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Recessive mosaicism in *ABCA12* causes a unique phenotype of segmental congenital ichthyosiform erythroderma mimicking erythrokeratodermia variabilis

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Consent for publication: the patient's parents provided written informed consent for the publication of this case report and any accompanying images.

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Abstract

We report a unique case of a 1-year-old boy presenting with nonpruritic erythematous patches and mild keratotic plaques, partially following the lines of Blaschko and mainly involving the extremities. Next-generation sequencing (NGS) revealed a heterozygous missense mutation c.4724C>T (p.Thr1575Met) and a *de novo* mosaic deletion mutation c.6861_6869del (p.Leu2288_Gly2290del) in the *ABCA12* (*NM_173076.3*) gene from the DNA of the patient's blood. Even more to the point, the lesional skin showed clinical improvement after 2 weeks of moisturizing treatment. Therefore, partial encapsulation treatment, widely used to enhance the percutaneous absorption of drugs, is suitable for mosaic ichthyosis given its localized skin lesions.

Introduction

ABCA12 belongs to a subfamily of adenosine triphosphate-binding cassette (ABC) transporters, which are important for lipid transport.[1] *ABCA12* was recognized as a key molecule in keratinocyte lipid transport. ABCA12 is a keratinocyte transmembrane lipid transporter protein associated with lipid transport in lamellar granules (LG) to the apical surface of granular layer keratinocytes.[2] Defective ABCA12 leads to disturbed lipid transport in the LG, including ceramide transport. Germline mutations in the *ABCA12* gene have been described in patients with autosomal recessive congenital ichthyoses, including congenital ichthyosiform erythroderma (CIE), harlequin ichthyosis (HI), and lamellar ichthyosis (LI).[3] Postzygotic compound allelic loss in autosomal recessive disorders is extremely rare and will not appear as the typical phenotype of the known germline mutation-associated disease.

A previous study reported the first rare case of blaschkoid CIE caused by mosaicism in *ABCA12* (a combination of a heterozygous germline mutation and a postzygotic mutation in the *ABCA12* gene).[4] Our study reported another unique acral phenotype of CIE mimicking erythrokeratodermia variabilis (EKV) with recessive mosaic *ABCA12* mutations, which has not been reported in the literature, broadening the mosaic manifestations of autosomal recessive congenital ichthyosis.

Case Report

A 1-year-old Chinese boy was recruited for this study. After written informed consent was obtained from the parents of the probands, a skin biopsy was performed, and skin and blood samples were

collected. Next-generation sequencing (NGS) was conducted on the DNA extracted from the patient's blood.

Next-generation sequencing

The TIANamp Blood DNA Kit (TianGen BioChemical Co., Ltd., Beijing, China) was used to extract genomic DNA. NGS using a custom enrichment kit targeting 745 genes associated with genodermatosis was performed to identify the pathogenic mutation (*Supplementary Table 1*). Meanwhile, NGS-based analysis of copy number variations (CNVs) was performed to identify copy number changes in these genes. Online silico programs PolyPhen2 (http://genetics.bwh.harvard.edu/pph2) and SIFT (http://sift.bii.a-star.edu.sg) were applied to predict the impact of novel missense mutations.

Immunofluorescence staining

To perform immunofluorescence staining, skin tissue sections were incubated overnight at 4°C with the primary antibody, rabbit anti-human ABCA12 antibody (1:200 dilution; GeneTex, Inc., CA, USA). The sections were then incubated with the appropriate secondary antibody at room temperature for 1 hour. Finally, the sections were visualized under a fluorescence microscope and photographed.

Clinical presentation

The patient was referred to our department for long-lasting symmetrical brown keratotic plaques with sharp borders. The erythematous and keratotic lesions were predominantly confined to the armpit, buttock, and limbs and had gradually developed and stabilized as the child grew (Figure 1). Keratotic plaques thinned and erythematous patches appeared after moisturizing treatment (*Supplementary Figure 1*). There was no collodion membrane at birth. The patient's palms and soles were not hyperkeratotic. Ectropion, eclabium, and hypoplasia of the ear lobes were not observed, and the hair, nails, and teeth were intact. Furthermore, intelligence and growth were slightly lower than expected, and the child had a history of congenital heart disease. The other family members did not show a similar skin disease. Histology of the affected skin showed hyperkeratinization, epidermal papillomatous hyperplasia, granular layer thickening, but sparse inflammation around the dermal vascular (*Supplementary Figure 2*). Due to the infant-onset presentation, a genodermatosis such as

EKV, H syndrome, and a mosaic form of CIE was suspected.

