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Research letter

Cardiomyopathy in patients with epidermolysis bullosa simplex with mutations in *KLHL24*

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DEAR EDITOR, Dominant mutations in *KLHL24*, encoding for kelch-like protein 24 (*KLHL24*), have been implicated in the

pathogenesis of epidermolysis bullosa simplex (EBS). So far, 26 patients from different ethnicities have been reported and all of them harboured a heterozygous *KLHL24* start codon mutation, with c.1A>G;p.Met1? being the most prevalent.¹⁻³ We aimed to expand the phenotypic spectrum by incorporating additional findings, in particular dilated cardiomyopathy, seen in a Dutch family.

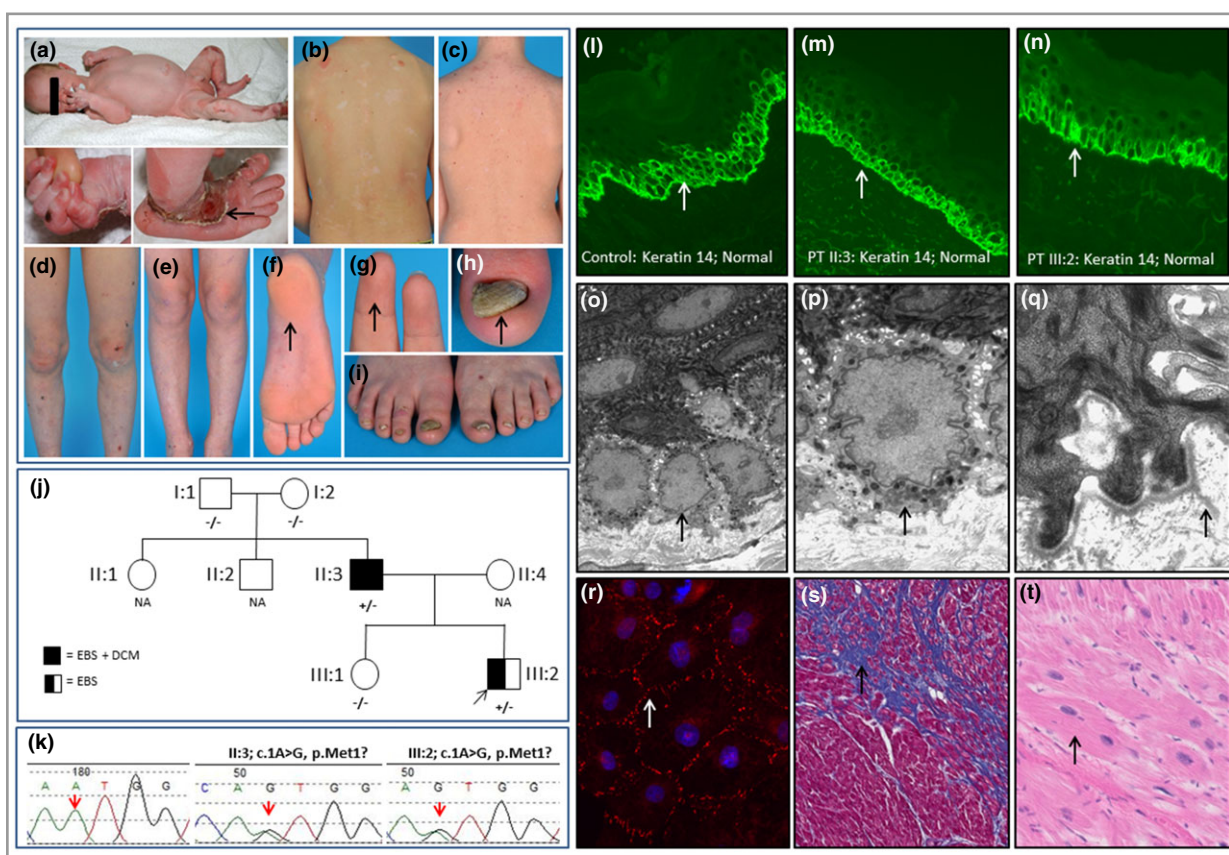


Fig 1. Epidermolysis bullosa simplex due to *KLHL24* (c.1A>G, p.1Met?) mutation. (a–h) Clinical photographs of the index patient showing (a) cutis aplasia at birth; (b, d) generalized blisters healing with scarring and hypo-/hyperpigmentation; (c, e) amelioration of phenotype at 14 years of years; (f) palmoplantar hyperkeratosis; (g) loss of dermatoglyphics; (h) congenital malrotation of the great toenail; and (i) nail dystrophy. Arrows point to the clinical features mentioned. (j) Family pedigree: filled black square indicates affected patient with skin fragility and cardiomyopathy (III:2); clear symbols indicate unaffected individuals (II:3 and III:2); (–) indicates wild-type allele and (+) indicates affected allele. NA, not available; EBS, epidermolysis bullosa simplex; DCM, dilated cardiomyopathy. (k) Sequence chromatograms of affected members depicting the mutation (c.1A>G, p.1Met?) in *KLHL24* (Ref Seq: NM_017644.3). (l–n) Immunofluorescence antigen mapping (IFM) showing normal staining for keratin 14 [green; clone: LL002 (Abcam, Cambridge, U.K.)] in (l) control tissue and (m, n) affected patients. (o–q) Transmission electron micrographs (TEM) showing a striking paucity of intermediate filaments in (o) basal cells along with (p) prominent subnuclear melanosomes. (q) Alternate thinning and thickening of lamina densa along with some blind off-shoots can also be seen. Arrows point to the TEM features mentioned. (r) IFM staining showing localization of *KLHL24* [red; clone: ab104089 (Abcam)] along the cell membrane on cultured normal human cardiomyocytes. (s) Masson's trichrome staining showing interstitial fibrosis and (t) haematoxylin and eosin staining showing cardiomyocyte hypertrophy in the explanted diseased heart in patient II:3.

