Inflammatory linear verrucous epidermal nevus should be genotyped to direct treatment and genetic counseling

To the Editor: Inflammatory linear verrucous epidermal nevus (ILVEN) is a clinical diagnosis based on persistent Blaschko-linear erythematous scaly and usually pruritic lesions. Sixteen patients with a clinical diagnosis of ILVEN as defined by published diagnostic criteria were recruited and consented under Research Ethics Committee approval for phenotypic, histological, and genotypic analysis. At the time of initiating this study in 2014 no genetic causes of ILVEN were known. Causative genetic variants since described are in *GJA1*,[1] *ABCA12*[2], *CARD14*,[3] *PMVK*[4], *NSDHL*,[4] *HRAS*[4] and *KRT10*.[4] Disease mechanisms thus far include germline X-linked variants, mosaic variants, and germline first hit with mosaic second hit.

Paired blood and affected skin DNA underwent deep whole exome sequencing (WES, mean 250X), $n = 14$, and if negative, skin DNA underwent targeted sequencing panel R327 (mosaic disorders, UK National Genomic Test Directory), $n = 8$. Two patients had a negative WES and did not go forward to next generation sequencing panel due to sample limitations. Two patients recruited late in the study had next generation sequencing panel first and did not proceed to WES.

We confirm here that ILVEN has multiple monogenic causes, with mutations in *NSDHL* ($n = 2$, germline, *NSDHL* c.613G > T, p.[G205T], c.603_604delTG, p.[H201fs*69], both picked up on WES), *PMVK* ($n = 1$, mosaic in blood and skin, no second variant detected in the same gene in skin, *PMVK* c.126delG, p.R42fs, picked up on WES), *HRAS* ($n = 1$, mosaic, *HRAS* c.37G > C, p.(G13R), picked up on panel, and *CARD14* ($n = 2$, mosaic, these 2 only previously published,[1] both picked up on WES). Ten patients had no pathogenic variants identified and we specifically excluded any variants in all previously described genes. No patients who were negative on WES had genes identified on a subsequent panel, suggesting that variants still unidentified are not in known mosaic genes, or if they are they are unlikely to be single nucleotide variants or short copy number changes.

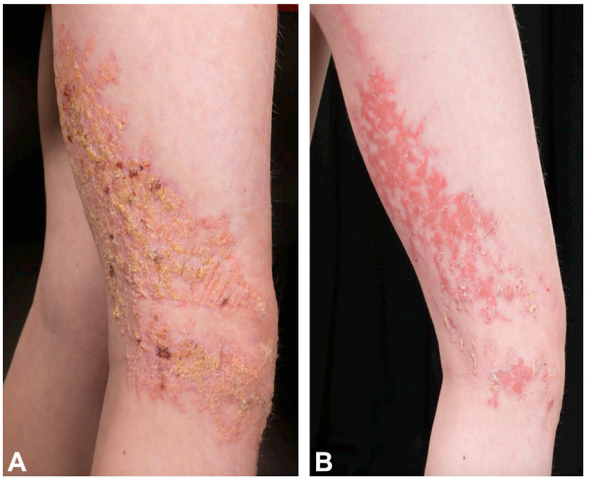

Fig 1. Clinical response to 2% cholesterol and 2% simvastatin topical treatment in patients harboring *NSDHL* variants is variable. **A** to **B,** Partial response is seen in a patient harboring a *NSDHL* variant with pretreatment condition seen in (**A**) and posttreatment condition in (**B**). This is in contrast with the complete and maintained response seen in another patient harboring an *NSDHL* variant (Supplementary Fig 1, *D-E*, available via Mendeley at https://data.mendeley.com/datasets/74shtt6skp/1).

Histology was highly variable between patients, even those with the same monogenic disease.[3] *PMVK* lesional histology did not demonstrate a cornoid lamella (Supplementary Fig 1, *B*, available via Mendeley at https://data.mendeley.com/datasets/74shtt6skp/1).

