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LETTER TO THE EDITOR

Case of epidermodysplasia verruciformis with a novel mutation of *TMC8*

Dear Editor,

Epidermodysplasia verruciformis (EV) is a rare genetic disorder caused by immunological abnormality against human papillomaviruses (HPV), leading to increased risk of development of cutaneous malignancies.[1] Mutations in *TMC6* and *TMC8* are associated with EV and account for approximately 75% of EV cases.[2] Here, we report the first case of EV with c.1824-1G>A mutation in *TMC8*.

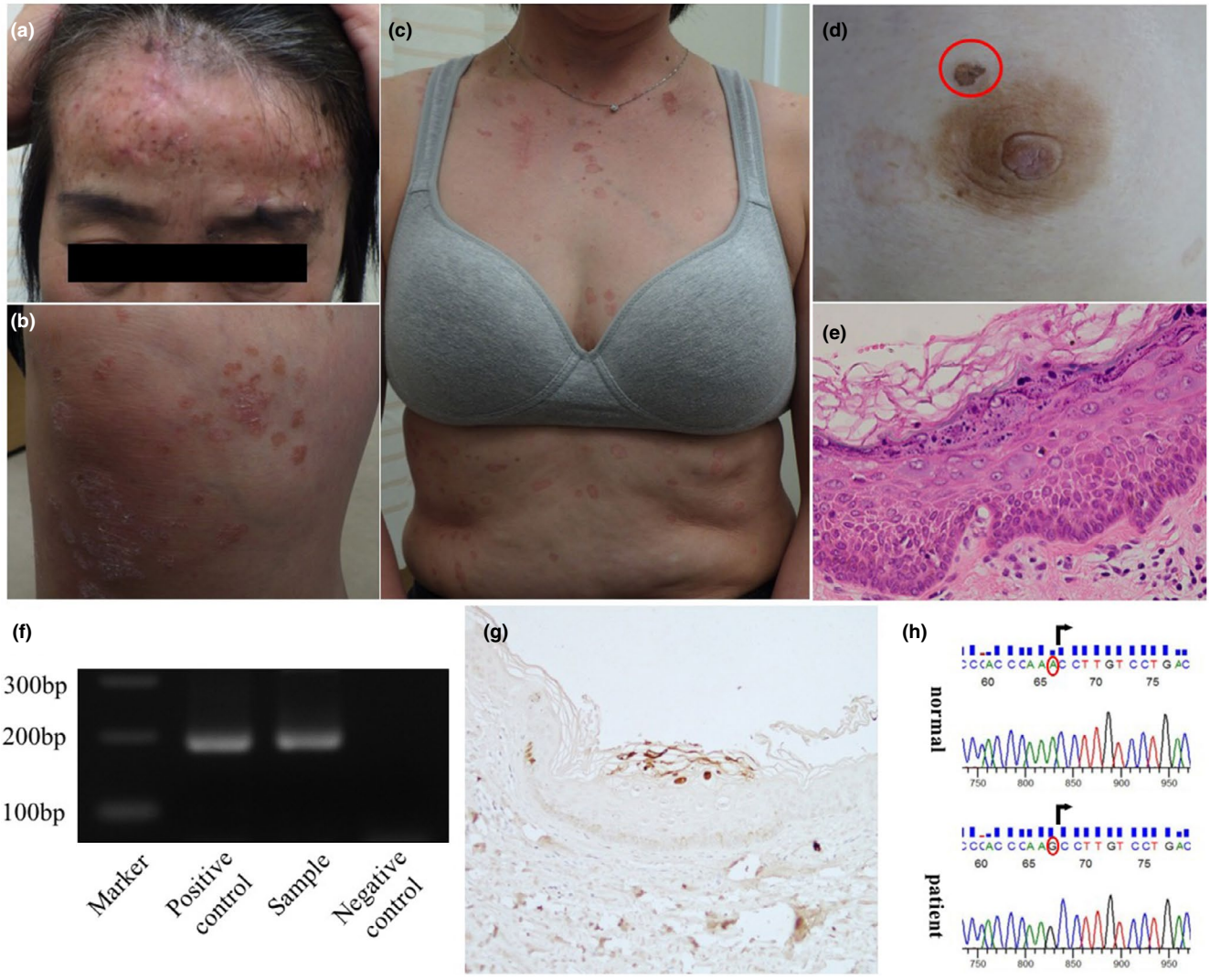

FIGURE 1 (a) Erythematous patches and surgical scars on the patient's forehead. (b) Brownish macules and scaly erythema on her lower limb. (c) Pigmented macules and erythema, which were partly annular, on her trunk. (d) A keratotic brownish macule (red circle) on her chest was biopsied. (e) Histopathological findings showed acanthosis with large cells containing basophilic cytoplasm and enlarged nucleus in the granular and spinous layers (hematoxylin–eosin, original magnification ×200). (f) In this case, polymerase chain reaction for human papillomaviruses (HPV) was positive. The first and last lanes indicate HPV type 16 and distilled water, which were used as the positive and negative controls, respectively. (g) Results of immunohistochemistry. The cells were positive for anti-HPV antibody (K1H8) in the cornified and granular layers (×200). (h) A novel mutation (c.1824-1G>A) at intron 14 in *TMC8* was identified]

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A 55-year-old Japanese woman with multiple skin cancers on her face was referred to our hospital. She had developed erythematous patches of the face since childhood, and the pigmented macules increased to all over the body from 10 to 20 years of age. She developed multiple actinic keratosis, Bowen's disease, and basal cell carcinoma on her face in her 50s and underwent surgical excision of each lesion at the former hospital. At the first examination, brownish macules and erythema, which were partly annular and scaly, were scattered throughout the body (Figure 1a–c). A skin biopsy taken from a keratotic brownish macule on her chest (Figure 1d) revealed