Familial pityriasis rubra pilaris in a Chinese family caused by a novel mutation in CARD14 gene

Sir,

Pityriasis rubra pilaris (PRP) (MIM# 173200) is a rare genodermatoses characterized by palmoplantar keratoderma and follicular hyperkeratotic papules. Generally, several follicular hyperkeratotic papules coalesce to form large, well-demarcated and scaly erythematous plaques interspersed by areas of normal skin.[1,2] Erythroderma may result in severe cases. Familial PRP is inherited in an autosomal dominant manner. In addition, the clinical symptoms of familial PRP usually start to appear at the time of birth or in the first few years of life and patients gradually develop diffuse palmoplantar keratoderma, prominent follicular hyperkeratosis, and erythema.[3]

In this study, we investigated a Chinese family with familial PRP in the Department of Dermatology, Dermatology Hospital, Southern Medical University, Guangzhou, China. All the family members participating in this study had given their informed consent. The ethics committee of Dermatology Hospital, Southern Medical University had approved the study in accordance with the Declaration of Helsinki.

The proband was a 3-year-old Chinese girl who was born healthy [Figure 1a], but began to develop palmoplantar keratoderma along with erythema at 2 years of age. This was followed by development of large patches of hyperkeratosis and erythema with waxy keratotic plaques and fine scales on the knees, ankles, soles and gluteal cleft [Figure 1b-g]. The surface of the keratotic plaques was covered with thin, hard, and rough scales. Biopsy from the right palm of the proband showed hyperkeratosis, acanthosis, and sparse lymphocytic infiltration in the superficial dermis [Figure 1h and i].

Proband's mother presented with palmar hyperkeratosis and erythema during her childhood but milder than the proband, and the rashes gradually eased with increasing age. Proband's nonidentical twin sister (III-2) had erythema and hyperkeratosis on palms and soles epidermis only, similar to but milder than in the proband [Figure 2a-c]. Proband's father was normal. Proband's maternal grandmother (I-2) and uncle (II-3) showed mild diffuse PPK without erythema.

General physical examination, systemic examination and developmental and cognitive assessment of the proband were normal. Dermatologic examination for dermatophytes and candida was negative from the hyperkeratotic skin of hands and feet of the proband. The rest of the skin and other ectodermal tissues were completely normal.

The patient and affected relatives were diagnosed with PRP according to the diagnostic criteria by two independent dermatologists.[4] To identify the genetic basis of the disease in this family, targeted next-generation sequencing and Sanger sequencing were performed. Targeted next-generation sequencing and Sanger sequencing identified a novel heterozygous mutation: c.2263C>T, p.Q755* in exon 16 of *CARD14* in the proband (III: 1) and in all the affected family members. This mutation was absent in the unaffected family members and in normal controls [Figure 2d and e]. This mutation co-segregated well with the disease phenotypes among the affected members in this family.

Here, we identified the first nonsense mutation in the human *CARD14* gene, which results in the formation of truncated

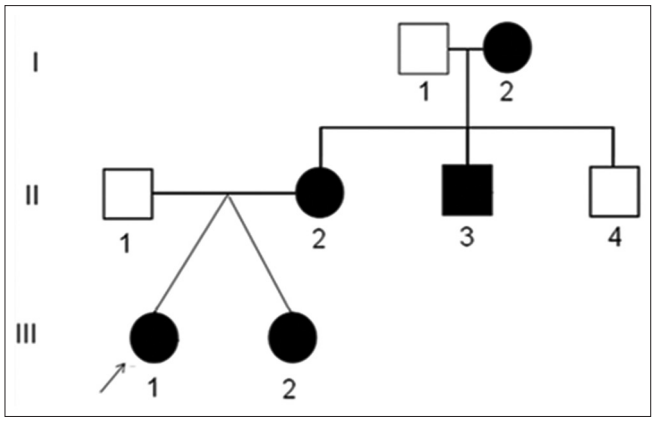

Figure 1a: Pedigree of the Chinese family with familial pityriasis rubra pilaris. Arrow indicates the proband (III-1)

