

A Postzygotic *TRPM4* Variant in a Patient with Inflammatory Linear Verrucous Epidermal Nevus

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Dear Editor,

Inflammatory linear verrucous epidermal nevus (ILVEN) is a rare mosaic skin disorder characterized by linear erythematous papules and plaques following Blaschko lines (1). Histopathologically, the epidermis exhibits acanthosis and papillomatosis with alternating parakeratosis and orthokeratosis (1). While the genetic basis for certain ILVEN cases was implicated, including postzygotic variants in *GJA1*, *CARD14* (2, 3), the molecular basis for most ILVEN remains undefined. *TRPM4* encodes transient receptor potential melastatin 4, a calcium-activated non-selective cation channel critical for regulating membrane potential. Pathogenic variants in *TRPM4* drive cardiac conduction block and cutaneous progressive symmetric erythrokeratoderma (PSEK) via gain-of-function (GoF) patterns (4, 5). While cardiac *TRPM4* variants exerted GoF properties predominantly via constitutive SUMOylation and impaired endocytosis, leading to a pathological increase in channel density at the plasma membrane (5), the PSEK-associated variants affect the gating activation of *TRPM4* (4). Recently, we identified a postzygotic *TRPM4* variant in a patient with generalized ILVEN and leukonychia (1). Here, we report on an ILVEN patient caused by a new postzygotic variant in *TRPM4*.

The patient, a 2-year-old girl, presented with asymptomatic linear papules and plaques along the left trunk and extremities since birth. Physical examination revealed reddish flat-topped papules coalescing to plaques distributed along Blaschko's lines on her left chest, axilla, upper and lower extremities, with yellowish verrucous keratotic plaques on her left palm (**Fig. 1a**). Histological examination of the lesion revealed acanthosis with alternating hyperkeratosis and parakeratosis and a mononuclear infiltration in the superficial dermis, consistent with ILVEN (**Fig. 1b**).

Whole-exome sequencing using genomic DNA extracted from lesional skin revealed a mosaic missense variant in *TRPM4* (c.2758A>G, p.Ile920Val, variant allele frequency 8%; RefSeq accession Number NM_017636), which was predicted to be "disease causing" and absent in public databases. We further performed laser-captured microdissection (LCM) followed by Sanger sequencing in the paraffin-embedded skin section. The variant was enriched in epidermal areas exhibiting parakeratosis or hyperkeratosis, whereas it was absent in the dermis or the normal epidermis (**Fig. 1c**), indicating that

the variant is postzygotic restricted to the affected epidermal lineages. The affected residue Ile920 is evolutionally conserved across species (**Fig. 1c**) and has not been recorded previously.

Next, we constructed the variant structure under Ca²⁺-free and Ca²⁺-bound situations using AlphaFold3 (<https://alphafoldserver.com>) to evaluate the functional impact of the Ile920Val mutant compared to the wildtype (models were downloaded from RCSB PDB) (**Fig. 1d**). Residue Ile920 was predicted to locate in the 4th–5th transmembrane helix (S4–S5) linker of *TRPM4*. We found an additional hydrogen bond between mutant residue Val920 and residue Gly917, which is a highly conserved residue also located in the S4–S5 linker (**Fig. 1c** and **d**). This new hydrogen bond was predicted to increase the linker rigidity and ability of electromechanical coupling to the pore, thereby facilitating the transduction of the preceding conformational changes from the S1–S4 domain to the pore and subsequent channel opening (**Fig. 1d**). Interestingly, structural analysis of the Ile920Val mutant reveals a radial expansion of the channel pores at the level of residues Gly976 and Ile1040 (**Fig. 1d**). Previous structural studies have identified Phe975 and Gly976 as the narrowest constriction points of the upper pore, while the side chains of Ile1040 in the S6 segment form a tight seal at the lower gate (6, 7). They are 2 narrowest constrictions of the ion channel which are located in the selectivity filter of the pore and intracellular gate of the S6 helix, respectively (6, 7), facilitating channel gating and ion permeation for the open state. In this way, the S4–S5 linker gearbox of the mutant *TRPM4*-Ile920Val predisposes the channel to a more readily openable state.

We have previously linked germline GoF variants (p.Ile1033Met and p.Ile1040Thr) in *TRPM4* to PSEK, and a postzygotic GoF variant (p.Ile909Ser) to ILVEN. All these variants were confirmed to enhance channel opening and elevate membrane potential through electrophysiological studies (1, 4). Compared to *TRPM4*-associated PSEK which is localized, self-healing with incomplete penetrance (4, 8), *TRPM4*-associated ILVEN is more severe and devastating. This correlates well with the more robust GoF extent of the Ile909Ser variant compared to the PSEK variants, which was demonstrated by our electrophysiological studies (1). Residue Ile909 locates to S4 terminus which is predicted to perturb the S4–S5 linker, while residues

