

Mutation p.Arg127Pro in the IA Domain of KRT16 Causes Pachyonychia Congenita in Chinese Patient: A Case Report of PC Associated with Acral Melanoma

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Abstract: Pachyonychia congenita (PC) is a group of rare hereditary disorders, characterised by hypertrophic nails and palmoplantar keratoderma (PPK), particularly localised to the pressure areas of the feet. At a molecular level, it is caused by mutations in genes encoding KRT6A, KRT6B, KRT6C, KRT16, or KRT17. To identify the underlying gene mutation in a Chinese family with PC presenting with disabling palmoplantar keratoderma and subsequent associated acral melanoma. Genomic DNA was extracted from peripheral blood samples of three available individuals in the Chinese family, which included the patient and his two unaffected sisters. The index patient presented with severe palmoplantar keratoderma as well as a newly diagnosed acral malignant melanoma (MM). Whole-exome sequencing (WES) was carried out with amplification of exon 1 of KRT16 by polymerase chain reaction (PCR). PCR products were then sequenced to identify potential mutations. We identified the proline substitution mutation p.Arg127Pro (c.380G>C) in our patient's IA domain of KRT16. The same mutation was not found in his sisters or unrelated healthy controls. The mutation (p.Arg127Pro (c.380G>C)) in KRT16 has been reported in Dutch patients with PC. However, it is the first such report of a patient with a PC of Chinese origin. In addition, the acral MM occurred under the background of genetic PPK caused by KRT16 mutation in this patient.

Keywords: pachyonychia congenita, Chinese patient, acral melanoma, mutation of gene

Introduction

Pachyonychia Congenita (PC; OMIM #167200 and #167210) is a group of rare hereditary ectodermal dysplasia disorders.¹ Classification of PC depends on specific keratin gene mutations, subdivided into five subtypes, namely PC-KRT6A, PC-KRT6B, PC-KRT6C, PC-KRT16, and PC-KRT17, based on the causative gene. Palmoplantar keratodermas (PPKs) are a heterogeneous group of conditions involving ectodermal dysplasia, displaying marked hyperkeratosis on the palms and soles. Notably, PPK is a common and major feature in patients with PC. Based on the pattern of hyperkeratosis, PPKs are generally classified into diffuse, focal (including striate), and punctate forms. Focal PPK features painful hyperkeratotic plaques on the palms and soles and is caused by mutations in KRT6C and KRT16 keratin genes, as well as other genes involving skin barrier function, such as DSG1 and TRPV.²⁻⁵ Here, we report a Chinese patient with PC and severe disabling focal PPK associated with the development of acral malignant melanoma.

Case Presentation

A 65-year-old unmarried Chinese male presented visibly thickened nails and skin on the soles of his feet since five years of age (Figure 1A and B). In addition to the marked and disabling painful symmetrical PPK, moderate nail hypertrophy



Figure 1 (A) Pedigree of the affected family, blood samples were from the second generation individuals because the patient's parents passed away. ■□○/◊ Signals indicate the affected, unaffected, passed away individuals and the proband, respectively. (B) hypertrophic and discolored fingernails were shown. (C) Focal and striated hyperkeratosis on the palms limited his finger stretch. (D) diffuse yellowish plantar hyperkeratosis and a large black neoplasm were shown on his left planta. (E) another aspect was shown of the dystrophy nails and palmoplantar keratoderma.

with rough and discolored surfaces was found on his fingernails and toenails. The painful PPK involving pressure areas restricted his ability to carry out manual labor. His palms displayed focal striated hyperkeratosis, and his soles featured more prominent thickened and diffuse hyperkeratosis, which limited his walking (Figure 1C–E). This led him to see dermatologists repeatedly for several decades. However, the patient just taken oral retinoids irregularly because of the adverse effects. The patient and his two sisters were clinically assessed, and no abnormal clinical features found in either of his sisters. His parents had previously passed away, but there were no records of clinical reports of skin or nail abnormalities. The patient then developed an ulcerated tumid lesion on the frontal aspect of his right plantar region (Figure 1D and E), following which a skin biopsy was undertaken with histology confirming malignant melanoma (Clark V was established, and the histopathological figures were shown in Figure 2). The patient present left inguinal lymph nodes enlargement; chest and abdominal computed tomography scan was performed and multiple nodules in both lungs were found, and metastatic tumor considered; in addition, multiple tumors were found in his liver and both sides of adrenal glands. Based on the clinical features and family history, a sporadic PC type 1 case associated with the development of acral melanoma was established.

