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Letter to the Editor

Incontinentia pigmenti in a female infant with somatic mosaicism due to the *IKBKG* variant

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Running title: Incontinentia pigmenti with somatic mosaicism of *IKBKG*

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Dear Editor:

Incontinentia pigmenti (IP) is a rare X-linked dominant genodermatosis characterized by typical skin lesions along Blaschko's lines, affecting the skin and other sites including teeth, nails, hair, eyes, and the nervous system¹. It is usually lethal in affected males, but females generally survive because of X-chromosome inactivation. Approximately 80% of female patients with IP carry the *IKBKG* gene deletion located on chromosome Xq28. In rare cases, male patients with IP could survive if they also have Klinefelter syndrome (47, XXY) or *IKBKG* somatic mosaicism^{2 3}. A 14-day-old female infant presented with blisters on her right forearm, abdomen, and thigh. She was born at term after 39 weeks and a day of pregnancy as the firstborn, without a family history of skin disorders, weighing 2,824 g, and was born out of a normal pregnancy and delivery. On day 2 after birth, she was noted to have small blisters on her right forearm. On day 4, acyclovir was administered; however, her skin condition did not

improve. Physical examination revealed the presence of erythematous vesicular eruptions that were arranged linearly and that followed Blaschko's lines on her right forearm and right lateral abdomen, with pigmentation on her right groin and thigh, and a keratotic papule on the her nipple (**Figs. 1a, 1b**). She showed no scalp hair loss and no abnormality in her teeth shape. No neurological or ophthalmic involvement was noted during the first 14 days. The mother was not observed for any mild symptoms that could have been indicative of IP. A skin biopsy of her right forearm revealed abundant eosinophils in intraepidermal vesicles and superficial dermis along with pigment incontinence in the dermis, which suggested IP (**Figs. 1c, 1d**). After obtaining informed consent from her parents, genomic DNA was extracted from the patient's peripheral blood. Polymerase chain reaction (PCR) of *IKBKG* showed no exon 4_10 deletion (**Fig. 1e**). Multiplex ligation-dependent probe amplification revealed no insert/deletion variants. Sanger sequence analysis detected no common deletions, nucleotide alterations, or copy number variations in *IKBKG*. Considering the possibility of low-frequency somatic mosaicism, quantitative nested PCR of *IKBKG* was performed and exon 4_10 deletion was confirmed⁴ (**Fig. 1e**). The human androgen receptor (HUMARA) X-chromosome inactivation assay showed no skewed X-chromosome inactivation, suggesting that the patient had somatic mosaicism due to the *IKBKG* variant in IP. The overall detection of the *IKBKG* variant has been reported to be relatively low at 77.6% and specifically at 65% for the detection of exon 4_10 deletion because of its complex genomic structure despite *IKBKG* being the only causative gene for IP⁵. Although cases of somatic mosaicism of male IP patients have been reported^{2 3}, a female patient with mosaicism of IP, as in our case, should be considered when patients feature much milder clinical symptoms without the detection of pathological variants of *IKBKG*, which will require a nested PCR study. No skewed inactivation detected in X-chromosome inactivation studies, such as the HUMARA assay for IP, would also be helpful for the consideration of low-frequency mosaicism.⁴.

Conflict of Interest

The authors declare that they have no conflict of interest.