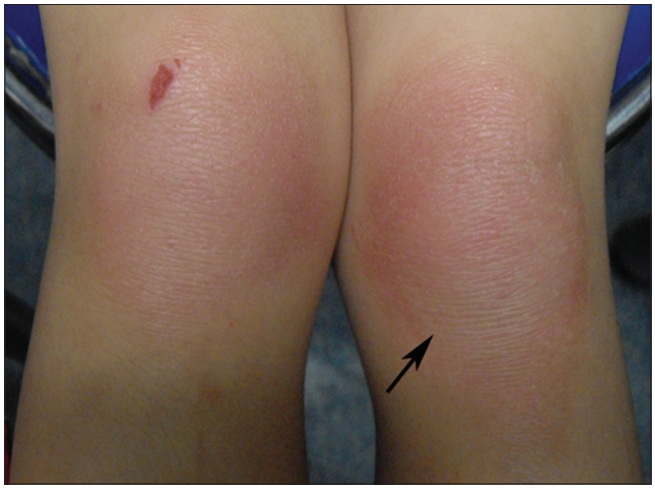

Figure 1c: Proband with erythematous scaly plaque on the patellar surfaces of knee

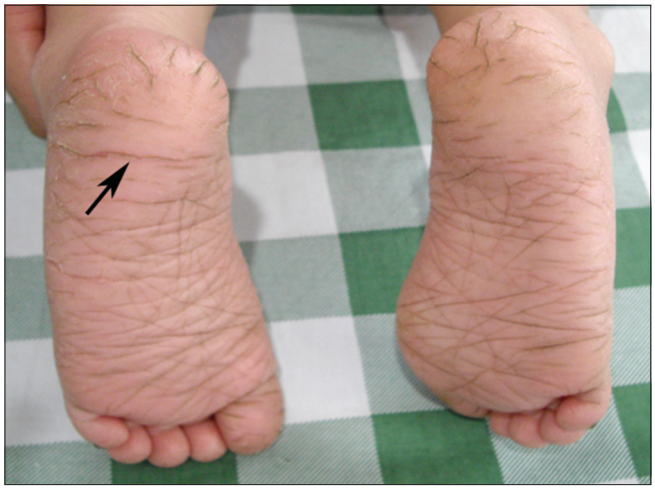

Figure 1e: Proband with erythematous scaly plaque on the plantar epidermis

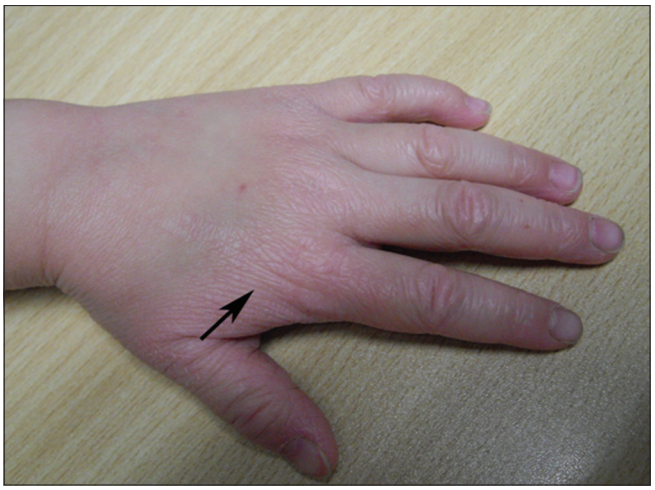

Figure 1b: Proband with hyperkeratosis and erythema having waxy keratotic plaques with fine scales on the dorsal surface of the hand