acanthosis with large cells composed of basophilic cytoplasm containing keratohyalin granules and enlarged nuclei in the granular and spinous layers (Figure 1e). Based on the EV diagnosis from the histopathological findings, HPV infection was considered possible and was analyzed. HPV was detected with polymerase chain reaction (PCR) using the CPI/CPIIS primer pair that could detect HPV types 5, 8, and 20, which are frequently detected in EV patients (Figure 1f).[3] Upon direct sequencing, HPV type 5, which is an oncogenic HPV at least in patients with EV, was detected. Immunohistochemically, HPV-positive cells were observed in the cornified and granular layers (Figure 1g). Mutation analysis of *TMC6* and *TMC8* revealed a homozygous c.1824-1G>A mutation in intron 14 of *TMC8* (Figure 1h). The frequency of this mutation was zero out of 1197, according to Human Genome Variation Database. A c.1824-1G>A mutation is located at the splice acceptor site and could cause splicing abnormalities. To analyze the pathogenicity of this mutation, we performed reverse transcription PCR (RT-PCR). The results revealed the presence of four pathological transcripts and there was no normal *TMC8* transcript (Figure S1). Therefore, the patient was diagnosed with EV caused by a *TMC8* mutation. There is neither family history of EV nor consanguinity between the patient's parents.

TMC8 has diverse roles; the TMC domain of *TMC8* binds to zinc transporter-1 (ZnT-1) and tumor necrosis factor (TNF) receptor-associated death domain protein (TRADD).[4] Activator protein 1 involved in the life cycle of HPV is downregulated by the binding of *TMC8*-ZnT-1. The apoptosis induced by TNF-α, which plays a role in the defense against HPV, is promoted through the combination of *TMC8* and *TRADD*.[4] The in-frame deletion of the C-terminal amino acids of the TMC domain in *TMC8* causes sensitivity to HPV; therefore, the C-terminal TMC domain could be important for *TMC8* function *in vivo*.[5]

To our knowledge, this is the first report of a patient with EV presenting a c.1824-1G>A mutation in *TMC8*. Further studies are needed to determine how this mutation affects *TMC8* function.

CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.