

# Focal Palmoplantar Keratoderma and Gingival Keratosis Caused by a *KRT16* Mutation

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## PRACTICE POINTS

- Focal palmoplantar keratoderma and gingival keratosis (FPGK) is a rare autosomal-dominant syndrome featuring focal, pressure-related, painful palmoplantar keratoderma (PPK) and gingival hyperkeratosis presenting as leukokeratosis.
- Focal pressure-related PPK and oral hyperkeratosis also are seen in pachyonychia congenita (PC), which is caused by mutations in keratin genes and is distinguished from FPGK by characteristic nail changes.
- A shared causative gene suggests that FPGK should be considered part of the PC spectrum.

To the Editor:

Focal palmoplantar keratoderma and gingival keratosis (FPGK) (Online Mendelian Inheritance in Man [OMIM] 148730) is a rare autosomal-dominant syndrome featuring focal, pressure-related, painful palmoplantar keratoderma and gingival hyperkeratosis presenting as leukokeratosis. Focal palmoplantar keratoderma and gingival keratosis was first defined by Gorlin<sup>1</sup> in 1976. Since then, only a few cases have been reported, but no causative mutations have been identified.<sup>2</sup>

Focal pressure-related palmoplantar keratoderma (PPK) and oral hyperkeratosis also are seen in pachyonychia congenita (PC) (OMIM 167200, 615726, 615728, 167210), a rare autosomal-dominant disorder of keratinization characterized by PPK and nail dystrophy. Patients with PC often present with plantar pain; more variable features include oral leukokeratosis, follicular hyperkeratosis, pilosebaceous and epidermal inclusion cysts, hoarseness, hyperhidrosis, and natal teeth. Pachyonychia congenita is caused by mutation in keratin genes *KRT6A*, *KRT6B*, *KRT16*, or *KRT17*.

Focal palmoplantar keratoderma and gingival keratosis as well as PC are distinct from other forms of PPK with gingival involvement such as Papillon-Lefèvre syndrome (OMIM 245000) and Olmsted syndrome (OMIM 614594). Papillon-Lefèvre syndrome is a rare autosomal-recessive disorder caused by mutations in the cathepsin C, *CTSC*, gene that exhibits erythematous, diffuse, transgradient PPK and early severe periodontitis. Olmsted syndrome is caused by autosomal-dominant gene mutations in transient receptor potential cation channel, subfamily V, member 3, *TRPV3*, and is characterized by severe bilateral transgradient PPK with leukoplakia of the tongue and buccal mucosa but also usually exhibits marked periorificial keratotic plaques, which facilitate exclusion of other phenotypically similar syndromes.<sup>3</sup>

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The authors report no conflict of interest.

This study was in part supported by National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grant R01AR068392 and the Yale Center for Mendelian Genomics grant U54 HG006504.

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doi:10.12788/cutis.0571

Despite the common features of FPGK and PC, they are considered distinct disorders due to absence of nail changes in FPGK and no prior evidence of a common genetic cause. We present a patient with familial FPGK found by whole exome sequencing to be caused by a mutation in *KRT16*.

