

# First Report of Pachyonychia Congenita Type PC-K6a in the Romanian Population

Anca CHIRIAC<sup>a,b,c</sup>, Cristina RUSU<sup>d,e</sup>, Alina MURGU<sup>d,e</sup>, Anca E CHIRIAC<sup>d</sup>, Neil J WILSON<sup>f</sup>, Frances J D SMITH<sup>g</sup>

<sup>a</sup>Department of Dermatology, Nicolina Medical Center, Iasi, Romania

<sup>b</sup>Department of Dermato-Physiology, Apollonia University, Iasi, Romania

<sup>c</sup>“Petru Poni” Institute of Macromolecular Chemistry, Romanian Academy, Iasi, Romania

<sup>d</sup>University of Medicine and Pharmacy “Grigore T Popa” Iasi, Romania

<sup>e</sup>“Sfanta Maria” Children Hospital, Iasi, Romania

<sup>f</sup>Centre for Dermatology and Genetic Medicine, Division of Biological Chemistry and Drug Discovery, School of Life Sciences, University of Dundee, Dundee, UK

<sup>g</sup>Pachyonychia Congenita Project, Salt Lake City, Utah, USA

## ABSTRACT

*Pachyonychia congenita (PC) is a rare autosomal dominant skin disorder, with unknown prevalence, although it is estimated there are between 2,000 and 10,000 cases of PC worldwide. The International PC Research Registry (IPCRR) has currently identified (as of November 2016) 746 individuals (in 403 families) with genetically confirmed PC. Heterozygous mutations, predominantly missense mutations, in any one of five keratin genes, KRT6A, KRT6B, KRT6C, KRT16, or KRT17 cause PC. The predominant clinical findings include plantar keratoderma, plantar pain and variable dystrophy of some or all toenails and/or fingernails. Oral leukokeratosis, follicular hyperkeratosis, cysts of various types and natal teeth may also be present. We report the first case of genetically confirmed PC from Romania due to a mutation in KRT6A, p.Arg466Pro.*

**Keywords:** pachyonychia congenita, oral leukokeratosis, nail dystrophy, palmoplantar keratoderma, plantar pain, keratin mutation

## INTRODUCTION

**P**achyonychia congenita (PC; MIM #615726, #615728, #615735, #167200, #167210) is a rare autosomal dominant genodermatosis that typically presents with plantar keratoderma, plantar pain and variable nail dystrophy (1). Oral leukokeratosis, follicular hyperkeratosis and cysts

of various types often occur. Natal teeth are associated with one subgroup of PC. Plantar calluses develop in early childhood as children start walking and the subsequent excruciating plantar pain that develops by the second decade of life is the most problematic complaint (2). This greatly affects their quality of life and they may require the use of canes, crutches or wheelchairs

Address for correspondence:

Anca Chiriac MD, PhD, Centrul Medical Nicolina, Str. Hatman Sendrea, Nr 2, Iasi, Romania

E-mail: [ancachiriac@yahoo.com](mailto:ancachiriac@yahoo.com)

Phone: 004072134999

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to aid mobility. Five keratin genes, *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, or *KRT17*, that are expressed in palmoplantar epidermis, the nail bed and mucosal tissues are associated with PC. A heterozygous mutation in any one of these five keratin genes results in PC. □

### CASE REPORT

A 10-year-old male child from a rural area presented to the Dermatology Clinic, Iasi, Romania. A diagnosis of pachyonychia congenita was made following a detailed clinical examination. He had distinct hypertrophic nail dystrophy of the feet and hands, with distal hyperkeratosis, curvature of nails especially on the fingers, which are wedge-shaped with yellowish discoloration (Figure 1). Thickening of all 20 nails occurred between one and four years of age. He had very painful focal plantar keratoderma, which affected his walking and limited his mobility, thereby greatly affecting his quality of life. Plantar calluses and blisters developed on the ball of his foot, his heel and between his toes around the age of one to four years. Around the same age, palmar keratoderma developed on his palms and fingers. Oral leukokeratosis covered the entire dorsal aspect of his tongue, affecting feeding and speaking; also, hoarseness of his voice was reported. Follicular keratosis was present on his upper limbs, especially on elbows and knees. Topical keratolytics and emollients were prescribed but with only slight benefit.

His mother was unaffected, but his father and sister were reported to have similar clinical manifestations involving the palms, soles and nails consistent with autosomal dominant inheritance of PC.

After being referred to the Pachyonychia Congenita Project ([www.pachyonychia.org](http://www.pachyonychia.org)), genetic testing was performed to confirm the clinical diagnosis. Worldwide, a number of services, including genetic testing (from saliva or blood), are freely provided by PC Project to PC patients who enroll in the International Pachyonychia Congenita Research Registry (IPCRR; <http://registry.pachyonychia.org/s3/IPCRR>). Blood samples were obtained from the child with informed consent and following ethical approval, respecting the principles of the Helsinki Accords. Genomic DNA was extracted using standard procedures and molecular genetic



**FIGURE 1.** Clinical features: a) focal plantar keratoderma; b) hypertrophic nail dystrophy of the toenails; c) hypertrophic nail dystrophy of the fingernails; d) oral leukokeratosis

testing was performed as described by Wilson *et al* (3).

