Focal Palmoplantar Keratoderma and Gingival Keratosis Caused by a KRT16 Mutation

Theodore D. Zaki, MD; Lynn M. Boyden, PhD; Erin Mathes, MD; Rong-hua Hu, BS; Jing Zhou, PhD; Erin Loring, MS; Jeffrey North, MD; Vikash Oza, MD; Keith A. Choate, MD, PhD

Focal Pressure-Related Palmoplantar Keratoderma and Oral Hyperkeratosis Caused by a KRT16 Mutation

To the Editor:

Focal palmoplantar keratoderma and gingival keratosis (FPGK) is a rare autosomal-dominant syndrome featuring focal, pressure-related, painful palmoplantar keratoderma 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.

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.

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 is caused by a KRT16 mutation.

Drs. Zaki, Boyden, Zhou, and Choate as well as Ms. Hu and Ms. Loring are from the Yale University School of Medicine, New Haven, Connecticut. Drs. Zaki, Zhou, and Choate as well as Ms. Hu are from the Department of Dermatology. Ms. Loring as well as Drs. Boyden and Choate are from the Department of Genetics. Dr. Choate also is from the Department of Pathology. Drs. Mathes and North are from the Department of Dermatology, University of California, San Francisco. Dr. Oza is from the Ronald O. Perelman Department of Dermatology, School of Medicine, New York University, New York.

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Correspondence: Keith A. Choate, MD, PhD, Department of Dermatology, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520 (keith.choate@yale.edu).

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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.\(^4\) 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.\(^5\) 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.\(^6\)

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.\(^2\) This study and our data together suggest that, similar to PC, there are multiple genes in which mutations cause FPGK.
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. 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 KRT16 mutation may reveal respective contributions of additional genetic variation and environmental effects to the variable clinical presentations.

REFERENCES