



# Compound Heterozygous Mutations in *TGM1* Causing a Severe Form of Lamellar Ichthyosis: A Case Report

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**Abstract:** We aimed to detect the pathogenic gene mutations in a patient with lamellar ichthyosis (LI). The genomic DNA of the patient was examined using high-throughput whole-exome sequencing to identify the causative mutations. Compound heterozygous mutations of c.1187G>T (p.Arg396Leu) and c.607C>T (p.Gln203\*) were found in the transglutaminase-1 gene (*TGM1*) on chromosome 14 of the proband. The mutations stated above have been reported to impair the function of TGM1 protein and to be pathogenic. Our data suggest that the proband carried compound heterozygous mutations of c.1187G>T(p.Arg396Leu) and c.607C>T(p.Gln203\*) in *TGM1*, which were in the *trans* position and the cause of his disease. We also found some dermoscopic in this patient which may be specific in LI.

**Keywords:** autosomal-recessive congenital ichthyosis, *TGM1*, lamellar ichthyosis, whole-exome sequencing

## Introduction

Lamellar ichthyosis (LI) is a rare autosomal-recessive inherited and genetically heterogeneous disease. It is one of the main skin phenotypes of autosomal-recessive congenital ichthyosis (ARCI).<sup>1</sup> There are eight genes reported to be related with LI: *TGM1*, *ABCA12*, *ALOXE3*, *ALOX12B*, *CERS3*, *CYP4F22*, *NIPAL4/ICHTHYIN* and *PNPLA1*.<sup>2</sup> *TGM1* mutations are not only the most common cause of LI, but also the main cause of ARCI.<sup>3,4</sup> The genotype–phenotype correlation of ARCI is not clear. Nevertheless, researchers have discovered that ARCI caused by *TGM1* mutations is linked significantly to the presence of collodion membrane at birth, ectropion, plate-like scales and alopecia.<sup>3</sup> Dermoscopic findings of LI are rare.<sup>5</sup> Thus, we investigated the genetical cause and dermoscopic features of the proband.

## Case Report

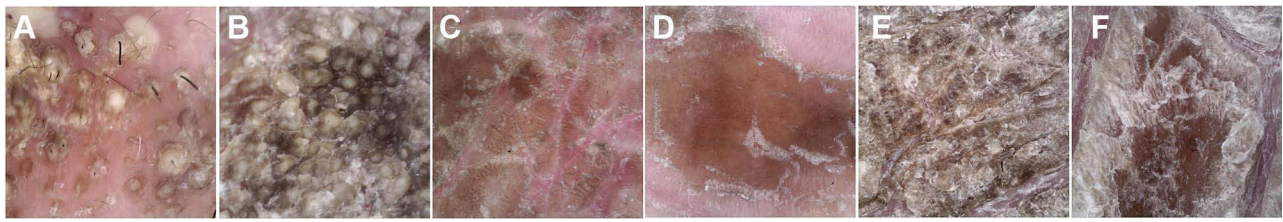
A 19-year-old male was admitted to our hospital with generalized squamous keratosis. He had been diagnosed as a collodion baby at birth, and later developed the lamellar form of ichthyosis gradually all over his body without systemic treatment. Following the ichthyosis, he had light-to-dark-brown ichthyotic keratotic scales with hair loss, ectropion, and incomplete eye closure (Figure 1). We magnified the scales on different areas of the proband with a dermoscope. Dermoscopy showed alopecia and pustules on his head (Figure 2A), greasy light-brown scales on his face (Figure 2B), “sheet-like” scales on his hand (Figure 2C), pre-thoracic skin (Figure 2D) and “bark-like” thickened scales with deep fissures between scales on the abdominal area (Figure 2E) and on his thigh (Figure 2F). The degree of hyperkeratosis differed in different parts of the skin. In general, scales on areas with thicker subcutaneous fat tended to be thicker. Histopathology (Figure 3) showed severe lamellar hyperkeratosis, mild hypertrophy of the spinous layer, and vacuolated degeneration of some spinous cells. In the stratum corneum, there were some cross-sections of hair shaft (arrows in Figure 3). One of those structures was highlighted and magnified in the upper right corner (red box in Figure 3). The proband's father denied consanguineous marriage or a similar family history.



