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SHORT COMMUNICATION

Lamellar Ichthyosis Caused by a Previously Unreported Homozygous *ALOXE3* Mutation in East Asia

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Autosomal recessive congenital ichthyosis (ARCI) includes a wide range of ichthyosis phenotypes, including harlequin ichthyosis, lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), and self-improving collodion ichthyosis (SICI) (1, 2). To date, 9 causative genes for ARCI have been identified (1, 2). *ALOXE3* is a causative gene in LI as well as CIE, and it encodes the eLOX-3 lipoxygenase, which is predominantly synthesised in the epidermis. ARCI caused by an *ALOXE3* mutation is very rare, with less than 30 families with the mutation reported in the literature. The previously reported cases with homozygous or compound heterozygous *ALOXE3* mutations were from Europe, North Africa, the Middle East, and South Asia (3–8). Here, we describe an LI patient with a previously unreported homozygous *ALOXE3* mutation in a consanguineous family from Japan and review ARCI cases with *ALOXE3* mutations.

CASE REPORT

The patient is a 58-year-old Japanese woman who presented with symptoms of ichthyosis since birth. Her parents were first cousins. She has 3 siblings, of which one has a similar ichthyosis phenotype (Fig. 1a). Ectropion was not reported at birth. She showed brown-to-gray scaling without erythroderma on her trunk and extremities (Fig. 1b). She did not show pal-

