Case Letter

A novel compound heterozygous variant in the *ABCA12* gene associated with mild palmoplantar keratoderma

Dear Editor,

Pathogenic variants in *ABCA12* are important causative genetic defects for autosomal recessive congenital ichthyoses (ARCI), including congenital ichthyosiform erythroderma, harlequin ichthyosis and lamellar ichthyosis, often accompanied by palmoplantar keratoderma (PPK).[1,2] Occasionally, specific *ABCA12* mutations have been linked to milder phenotypes, including erythrokeratodermia variabilis et progressiva and pityriasis rubra pilaris.[2,3] This report presents a case of isolated PPK resulting from variants in the *ABCA12* gene and reviews such reported mild cases associated with *ABCA12* variants.

A 31-year-old healthy woman, employed as a teahouse manager, presented with progressive thickening of the palms and soles since seven years of age, without significant discomfort. On examination, she exhibited mild, thick, yellowish plaques on weight-bearing sites of the palmoplantar areas, notably on the finger flexors and calcaneal regions [Figures 1a, 1b and 1c]. There was no evidence of hyperhidrosis, transgradiens, or a sponge-like appearance after water immersion. No cutaneous involvement suggestive of ichthyosis was noted in other areas of the body, and no abnormalities of nails, hair, or teeth were observed. Family history was noncontributary [Supplementary Figure 1]. Histological examination of the keratotic lesion from the right thumb showed orthohyperkeratosis and acanthosis without acantholysis [Figure 1d].

After informed consent and approval from the ethics committee of the institute, peripheral blood samples were taken from the patient and her parents. Whole-exome sequencing identified a novel compound heterozygous variant in the *ABCA12* gene in the proband, which was confirmed by Sanger sequencing. This included the duplication variant c.7659_7662dupGAGT (p.Q2555Efs*20) in exon 52, and the missense variant c.7386G>C (p.M2462I) in exon 50, inherited from her mother and father, respectively [Figure 2a]. These observed variants

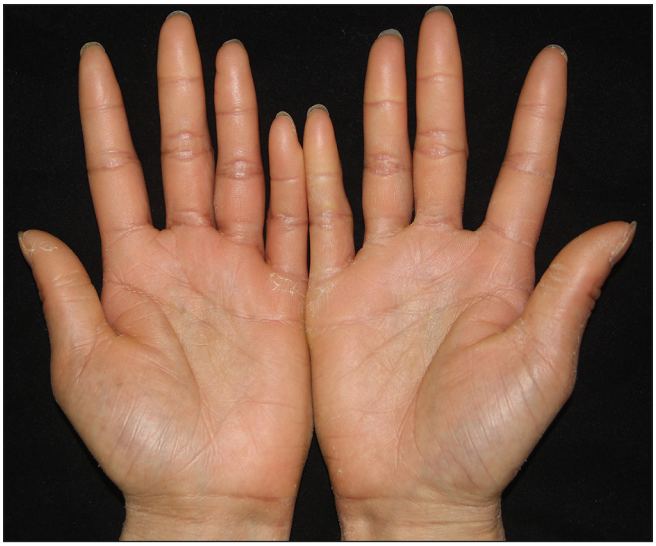

Figure 1a: Mild, thick, yellowish plaques of the palms, notably on the finger flexors.

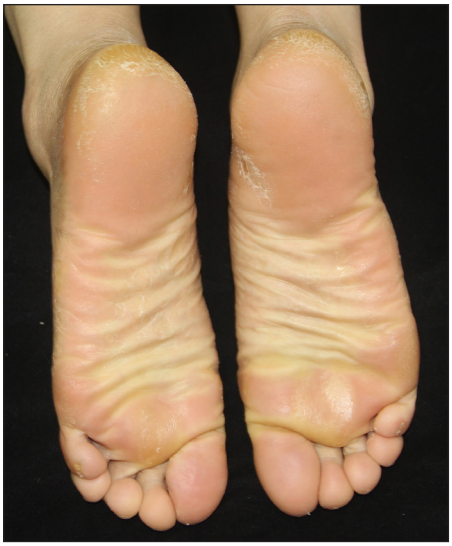

Figure 1b: Thick, yellowish plaques on weight-bearing sites of the plantar areas.