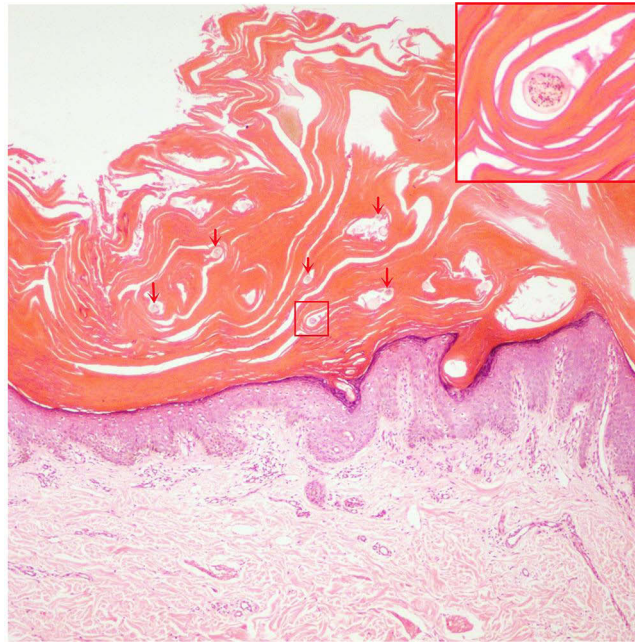
**Figure 1** Clinical features of the patient: dark, thickened and tightened lamellar scales spread over almost all the skin surface with hair loss and ectropion.

The clinical diagnosis was severe LI. High-throughput whole-exome sequencing was requested to further identify the cause.

After obtaining written informed consent, we extracted genomic DNA from the peripheral blood of the patient and his father. Mutation sites were identified by whole-exome sequencing with the genomic DNA of the proband. Whole-exome sequencing was based on a high-throughput sequencing platform with a paired-end strategy. We used the xGen Exome Research Panel from IDT (<https://eu.idtdna.com/>) for mutation capture. We screened for pathogenic mutations based on American College of Medical Genetics and Genomics guidelines.<sup>6</sup> Pathogenic mutations that correlated with the patient's clinical phenotype were verified using Sanger sequencing of genomic DNA of the proband and his parents.



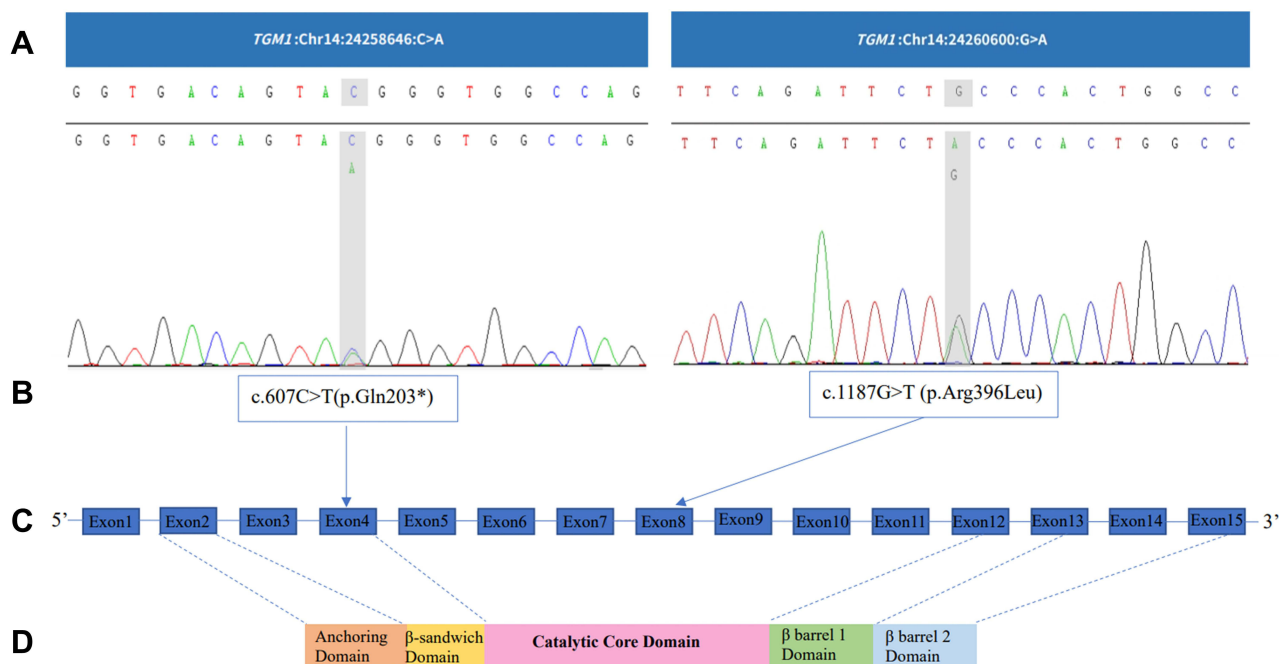
**Figure 2** Dermoscopic features of the patient. Dermoscopy ( $\times 50$  magnification) shows alopecia and pustules on his head (A), greasy light-brown scales on his face (B), "sheet-like" scales on his hand (C), pre-thoracic skin (D) as well as "bark-like" thickened scales with deep fissures between scales on the abdominal area (E) and on his thigh (F).