After obtaining informed consent from the participating individuals and ethical approval of the Review Board of the First Affiliated Hospital of Huzhou University, which complied with the Helsinki Accord, genomic DNA was extracted from peripheral blood using the universal genomic DNA extraction kit (TaKaRa, Shiga, Japan). The blood sample was collected two years before his occurrence of melanoma. Whole-exome sequencing (WES) was performed on the patient, and all exons of KRT16 were directly sequenced (Table 1).

Discussion

The results of WES found that mutations in several exon regions were found, including KRT16, ABCB9, CASP14, PEX1, and PLEC (Table 1). Sanger sequencing confirmed a heterozygous missense mutation c.380G>C (p.R127P) variant in exon 1 of KRT16 (Figure 3), resulting in an Arg to Pro change in residue 127 of the protein. This mutation was not detected in his unaffected sisters or 100 unrelated normal individuals. This identical variant was found in Dutch

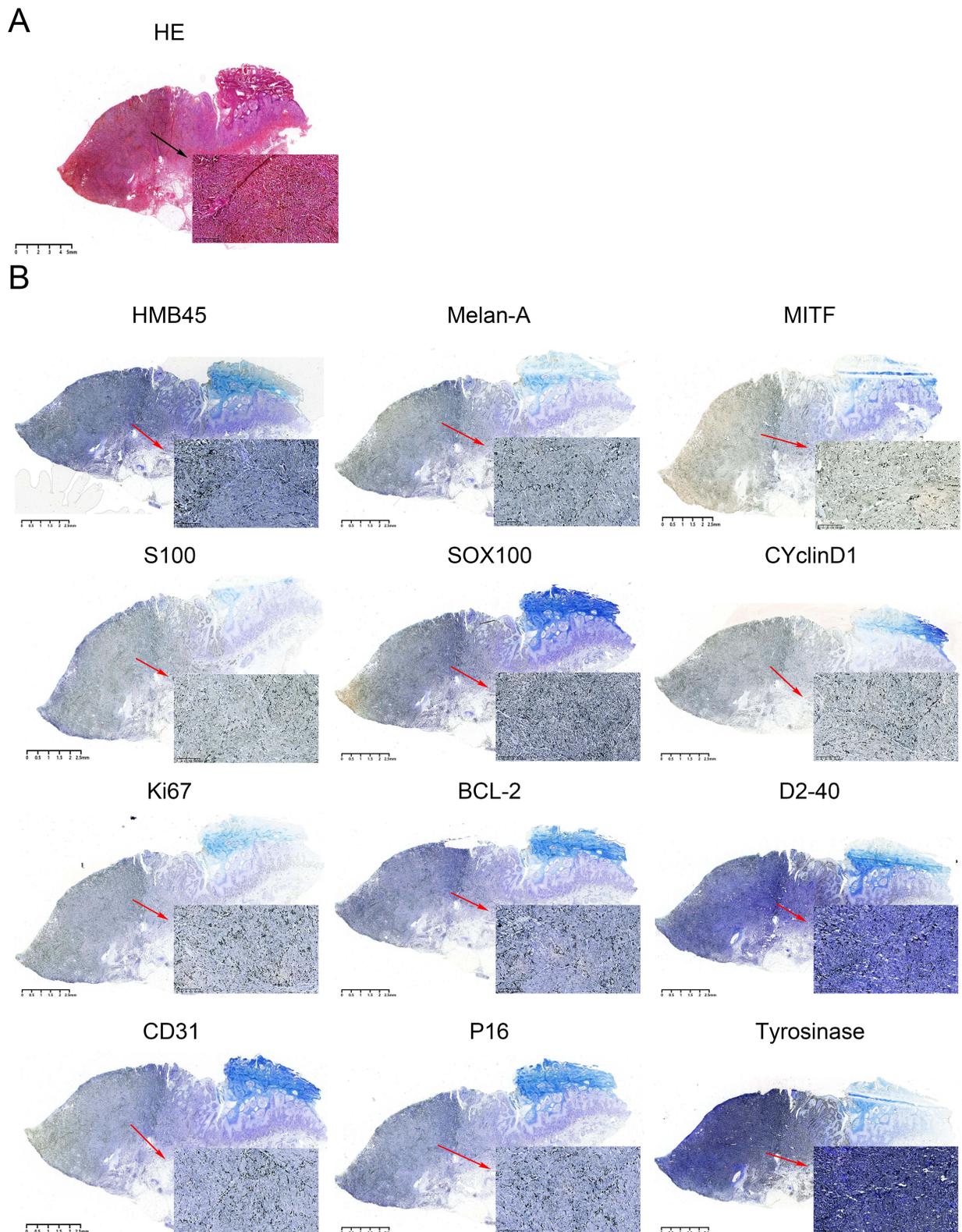


Figure 2 Histopathological figures of skin biopsy. **(A)** HE staining. **(B)** IHC staining of HMB45, Melan-A, MITF, S100, SOX10, CyclinD1, Ki67, BCL-2, D2-40, CD31, P16, and tyrosinase protein (magnification: 100 \times).

