LETTER TO THE EDITOR

Identification of a novel lethal form of autosomal recessive ichthyosis caused by UDP-glucose ceramide glucosyltransferase deficiency

KEYWORDS: ceramide, collodion, glucosylceramide, ichthyosis, UGCG

To the Editor:

The skin barrier function is achieved through a complex interplay of specialized cellular mechanisms and extracellular components. Ichthyosis is one phenotypic consequence of failure of this interplay, and is characterized by an excessively dry and scaly skin. There are many subtypes that range in severity from very mild to lethal. Single gene defects are the most frequent cause and range from the extremely common Filagrin-related ichthyosis vulgaris to the very rare PHGDH-related Neu-Laxova syndrome. Many patients, however, remain genetically uncharacterized. We propose UDP-glucose ceramide glucosyltransferase (UGCG)-related ichthyosis as a novel form based on a sole Saudi family.

The index patient was born at 37 weeks to a healthy 31-year-old G3P2AB0 mother following a pregnancy complicated by polyhydramnios. Delivery was vaginal with normal growth parameters (weight 2.8 kg, length 42 cm and OFC 33 cm). He was covered with a collodion membrane, and the skin was shiny and taught with joint contractures (Figure 1). He died at age 2 weeks because of severe hypernatremic anuric renal failure. Both parents are from the same tribe but denied recognizable consanguinity. In addition to their healthy daughter, they had lost a daughter with a remarkably identical phenotype to the index (polyhydramnios, collodion membrane, hypernatremic dehydration and death at 2 months of age). Lack of cholestasis in both affected children made ARC (arthrogryposis, renal dysfunction and ichthyosis) syndrome unlikely. There were no additional affected relatives. Family was enrolled using an IRB-approved research protocol (KFSHRC RAC#2121053) and whole exome sequencing of the index was performed as described before. Priority was given in determining variant candidacy to those in known ichthyosis genes. When none was identified, we considered variants in novel genes that reside within the autozygome given the family history. This highlighted a novel homozygous truncating

FIGURE 1  (A) Clinical photograph of the index showing shiny taught skin with associated joint contractures (a separate consent to publish this photograph was obtained from the parents). (B) Graph of UDP-glucose ceramide glucosyltransferase (UGCG) with the sequence chromatogram
variant in UGCG:NM_003358:exon2:c.142dupA within ~8 Mb autosome interval. This variant predicts NMD and/or frameshift (p.(Ser48Lysfs*18)). Sanger sequencing confirmed parents and unaffected sister to be heterozygous for the variant, which was absent in gnomAD and 3376 ethnically matched exomes (Figure 1).

Glycosphingolipids (GSLs) are ubiquitous components of cell plasma membranes in mammals. Glucosylceramides (GlcCers) are the main GSLs of the epidermis where they are shuttled into lamellar bodies (LBs) with the help of ABCA12. Upon LBs exocytosis, β-glucocerebrosidase, with the help of the activator protein, releases ceramides (the major component of the skin lipid barrier) from GlcCer in the extracellular space of the stratum corneum. Mouse models for each of these components of ceramide metabolism have been described and a severely impaired skin barrier function was a common phenotype, and ABCA12 mutations are a major cause of severe autosomal recessive ichthyosis in humans. UGCG catalyzes the synthesis of GlcCers and its complete knockout is early embryonic lethal.3 However, keratinocyte-specific conditional knockout was found to result in a severely impaired skin barrier defect that is identical to that seen in other ichthyosis mouse models.4,5 The pathogenesis of ichthyosis is thought to result from a combination of abnormal extrusion of lipid-lamella, and abnormal skin ceramide metabolism. We note that the homozygous truncating variant in our family abolishes the C-terminal catalytic domain of UGCG, which predicts at least a severely impaired enzyme. Lack of biological material did not allow us to pursue further characterization of the variant (eg, NMD) or its effect on skin lipidome. The remarkably similar phenotype of UGCG mutation-positive patients and of the conditional knockout mouse supports the notion that the mutation is causal. Our report, therefore, suggests the expansion of inborn errors of lipid metabolism in skin that manifest as ichthyosis to include UGCG-related disease. It will be of interest to observe in future reports the effect of milder biallelic UGCG mutations in humans especially because we cannot exclude the possibility of a dual molecular diagnosis for ichthyosis and contractures in this family.

ACKNOWLEDGEMENT

We thank the family for allowing us to publish their data. We also thank the team at Medical Diagnostic Laboratory for their help with the clinical exome testing.

ORCID

F.S. Alkuraya http://orcid.org/0000-0003-4158-341X

REFERENCES