declare that there is no conflict of interest.

Acknowledgements

We thank all the patients for their participation in this research and clinicians who have helped us and sent DNA from families in this study: Prof. M.F. Jonkman and Dr. A.J. van Essen, Groningen, The Netherlands; Prof. J.A. McGrath, The Guy’s, King’s College and St. Thomas’ Hospitals’ Medical School, London, UK; Prof. R. Hennekom and Dr. A. Taylor, Great Ormond Street Hospital, London, UK; Dr. E. J.C. Stewart, Leigh Infirmary, Leigh, UK; Dr. K Batta, Watford General Hospital, UK and Dr. D. Shurman, Thomas Jefferson University Hospital, Philadelphia, USA. We are grateful to the International Pachyonychia Congenita Consortium for clinical input and patient recruitment. FJDS is supported by Pachyonychia Congenita Project and DEBRA UK (WHIM and EBL).

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