Table I WES Method Detected Mutations in Several Exon Regions

Chr	Start	End	Ref	Alt	Func.ref Gene	Gene.ref Gene	Exonic Func. ref Gene	AA Change.ref Gene
chr17	39768561	39768561	C	G	Exonic	KRT16	Nonsynonymous SNV	KRT16:NM_005557:exon1:c.G380C:p.R127P
chr12	123424824	123424824	G	C	Exonic	ABCB9	Nonsynonymous SNV	ABCB9:NM_001243013:exon8:c.C1388G:p.S463C,ABCB9:NM_019624:exon8:c.C1448G:p.S483C,ABCB9:NM_001243014:exon9:c.C1577G:p.S526C,ABCB9:NM_019625:exon9:c.C1577G:p.S526C,ABCB9:NM_203444:exon9:c.C1577G:p.S526C
chr19	15166345	15166345	G	A	Splicing	CASPI4	0	0
chr7	92148308	92148308	C	A	Splicing	PEX1	0	0
chr8	145004104	145004104	C	T	Exonic	PLEC	Synonymous SNV	PLEC:NM_201378:exon22:c.G2697A:p.T899T, PLEC:NM_201379:exon22:c.G2673A:p.T891T, PLEC:NM_201380:exon22:c.G3150A:p.T1050T, PLEC:NM_201381:exon22:c.G2643A:p.T881T, PLEC:NM_201382:exon22:c.G2739A:p.T913T, PLEC:NM_201383:exon22:c.G2751A:p.T917T, PLEC:NM_201384:exon22:c.G2739A:p.T913T, PLEC:NM_000445:exon23:c.G2820A:p.T940T

origin, reported by Smith,⁶ presented in the Human Gene Mutation Database (HGMD) and then reviewed by Xu and Liao.⁷ No other mutations were detected in KRT6 and KRT17 genes in this patient.

Relative reports found that various keratin mutations cause several cutaneous disorders, with PC arising from mutations in KRT6A, KRT6B, KRT6C, KRT16, and KRT17 genes.⁸ Keratin 16 is mainly expressed in the palmo-plantar epidermis. Structurally, the keratin comprises α -helical rod domains and non-helical linkers and can be divided into four parts (domain 1A, 1B, 2A, and 2B), respectively. Functionally, the highly conserved sequences of the α -helical rod domain on exon 1 generally correlate with PPK. These regions are considered important for end-to-end overlap interaction during the keratin elongation filament assembly and network formation Phase 4. In cases with KRT16 mutations, dystrophic nails and prominent PPK (typically non-epidermolytic) are the predominant features; however, mutations in KRT16 can also be associated with disabling painful PPK but with mild or no nail involvement.⁹

Twenty-one missense mutations in KRT16 have been reported in The Human Gene Mutation Database (HGMD, <http://www.hgmd.cf.ac.uk/ac/search.php>). A previously identified mutation was found in exon 1 of KRT16, c.380G>C (p.Arg127Pro).⁶ Compared with this patient, the mutation c.380G>C (p.Arg127Pro) occurs within the highly conserved region of the 1A, helix initiation motif, with proline (Pro) reported to affect the α -helical tertiary structure.¹⁰ On the one hand, mutations in the same codon can lead to varying clinical features between cases and families. Compared with Pro substitution, other amino acid changes, such as Cys, Ser, and His substitutions, are associated with milder PPK and nail involvement. On the other hand, the site of codon mutations can influence the severity of the disease. Compared with the amino acid changes of Arg>Pro and Leu>Pro in the 2B region, those cases with the same mutation in the 1A region of KRT16 developed more diffuse palmoplantar hyperkeratosis and severe nail involvement. The mutations in codons 125, 127, and 132 of the 1A region of KRT16 are most commonly responsible for PC-1, and proline substitution mutations at codons 127 or 128 may lead to more severe palmoplantar keratoderma.¹⁰

In addition, KRT16 maintains promoting proliferation signaling under higher stress conditions,¹¹ which might contribute to more severe plantar hyperkeratosis than that on the palms. We just found that in this patient, the type and degree of hyperkeratosis varied between the palms and soles, with more severe and disabling diffuse hyperkeratosis

