Abstract

Pachyonychia congenita (PC) is a rare autosomal dominant genetic skin disorder due to a mutation in any one of the five keratin genes, KRT6A, KRT6B, KRT6C, KRT16, or KRT17. The main features are palmoplantar keratoderma, plantar pain, and nail dystrophy. Cysts of various types, follicular hyperkeratosis, oral leukokeratosis, hyperhidrosis, and natal teeth may also be present. Four unrelated Indian families presented with a clinical diagnosis of PC. This was confirmed by genetic testing; mutations in KRT17 were identified in all affected individuals.

Key Words: Cysts, keratin, keratin mutation, nail dystrophy, pachyonychia congenita, palmoplantar keratoderma, plantar pain

Introduction

Pachyonychia congenita (PC) is a rare autosomal dominant genodermatosis which is caused by a mutation in any one of the five keratin genes, KRT6A, KRT6B, KRT6C, KRT16, or KRT17.[1] There are an estimated 5000–10,000 cases worldwide.[2] PC affects all ethnic backgrounds and the same mutations are found among various nationalities. More than 100 distinct mutations have now been identified resulting in an array of PC phenotypes (www.pachyonychia.org). PC is characterized by a triad of dystrophy of some or all toenails and/or fingernails, plantar keratoderma, and plantar pain. Other associated features are cysts of various types, follicular hyperkeratosis, oral leukokeratosis, hyperhidrosis, and natal teeth.[1]

Historically, PC was divided into two subgroups, PC-1 and PC-2.[4,5] However, this classification is based on case series and isolated case reports. PC has features overlapping with other palmoplantar keratodermas (PPKs), but the modern-day discriminator is mutational analysis. Over the past 10 years, the PC project (www.pachyonychia.org) has gathered data on over 700 genetically confirmed PC patients, which have been compiled in the International PC Research Registry (IPCRR). Based on these more extensive data, the classification was revised in 2011 according to keratin mutation subtypes, i.e., PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17 that correspond to mutations in the KRT6A, KRT6B, KRT6C, KRT16, and KRT17 genes, respectively.[3,6] The clinical features of all five subtypes overlap and although there are some differences that distinguish between them, confirmation by genetic testing provides the definitive diagnosis. PC-K17 individuals have multiple cysts that develop at puberty, and milia are often present in young children. The presence of natal teeth indicates PC-K17 (though...
not all PC-K17 cases have natal teeth). Plantar pain in PC-K17 is highly variable between individuals. Those with PC-K6a, in general, have high levels of plantar pain, 20/20 nail involvement, and oral leukokeratosis. PC-K6b and PC-K6c mostly present with milder and less nail involvement and milder plantar keratoderma than other subtypes. PC-K16 individuals have painful plantar keratoderma and more palmar keratoderma. Nail involvement varies from extremely hypertrophic nails to few or no nails involved and certain mutations in KRT16, p. Asn125Ser and p.Arg127Cys, are known to be associated with mild or no nail involvement.[7]

These four families with mutations in KRT17 are the first-reported cases from India with PC to be reported with genetic testing to confirm the clinical diagnosis.

Case Report

The proband from Family 1 was a 30-year-old female who presented with complaints of multiple cysts on the neck, trunk, axillae, extremities, and abdomen [Figure 1] with thickened nails and plantar keratoderma. The onset of skin lesions began at the age of 18 years. The patient gave history of natal teeth. Her daughter was similarly affected [Figure 2]. Features were noted when she was younger which could have been due to increased awareness of the disease within the family. The cutaneous features and clinical course of the disease were in keeping with PC as described in literature, although plantar pain was strikingly absent. Plantar pain is the most common finding in patients of PC and has been reported in nearly 90% of patients above the age of 10 years.[3] For all cases in this report, genomic DNA was extracted from peripheral blood leukocytes using standard procedures or from saliva collected in an Oragene DNA sample collection kit (DNA Genotek, Ontario, Canada) and extracted according to the manufacturer’s protocol. Samples were obtained by the IPCRR with informed consent and ethical approval from the Western Institutional Review Board that complies with principles of the Helsinki Accord. Mutation analysis was performed as described by Wilson et al. in 2014.[1] A heterozygous missense mutation in KRT17, K17 p. Met88 Lys, c.263T>A, was identified in Family 1 in both the proband and her daughter; this is a previously reported mutation.[8]