**Figure 3** Histology (hematoxylin and eosin,  $\times 100$  magnification) shows severe lamellar hyperkeratosis, mild hypertrophy of the spinous layer, and vacuolated degeneration of some spinous cells. In the stratum corneum, there were some cross-sections of hair shaft (arrows). One of those structures was highlighted and magnified in the upper right corner (red box).

Two known heterozygous variants on *TGMI* gene were identified in the genomic DNA of the proband. One was c.1187G>T (p. Arg396Leu) (NM\_000359.3; exon 8) on Chr14:24260600 (NC\_000014.9), which was inherited from his father. The other was c.607C>T (p.Gln203\*) (NM\_000359.3; exon 4) on Chr14:24258646 (NC\_000014.9) (Figure 4). According to the American College of Medical Genetics and Genomics guidelines,<sup>6</sup> the proband carried two mutant loci (c.1187G>T and c.607C>T) and, although only the father was tested for carriage (the mother was not tested), we found that the father carried only the mutation at the c.1187G>T locus. Hence, we assumed that the two variant loci in the proband were in the *trans* position according to the Mendelian law.

The *TGMI* mutations in exon 8 and exon 4 have been reported to be pathogenic.<sup>1,7-11</sup> The former, c.1187G>T (p. Arg396Leu), located in the catalytic core domain of transglutaminase 1 (TGase-1), forms a compound heterozygous state with pathogenic variant (c.919C>T, c.160C>T, c.1135G>C) or suspected pathogenic variant (c.652G>A) and thus leads to ichthyosis.<sup>1,7,8</sup> In vitro study, it is reported that c.1187G>T (p.Arg396Leu) affects the structure of the enzyme and influences the catalytic reaction.<sup>1</sup> The latter, located in the  $\beta$ -sandwich domain of TGase-1, is reported to cause severe LI with ectropion and alopecia in addition to the typical thick lamellar scales on the trunk and extremities in a Chinese patient with c.607C>T (p.Gln203\*) homozygous mutation. Moreover, in situ *TGMI* assays have revealed a loss of TGase-1 cDNA and an absence of transglutaminase activity in the skin.<sup>11</sup> In another Chinese patient with LI in which



**Figure 4** *TGM1* mutations. (A) and (B) *TGM1* mutations in the proband. (C) *TGM1* structure. *TGM1* has 15 exons and the translation start is located in the second exon.<sup>26</sup> (D) Protein domains of *TGM1*. It consists of five chains (817 amino acids): anchoring domain (1–92),  $\beta$ -sandwich domain (94–246), catalytic domain (247–572),  $\beta$ -barrel 1 domain (573–688), and  $\beta$ -barrel-2 domain (689–817).<sup>19</sup>

this variant and the pathogenic variant c.944G>A formed a compound heterozygous state, in addition to erythema and scaling, external ear deformities were observed.<sup>9</sup>

The proband was eventually diagnosed with severe LI caused by *TGM1* compound heterozygous mutations. He was treated with acitretin (20 mg/day, P.O.) and topical agents (Vaseline™ and tazarotene). Unfortunately, the patient was lost during follow-up.

