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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Increased pachyonychia congenita severity in patients with concurrent keratin and filaggrin mutations

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Summary

Pachyonychia congenita (PC), a rare autosomal-dominant keratin disorder caused by mutations in keratin genes KRT6A/B, KRT16 or KRT17, is characterized by painful plantar keratoderma and hypertrophic nail dystrophy. Loss-of-function mutations in the filaggrin (FLG) gene underlie the most prevalent skin disorder of cornification, ichthyosis vulgaris (IV), which presents with generalized scaling and is also associated with atopic dermatitis. Recently, FLG mutations have been reported to increase phenotype severity of X-linked ichthyosis and alopecia areata. We report a parent–child trio in which the mother and the son have PC and the father has IV. Both the mother and the son are carriers for the KRT16 mutation p.Leu132Pro. The son, who is much more severely affected than his mother, in addition carries the heterozygous FLG mutation p.R2447X, which was inherited from the father. This observation suggests that coinheritance of mutations in KRT16 and FLG may aggravate the PC phenotype and that FLG could serve as a genetic modifier in PC.

Pachyonychia congenita (PC) is a rare autosomal-dominant ectodermal dysplasia which can be divided into two major subtypes.1,3 Patients with PC-1 (OMIM 167200, Jadassohn–Lewandowsky syndrome) present with hypertrophic nail dystrophy, painful diffuse or focal symmetrical hyperkeratosis of palms and soles sometimes associated with erosions, follicular keratosis on the extensor surfaces of the extremities and oral leucokeratosis.3 Individuals with PC-2 (OMIM 167210, Jackson–Lawler type) additionally show epidermoid cysts, neonatal teeth and leucokeratosis of the larynx and trachea.4 At the molecular level, PC-1 is caused by dominant-negative mutations in keratin genes KRT6A and KRT16 whereas PC-2 is due to mutations in KRT6B and KRT17.5–7 Keratin 16 and 17 are expressed in differentiated epithelial structures such as nail beds, palmoplantar epidermis and mucosa, which comprise the affected tissues in PC-1.2,6 Because of phenotype variations in patients carrying the same genotype, it was hypothesized that genetic or environmental modifiers could influence the genotype–phenotype relationship;2,8 however, until now this has not been confirmed.

In 2006, loss-of-function mutations in the gene coding for filaggrin (FLG) were discovered as the molecular basis of ichthyosis vulgaris (IV), the most common hereditary disorder of cornification in humans. The same mutations are also strongly associated with atopic eczema.9,10 Recently, it was reported that coinheritance of FLG mutations increases phenotype severity of X-linked ichthyosis11 and alopecia areata.12 We present the first case report of a patient with concurrent KRT16 and FLG mutations showing an increased PC severity, indicating that FLG could serve as a genetic modifier in PC.

Case report

A 46-year-old Austrian woman (Figs 1a–d and 2) and her 20-year-old son (Fig. 1e–h) presented with typical PC-1 with onset at 1 year of age. Findings included hypertrophic dystrophy of the fingernails and toenails, painful diffuse symmetrical hyperkeratosis of the soles and mild follicular keratosis on the extensor surfaces of the extremities. Strikingly, the son was much more severely affected than his mother. In addition to the findings of his mother, he also showed palmar hyperkeratosis, plantar macerations and large blisters, oral leucokeratosis and palmar hyperlinearity (Fig. 1e–h).

Mother and son lived in the same household with similar environmental conditions. While the mother worked as a secretary, her son was a student. He had previously experienced a deterioration of his plantar calluses during increased physical activity (walking) when temporarily jobbing in a parcel service. At the time of the present study, with avoidance of physical activity, his cutaneous symptoms had returned to baseline. Even though the mother showed stronger symptoms of PC during childhood, she was never as severely affected as her son. Treatment consisted of topical emollients in both patients. In addition, 32 years previously the mother had received a
Fig 1. Phenotype of the index patient (a–d) and her son (e–h) showing the typical features of pachyonychia congenita type 1. Note the more severe phenotype in the son with involvement of the distal nail surfaces, palmar hyperkeratosis and hyperlinearity, plantar macerations, large blisters and calluses.
course of oral etretinate (Ro-A-Vit 10-9359; Hoffmann-La Roche, Vienna, Austria) 25 mg twice daily for about 4 weeks, but treatment was discontinued because of increased plantar blistering and pain. Taken together, it was unlikely that environmental factors were solely responsible for the differences in phenotype severity between mother and son.