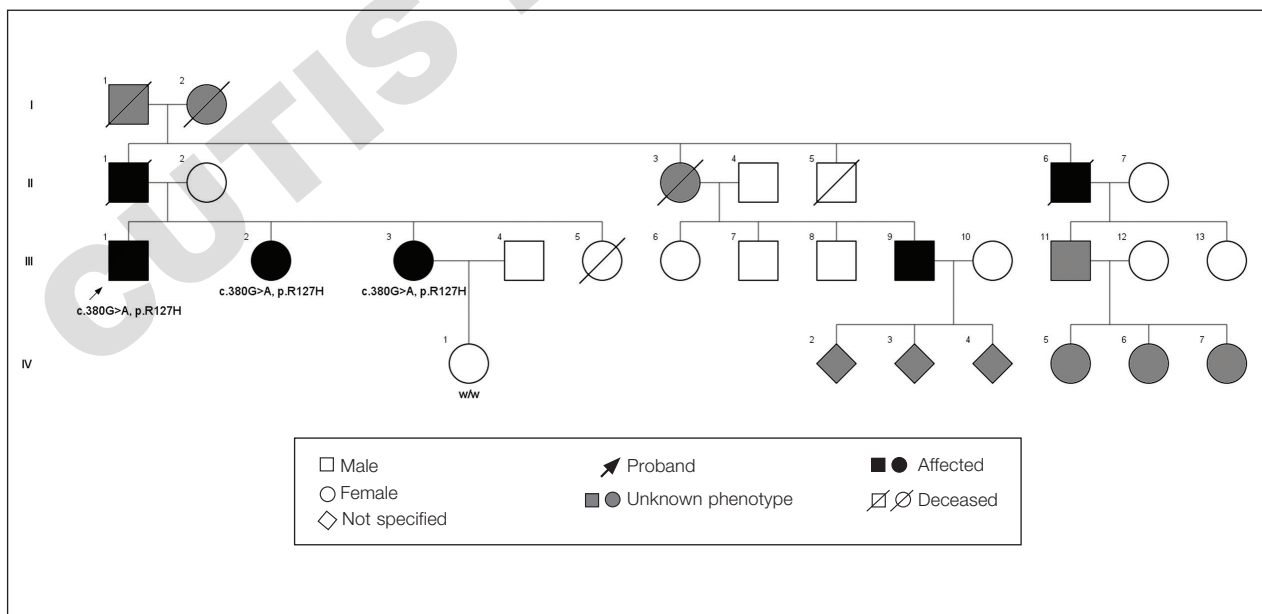
The proband was a 57-year-old man born to unrelated parents (Figure 1). He had no skin problems at birth, and his development was normal. He had painful focal keratoderma since childhood that were most prominent at pressure points on the soles and toes (Figure 2A), in addition to gingival hyperkeratosis and oral leukokeratosis (Figure 2B). He had no associated abnormalities of the skin, hair, or teeth and no nail findings (Figure 2C). He reported that his father and 2 of his 3 sisters were affected with similar symptoms. A punch biopsy of the right fifth toe was consistent with verrucous epidermal hyperplasia with perinuclear keratinization in the spinous layer (Figure 3A). A gingival biopsy showed perinuclear eosinophilic globules and basophilic stranding in the cytoplasm (Figure 3B). His older sister had more severe and painful focal keratoderma of the soles, punctate keratoderma of the palms, gingival hyperkeratosis, and leukokeratosis of the tongue.

Whole exome sequencing of the proband revealed a heterozygous missense mutation in *KRT16* (c.380G>A, p.R127H, rs57424749). Sanger sequencing confirmed this mutation and showed that it was heterozygous in both of his affected sisters and absent in his unaffected niece (Figure 1). The patient was treated

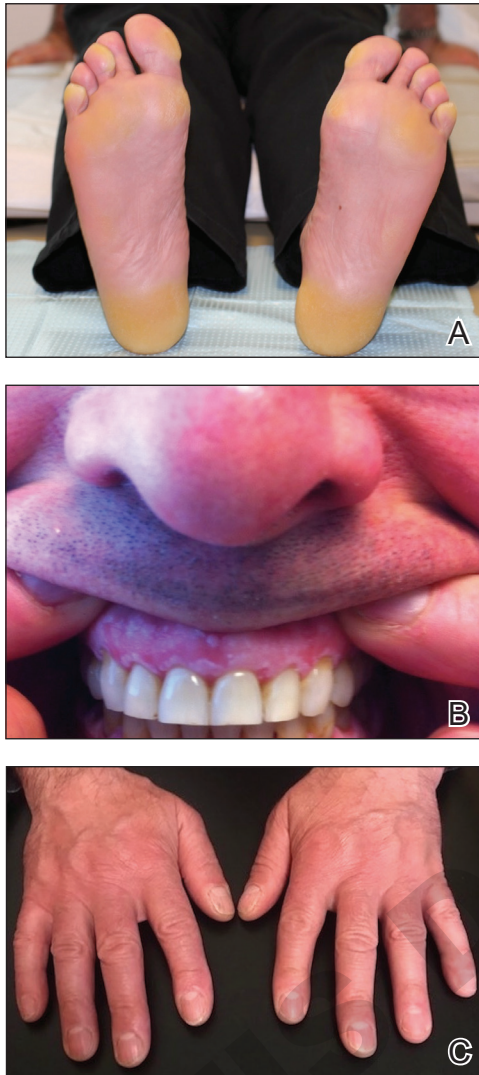
with topical and systemic retinoids, keratolytics, and mechanical removal to moderate effect, with noted improvement in the appearance and associated pain of the plantar keratoderma.

