Lipoid proteinosis (LP, OMIM 247100), also known as Urbach-Wiethe disease, is a rare autosomal recessive multisystem disorder which is characterised by various degrees of scarring and hyaline-like deposition. LP primarily involves skin and mucosal membranes of the upper aerodigestive tract, leading to hoarseness, dysphagia, abnormal tongue movement, and in severe cases respiratory difficulty (1, 2). Histologically, LP is characterised by widespread intercellular deposits of periodic acid–Schiff (PAS)-positive hyaline material in the dermis (2). The genetic cause of LP has been mapped to the extracellular matrix protein 1 (ECM1) gene on chromosome 1q21.2 (3). Among 50 mutations reported to date, 9 are missense, 16 are nonsense, 6 are splicing variants and 19 are in- or out-of-frame insertions or deletions (<100 bp, except for an 1163-bp deletion) (3). Here we report a germline 5141-bp deletion spanning 76% of ECM1 coding sequence and 28% of the neighbouring long intergenic non-coding RNA a1 (ncRNA-a1) in a consanguineous Chinese family.

CASE REPORT

The proband was a 22-year-old Chinese Han man born to consanguineous first-cousin parents (Fig. 1a). At the age of 7 months, he presented with recurrent, generalised blistering and pustules with erosions involving skin and oral mucosae which was diagnosed as “impetigo”. Most of the skin lesions resolved spontaneously within 2 weeks with scarring, despite several episodes of recurrence documented until the age of 8 years. His oral erosions persisted following the onset, and he had restricted mouth opening and a hoarse voice. Progressive scalp alopecia developed in the first year of life. He had no history of neurological or psychiatric deficits. The parents were clinically unaffected.

On examination, waxy beaded papules were observed on the margins of both upper eyelids and left nasolabial fold (Fig. 1b). Several acneliform atrophic scars were noted on his face and nape. Skin thickening was prominent on his forehead (Fig. 1c). Bilateral punctuate hyperkeratotic papules dispersed on his hands and feet, some of which coalesced into plaques. He had diffuse alopecia on his scalp, which accentuated on the parietal and occipital regions (Fig. 1c). Skin pigmentation and nails were normal. Intraoral examination revealed yellow-white infiltrations on his oral mucosae, gingival overgrowth and hypodontia (Fig. 1d). His lips, tongues and buccal mucosae were thickened with reduced movement (Fig. 1e). Laboratory investigations showed elevated serum protein level (81 g/l) and creatine kinase (270 U/l). Complete blood count and liver function tests were within normal limits.

Histopathology of biopsies taken from his tongue revealed hyperkeratosis with acanthosis and elongated rete ridges. In the lamina propria of his buccal mucosae, there was diffuse deposition of hyaline-like material positive for PAS staining and negative for Congo red staining, indicating the presence of glycoproteins. PAS staining also revealed thickening of the basal membrane (data not shown).

This study was approved by the Clinical Research Ethics Committee of Peking University First Hospital. All family members provided written informed consent for participation. Genomic DNA was extracted from peripheral blood of the patient and parents. Ten exons and flanking sequences of ECM1 were amplified by PCR using intronic primers, followed by gel purification and direct sequencing.

While no pathogenic mutations were found in ECM1 exons 1–5, primers specific for exons 6–10 failed to produce any amplicons in the patient but were able to amplify those of a normal control, suggesting a possible homozygous deletion. To find the deletion breakpoints, we employed PCR-based strategies with multiple
The mutation also deleted part of the ncRNA-a1, which belongs to a class of non-coding RNAs that have recently been linked to epigenetic control of chromatin, X-chromosome inactivation, imprinting, along with the regulation of epidermal differentiation (13). In mammalian skin, these RNAs have been confirmed to regulate the pathogenesis of melanoma, ultraviolet-induced skin injury and psoriasis (13). By phorbol ester-induced keratinocyte differentiation and siRNA experiments, Örom and colleagues (14) showed that full-length ncRNA-a1 could positively regulate the neighbouring ECM1 in an enhancer-like manner, whereas shortened ncRNA-a1 had decreased regulatory functions. Therefore, we deduce that, in our patient, loss of ~28% of ncRNA-a1 sequence is likely to decrease the transcription level of the already mutated ECM1. However, whether the joint deletion has contributed to the aforementioned uncommon LP phenotypes (alopecia and hypodontia) is yet to be elucidated.

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