SHORT COMMUNICATION

Somatic Variants of *KRT1/KRT10* Identified by Next-generation Sequencing in Patients with Epidermal Nevi

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Submitted Jun 6, 2024. Accepted after revision Sep 18, 2024
Published Oct 22, 2024. DOI: 10.2340/actadv.v104.40958. Acta Derm Venereol 2024; 104: adv40958

Epidermal nevus (EN) is a benign hamartomatous skin lesion typically manifesting within the first year of life, characterized by localized verrucous epidermal thickening following Blaschko's lines (1, 2). EN is considered a result of genetic mosaicism mainly caused by somatic variants in keratin genes (1). However, detecting these variants poses a challenge due to their low frequency in peripheral blood, necessitating the use of more precise methods beyond universal next-generation sequencing (NGS).

Here, we describe 3 patients diagnosed with ENs resulting from low-frequency somatic variants in *KRT1* or *KRT10*, including 2 unreported variants. Written informed consents were obtained. The research was approved by the Ethics Committee of the Institute of Dermatology of the Chinese Academy of Medical Sciences and Peking Union Medical College (2019-Clinic-005).

CASE REPORTS

All the patients exhibited classic clinical manifestations of EN, characterized by asymmetrical hyperkeratotic plaques along Blaschko's lines. Patient 1, a 4-year-old female, presented with narrow-band lesions extensively distributed on the trunk, buttocks, and flexural aspects of the limbs. Patient 2, a 41-year-old male, exhibited broad-band lesions predominantly on the buttocks, abdomen, and groin, accompanied by widespread erythema, hyperkeratotic patches, and desquamation. Patient 3, a 33-month-old male child (**Fig. 1**A), displayed lesions in a narrow-band pattern scattered on the trunk and limbs. None of them had a related family history or other associated systemic symptoms.

To ascertain the genetic aetiology, we first isolated the patients' DNA from peripheral blood to perform the Skin NGS panel (MyGenostics, Beijing, China), which is the custom exome sequencing panel containing 723 genodermatosis-targeted genes. Subsequent polymerase chain reaction (PCR)–NGS (10,000×) was accomplished for further verification of the variant ratio.

RESULTS

Patient 1's result showed a pathogenic mosaic variant of *KRT10* c.467G>A (p.A156H) with a variant ratio of 23.6784% (8618/36,396). This is an unreported pathogenic missense variant with allele frequency of 0.000008238 (ExAC database), predicted to be deleterious (SIFT), probably damaging (PolyPhen) and disease-causing (MutationTaster). Patient 2's result revealed a mosaic variant of *KRT10* c.466C>T (p.R156C) with a variant ratio of 13% (1190/9236), which is a reported pathogenic variant of EN and epidermolytic hyperkeratosis (2, 3). However, no genetic variant was discovered in Patient 3's peripheral blood DNA. Therefore, we obtained a biopsy specimen of his affected skin. A heterozygous *KRT1* c.551T>C (p.I184T) variant was detected with a variant ratio of 18% (26,186/142,033) in DNA extracted from his affected skin tissue. This variant was not found in the ExAC database, and was predicted to be deleterious (SIFT), probably damaging (PolyPhen) and disease-causing (MutationTaster). Sanger sequencing confirmed all the genomic variants in the 3 patients (Fig. 1B–D).

ENs are regarded as benign skin mosaicism disorders affecting the epidermis and skin appendages, and can occasionally involve other organ systems, including skeletal, neurological, and ophthalmological systems, which is termed EN syndrome (4, 5). ENs may also appear with malignant tumours of skin or other systems (6). Thus, a complete assessment of affected patients is essential, and more accurate detection techniques are needed for genetic counselling (7). For EN patients with fertility aspirations, sperm genetic testing and pre-implantation genetic testing could be used to reduce the potential genetic risks to their offspring (8).

DISCUSSION

To date, 9 articles have reported cases of EN caused by somatic variants of keratin genes, mainly *KRT1*, *KRT2*, and *KRT10*. Genetic testing methods have gradually improved (1, 2, 9, 10). Initially, genomic DNA from skin lesions was detected through PCR (2). Subsequent advancements, such as whole-exome sequencing, have enabled testing of lower-ratio somatic heterozygous variants in affected skin tissues (9). The application of NGS facilitated discovery of somatic variants from not only the patient's affected skin but also peripheral blood. Diociaiuti et al. (10) detected a *KRT2* c.556A>G somatic variant in a patient with EN through NGS using a customized ichthyosis gene panel through both blood (estimated variant ratio of 1.5%) and affected skin (variant ratio of 25%). On the above basis, we initially combined high-depth skin panel sequencing with high-depth sequencing of pathogenic sites.