The cutaneous findings identified in our patients (III:2 and II:3) are mostly consistent with previous reports,^{1–3} except for a few additional findings that included loss of dermatoglyphics, hypohidrosis and congenital malrotation of the great toenails (Fig. 1). Intriguingly, the affected father (II:3) had also developed a rapidly progressive dilated cardiomyopathy of unknown aetiology at the age of 18 years for which a cardiac transplantation was necessary within a year of the first clinical signs being seen. Immunofluorescence antigen mapping (IFM) of skin biopsies showed normal staining intensities for a set of diagnostic epidermal proteins, including keratins 5 and 14 in both the affected members (Fig. 1). However, electron microscopy revealed a striking paucity of intermediate filaments in the basal keratinocytes along with numerous and prominent mitochondria,³ suggesting that, although present, keratins 5 and 14 are not able to form a proper intermediate filament network, thereby pointing to a diagnosis of EBS. In addition, we also observed large subnuclear melanosomes, abnormal thinning and thickening of lamina densa with few re-duplications and blind offshoots (Fig. 1). Whole-exome sequencing followed by Sanger sequencing confirmed the presence of a heterozygous *KLHL24* mutation (c.1A>G, p.Met1?) in both the affected individuals (Fig. 1).

Although these findings explained the skin phenotype, it remained unclear whether the mutation in *KLHL24* was responsible for the pathogenesis of cardiomyopathy in the father as well. Histological features of the explanted heart showed diffuse myocyte hypertrophy and moderate-to-strong interstitial fibrosis with no infiltrate, signs of stacking or cardiomyocyte disarray (Fig. 1), consistent with a diagnosis of dilated cardiomyopathy. Considering the possibility that he might have had a cardio-cutaneous syndrome or a second genetic condition due to a mutation in a gene causing isolated dilated cardiomyopathy, molecular analysis of genes implicated in the pathogenesis of epidermolysis bullosa, cardio-cutaneous syndromes, hereditary cardiomyopathies and related disorders was performed but did not reveal any pathogenic variations (available upon request). Interestingly, He et al. also noted dilated cardiomyopathy in a 43-year-old patient, although the age of onset in this patient was unclear.² Furthermore, Hedberg-Olfers et al. reported two patients with a homozygous *KLHL24* nonsense mutation (c.1048G>T, p.E350*) associated with hypertrophic cardiomyopathy, and validated the association in a zebrafish model.⁴

To better understand this cardiac association, we performed IFM staining on human embryonic stem cell 9-derived cardiomyocytes for the presence of *KLHL24*.⁵ Surprisingly, we observed a clear positive staining of *KLHL24* along the cell membrane in a distribution pattern similar to other intercalated disc proteins involved in cardiocutaneous syndromes (Fig. 1), extending the RNA expression data of *KLHL24* in the heart,¹ and providing a clue for a possible cardiocutaneous syndromic association. Notably, his affected 14-year-old son had a borderline enlarged left ventricle (dimensions in the 95th percentile) on two-dimensional

echocardiography, whereas his unaffected 18-year-old daughter and parents (mother aged 70 years and father aged 71 years) did not show any cardiac abnormalities. Cardiomyopathy was not reported in the rest of the family. This further strengthens the hypothesis that the cardiomyopathy might, indeed, be caused by the *KLHL24* mutation and not by unrelated genetic factors.

Given that *KLHL24* is shown to be widely expressed in tissues other than skin like brain, kidney, liver, lung and pancreas,¹ we also screened our patients for possible abnormalities in those organs. The affected father, besides the cardiomyopathy, suffers from short- and long-term memory problems, and muscular weakness with slight ptosis. Renal dysfunction was also noted; however, this could also be attributed to the long-term use of ciclosporin for his heart transplant. His affected 14-year-old son, besides his borderline enlarged heart, reported concentration and learning problems. No other extracutaneous features were found on screening.

Altogether, the emerging picture is that of a *KLHL24* mutation causing a syndromic rather than a skin-only type of epidermolysis bullosa, in which cardiomyopathy may be a dominant symptom. Other new features in our cases include cutaneous findings, such as loss of dermatoglyphics, hypohidrosis and congenital malrotation of great toenails, in addition to mental problems. Future studies are needed to reveal whether these symptoms are, indeed, part of the *KLHL24*-related phenotype. The reason that cardiomyopathy has been described in only a few of the previously reported patients may be related to the fact that most of them were under 15 years of age and the symptoms likely display an age-dependent penetrance and/or need additional triggers. We therefore recommend screening all patients with *KLHL24* mutations for extracutaneous manifestations, particularly cardiomyopathy, from the early teens onwards.

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