## Discussion

*TGM1* (NM\_000359.3), located on chromosome 14 (NC\_000014.9), is a gene that contains 15 exons encoding 817 amino acids and expresses TGase-1, which is a calcium-dependent, catalytic membrane-binding enzyme that plays an important part in formation of the epidermal keratinized envelope. TGase-1: (i) acts as a scaffold to organize secreted extracellular lipids into a continuous lamellar membrane that mediates the permeability barrier function and prevents water loss; (ii) constitutes a mechanical barrier to prevent infection.<sup>12–14</sup> *TGM1* mutations can lead to varying degrees of transglutaminase deficiency, which impairs protein crosslinking and esterification of epidermis-specific ceramides during formation of keratinocyte proteins and lipid envelopes, and disrupts the skin-barrier function.<sup>15</sup>

Homozygous or compound heterozygous mutations on *TGM1* lead to ARCI1, an autosomal recessive inherited disease which has two clinical phenotypes, LI and NCIE, and causes LI in most cases and NCIE in some cases.<sup>16</sup> LI presents as generalized brown or dark lamellar hyperkeratosis with or without erythema. NCIE presents as a distinct erythema covered with fine grayish-white scales. LI and NCIE may show scarring alopecia.<sup>17</sup> *TGM1* mutations are associated with certain clinical manifestations: collodion membrane at birth, hair loss, hearing problems, eye problems, and skin odor.<sup>18</sup> However, clinical phenotypes cannot be inferred from genotypes, and even identical genotypes can lead to different clinical phenotypes.<sup>19</sup>

A genetic diagnosis is the “gold standard” for the diagnosis of hereditary diseases. The common method is whole-exome sequencing of DNA extracted from peripheral blood and data analyses for possible pathogenic variants. Validation is undertaken by Sanger sequencing. In autosomal-recessive ichthyosis, novel (especially) missense mutations must be identified by enzyme-activity assays to determine their pathogenicity.<sup>20</sup> Alternatively, they can be verified by immunofluorescence blotting, which determines whether the mutated gene is pathogenic by comparing expression of the mutated

gene with that of the wild-type protein.<sup>21</sup> Besides, computational analysis serves as a selective and attractive molecular approach. For instance, structural modeling has revealed that compound heterozygous missense mutations located in the catalytic core domain can lead to a significantly impaired structural stability of transglutaminase protein.<sup>22</sup>

Researchers have discovered (through dermoscopy) many keratotic plugs in the cristae cutis where eccrine sweat pores are present. They believe these will block sweat glands and are the cause of hypohidrosis in LI.<sup>4</sup> In a study by Yang and colleagues, scales covered the cristae cutis but not the sulci cutis, in accordance with our findings. In our study, we also found the degree of hyperkeratosis differed in different parts of the skin and scales on areas with thicker subcutaneous fat tended to be thicker which may serve as another characteristic dermoscopic feature of LI. Yet further researches are needed.

Biopsy of ARCI-TGM1 cases often reveals non-specific features such as hyperkeratosis with focal parakeratosis, a slightly thickened granular layer, and mild-to-moderate psoriasiform hyperplasia.<sup>23</sup> In this case, except for those non-specific features, we also found some cross-sections of hair shaft in the stratum corneum in hematoxylin eosin stain of abdominal skin biopsy as a result of the over-thickened stratum corneum.

Acitretin is first-line treatment of LI in adults because it improves hyperkeratosis, hypohidrosis, hair regrowth, ectropion, hearing, and daily skin care. Emollients are recommended for patients with ichthyosis, and are used at least twice-daily, after bathing. Other topical therapies include lubricating agents, keratolytic agents, or topical retinoids depending on the overall lesions of the patient.<sup>24</sup> Patients with ectropion require regular eye examinations, long-term use of eye lubricants, and eyelid massage to reduce ocular symptoms. Eyelid skin grafts may be considered in patients with more severe ectropion, but only as third-line treatment.<sup>25</sup>

## Conclusions

The proband carried two pathogenic variants in *TGM1* (c.1187G>T and c.607C>T). These compound heterozygous mutations were the causes of LI in the proband, and were in the *trans* position. Dermoscopy revealed keratotic scales anastomotic to the crista cutis, which led to a highlighted sulci cutis presenting like a fissure. The thickness of plate-like scales differed in different parts of the body, from sheets to bark-like. We found scales on areas with thicker subcutaneous fat tended to be thicker. Histology showed cross-sections of hair shaft in the stratum corneum, which is a sign of the over-thickened stratum corneum.

## Ethics Approval

The patient's informed consent for publication of the case details, including publication of the patient's images, was obtained, and the study was approved by the Ethics Committee of the Second Hospital of Jilin University.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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