We have herein reported 3 cases of EN due to somatic mosaicism variants of *KRT1* or *KRT10*. Two previously

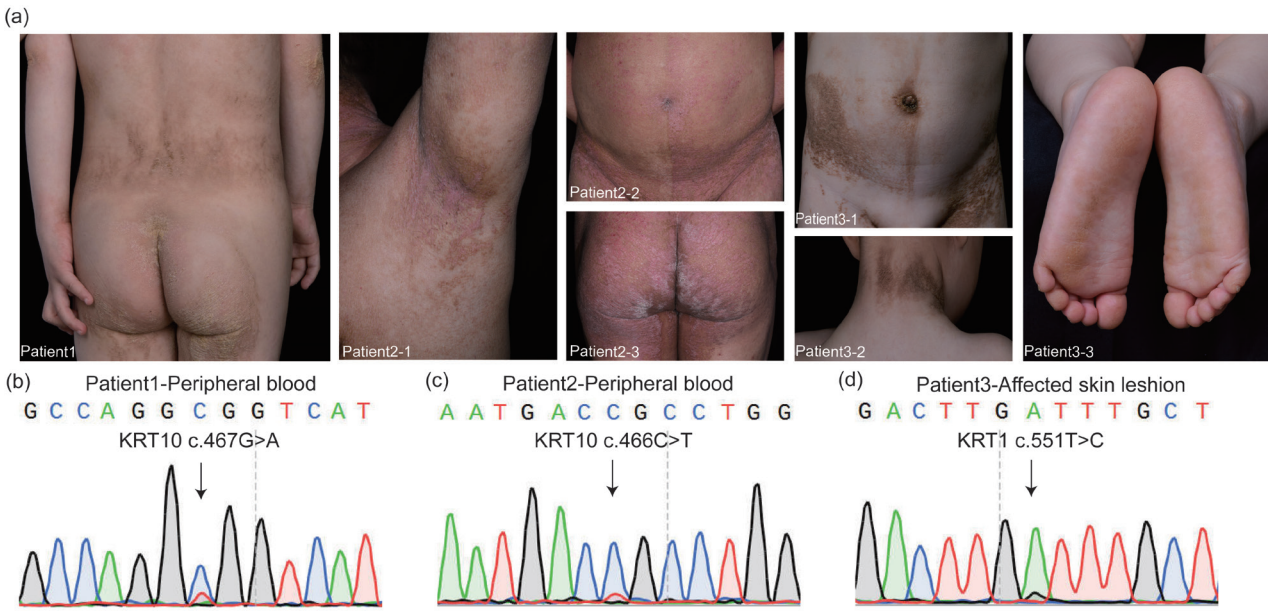

Fig. 1. Patients' clinical and genetic features. (A) Patient 1: Verrucous hyperkeratotic plaques on the trunk, buttocks, and flexural aspects of the limbs; Patient 2: Hyperkeratotic plaques covering the buttocks, abdomen, and groin, accompanied by widespread erythema, hyperkeratotic patches, and desquamation; Patient 3: Scattered hyperkeratotic plaques along Blaschko's lines, especially on the trunk and limbs. (B) A *KRT10* c.467G>A somatic mosaic variant was detected from Patient 1's peripheral blood. (C) A *KRT10* c.466C>T somatic mosaic variant was detected from Patient 2's peripheral blood. (D) A *KRT1* c.551T>C somatic mosaic variant was detected from Patient 3's affected skin tissue.

unreported variants were found: *KRT10* c.467G>A (p.A156H) and *KRT1* c.551T>C (p.I184T). Our detection method accurately identified the mosaic proportions in both blood and tissue samples.

In general, mosaicism involving multiple organ systems (both the skin and the blood system are affected) tends to occur in the early stages of embryonic development, while mosaicism confined to a single organ or tissue is the result of somatic variants that occur later in embryonic development (11). To optimize efficiency, we suggest blood sampling for patients with extensive lesions and tissue sampling for those with partial lesions. This approach is crucial for ensuring precise diagnosis, minimizing the risk of misdiagnosis, and should be integrated into clinical practice.

ACKNOWLEDGEMENTS

Funding sources: This work was supported by grants from the CAMS Innovation Fund for Medical Sciences (CIFMS) (2021-I2M-1-018).

IRB approval status: The research was approved by the Ethics Committee of the Institute of Dermatology of the Chinese Academy of Medical Sciences and Peking Union Medical College (2019-Clinic-005).

The authors have no conflicts of interest to declare.

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