A heterozygous mutation – p.Arg466Pro (c.1397G>C) – was identified in *KRT6A* within the helix termination motif, a known mutation hotspot region. No other family members were available for testing. This mutation has been previously reported once, in a family of Indian origin (4). □

### DISCUSSION

Dominant-negative mutations in any of the five keratin genes *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, or *KRT17* (3) underlie the pathogenesis of PC. In 2011, the analysis of clinical and molecular information from more than 250 cases of genetically confirmed PC collated by the IPCRR showed a clinical overlap between the historical subtypes of PC, PC-1 and PC-2. Consequently, the nomenclature was revised based on the genotype: those with mutations in *KRT6A* were named PC-K6a, those with mutations in *KRT17* were called PC-K17, and so on (1, 5).

In November 2016, the continuing expansion of the IPCRR has resulted in the identification of 746 genetically confirmed cases (in 403 families) of PC worldwide. Of these, 231 (31%) cases were spontaneous and 515 (69%) familial; there was no ethnic or gender bias. From these data, some general genotype-phenotype correlations have been identified as described below ([www.pachyonychia.org](http://www.pachyonychia.org)) (1, 2). Individuals with

mutations in PC-K6a form the largest group within the IPCRR (38%) and typically present with severe, painful plantar keratoderma, nail dystrophy and oral leukokeratosis. Plantar keratoderma usually occurs before the age of 5 and is extremely painful, having a negative impact on quality of life. Palmar keratoderma may also be present. Thickening of the fingernails and toenails is characteristic; often all 20 nails are affected since birth or early childhood and may be either extremely thickened or terminate prematurely. Follicular hyperkeratosis may be present on elbows, knees or other sites of friction especially in children and lessens with time. A number of patients have various types of cysts. Some children (4-12 years of age) experience extreme pain with the first bite or first swallow that lasts for approximately 15-25 seconds and lessens with age.

PC-K6b affects a much smaller group of patients than PC-K6a (9%) and is generally considered milder than PC-K6a. It is often not evident at birth but shows signs in childhood. The most consistent and challenging feature is the painful plantar keratoderma. The number of toenails and fingernails affected is variable, with less than 50% of individuals having any fingernail dystrophy. Cysts and follicular hyperkeratosis are reported in many cases; oral leukokeratosis is present in a small number of cases. The mildest form of PC is due to mutations in *KRT6C*, but those with PC-K6c are also by far the smallest subgroup of patients within the IPCRR (only 3%); therefore, there are very few data available.

For those diagnosed with PC-K16 (33%), painful plantar keratoderma is the most challenging feature. PC-K16 is not usually present at birth but it is evident before the age of 14. More than 50% have constant palmar keratoderma with fissures and associated pain. Nail dystrophy presents as very thickened nails or, in the case of some specific mutations, with little/no nail dystrophy (6). Oral leukokeratosis, cysts and follicular hyperkeratosis occur in a small number of cases.

To date, approximately 17% of PC patients within the IPCRR have mutations in *KRT17*. Natal teeth are a key feature of PC-K17 (though not present in all cases of PC-K17). Cysts (steatocysts) occur in almost all individuals with PC-K17. They develop around puberty, continuing during adulthood and are often the most troublesome feature. Nail dystrophy is frequently observed

since birth or early childhood. Follicular hyperkeratosis also occurs. PC-K17 individuals exhibit variable expression of plantar keratoderma and highly variable pain levels; oral leukokeratosis is present in a small number of cases.

Due to the rarity of PC gaining, a correct clinical diagnosis can be difficult. In this case, several previous visits to clinic had pointed towards alternative diagnoses. The oral leukokeratosis was thought to be chronic oral candidiasis, for which he was treated but with no effect; this diagnosis was later excluded following laboratory investigations, including direct microscopic examination and culturing a scraping from a lesion. His nail dystrophy was diagnosed as onychomycosis and subsequently treated by systemic and local aggressive antifungal therapy. Although nail infections are sometimes a problem, they are not the cause of his hypertrophic nail dystrophy. The hoarseness of his voice was misdiagnosed as chronic laryngitis. Although these are not uncommon misdiagnoses in babies and young children with nail, oral and/or plantar keratoderma involvement, a diagnosis of PC should be considered (2).

Confirmation of a clinical diagnosis by genetic testing is important to ensure appropriate care and genetic counseling. Other rare skin disorders can be confused with/appear like PC due to similarity of some clinical features (3). These include autosomal dominant disorders; Clouston syndrome/hidrotic ectodermal dysplasia, which presents with hypertrophic nail dystrophy; palmo-plantar keratoderma and variable hypotrichosis (due to mutations in the gap junction beta-6 gene (*GJB6*), which encodes connexin 30, *Cx30*); Olmsted syndrome, characterized by painful palmo-plantar keratoderma with/without periorificial hyperkeratosis; pseudoainhum and alopecia (caused by mutations in the transient receptor potential cation channel subfamily V, member 3, *TRPV3*); and striate palmo-plantar keratoderma (due to mutations in desmoglein 1, *DSG1*, a calcium-binding transmembrane glycoprotein).

Detailed information on management and caring for PC are available on the PC Project website ([www.pachyonychia.org](http://www.pachyonychia.org)). Patients care for their main complaints themselves by regularly trimming/filing/grinding and paring calluses and by filing/grinding/clipping nails (7). Pain medication may be necessary to deal with the plantar pain. Although at present there is no specific

treatment for PC, a number of ongoing research projects develop an effective therapy. Identifying and documenting further cases of PC will aid and promote the planning of future clinical trials for this rare disorder. Here we report the first case of PC-K6a from Romania and add it to the IPCRR. □

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