Genetic analyses revealed a heterozygous dominant missense mutation in the keratin 16 gene, namely p.Leu132Pro, in both the mother and her son. The histology of plantar skin showed acanthosis and compact hyperkeratosis with focal parakeratosis consistent with the diagnosis of PC. Except for the more prominent hyperkeratosis in the son compared with the mother, which is consistent with the clinical picture, no further histological differences could be detected. Staining for KRT16 revealed expression throughout the epidermis in both patients (Fig. 3d–f). While there was strong immunohistochemical staining for FLG using a mouse monoclonal antibody (Novocastra, Newcastle upon Tyne, U.K.) in the mother and in a control individual, the son showed decreased FLG expression with a reduced stratum granulosum layer (Fig. 3a–c).

The 68-year-old father displayed features consistent with moderate IV, characterized by fine scaling on the extensor surfaces of the extremities, keratosis pilaris on the upper arms and palmoplantar hyperlinearity (Figs 2 and 4). A screen for the common European FLG mutations R501X, 2282del4, R2447X and S3247X, using a TaqMan allelic discrimination analysis.
ascribed to the hypothesis that the phenotype variation in this family can be modifying genetic factor. Based on this observation we lessence, was never affected as severely as her son, points to a that the mother throughout life, including childhood and ado-
sufficiently explain the striking phenotype differences. The fact that imposing role in phenotype severity, in this family it does not
the possibility that environmental trauma may play a super-
als with abnormalities in both FLG and KRT16.

Discussion
Because patients with PC due to keratin mutations can show phenotype variation even when carrying the same genotype, it was hypothesized that the genotype–phenotype relationship is influenced by additional environmental or genetic modifiers.2,8 The present case report suggests that concomitant FLG mutations can act as genetic modifiers of the PC phenotype. It appears unlikely that the more pronounced PC-1 phenotype of the son is due to environmental effects, because both individuals live in the same household with similar working and leisure conditions. Although we cannot completely exclude the possibility that environmental trauma may play a superimposing role in phenotype severity, in this family it does not sufficiently explain the striking phenotype differences. The fact that the mother throughout life, including childhood and adolescence, was never affected as severely as her son, points to a modifying genetic factor. Based on this observation we hypothesize that the phenotype variation in this family can be ascribed to the FLG genotype, i.e. concomitant mutations p.Leu132Pro in KRT16 and p.R2447X in FLG in the son. This assumption is substantiated by two recent reports, describing that coinheritance of FLG mutations can aggravate phenotype severity in other cutaneous disorders.1,11

The epidermal keratins are intermediate filament proteins that form the cytoskeletal network of keratinocytes. Mutations in KRT16 result in accumulation of defective keratins within the cytoplasm, aberrant intermediate filament organization, increased epithelial fragility and hyperproliferation of mechan-

assay as described previously,11 identified the heterozygous mutation p.R2447X in the son and his father.

In summary, while the index patient carried the p.Leu132-Pro mutation in KRT16 and her husband the p.R2447X mutation in FLG, their son inherited both mutations. Past medical history and recent laboratory findings of both patients with PC were unremarkable. A detailed family history did not reveal other family members affected by PC and the examination of the mother’s father and sister did not show any cutaneous fea-
tures. There was no history or current evidence for atopic dermatitis, allergic rhinitis or asthma in the family.

Fig 4. Phenotype of the father presenting with characteristic features of ichthyosis vulgaris. (a) Fine scaling on the extensor surfaces of the lower extremities. (b) Hyperlinearity of the palms. (c) Keratosis pilaris on the upper arms.

References


