

Unique variants in the *FLG* gene and *FERMT1* gene in a Chinese patient with ichthyosis and Kindler syndrome



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INTRODUCTION

Ichthyosis vulgaris (IV) is usually easily diagnosed based on clinical manifestations including dry skin history, scales on both calves, and excessive keratinization on the extensor aspect of the limbs. Gene variants are commonly found on the *FLG* gene.

CASE REPORT

A 13-year-old student presented with symptoms since the age of 2 when peanut-sized erythema and mild desquamation developed on the posterior neck. Keratinization on the extensor surfaces of the limbs and peanut-sized erythema on the flexor surfaces began appearing at the age of 6. By the age of 9, the erythema and desquamation on the posterior neck had spread to the entire neck. The symptoms worsened in winter and lightened in summer. The patient's mother had a history of dry skin. On examination, the skin of the torso and limbs was dry with few scales. Round brown dyspigmentation was observed on the skin overlying the knees. Reticular erythema and telangiectasia were seen on the neck. Symmetrical and clear atrophic erythema and telangiectasia were on both axillae. Rough and light red erythema with scales and slight rhagades were on both elbows, palm metatarsals, fingers, dorsal hands, and popliteal fossae, and diamond and polygonal scales appeared on both calves. Wax drop phenomenon, film phenomenon, and Auspitz sign were negative (Fig 1). The rub test and the Nikolsky sign were negative. A skin biopsy was taken from the right axillae, with hematoxylin-eosin and elastic fiber staining. (Fig 2).

Through gene high-throughput sequencing and Sanger verification, we found that the *FLG* gene had

Abbreviations used:

ACMG: American College of Medical Genetics and Genomics
IV: ichthyosis vulgaris
REVEL: rare exome variant ensemble learner

2 variants of uncertain significance, c.7945delA and c.11093G>A, and the *FERMT1* gene had one pathogenic variant, c.1343T>A (Table I).

C.7945delA leads to amino acid change p.S2649Vfs*94, which is a frameshift variant. The pathogenicity of this variant in IV has been reported in the Human Gene Mutation Database. According to the American College of Medical Genetics and Genomics (ACMG) guidelines,¹ this mutation was preliminarily determined to be pathogenic. C.11093G>A, nucleotide number 11093 in coding region mutating from guanine to adenine, leads to amino acid change p.G3698D, amino acid number 3698 mutating from glycine to aspartic acid, which is a missense variant. The Human Gene Mutation Database did not report the correlation of the locus. According to the ACMG guidelines,¹ the clinical significance of this variant is still uncertain.

C.1343T>A, nucleotide number 1343 in the coding region mutating from thymine to adenine, leads to amino acid change p.M. 448K, amino acid number 448 mutating from methionine to lysine, which is a missense variant. According to the ACMG guidelines,¹ the clinical significance of this variant is still uncertain.

Additionally, we use the REVEL (rare exome variant ensemble learner)² and polyPhen 2 to predict the pathogenicity of variants. According to the

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Fig 1. Clinical features. skin lesions presented on the axillae, elbows, metacarpophalangeal joints and wrists, and knees and calves.

prediction, the variant of *FERMT1*, C.1343T>A, is pathogenic. The variant of *FLG*, c.7945delA, is unknown, and the variant of *FLG*, c.11093G>A, is benign. The variant of *FERMT1* is related to Kindler syndrome. The patient's parents and sister have the heterozygotic variant, and he has the homozygous variant. They all denied a family history of similar or inherited diseases.

Both *FLG* gene site, c.11093G>A, and *FERMT1* gene site, c.1343T>A, were not previously reported.

DISCUSSION

In this case, the patient's atrophic erythema and telangiectasia on the neck could not be simply explained by ichthyosis. Although it is atypical, the diagnosis of Kindler syndrome should also be considered. No typical changes of psoriasis were found on pathologic examination.