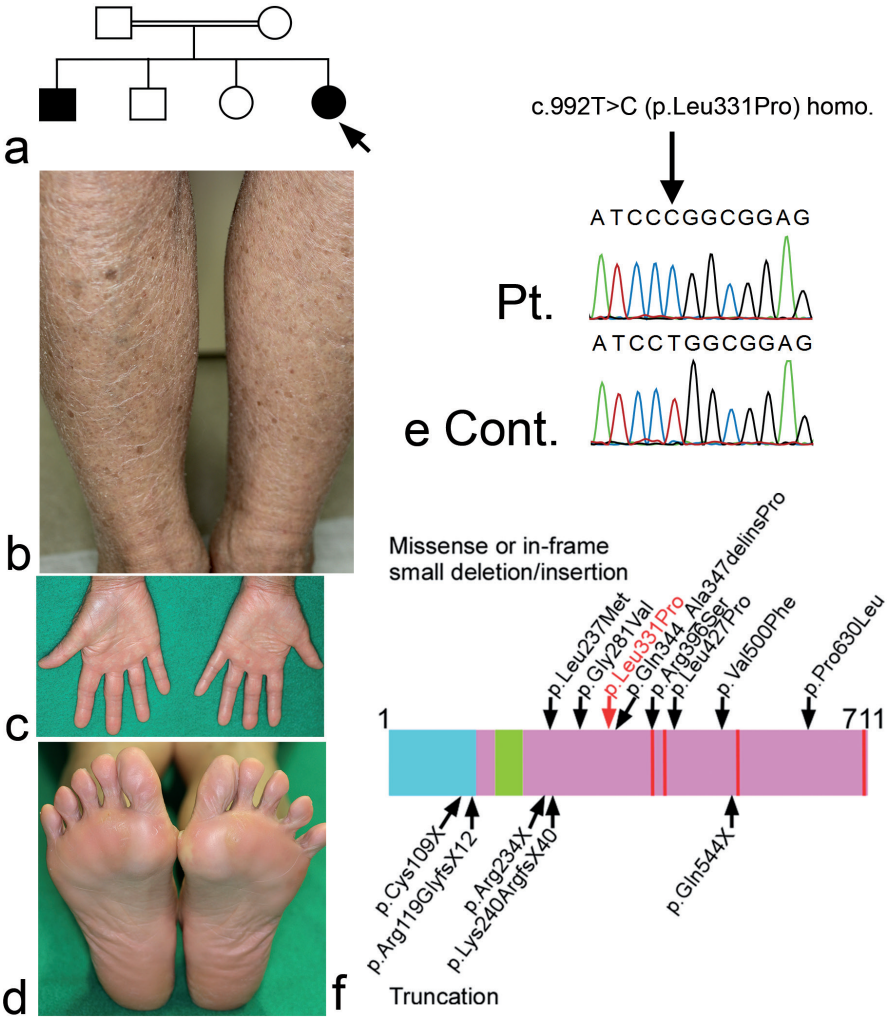

Fig. 1. Pedigree, clinical features, and *ALOXE3* sequence data of the patient; sequence alignments around the missense mutation; and a summary of known *ALOXE3* mutations. (a) Pedigree of the patient. (b) The patient showed brown-to-gray scaling bilaterally on the lower legs. (c) The patient did not show palmar keratosis. (d) The patient showed mild plantar hyperkeratosis. (e) Sequence data of *ALOXE3* in the patient with the mutation and a control without the mutation. The arrow indicates c.992T>C (homozygous). (f) The eLOX-3 protein domain structure and *ALOXE3* mutations from this study and the literature. The previously unreported missense mutation identified in this study, p.Leu331Pro, is shown in red. A blue box and a green box indicate the N-terminal β-barrel LH2 domain and an inserted specific extra domain, respectively. Pink boxes indicate C-terminal catalytic lipoxygenase domain from amino acid position 126. Putative iron ligands of the active sites are in red.

mar keratosis or alopecia, but did show mild plantar keratosis during middle age (Fig. 1c, d).

Following ethical approval, informed written consent was obtained in compliance with the Declaration of Helsinki guidelines. The coding regions, including the exon-intron boundaries of *TGM1, ABCA12, ALOX12B*, and *ALOXE3*, were amplified from genomic DNA by PCR as described elsewhere (3). Direct sequencing of the patient's PCR products revealed that the patient had a homozygous *ALOXE3* mutation, c.992T>C (p.Leu331Pro) (gene accession number: NM_021628.2) (Fig. 1e). p.Leu331Pro was analysed using SIFT (http://sift.jcvi.org/) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/). The SIFT score was 0.000 and PolyPhen-2 score was 1.000; both scores predicted that p.Leu331Pro had damaging effects. We found no mutation in the other 3 genes tested. c.992T>C was not detected in the 200 control alleles (100 control individuals, data not shown). Thus, the patient was diagnosed as having LI caused by the homozygous *ALOXE3* mutation.

DISCUSSION

All previously reported ARCI cases with *ALOXE3* mutations have been in families from Europe, North Africa, the Middle East, and South Asia (Fig. 1f, Table SI[1]). To our knowledge, the present patient is the first case with *ALOXE3* mutations in a family from East Asia. Our case suggests that *ALOXE3* mutations are possibly found in families worldwide. We reported more than 50 Japanese cases of ARCI that had *TGM1, ABCA12, ALOX12B*, or *CYP4F22* mutations (2, 9, 10). Although we do not have data indicating how often patients with ichthyosis are offered genetic testing in Japan, no other patients with *ALOXE3* mutations have been found to date. We hypothesise that the carrier rate of ichthyosis-causing *ALOXE3* mutations may be very low in Japan.

We reviewed 39 cases of ARCI from 29 families that had *ALOXE3* mutations, including the case described here (3–8) (Table SI[1]). Thirteen *ALOXE3* mutations have been reported (Fig. 1f). Truncation mutations, missense mutations, and an in-frame small deletion/insertion mutation have been reported. The truncation mutations include nonsense mutations, a deletion mutation resulting in a frame shift, and a splice site mutation. In 2 cases, *ALOXE3* mutations were identified only in one allele. In the literature (Table SI[1]), ARCI phenotypes caused by *ALOXE3* mutations were categorised as CIE, LI, and SICI. In 3 cases, clinical features were not described, and their ARCI phenotypes were unknown.

In conclusion, the present case clearly indicates that *ALOXE3* is a possible causative gene in East Asian ARCI patients.

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The authors declare no conflicts of interest.

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[1]https://doi.org/10.2340/00015555-2022