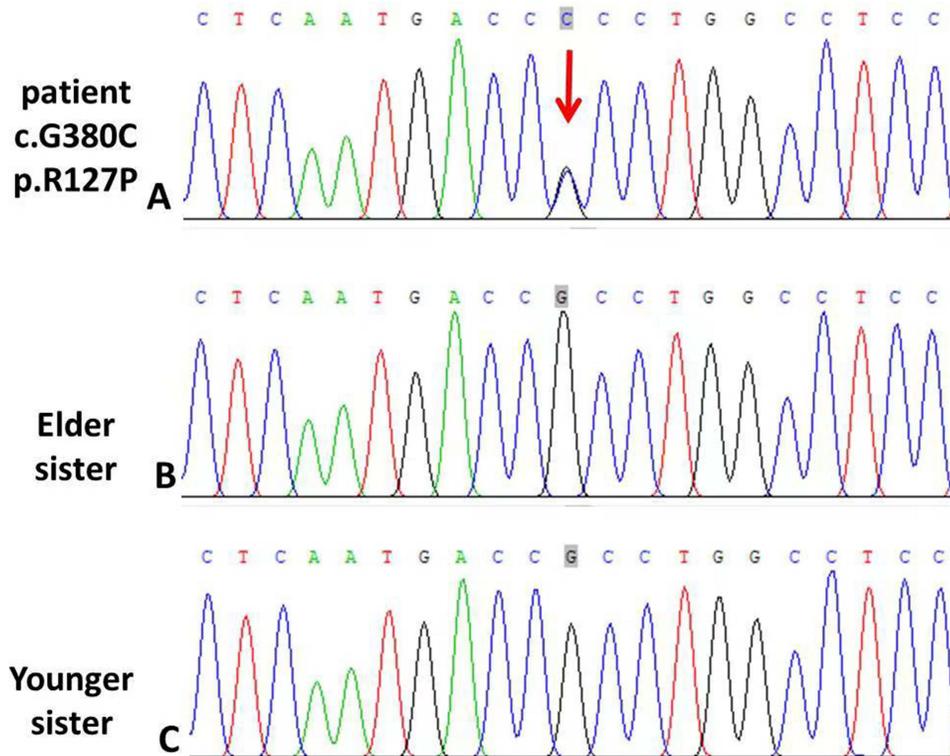


Figure 3 Sequence analysis of the exon 1 of KRT16 from the patient compared with his unaffected sisters. (A) Patient was shown that a heterozygous missense mutation c. G380C, p.Arg127Pro (Red arrow); (B) Sequence analysis of the exon 1 of KRT16 from elder sister; (C) Sequence analysis of the exon 1 of KRT16 from younger sister.

on the plantar aspect, which restricted his walking, and striated milder hyperkeratosis on his palms. This patient also developed an acral MM on his right plantar aspect. Given the absence of reports of the cases with simultaneous development of acral MM and PC, it raises the consideration that mechanical stress may deteriorate the destructed sole in a PC patient with KRT16 mutation. Several cases with Nagashima-type palmoplantar keratoderma, Mal de Meleda, or Papillon-Lefèvre syndrome have been reported associated with MM.¹² However, no PC patient that simultaneously developed acral MM was reported. KRT16 also plays a role in regulating mitochondrial function and causing oxidative stress in PC and related keratin-based skin disorders.¹³ Relative paper clarified that six hub genes, including FABP5, IVL, KRT6A, KRT15, KRT16, and TIMP2, were significant value in predicting transformation from nevi to melanoma.^{14,15} In addition, in this case report, we found that the mutation of KRT16 in PC correlated with the occurrence and transformation of melanoma. To clarify whether KRT16 mutation is closely related to the conversion of PC to MM is the key point of our next work.

Conclusion

We first report the previously reported mutation c.380G>C (p.Arg127Pro) on exon 1 of KRT16 occurring in a Chinese patient, with PC presenting with severe disabling FPPK. This patient also developed a co-existent acral MM. Additional pedigrees are needed to verify the correlation between genotype and phenotype. In consideration of the acral MM that occurred under the background of genetic PPK caused by KRT16 mutation in this patient, additional factors such as mechanical stress should also be highlighted for providing a valuable clue for guiding the treatment and follow-up of patients with severe PPK.

Consent Statement

The patient had given written informed consent for the publication of his clinical details and accompanying images. The human study was approved by the Ethics Review Committee on Human Research of Taizhou Second People's Hospital (TZEY-LW-202305).

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Disclosure

The authors have no conflicts of interest to declare in this work.

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