The result of gene high-throughput sequencing also conforms to the report by Smith et al³ that IV is related to *FLG* variant and is an incomplete exogenous autosomal dominant mode of

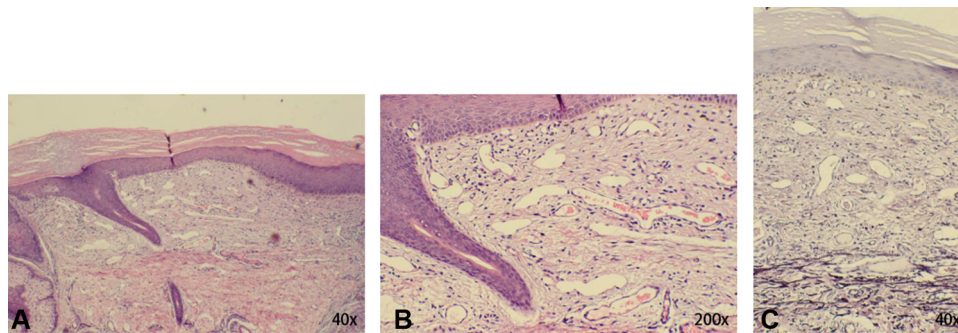


Fig 2. **A** and **B**, Hyperkeratosis, focal thickening of stratum granulosum, atrophy and thinning of epidermis, flattening and disappearance of epidermal papillae, vascular hyperplasia, dilation and hyperemia in the papillary dermis, a small number of lymphocytes, and pigment phagocytes infiltration around the blood vessels. **C**, Dermal papillae and dermal superficial elastic fibers reduce, break, and disappear. (**A** and **B**, Hematoxylin-eosin stain; **C**, elastic fiber staining.)

Table I. The patient's 2 variants of *FLG* gene and 1 variant of *FERMT1* gene

Gene	Chromosomal location	Transcript; exon	Nucleotide, amino acid	Hom/Het	Frequency	Inheritance patterns	Source of variation
<i>FLG</i>	chr1-152279416-152279417	NM_002016 ; exon3	c.7945delA (p.S2649Vfs*94)	Het	0.00350	AD	Mother
<i>FLG</i>	chr1-152276269	NM_002016 ; exon3	c.11093G>A (p.G3698D)	Het	—	AD	Father
<i>FERMT1</i>	chr20-6068452	NM_0176 71; exon11	c.1343T>A (p.M448K)	Hom	—	AR	Parents

AD, Autosomal dominant; AR, autosomal recessive; Het, heterozygote; Hom, homozygote.

inheritance. The patient's parents are defective gene carriers. Regarding the severe ichthyosis symptoms, Chen et al⁴ reported that the reduction or deletion of profilaggrin and filaggrin can be seen in the skin biopsy of IV patients, and the degree of reduction and clinical manifestations were significantly increased when *FLG* gene defects were combined to form compound heterozygotes. Therefore, it was speculated that the compound heterozygote that resulted from the *FLG* gene defect significantly aggravated the impairment of skin barrier function and exacerbated the clinical symptoms.

Lai-Cheong et al⁵ reported that *FERMT1* is the pathogenic gene of Kindler syndrome. The main clinical features of Kindler syndrome are blistering, particularly in trauma-prone sites, and progressive poikiloderma and skin atrophy, especially on the dorsal aspect of the hands and feet. Nevertheless, the patient was unable to meet the diagnostic criteria for Kindler syndrome, and no relevant research of Kindler syndrome reported a variant at the C.1343T>A site of the *FERMT1* gene.

According to the prediction of REVEL, the variant of *FERMT1*, C.1343T>A, is pathogenic. The variant of

FLG, c.7945delA, is unknown, and the variant of *FLG*, c.11093G>A, is benign.

Referring to the complex and atypical symptoms of this patient, we made 2 hypotheses. First, the variants of the *FLG* gene and the *FERMT1* gene simultaneously displayed 2 independent and different clinical manifestations. Second, the symptoms may be owing to the variants of the *FLG* gene, which severely impairs the function of skin barrier. It may have a modifying effect on the symptoms of Kindler syndrome due to the variant of the *FERMT1* gene. The mechanism and correlation between the *FLG* gene and the *FERMT1* gene need further studies to verify, such as western blot analysis.

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