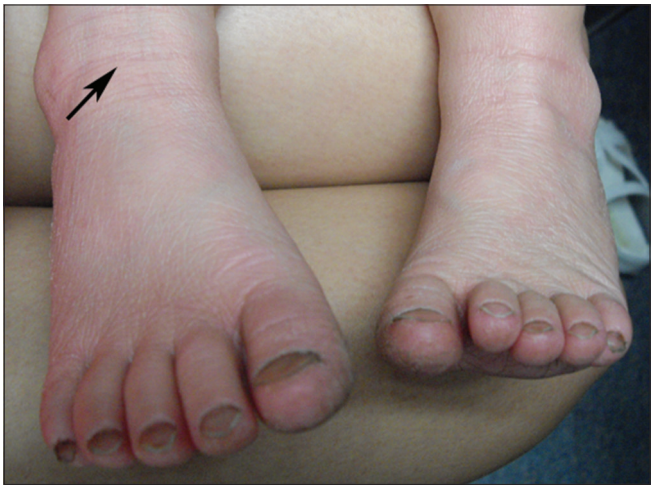

Figure 1d: Proband with erythematous scaly plaque on the tarsus

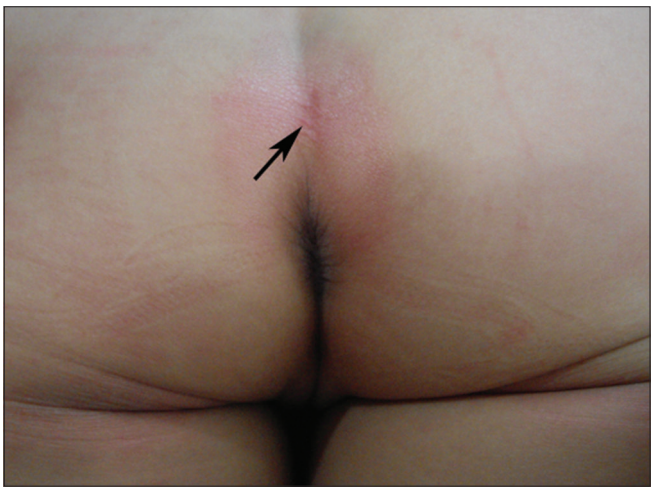

Figure 1f: Proband with erythematous scaly plaque on the gluteal sulcus

CARD14 protein in this three-generation Chinese family with familial PRP. This nonsense mutation leads to complete loss of the GuK domain from the *CARD14* protein. This mutation is a *loss-of function* mutation according to the variants interpretation guidelines of the American College of Medical Genetics and Genomics.[5]

