

A novel mutation resulting in keratin 1–linked palmoplantar keratoderma with epidermolytic ichthyosis



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INTRODUCTION

Transgrediens et progrediens palmoplantar keratoderma (PPK), also known as Greither's disease, is a rare entity that was originally described in 1952.¹ It is characterized by diffuse keratoderma of the palms and soles that extends to the dorsal aspects of the hands and feet, with erythematous borders.^{2,3} Characteristically, the keratoderma involves the skin over the Achilles tendon and is associated with hyperhidrosis.^{2,3} Patients may develop hyperkeratotic plaques on knees, elbows, or flexural areas.^{2,3}

To date, reported cases of Greither's disease demonstrate phenotypic variability, adding to the diagnostic challenge that cases of PPK often present. Although the etiology of Greither's disease is not fully elucidated, several authors have proposed that defects in the keratin 1 gene (*KRT1*) may be an important pathophysiologic component of this disease.²⁻⁵ In this report, we describe a case of keratin 1–linked palmoplantar keratoderma with epidermolytic ichthyosis in which a previously unreported mutation in *KRT1* was discovered. Although we favor classifying PPKs according to genetic testing, we recognize that this case could also be described as Greither's disease, using the historical eponymous naming system based on morphology and associated features.

CASE REPORT

A 16-year-old adolescent with reported history of atopic dermatitis and recurrent superficial bacterial infections presented to our dermatology clinic for

Abbreviation used:

KRT1: keratin 1 gene
PPK: progrediens palmoplantar keratoderma

evaluation of a rash on the bilateral aspect of his knees, in addition to thickened palms and soles. His mother endorsed that the thickened palms had been present since infancy; however, she denied a history of blistering or erosions, or presence of a collodion membrane during the neonatal period. She also denied family history of similar findings. On physical examination, the bilateral aspect of the palms revealed keratoderma extending to the volar portion of the wrists and dorsal portion of the hands (Fig 1). Hyperkeratotic plaques were also observed on the extensor surfaces of the bilateral aspect of the knees (Fig 2) and elbows. A shave biopsy, obtained from the right elbow and evaluated with hematoxylin-eosin staining, demonstrated hyperkeratosis, digitated acanthosis, hypergranulosis with perinuclear vacuolization, and indistinct cell borders consistent with epidermolytic hyperkeratosis (Fig 3). Because of these clinical and histopathologic findings, our patient was referred for genetic testing. The results revealed a frameshift mutation within *KRT1* starting with codon glycine 594, changing this amino acid to an arginine residue (Fig 4). This c-terminus frameshift variant, c.1780_1787delGGCGGCGG, is predicted to produce a keratin molecule with an aberrant, elongated tail domain. We believe that this clinical picture, in correlation with histopathologic

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Fig 1. Transgrediens et progrediens palmoplantar keratoderma on the palmar aspect of the hand.



Fig 2. Hyperkeratotic plaque on the knee.

findings and genetic testing, is consistent with a diagnosis of keratin 1–linked PPK with epidermolytic ichthyosis. Our patient is currently being managed with 40% urea cream to hyperkeratotic plaques daily, 10 mg of acitretin daily, and chlorhexidine skin cleanser 3 times weekly. Although this regimen has decreased the incidence of superficial bacterial infections and malodor, it has provided only modest benefit for the hyperkeratotic plaques and PPK. Our patient was also referred to a geneticist for counseling.

DISCUSSION

Keratins are a vital intermediate filament for epithelial cell structure.⁵ It is known that K1, a type 2 keratin, dimerizes with type 1 keratins 9 and 10 in the epidermis of palmoplantar skin.^{5,6} However, the relationship between various genetic defects in these keratins and their resulting clinical phenotype is complex.