All patients were given a trial of therapy under hospital Drug and Therapeutics Committee approval with 2% cholesterol/2% simvastatin in Unguentum Merck, applied topically twice a day for 3 months to 1 clearly designated area of affected skin. Maintained substantial response was seen in 4 children, 2 with *NSDHL* variants (Fig 1, *A* and *B*, Supplementary Fig 1, *D-E*, available via Mendeley at https://data.mendeley.com/datasets/74shtt6skp/1), 1 with the *PMVK* variant, and a fourth with no identified causative genotype. Although response was expected in these patients from the literature, the high degree of variability even within the same monogenic disease was not. For example, 1 patient with *NSDHL* cleared completely within 3 months and has not relapsed despite discontinuing therapy for over a year (Supplementary Fig 1, *D-E*, available via Mendeley at https://data.mendeley.com/datasets/

74shtt6skp/1), whereas the other never had full clearance (Fig 1, *A* and *B*). Transient and/or milder clinical responses were reported in the remainder of our cohort. Baseline serum cholesterol and triglycerides were normal in the 8/16 patients in whom it was measured, as were follow-up measurements for the 3 who continued.

ILVEN is therefore highly heterogeneous genetically, with a substantial proportion of cases still unsolved, and importantly genetic diagnosis has implications for management. Other than topical cholesterol/statin for *NSDHL* and *PMVK*, skin disease from mutations in *CARD14* including ILVEN responds to ustekinumab.[3,5] In parallel to directing drug therapy, genetic diagnosis has implications for counseling. All variants described in this study arose de novo; however, in the majority of cases these are at least theoretically compatible with life if passed on to offspring in the germline.

Our data support routine genotyping in patients with a clinical diagnosis of ILVEN, to direct treatment and genetic counseling, with histology being of limited use in differentiating between causes. Variable therapeutic outcomes within the same monogenic disease suggest other unestablished confounding factors.

Satyamaanasa Polubothu, MD, PhD,[a,b,c] Melissa Riachi, PhD,[a,b] Paulina Stadnik, PhD,[a] Olumide Ogunbiyi, MSc,[d] Regula Brändli-Wälchli, MD,[c] Thomas Cullup, MD,[e] Neil J. Sebire, MD,[d] Alan Pittman, PhD,[f] and Veronica A. Kinsler, MD, PhD[a,b,c]

From the Genetics and Genomic Medicine, UCL GOS Institute of Child Health, London, UK[a]; Mosaicism and Precision Medicine Laboratory, The Francis Crick Institute, London, UK[b]; Paediatric Dermatology, Great Ormond St Hospital for Children, London, UK[c]; Paediatric Pathology, Great Ormond St Hospital for Children, London, UK[d]; North Thames Genomic Laboratory Hub, Great Ormond Street Hospital, London, UK[e]; and Genetics Research Centre (A.P.), St George's University of London, London, UK.[f]

Drs Polubothu, and Riachi contributed equally and are first authors.

Funding sources: UK National Institute of Health and Social care Research (NIHR grant 300774), Great Ormond Street Hospital Childrens' Charity (GOSHCC) Livingstone Skin Research Centre, Biomedical Research Centre at Great Ormond St Hospital for Children NHS Foundation.

Patient consent: Consent for the publication of recognizable patient photographs or other identifiable material was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

IRB approval status: Written informed consent was obtained in line with Research Ethics Committee approvals 12/LO/1522 and 17/LO/1783.

Key words: genetic counseling; genotype; ILVEN; mosaicism; sequencing; topical therapy.

Correspondence to: Veronica A. Kinsler, MD, PhD, The Francis Crick Institute, 1 Midland Rd, London, NW1 1AT, UK

E-mail: v.kinsler@ucl.ac.uk

Twitter handle: @KinslerLab

Conflicts of interest

None disclosed.

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https://doi.org/10.1016/j.jaad.2024.01.075