Phenotypic heterogeneity is common in PC, though PC due to *KRT6A* mutations demonstrates more severe nail disease with oral lesions, cysts, and follicular hyperkeratosis, while PC caused by *KRT16* mutations generally presents with more extensive and painful PPK.<sup>4</sup> *KRT16* mutations affecting p.R127 are frequent causes of PC, and genotype-phenotype correlations have been observed. Individuals with p.R127P mutations exhibit more severe disease with earlier age of onset, more extensive nail involvement and oral leukokeratosis, and greater impact on daily quality of life than in individuals with p.R127C mutations.<sup>5</sup> Cases of PC with *KRT16* p.R127S and p.R127G mutations also have been observed. The *KRT16* c.380G>A, p.R127H mutation we documented has been reported in one kindred with PC who presented with PPK, oral leukokeratosis, toenail thickening, and pilosebaceous and follicular hyperkeratosis.<sup>6</sup>

Although patients with FPGK lack the thickening of fingernails and/or toenails considered a defining feature of PC, the disorders otherwise are phenotypically similar, suggesting the possibility of common pathogenesis. One linkage study of familial FPGK excluded genetic intervals containing type I and type II keratins but was limited to a single small kindred.<sup>2</sup> This study and our data together suggest that, similar to PC, there are multiple genes in which mutations cause FPGK.



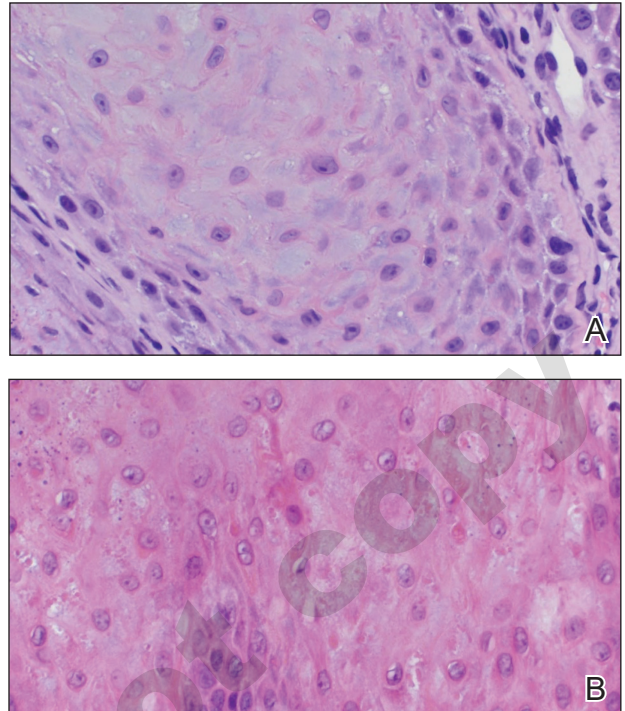
**FIGURE 1.** Pedigree of a family (generations I, II, III, and IV) showing focal palmoplantar keratoderma and gingival keratosis in those heterozygous for *KRT16* mutation p.R127H. Individuals III:1 (proband), III:2, and III:3 were heterozygous for *KRT16* mutation c.380G>A, p.R127H as indicated; individual IV:1 did not carry this mutation and was designated wild-type/wild-type (w/w). Intergeneration transmission of the disease to males and females supports autosomal-dominant inheritance.



**FIGURE 2.** A, Painful focal keratoderma most prominent at pressure points on the soles and toes. B, Gingival hyperkeratosis and oral leukokeratosis. C, Nails without thickening of plates or discoloration.

Murine *Krt16* knockouts show distinct phenotypes depending on the mouse strain in which they are propagated, ranging from perinatal lethality to differences in the severity of oral and PPK lesions.<sup>7</sup> These observations provide evidence that additional genetic variants contribute to *Krt16* phenotypes in mice and suggest the same could be true for humans.

We propose that some cases of FPGK are due to mutations in *KRT16* and thus share a genetic pathogenesis with PC, underscoring the utility of whole exome sequencing in providing genetic diagnoses for disorders that are genetically and clinically heterogeneous. Further biologic investigation of phenotypes caused by



**FIGURE 3.** Histologic findings in a patient heterozygous for *KRT16* mutation p.R127H. A, A punch biopsy of the right fifth toe showed verrucous epidermal hyperplasia with perinuclear keratinization in the spinous layer (H&E, original magnification  $\times 40$ ). B, A gingival biopsy showed perinuclear eosinophilic globules and basophilic stranding in the cytoplasm (H&E, original magnification  $\times 40$ ).

*KRT16* mutation may reveal respective contributions of additional genetic variation and environmental effects to the variable clinical presentations.

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