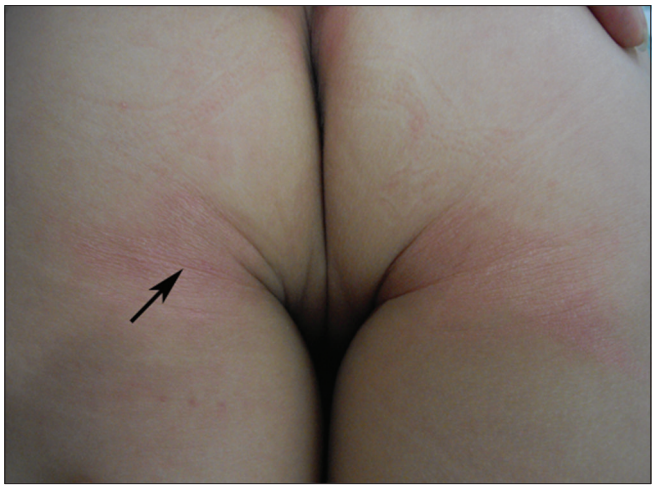

Figure 1g: Proband with erythematous scaly plaque in the gluteal cleft

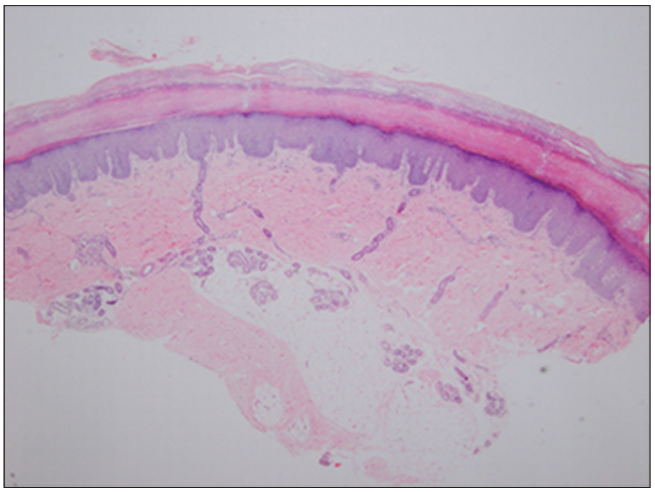

Figure 1h: Biopsy from right palm shows hyperkeratosis, acanthosis and sparse lymphocytic infiltration in the superficial dermis in low magnification (60X)

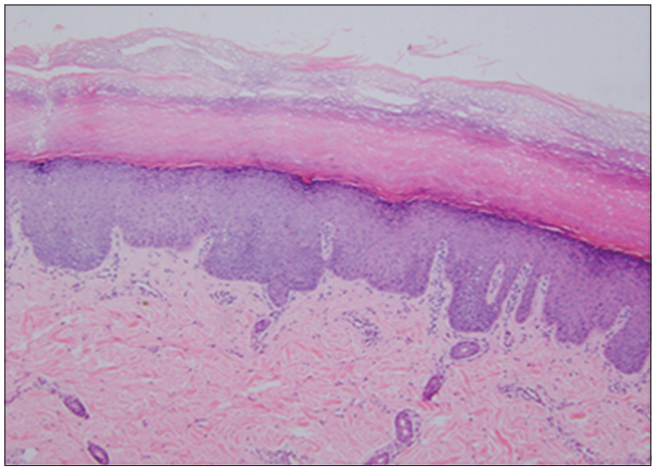

Figure 1i: Biopsy from right palm shows hyperkeratosis, acanthosis and sparse lymphocytic infiltration in the superficial dermis in high magnification (100X)

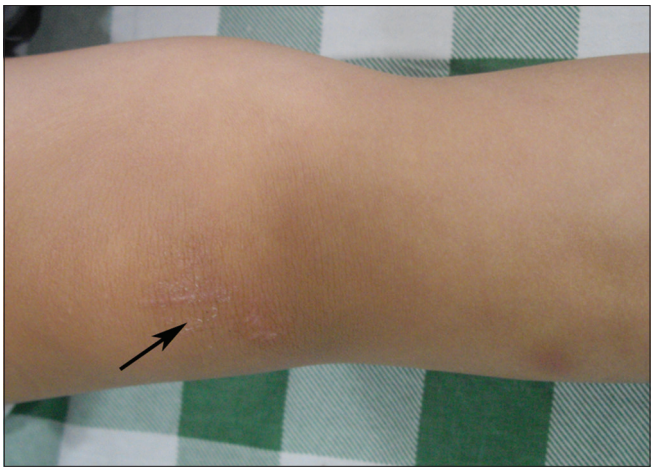

Figure 2a: Proband's sister's clinical symptoms and Sanger sequencing. Proband's younger sister (III-2) with hyperkeratosis and erythema having waxy keratotic plaques with fine scales in the patella surfaces of knee