Mutation analysis

NGS revealed a heterozygous missense mutation c.4724C>T (p.Thr1575Met) and a *de novo* mosaic deletion mutation c.6861_6869del (p.Leu2288_Gly2290del) in the *ABCA12* (*NM_173076.3*) gene in the blood samples. Both mutations were confirmed with Sanger sequencing (*Supplementary Figure 3*). Notably, the variant allele frequency (VAF) of the deletion mutation c.6861_6869del was approximately 50% (97/205) in the affected tissue and 30% (58/191) in the blood sample. In addition, a germline heterozygous mutation – c.4724C>T (p.Thr1575Met) in exon 31 of *ABCA12* – was identified and shown to be inherited from the mother. This previously unreported variant was absent in 100 unrelated Chinese control individuals and in public databases such as the 1000 Genomes Project and HapMap8. However, it is listed in Genome Aggregation Database (gnomAD) and in more recent versions of Single Nucleotide Polymorphism Database (dbSNP; current build 156) and dbSNP135. Both novel variants were predicted to be "possibly damaging" by PolyPhen-2 and "deleterious" by the Sorting Intolerant from Tolerant (SIFT) algorithm. No additional pathogenic variants were detected in genes associated with EKV, H syndrome, or congenital ichthyosiform erythroderma (*ALOX12B*, *ALOXE3*, *GJB4*, *LOR*, and *SLC29A3*, among others).

Immunofluorescence analysis

Immunofluorescence analysis revealed that *ABCA12* was stained in the granular layer in a standard control (*Supplementary Figure 4 A,B*). In contrast, in the skin of the patient, *ABCA12* was only faintly stained (*Supplementary Figure 4 C,D*).

Discussion

The clinical differential diagnosis of our case includes CIE and EKV. Classic CIE with a germline mutation is characterized by fine, whitish scales on an erythematous background over the whole body; it is reportedly caused by mutations in *ABCA12*, *ALOX12B*, *ALOXE3*, *CERS3*, *CYP4F22*, *NIPAL4*, *PNPLA1*, and *TGM1*. Specific mutations in the ABCA12 lipid transporter are known to cause different phenotypes like HI, CIE, and LI.

EKV is a rare genodermatosis associated with keratinisation disorders. It has been associated with

mutations in *GJB3*, GJA1, and *GJB4*, which encode Connexin 31 and Connexin 30.[5,6] Connexins are the protein constituents of gap junctions in the stratum granulosum of the epidermis, which provide a mechanism for synchronized cellular response, facilitating metabolic and electronic functions of the cell. The Connexin 31 and 30.3 are involved in keratinocyte differentiation. Based on the genetic factor, EKV presents itself usually within the first years of life, as in our patient, but it rarely arises later in childhood.[7] Clinically, the condition is characterized by the presence of erythematous patches accompanied by fixed hyperkeratotic plaques.[8] Transient, irregularly shaped, bright-red patches develop and change in size and location over time. In contrast, the fixed, sharply demarcated, geographic hyperkeratotic plaques are typically distributed symmetrically over the extensor surfaces of the limbs, as well as in the axillary, inguinal, and gluteal regions.

Approximately 50% of EKV patients have palmoplantar keratoderma. The diagnosis, therefore, depends on the clinical features and family history. The main distinguishing feature of EKV is transient lesions, which were not observed in our case.

The missense mutation c.4724C>T (p.Thr1575Met) is maternally inherited; the frequency in unselected individuals of this missense mutation is 0.000150. A mutation in the same amino acid residue, c.4723A>C (p.Thr1575Pro), has been reported in the literature.[9] In-frame deletion mutation c.6861_6869del (p.Leu2288_Gly2290del) in the *ABCA12* gene has not been reported, but similar mutations with 3-bp deletion, such as c.6443_6445delCAC, c.4158_4160delTAC, were reported to be pathogenic.[1,10] Immunofluorescence analysis revealed that ABCA12 was only faintly stained in the granular layer in comparison with controls, suggesting that the two mutations decreased the expression of ABCA12.