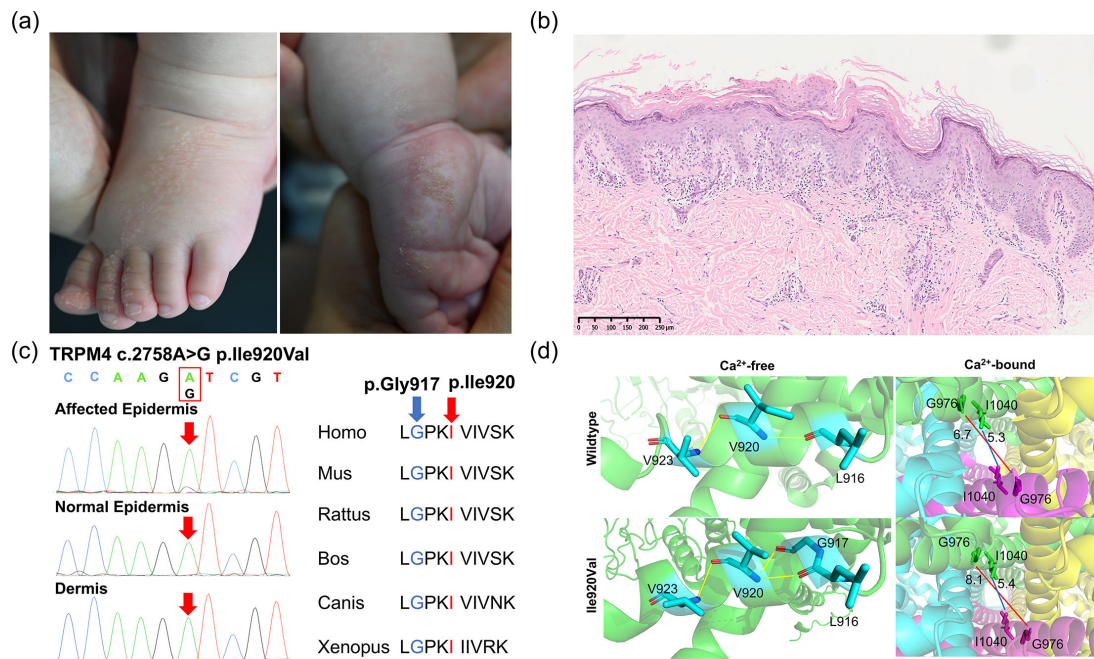


Fig. 1. (A) Linear erythematous papules and plaques distributed along the Blaschko lines on the left trunk, upper and lower extremities, as well as parts of the palms and soles with punctate or spicular hyperkeratosis. (B) Haematoxylin-eosin staining of skin lesion showed hyperkeratosis and parakeratosis, hypergranulosis, characteristic necrosis of the granular layer and perivascular mononuclear infiltration in the superficial dermis. Scale bar=250 µm. (C) The Sanger sequencing showed the mosaic TRPM4 variant in the damaged epidermis, normal epidermis and dermis. The multiple alignment showed residues Gly917 and Ile920 are highly conserved among species (right). (D) Modelling and prediction of TRPM4^{wildtype} (PDB code 6BQR and 6BQV) and TRPM4^{Ile920Val} (AlphaFold3-predicted structures). The yellow dashed lines represent the hydrogen bonds (left) and distances between 2 atoms (right). The TRPM4^{Ile920Val} shows new hydrogen bond linking Val920 to Gly917 and higher distance for Gly976 and Ile1040 in tetramers.

Ile1033 and Ile1040 locate in the pore domain. We hypothesize that variants affecting the S4–S5 linker might result in overwhelming functional gain, leading to a lethal phenotype in a germline heterozygote, and patients could only survive with embryonic mosaicism of these variants.

Various therapeutic approaches have been attempted for TRPM4-associated skin disorders with certain therapeutic effects achieved. Methotrexate has shown benefits in one of TRPM4-associated PSEK cases after failure of acitretin and secukinumab treatment (8). EGFR inhibitor (EGFRi) erlotinib has been shown to improve palmoplantar keratoderma in TRPV3-associated Olmsted syndrome (9). In our recent report of ILVEN, we further proposed that gain of function in TRPM4 channel increases membrane potential, potentially facilitating TRPV3 activation and subsequent EGFR/MAPK/ERK signalling (1). Consistently, oral erlotinib was beneficial in that patient, implicating the efficiency of EGFRi in TRPM4-associated ILVEN. However, given the limited extent of lesions in this patient, systemic erlotinib was not suggested due to its potential severe adverse effects. Topical EGFRi or other locally delivered pathway-directed therapies may be more suitable for TRPM4-associated ILVEN in the future.

In summary, we link a S4–S5 linker variant in TRPM4 to ILVEN. Our study sheds a light on the

pathogenic mechanisms and possible therapeutic targets for ILVEN. Further researches are warranted to identify additional TRPM4 variants in ILVEN and investigate the potential efficacy of the inhibitors targeting TRPM4 or its downstream pathways for ILVEN.

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The authors have no conflicts of interest to declare.

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