A 37-year-old female from Family 2 presented as a spontaneous case with thickened finger and toenails, plantar keratoderma, mild plantar pain, multiple cysts, and natal teeth [Figures 1 and 2]. She had no oral leukokeratosis or follicular keratosis. A previously reported heterozygous missense mutation was identified, K17 p.Leu95Pro.c.284T>C.[1,9]

In Family 3, a 30-year-old male presented with painful plantar keratoderma, palmar keratoderma, thickening of all finger and toenails, oral leukokeratosis, natal teeth, and multiple cysts [Figure 2]. By direct DNA sequence

Figure 1: Mild to severe plantar keratoderma (a) Family 1 (affected daughter) and (b) Family 3. Thickened finger and toenails, (c) Family 1 (affected daughter), (d) Family 4, (e) Family 3, and (f) Family 2

Figure 2: Multiple cysts present on the neck, axillae, and abdomen: (a and c) proband from Family 1, (b and d) the affected individual from Family 2. (e) Affected individual from Family 4 showing natal teeth
A 6-month-old girl from Family 4 presented with multiple milia on her face and thickening of all finger and toenails [Figure 2]. She had two natal teeth but no oral leukokeratosis [Figure 1]. Her parents were unaffected. She was found to have a previously reported heterozygous missense mutation in KRT17, K17 p.Leu99Pro, c.296T>C.\(^1,9\)

**Discussion**

Here, we report mutations in KRT17 as the cause of PC in all 4 families (5 individuals) from India. For individuals from Families 1, 2, and 3, the predominant feature and main complaint was multiple cysts [Table 1]. Typical of young children with PC-K17, the young girl in Family 4 had multiple milia and will likely develop cysts around puberty. Thickening of the finger and toenails started very early in childhood, and for each of the five cases, all twenty nails were affected [Table 1]. Two of the four adults reported plantar pain, and in one case, this was extremely painful often requiring medication. These features along with the presence of natal teeth are very typical of the PC-K17 form of PC [Table 1]. Summary of the clinical data of the five Indian cases and 109 (including these five cases) genetically confirmed PC-K17 cases in the IPCRR is shown in Table 2. All these mutations have been previously reported in different ethnic populations.

The lack of awareness regarding this disease and the paucity of genetic testing in suspected cases could be one of the reasons for the rarity of reported cases. We hope that this report will heighten awareness among dermatologists in developing countries to consider a diagnosis of PC when a patient presents with the triad of nail involvement, plantar pain, and PPK often accompanied with cysts, follicular hyperkeratosis, oral leukokeratosis, hyperhidrosis, and natal teeth and to confirm the initial diagnosis by genetic testing. PC Project provides free services including physician consultations, genetic testing and other support services to PC patients worldwide. Nearly 15% of those clinically diagnosed with PC and referred to the IPCRR (www.pachyonychia.org) are found to have a condition other than PC. This observation demonstrates the importance of obtaining a genetic confirmation of the disorder. The expanding database of molecular and clinical data collected by the IPCRR is of huge benefit in the development of future clinical trials.

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**Conflicts of interest**

There are no conflicts of interest.

**Table 1:** Summary of the clinical data and mutations of the 5 Indian cases

| Family | Sex/age | Mutation-protein change | DNA change | Unreported or previously reported | Familial or Spontaneous | Cysts | Thickened nails | Plantar pain | Oral leukokeratosis | Follicular hyperkeratosis | Natal teeth |
|--------|---------|-------------------------|------------|----------------------------------|-------------------------|-------|---------------|-------------|---------------------|------------------------|------------|
| 1      | Female - proband age 30 years | K17 p.Met88Lys | c.263T > A | Previously reported | Familial | Multiple | No | Yes | Yes | No | Yes |
| 2      | Female - daughter age 5 | K17 p.Met88Lys | c.263T > A | Previously reported | Familial | Multiple | Yes | Yes | Yes | No | Yes |
| 3      | Female - age 37 years | K17 p.Asn92Ser | c.275A > G | Previously reported | Spontaneous | Multiple | No | Yes | No | No | Yes |
| 4      | Male - age 30 years | K17 p.Asn92Ser | c.275A > G | Previously reported | Spontaneous | Multiple | No | Yes | No | No | Yes |
| 5      | Female - age 6 months | K17 p.Leu99Pro | c.296T > C | Previously reported | Spontaneous | Multiple | No | Yes | No | No | Yes |