Cutaneous mosaicism is readily visualized because affected tissue often follows predetermined patterns, such as lines of Blaschko. However, the clinical manifestations in our patient did not fit the typical classification of cutaneous mosaicism reported in the literature, possibly because of the relatively high deletion mutation rate in blood cells. A relatively mild phenotype with mild erythrokeratoderma may be attributed to the combination of a missense mutation and an in-frame deletion mutation in the *ABCA12* gene. Our patient's lesions were partially following the lines of Blaschko but mainly along the extremities. A relatively severe phenotype caused by the combination of a germline mutation and an acquired postzygotic mutation in *ABCA12* has been reported. The phenotype and histology of a patient's biopsy reported by van Leersum *et al.* showed many

similarities to those of the patient presented in this manuscript.[4]

Offspring of our patient had a 50% likelihood of being a carrier of the germline mutation c.4724C>T. Gonadal mosaicism of a postzygotic mutation c.6861_6869del (p.Leu2288_Gly2290del) in the patient could not be excluded and will depend on the mutation ratio in sperm. In this case, the phenotype could be explained by the combination of a germline mutation and an acquired postzygotic mutation in *ABCA12*, resulting in the diagnosis of a mosaic manifestation of autosomal recessive congenital ichthyosis.

After confirming the diagnosis in our patient, the keratotic plaques thinned, and erythematous patches appeared after moisturizing treatment. The lesional skin showed clinical improvement after 2 weeks of partial encapsulation treatment. Therefore, partial encapsulation treatment, widely used to enhance the percutaneous absorption of drugs, was suitable for mosaic ichthyosis given its localized skin lesions.

Conclusions

We report a unique recessive mosaic phenotype of segmental CIE mimicking EKV due to one inherited germline missense mutation and another postzygotic deletion mutation in the *ABCA12* gene. This report delineates the somatic mutation analysis that may be employed when faced with a comparable diagnostic challenge characterized by manifestations indicative of genetic mosaicism.

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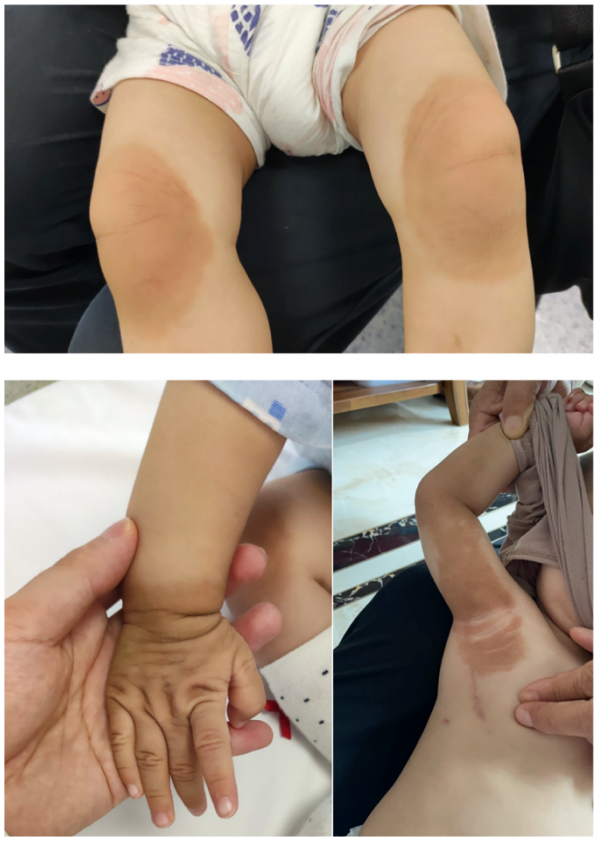
Figure 1. Clinical findings of the case. phenotype of segmental congenital ichthyosiform erythroderma.



Online Supplementary Material:

Supplementary Figure 1. Comparison before and after treatment. Keratotic plaques thinned, and erythematous patches appeared after moisturizing treatment.

Supplementary Figure 2. Histological findings of the case. Hematoxylin-eosin staining of the skin (bar, 200μm).

Supplementary Figure 3. Sanger sequencing shows the presence of both mutations in the blood samples. **A**) *De novo* mosaic deletion mutation c.6861_6869del (p.Leu2288_Gly2290del); **B**) heterozygous missense mutation c.4724C>T (p.Thr1575Met) in the *ABCA12* gene.

Supplementary Figure 4. Immunofluorescence staining showed that ABCA12 was prominently localized in the granular layer of the epidermis in control skin (**A**, **B**). In contrast, patient skin displayed only faint ABCA12 staining (**C**, **D**). Cryosections were incubated with a rabbit polyclonal anti-human ABCA12 antibody (1:200 dilution; GeneTex). Blue staining (DAPI) indicates nuclei. Scale bar = 50 μm.

Supplementary Table 1. List of genes included in the panel.