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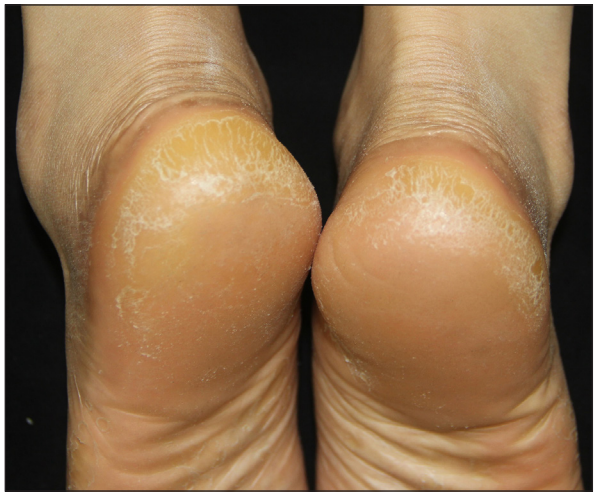

Figure 1c: Thick, yellowish plaques on the calcaneal regions.

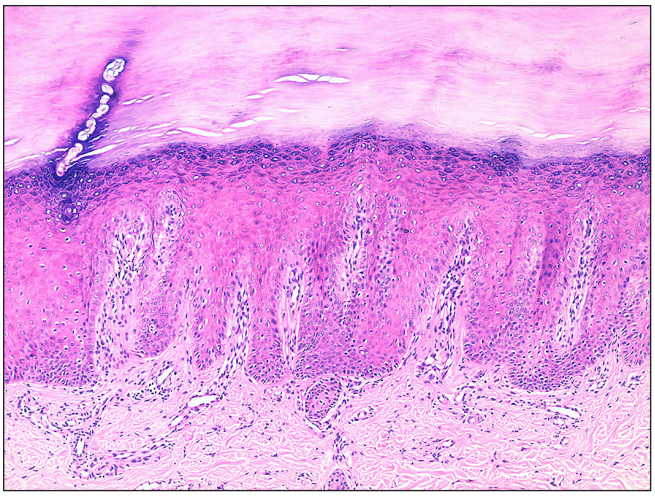

Figure 1d: Orthohyperkeratosis and acanthosis without acantholysis (Haematoxylin-eosin, 100×).