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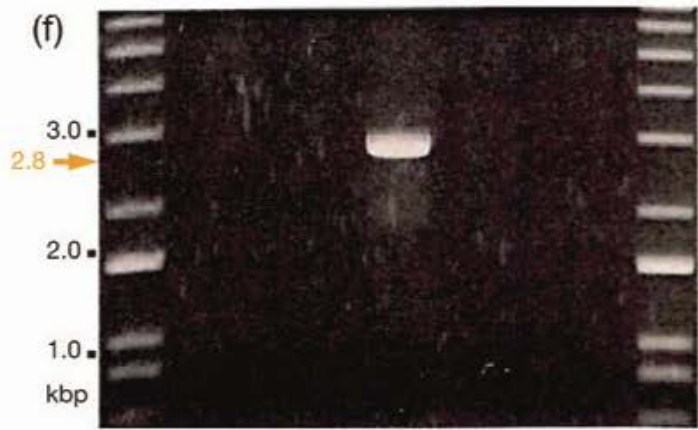
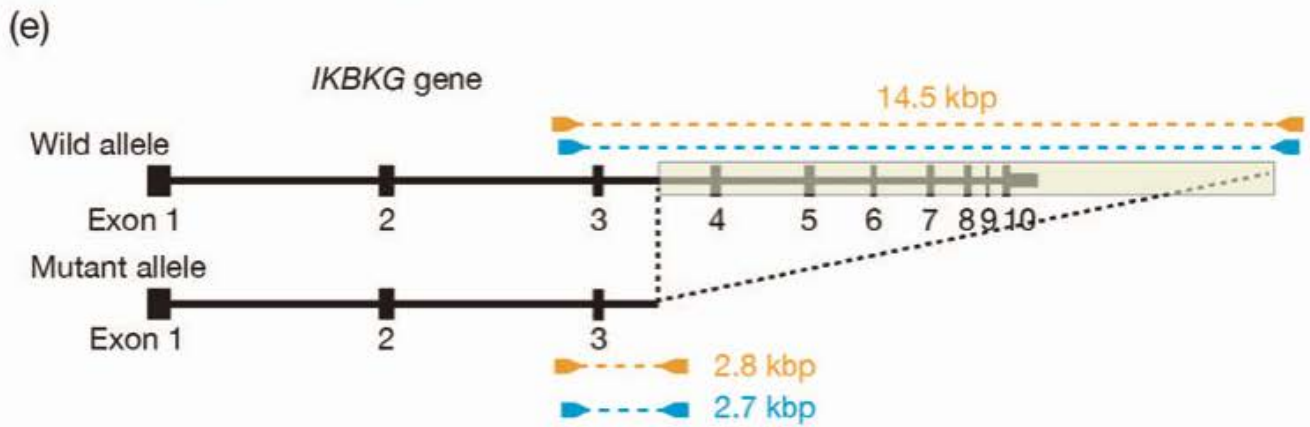
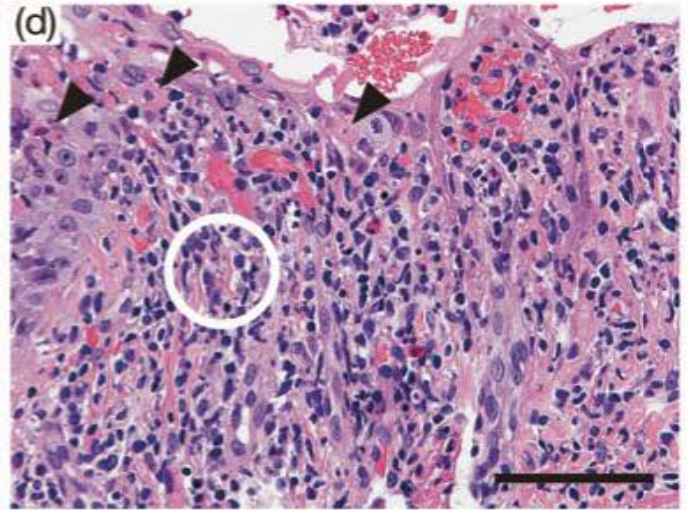
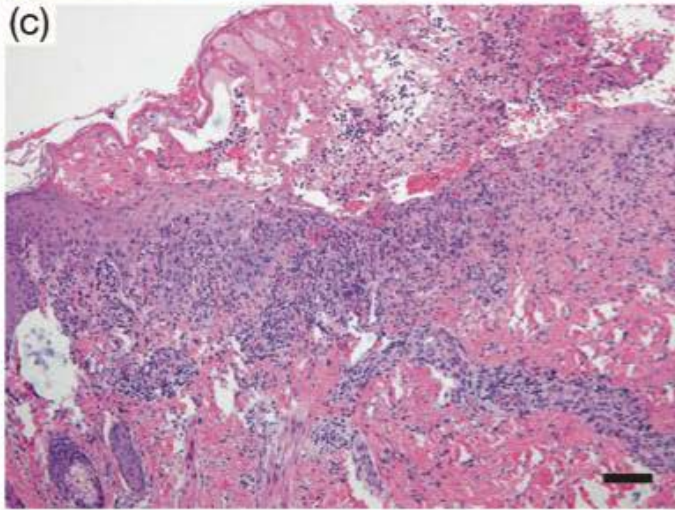
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Figure Legend

Figure 1. Clinical and histopathological features and genetic study results for *IKBKG*

Vesicular lesions on the right forearm (**a**) and erythema with a whirling appearance on the right flank (**b**) following Blaschko's lines. A biopsy specimen showing abundant eosinophils in the intraepidermal vesicles and superficial dermis, along with pigment incontinence in the dermis (white circle) and the apoptotic epidermal cells (arrowheads). (hematoxylin and eosin staining, scale bar = 100 μ m (**c**), scale bar = 20 μ m (**d**)) (e) Schematic illustration of the primer design of detection of exon4_10 deletion for wild and mutant allele with PCR (orange) and nested PCR (blue), respectively. (**f**) Polymerase chain reaction (PCR) amplification of *IKBKG* showing no exon 4_10 deletion to detect for a 2.8-kb-sized product in the DNA samples collected from the patient's peripheral blood sample (left panel). In nested PCR of *IKBKG*, we identified a 2.7-kb amplified product, indicating a low-frequency mosaicism of exon 4_10

deletion (right panel).



Patient
Affected Pt's control
Wild-type control
Negative control

Patient
Affected Pt's control
Wild-type control
Negative control