\(^1,9\) Agarwala, et al. Keratin 17 mutation in Pachyonychia Congenita.
Table 2: Summary of the clinical data of the 5 Indian cases and 109 (including these 5 cases) genetically confirmed pachyonychia congenita-K17 cases in the International Pachyonychia Congenita Research Registry

| Variable                           | India (n=5) (%) | PC-K17 (n=109) (%) |
|-----------------------------------|-----------------|--------------------|
| **Toenails, thickened**           | 5 of 5 (100)    | 106 of 109 (97)    |
| All 10 toenails thickened         | 5 of 5 (100)    | 82 of 109 (75)     |
| 7-9 toenails thickened            | 0 of 0 (0)      | 10 of 109 (9)      |
| 4-6 toenails thickened            | 0 of 0 (0)      | 7 of 109 (6)       |
| 1-3 toenails thickened            | 0 of 0 (0)      | 7 of 109 (6)       |
| **Age at onset-toenails**         |                 |                    |
| Birth or <1 year                  | 4 of 5 (80)     | 72 of 106 (68)     |
| 1-4 years old                     | 1 of 5 (20)     | 24 of 106 (23)     |
| 5-14 years old                    | 0 of 5 (0)      | 9 of 106 (8)       |
| 15 years and over                 | 0 of 5 (0)      | 1 of 106 (1)       |
| **Fingernails, thickened**        |                 |                    |
| All 10 fingernails thickened      | 5 of 5 (100)    | 47 of 109 (43)     |
| 7-9 fingernails thickened         | 0 of 5 (0)      | 11 of 109 (10)     |
| 4-6 fingernails thickened         | 0 of 5 (0)      | 26 of 109 (24)     |
| 1-3 fingernails thickened         | 0 of 5 (0)      | 9 of 109 (8)       |
| **Age at onset-fingernails**      |                 |                    |
| Birth or <1 year                  | 4 of 5 (80)     | 66 of 93 (71)      |
| 1-4 years old                     | 1 of 5 (20)     | 19 of 93 (20)      |
| 5-14 years old                    | 0 of 5 (0)      | 5 of 93 (5)        |
| 15 years and over                 | 0 of 5 (0)      | 3 of 93 (3)        |
| **Plantar keratoderma**           |                 |                    |
| Always (never completely go away) | 4 of 5 (80)     | 86 of 109 (79)     |
| Sometimes (feet clear up completely at times) | 0 of 5 (0) | 12 of 109 (11) |
| Seldom (feet are usually clear/symptoms) | 0 of 5 (0) | 4 of 109 (4) |
| **Age at onset-plantar**          |                 |                    |
| Birth or <1 year                  | 0 of 4 (0)      | 12 of 86 (14)      |
| 1-4 years old                     | 2 of 4 (50)     | 28 of 86 (33)      |
| 5-14 years old                    | 1 of 4 (25)     | 35 of 86 (41)      |
| 15 years and over                 | 1 of 4 (25)     | 12 of 86 (14)      |
| **Plantar pain**                  |                 |                    |
| Often require medication to handle pain | 1 of 4 (25) | 16 of 86 (19)   |
| Very painful, but do not use medication | 0 of 4 (0) | 25 of 86 (29) |
| Somewhat painful                  | 1 of 4 (25)     | 31 of 86 (36)      |
| **Palmar keratoderma**            |                 |                    |
| Always (never completely go away) | 1 of 5 (20)     | 16 of 109 (15)     |
| Sometimes (clear up completely at times) | 1 of 5 (20) | 17 of 109 (16) |
| Seldom (hands are usually clear/symptoms) | 0 of 5 (0) | 22 of 109 (20) |
| **Oral leukokeratosis**           |                 |                    |
| 1 of 5 (20)                       | 29 of 109 (27)  |                    |
| **Cysts**                         |                 |                    |
| 5 of 5 (100)                      | 101 of 109 (93) |                    |
| **Follicular hyperkeratosis**     | 2 of 5 (40)     | 71 of 109 (65)     |
| **Natal or prenatal teeth**       |                 |                    |
| 5 of 5 (100)                      | 82 of 109 (75)  |                    |

PC: Pachyonychia congenita, IPCRR: International Pachyonychia Congenita Research Registry

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