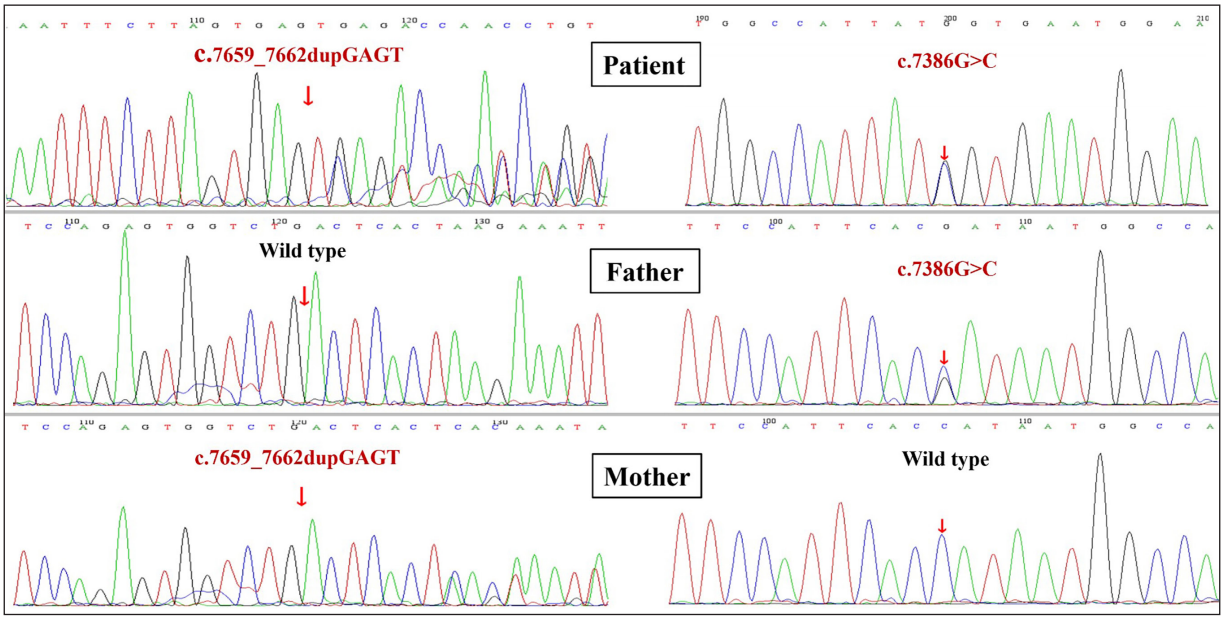

Figure 2a: Genetic analysis (sequence chromatogram) showing compound heterozygous variants in the C-terminus of *ABCA12*, including c.7659_7662dupGAGT (p.Q2555Efs*20) and c.7386G>C (p.M2462I). (A: Adenosine, C: Cytosine, T: Thymine, G: Guanine).

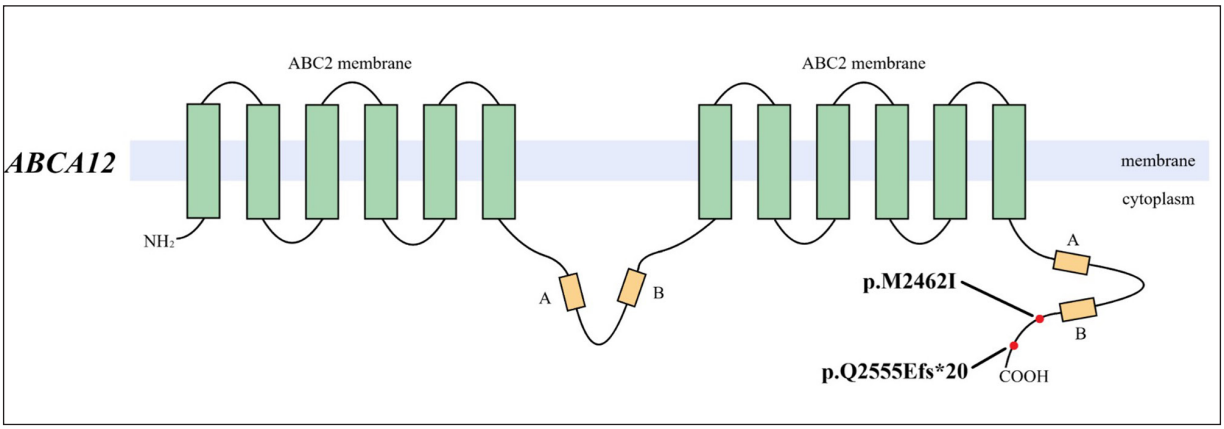

Figure 2b: Schematic representation of the *ABCA12* structure showing the identified variants located in the C-terminus. (COOH: carboxylic acid).

Table 1: *ABCA12*-associated mild keratinisation disorders

Clinical phenotype	Genetic basis	Reference/PMID
EKV or EKVP	Compound heterozygous: p.N678Rfs*10; c.2866-8T>A Compound heterozygous: p.D844G;p.P1938S Compound heterozygous: p.Y1929*; p.E2284D	Sun Q, *et al*. [2] PMID: 34851365
	Compound heterozygous: H1471R; T1534M	Terrinoni A, *et al*.[4] PMID: 37762265
	Compound heterozygous: p.P2416L; p.Y1218C	Liu Y, *et al*.[3] PMID: 38085035
PRP	Homozygous: p.T1534M Homozygous: p.R2426W	Takeichi T, *et al*.[6] PMID: 37752865
Nevoid form of CIE	Recessive mosaicism: p.I1257Nfs*4; p.E1227K	van Leersum FS, *et al*.[5] PMID: 31206590
Mild CIE with periodic exacerbation	Compound heterozygous: p.N2184I; p.I2307Rfs*14	Wada Y, *et al*.[7] PMID: 28771802
Isolated PPK	Compound heterozygous: p.Q2555Efs*20; p.M2462I	Our case

