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Clinical and molecular findings of pachyonychia congenita type 2 (PC-2)

Francisco Cammarata-Scalisi[1], Ken Natsuga[2], Ellen Toyonaga[2], Wataru Nishie[2], Hiroshi Shimizu[2], Frances Stock[3], Melisse Milano[4], Pierina Petrosino[4], Asmiria Arenas de Sotolongo[4] and Yoel Medina[5]*

[1]Medical Genetics Unit, Department of Child Care and Pediatrics, Universidad de Los Andes, Mérida, Venezuela; [2]Department of Dermatology, School of Medicine, Hokkaido University, Sapporo, Japan; [3]Pediatric Oncology Unit, Instituto Autónomo Hospital Universitario de Los Andes, Mérida, Venezuela; [4]Anatomical Pathology Unit, Universidad de Los Andes, Mérida, Venezuela; [5]Universidad de Los Andes, Mérida, Venezuela

Abstract

Pachyonychia congenita is a group of autosomal dominant inheritance pattern disorders characterized by hypertrophic nail dystrophy. There are two main clinical subtypes: type 1 and 2. Pachyonychia congenita type 2 is readily differentiated from type 1 by multiple steatocysts and/or presence of natal teeth and can be confirmed by mutations of KRT6B and KRT17. We report the case of a 33-year-old female patient with the missense mutation in KRT17 gene (c.280C>T, p.Arg94Cys) and discuss the several clinical features found with this mutation in the literature. (Gac Med Mex. 2015;151:253-5)

Corresponding author: *Francisco Cammarata Scalisi, francocammarata19@gmail.com*

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Introduction

Pachyonychia congenita (PC) is a group of disorders with an autosomal dominant inheritance pattern characterized by hypertrophic ungual dystrophy. There are two main clinical subtypes: type I (OMIM 167200), also known as Jadassohn-Lewandowsky, and type II (OMIM 167210), or Jackson-Lawler syndrome[1]. Frequently it has an oligosymptomatic presentation and can occur with hyperhidrosis, palmoplantar keratoderma, oral leukoplakia and keratosis pilaris[2]. PC-2 is differentiated from PC-1 by the presence of multiple steatocysts (MS) and/or natal teeth. PC-2 is caused by mutations in the *KRT6B* keratin gene, located at 12q13.13, which codifies for cytoskeletal 17 type I keratin[1].

MS (OMIM 184500) is an infrequent entity characterized by multiple dermal cysts originating in polysebaceous glands[2]. It has an autosomal dominant inheritance pattern or sporadic in nature. It appears during adolescence as multiple asymptomatic cysts in the axillary area, the trunk, the scrotum and proximal areas of the limbs, due to a high density of pilosebaceous units developing in these zones; it is infrequent in the face and the scalp[3]. Same as PC-2, MS is caused by mutation of the *KRT17* gene[4]. Next, we present the case of a 33-year old female patient with a missense mutation in the *KRT17* gene (c.280C>T, p.Arg94Cys) and different clinical findings reported in the literature with this mutation are reviewed.

Correspondence:
*Francisco Cammarata Scalisi
Unidad de Genética Médica
Departamento de Puericultura y Pediatría
Facultad de Medicina, Universidad de Los Andes (ULA)
Instituto Autónomo Universidad de Los Andes
Nivel Mezzanina
Mérida, 5101, Venezuela
E-mail: francocammarata19@gmail.com

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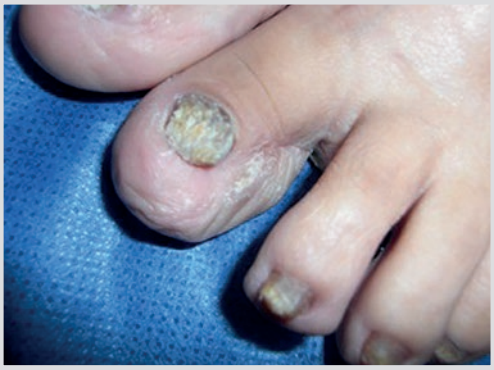

Figure 1. *Brown-yellowish colored toenails with thickening and dyskeratosis.*

Presentation of the case

This is the case of a 33-year old woman, with controlled hypertension, who had a yellowish-brown defect of the toenails since birth; thickening and dyskeratosis became later evident (Fig. 1). During adolescence, multiple lesions appeared on the face, the neck and the trunk, including the genital area, with cystic appearance, hard consistency, flesh tone or yellowish colored and variable size (0.4-1.6 cm), consistent with steatocystoma. The mother of the patient, as well as five maternal uncles and her maternal grandmother had nails and skin conditions.

The histopathological study revealed a cystic formation lined with stratified epithelial cells, with no distinct cellular bridges and with peripheral cell layers disposed in palisade. These cells didn't show a granular layer and those close to the light were tumescent with more discolored cytoplasm. Observed keratinization was abrupt and compact in the wall thickness, and a small sebaceous acinus was identified, which are findings consistent with steatocystoma.

