Novel Mutations in Extracellular Matrix Protein 1 Gene in a Chinese Patient with Lipoid Proteinosis

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Key words: Extracellular Matrix Protein 1; Lipoid Proteinosis; Mutation

Lipoid proteinosis (LP, OMIM 247100), also known as Urbach-Wiethe disease or lipoidosis cutis et mucosae, was first described by Urbach and Wiethe[1] in 1929. It is a rare autosomal recessive genodermatosis characterized by hoarseness from early infancy, distinctive skin and neurological manifestations, and cutaneous lesions. It affects mucosal membranes of the upper respiratory tract, upper digestive tract, central nervous system, lymph nodes, and striated muscles. Hamada[2] identified the genetic defect to be a loss-of-function mutation or reduced expression of the gene encoding extracellular matrix protein 1 (ECM1) on chromosome 1q21 in 2002. So far, approximately, 300 cases have been reported. This article reported a case with clinical and molecular findings compatible with LP.

A 25-year-old male patient was admitted to Peking Union Medical College Hospital on June 21, 2015. He had mild hoarseness and skin lesions since early childhood. The skin lesions occurred successively including vesicles, pustules, bullae, and hemorrhagic crusted eruptions on the face and limbs due to minor trauma. The skin was eventually thickened with waxy, yellow papules or verrucous plaques and nodules. Pock-like or acneiform scars occurred on the face. Physical examination revealed warty, infiltrated plaques on the extensor aspects of the forearms and elbows. Beaded papules also appeared on the eyelids and yellow papules in the oral cavity [Figure 1]. The patient had a younger brother who was not affected. No evidence of consanguinity in his family was found.

The histology results showed hyaline materials deposited mainly in the papillary dermis and around blood vessels, sweat duct, hair follicles, and muscle nap, those were positive for periodic acid-Schiff (PAS) staining [Supplementary Figure 1]. To obtain a definitive molecular confirmation of LP in this patient, we analyzed the *ECM1* gene. A sequence analysis of the patient revealed a novel compound heterozygous mutation (p.A44T/p.R392W) in exon 3 and exon 8. The mutation c.130G>A transversion had altered the Ala/A-44 codon (GCA) to Thr/T-44 codon (ACA), designated p.A44T. The mutation c.1174C>T transversion had altered the Arg/R-392 codon (CGG) to Trp/W-392 codon (TGG), designated p.R392W [Supplementary Figure 2]. The polymerase chain reaction (PCR) products were directly Sanger sequenced. Both identified mutations were not found in 100 normal controls by direct sequencing. PCR can provide a definitive diagnosis for this patient.

LP is a rare autosomal recessive genodermatosis that occurs worldwide but more commonly in the northern part of South Africa. Clinical manifestations ranged from benign dermatological involvement to neurological involvement. Most of the manifestations occur due to the deposition of PAS-positive hyaline materials in dermis and submucosa. The first clinical manifestation is hoarseness of the cry or voice after birth, caused by infiltration of the vocal cords.[3] LP is caused by

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Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.193446

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Received: 29-07-2016 **Edited by:** Yuan-Yuan Ji
How to cite this article: Bai X, Liu JW, Ma DL. Novel Mutations in Extracellular Matrix Protein 1 Gene in a Chinese Patient with Lipoid Proteinosis. Chin Med J 2016;129:2765-6.