In our patient, the clinical appearance of diffuse, transgrediens PPK, with onset during infancy, and hyperkeratotic plaques on the bilateral aspect of the knees and elbows is consistent with Greither's disease.¹⁻³ However, hyperhidrosis, a classic

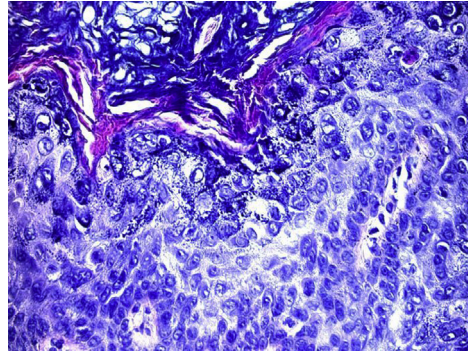


Fig 3. Hematoxylin-eosin results from biopsy showed hyperkeratosis, digitated acanthosis, hypergranulosis with perinuclear vacuolization, and indistinct cell borders consistent with epidermolytic hyperkeratosis.

component of this disease, was not a prominent feature in our patient.¹⁻³ Furthermore, he lacked extracutaneous findings and transient or migratory erythema, making other distinct entities with diffuse PPK with transgrediens less likely.³

The rarity and phenotypic heterogeneity of PPKs, including Greither's disease, makes them a challenging group of diagnostic entities. Early reports considered various clinical presentations as types of Greither's disease, stating that multiple genetic mutations can result in the disease and that it may be hallmarked by a wide phenotypic spectrum.⁷ However, recent literature aims to separate diagnoses by genetic makeup, relying less on strict clinical criteria and more on chromosomal analysis. Given the clinical picture, histopathologic findings, and genetic testing observed in our patient, we believe this case is most accurately described as keratin 1–linked PPK with epidermolytic ichthyosis.

KRT1 mutations have been implicated in a number of distinct keratodermas, highlighting the clinical variability that these mutations can impart.^{5,6} To our knowledge, the *KRT1* mutation observed in our patient has not previously been published as a pathogenic variant or observed in large population cohorts.⁸

This case underscores a unique and challenging diagnosis and supports the increasing body of evidence that *KRT1* mutations may result in heterogeneity of phenotypes. Furthermore, our case highlights a novel *KRT1* defect. Although a pragmatic approach to patients with PPK that is focused on history, physical examination, and histologic evaluation is essential, we suggest genetic testing also be considered. Genetic testing not only offers improved diagnostic certainty for patients but also will allow establishment of a more objective

Gene	Coding DNA	Variant	Zygosity	Classification
KRT1	c.1780_1787delGGCGGCGG	p.Gly594ArgfsX57 (G594RfsX57)	Heterozygous	Likely Pathogenic Variant

Fig 4. Novel variant in *KRT1*, resulting in a molecule with an aberrant, elongated tail domain.

genotype-phenotype correlation for individuals with *KRT1* mutations. This information will allow physicians to efficiently and successfully counsel patients on their diagnosis and prognosis. Additionally, through a greater understanding of the underlying pathogenesis, it is plausible that advancements in treatment modalities will be made.

REFERENCES

1. Greither A. Keratosis extremitatum hereditaria progrediens with genetic dominant. *Hautarzt*. 1952;3(5):198-203.
2. Gach JE, Munro CS, Lane EB, Wilson NJ, Moss C. Two families with Greither's syndrome caused by a keratin 1 mutation. *J Am Acad Dermatol*. 2005;53(5 suppl 1):S225-S230.
3. Sakiyama T, Kubo A. Hereditary palmoplantar keratoderma "clinical and genetic differential diagnosis". *J Dermatol*. 2016; 43(3):264-274.
4. Singh T, Yadav S, Dhillon K, et al. Greither's disease: a case report. *Int J Adv Med*. 2015;2(3):291-293.
5. Kimyai-Asadi A, Kotcher LB, Jih MH. The molecular basis of hereditary palmoplantar keratoderms. *J Am Acad Dermatol*. 2002;47(3):327-346.
6. Terron-Kwiatkowski A, Paller AS, Compton J, Atherton DJ, McLean WHI, Irvine AD. Two cases of primarily palmoplantar keratoderma associated with novel mutations in keratin 1. *J Invest Dermatol*. 2002;119(4):966-971.
7. Irvine AD, Paller AS. Inherited disorders of keratinization. *Curr Probl Dermatol*. 2002;14(3):77-115.
8. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536(7616):285-291.