The *KRT6A, KRT6B, KRT16* and *KRT17* genes were sequenced by means of genomic DNA extraction from a sample of saliva. The analysis revealed a heterocygous mutation (c.280C>T, p.Arg94Cys) in the *KRT17* gene (Fig. 2). Additionally, single-nucleotide polymorphisms were detected in the *KRT6A* (rs17845411, rs376545, rs17099719, rs12581781), *KRT6B* (rs428894, rs445185, rs11860693, rs388626) and *KRT16* (rs7406899) genes. The numbering of single nucleotide polymorphisms is registered in the dbSNP database of the National Center for Biotechnology Information. Aminoacid changes were also found (c.482C>A, p.Ala161Val, heterocygous) in the *KRT16A* gene and (c.55G>A, p.Gly19Arg, heterocygous) in *KRT16.* Both these aminoacid changes do not appear in the dbSNP database or in the 1,000-genome browser. This study was conducted at the Department of Dermatology of the Medicine School from the Hokkaido University in Sapporo (Japan).

Discussion

PC is a rare genodermatosis that produces significant ungual hyperkeratosis. It was described for the first time in 1716 by Carl Musaeus in a doctoral dissertation. In 1904, Muller C described a case of PC, and in 1906, Jadassohn and Lewandowsky F observed another case; since then, it has been known with both these eponyms[5]. In Venezuela, the first case was documented in 1964, in a degree thesis with the title "Contribution to the study of genodermatoses in Venezuela"[6].

PC is a group of keratinization abnormalities caused by mutation of one of four keratin genes[7]. As previously mentioned, alterations in the *KRT17* gene can appear in PC-2 and SM[2], since cytokeratin 17 is

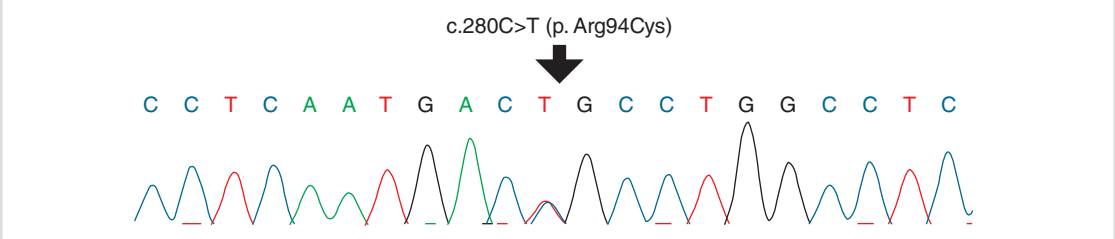

Figure 2. *Missense, heterocygous mutation (c.280C>T, p.Arg94Cys), in the KRT17 gene, which produces an arginine aminoacid change in position 94 to cysteine in cytoskeleton 17 type I keratin.*

expressed primarily in the ungual bed, pilous follicles and sebaceous glands[5]. Half of the cases are caused by *de novo* mutations, such as the present case; intra-familial phenotypical variations are of unknown causation[2].

Cytokeratins are heterodimeric proteins that form the intermediate filaments of the epithelial cells cytoskeleton. All of them have a similar protein structure, which consists of a central helical domain that mediates the polymerization of these proteins to form keratin tonofilaments. This central circular domain is subdivided in segments: 1A, 1B, 2A and 2B, and in flexible ligands: L1, L12 and L2. Sequences in helix 1A initiation and helix 2B termination are the most important hotspots for intermediate filaments assembly and it is there where mutations resulting in these entities are produced[5].

The mutation of the cytosine to thymine transition-type in *KRT17* gene commented in this report was initially presented by Covello et al.[8] in two families that produced a substitution of the aminoacid arginine by cysteine in position 94 of the protein. This resulted in abolition of the recognition site for the restriction enzyme *Aci* I. Although both these families had the same mutation, one, of American Caucasian origin, had PC-2 and MS, and the other one, of Dutch Caucasian origin, had only MS. Subsequently, this mutation was found in China in patients with MS[9]. Finally, a family from the Middle East had this homozygous form of mutation and clinically showed PC-2, blistering lesions with fissures in addition to ulcers in hands and feet, follicular hyperkeratosis and alopecia. Both the studied mutation and (c.275A>G, pAsn92Ser) have been the most commonly found in the *KRT17* gene and both show phenotypical variation, frequently producing PC-2 and occasionally MS[10].

Therefore, the commented case represents the fifth familial case with the (c.280C>T, p.Arg94Cys) mutation in the *KRT17* gene, which produces both PC and MS. In this case, intra-familial variation of unknown causation occurred, as well as inter-familial variation when compared with cases reviewed in the literature. It is the first time this mutation is documented in Latin America and this illustrates its wide distribution throughout the world. In addition to the studied mutation, the patient showed canges not previously found in the *KRT6A* and *KRT16* genes and single nucleotide polymorphisms were detected in the *KRT6A, KRT6B* and *KRT16* genes.

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