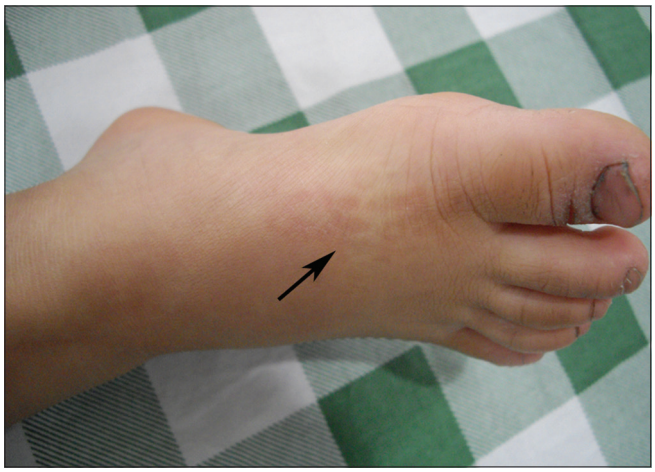

Figure 2b: Proband's sister's clinical symptoms and Sanger sequencing. Proband's younger sister (III-2) with hyperkeratosis and erythema having tarsus

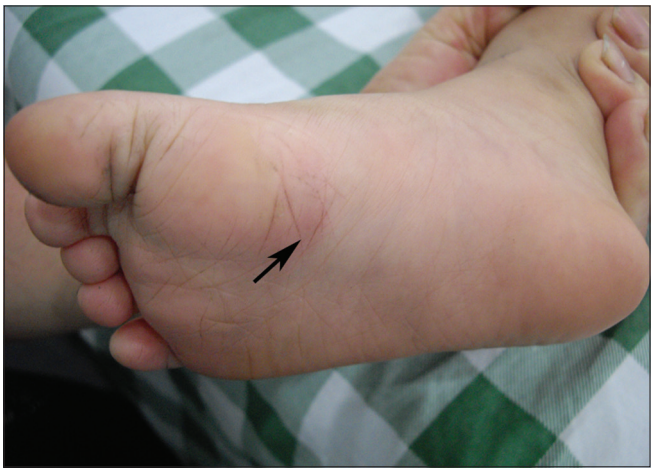

Figure 2c: Proband's sister's clinical symptoms and Sanger sequencing. Proband's younger sister (III-2) with hyperkeratosis and erythema having plantar epidermis

Our studied mutation is the first *loss-of-function* mutation which results in complete loss of the GuK domain of *CARD14* protein. Familial PRP is an autosomal dominant genodermatoses, so it is quite expected that all the affected family members showed

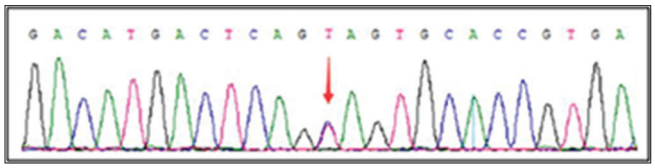

Figure 2d: Sanger sequencing of *CARD14* identified a cytosine to thymine substitution at cDNA position c.2263C > T

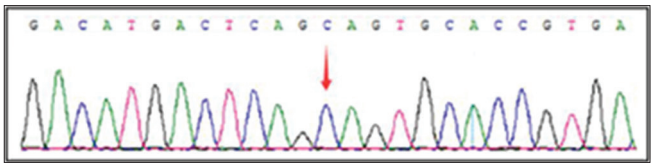

Figure 2e: The wild-type sequence from unaffected family members and normal control individuals (GenBank Accession: NM_024110.4)

a similar disease phenotype as they are harboring the same pathogenic mutation in a heterozygous state.[3] However, in this family, we found a spectrum of disease phenotype categorized as severe, moderate, and mild. The proband had severe phenotype, while proband's mother and nonidentical twin sister had moderate phenotype, and proband's maternal grandmother and uncle had mild phenotype, although all of them were harboring the same heterozygous nonsense mutation in *CARD14* gene. This can be explained by reduced penetrance and variable expressivity.[3] In this family, the extreme interindividual phenotypic diversity in the disease symptoms might be caused by the differences in the genetic background and the presence of "modifier genes" in each of the individuals.[2,3]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment

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Nil.

Conflicts of interest

There are no conflicts of interest.

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