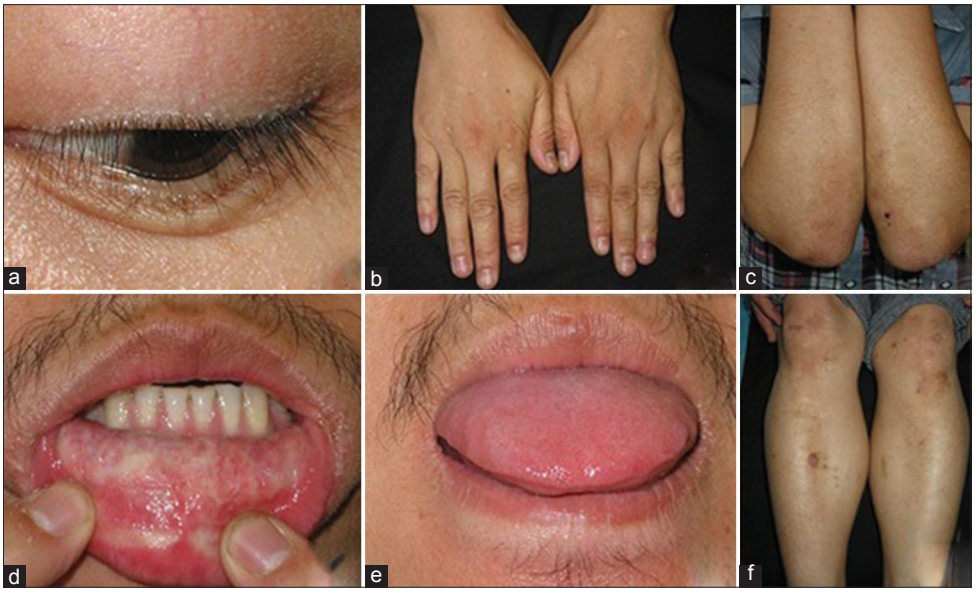

Figure 1: Clinical presentation of the 25-year-old male patient with lipoid proteinosis. (a) Beaded papule on the upper eyelid margin is inconspicuous; (b, c and f) mild scar formation in frictional area; (d) yellow-white infiltrates on the oral mucosa; (e) limited tongue movement.

loss-of-function mutations in *ECM1* gene.[2] The discovery of the mutations in *ECM1* allows accurate diagnoses to be made using gene sequencing. *ECM1* has effects on epidermal differentiation, binding to dermal collagen and proteoglycan and regulating angiogenesis. It expresses fibrous proteins on the basement membrane and growth factor by binding to proteoglycan. It also plays an important role on skin homeostasis.[4] The *ECM1* gene was mapped to chromosome 1q21.2, which has 10 exons. Almost half of all the mutations are located within exons 6 and 7.[5] Gene sequencing can improve diagnostic accuracy and offer a less invasive diagnostic test than a skin biopsy.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Acknowledgment

We are grateful to the patient's family for their contribution and participation in this clinical report. We also thank our colleagues Mr. Wei Wang and Mr. Jing Xie for their help in collecting blood samples.

Financial support and sponsorship

This study was supported by a grant of National Natural Science Foundation of China (No. 81371723).

Conflicts of interest

There are no conflicts of interest.

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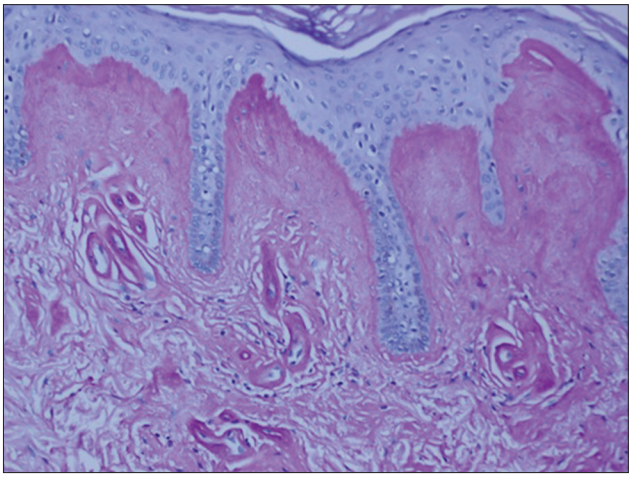
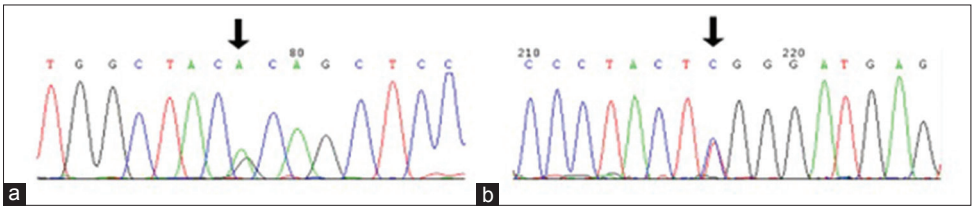


Supplementary Figure 1: Histological presentation in the patient with lipoid proteinosis. Periodic acid-Schiff staining showed accumulation of hyaline material in the dermis and eosinophilic material in the papillary dermis (PAS×200).



Supplementary Figure 2: Sequence analysis of the patient revealed a compound heterozygous mutation. (a) Mutation p.A44T in exon 3; (b) mutation p.R392W in exon 8.