EKV, erythrokeratodermia variabilis; EKVP, erythrokeratodermia variabilis et progressive; PRP, pityriasis rubra pilaris; PPK, palmoplantar keratoderma; CIE, congenital ichthyosiform erythroderma.

have not been reported from the databases of single nucleotide polymorphisms, ExAC, 1000 genomes, gnomAD, and Exome Variant Server (EVS). Both the variants were predicted to be detrimental using Sorting Intolerant From Tolerant PolyPhen-2, MutationTaster, and Genomic Evolutionary Rate Profiling [Supplementary Figure 2-3]. These variants are classified as uncertain significance according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Moreover, any other disease-causing variants associated with PPK were not detected. Given the genetic defects and clinical features, the diagnosis of isolated PPK associated with *ABCA12* variants was established.

The *ABCA12* protein, consisting of 2595 amino acids encoded by 53 exons, plays a crucial role in skin metabolism and keratinisation.[1,2] This ATP-binding cassette transporter facilitates the transport of lipid glucosylceramides, crucial for forming the extracellular lamellar membrane.[1,2] Disturbances in *ABCA12* function can lead to impaired lamellar granules, disrupting intercellular lipid deposition and skin barrier function.[1,2] Consequently, hyperkeratosis occurs due to compensatory hyperproliferation of keratinocytes.[1]

The clinical severity often correlates with the nature of mutations affecting *ABCA12* function. For example, potentially fatal harlequin ichthyosis often results from loss-of-function truncating mutations, while biallelic missense mutations typically lead to milder phenotypes like congenital ichthyosiform erythroderma or lamellar ichthyosis. [1,2]

Recent reports have linked *ABCA12* mutations to relatively milder keratinisation disorders[2-7] [Table 1]. Several *ABCA12* variants have been identified in erythrokeratodermia variabilis, an otherwise dominant disorder resulting from connexin gene defects.[2,3] Terrinoni *et al*. also identified a compound heterozygous mutation in *ABCA12* (exon 30 and exon 31) in a family displaying an variabilis et progressiva phenotype.[4] Their evaluation of glucosyl-ceramides in the upper epidermal layers suggested a partial depletion of *ABCA12* function in the mild phenotype, characterised by reduced and patchy hydroxy ceramide deposition.[4] *ABCA12* variants also cause a blaschkoid form of congenital ichthyosiform erythroderma due to recessive mosaicism.[5] Additionally, cases resembling pityriasis rubra pilaris have been described in association with *ABCA12* variants.[6] These mild cases often involve unique missense changes in *ABCA12*, not leading to complete loss of function.[6]

In our case, isolated PPK without generalised ichthyosis was noted. The identified causal mutations, located in exon 50 and 52, might cause a potential mild loss of protein function in the C-terminus of *ABCA12* [Figure 2b], offering a plausible explanation for the observed mild phenotypes. Given that lesions are localised in weight-bearing and friction areas, environmental factors like pressure might contribute to hyperkeratotic lesions in individuals with a genetic background of hypomorphic *ABCA12* variants. However, further functional studies are necessary to validate this hypothesis.

In conclusion, we identified a novel compound heterozygous variant in the *ABCA12* gene in a patient presenting with a mild form of isolated PPK. Our study expands the phenotypic spectrum associated with *ABCA12* variants and underscores the genetic heterogeneity of isolated PPK. Further research is crucial for elucidating precise genotype–phenotype correlations for *ABCA12* mutations, particularly in cases with mild phenotypes.

Ethical approval statement: The research/study was approved by the Institutional Review Board at Ethics Committee Biomedical Research, West China Hospital of Sichuan University, number IRB No. 202304705, dated 2023.12.05.

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