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Identification of a novel mutation in the *ST14* gene in an Iranian family with ichthyosis and hypotrichosis

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Abstract

Inherited ichthyosis is a heterogeneous group of rare cutaneous disorders characterized by hyperkeratosis and scaly skin. So far, only a few genetic studies on ichthyosis have been performed in Iran. Herein, we reported a family with two cases of ichthyosis and hypotrichosis that were investigated by whole exome sequencing. Targeted data analysis identified a novel nonsense variant c.1243C>T (p.Gln415Ter) located at exon 11 of the *ST14* gene in the proband. Sanger sequencing showed co-segregation of this mutation with the disease in this family. Further studies are needed to develop knowledge about the spectrum of changes in this gene and their effects on protein function and disease phenotype.

Keywords: whole genome sequencing, skin disorder, genetic, hereditary, phenotype

Introduction

Inherited ichthyosis is a family of rare genetic skin disorders, which are characterized mainly by mild to severe localized or generalized hyperkeratosis and scaly skin [1-6]. Inherited ichthyosis is divided into syndromic and non-syndromic groups according to the presence or absence of associated clinical features [7].

So far, over 50 genes have been identified to be associated with autosomal dominant, autosomal recessive, and X-linked types of ichthyosis [6, 8]. Owing to a large number of genes involved in ichthyosis and scattering of mutations along the length of these genes, traditional gene-by-gene Sanger sequencing of all the associated genes would be labor intensive, time consuming, and highly costly. In recent years next-generation sequencing has provided a high-throughput and cost-effective approach for detection of mutations causing hereditary ichthyosis [8, 9].

Iran is a country with a high rate of consanguineous marriages (38.6%), [10]. Despite the importance of increasing knowledge on the genetic causes of inherited ichthyosis in choosing the best strategy for molecular diagnosis of this disease, studies on this condition are limited in Iran [9, 11, 12]. In this study, the whole exome sequencing method was used to find the genetic cause of the ichthyosis in an Iranian family with two affected members.

Case Synopsis

A 40- year-old man of Persian descent from north of Iran was referred to the Molecular Medicine Department, Pasteur Institute of Iran for further evaluation of dry skin and hypotrichosis since birth. Physical examination showed diffuse dry skin and mild hypotrichosis with mild facial involvement (on forehead) but without palmar/plantar involvement, or periorbital erythema. Severe dry eyes, thin sclera, and chronic meibomian gland dysfunction were also found in the eye examination. Hair shaft examination

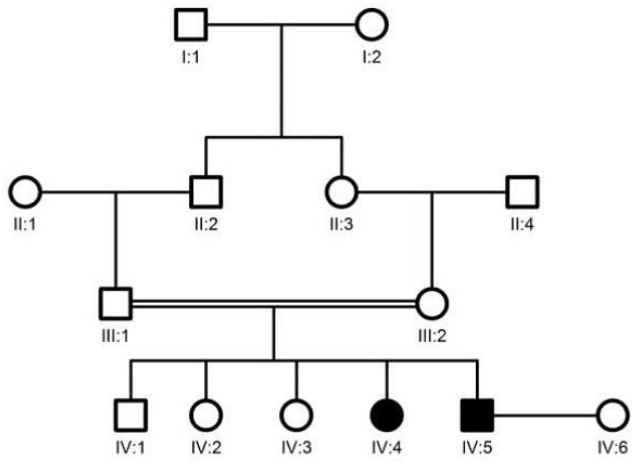

Figure 1*: Pedigree of the Iranian family with two affected individuals with confirmed ichthyosis.*

showed hair diameter variation, trichoschisis, and irregular twisting (pseudo pili torti).

The proband was born to a consanguineous marriage and had a positive family history of skin disease with a similar presentation in one of his sisters. No other affected family members were reported. The family pedigree is shown in **Figure 1**. Participants in the study completed a questionnaire and signed an informed consent form. This study was confirmed by the ethics committee of our institution.

Peripheral blood samples were obtained from the proband and his family members. Genomic DNA was extracted using the salting out method according to standard protocol [13]. Whole exome sequencing was done using Illumina HiSeq 2000 (Macrogen, South Korea). The Human Phenotype Ontology browser (HPO-Browser; http://compbio.charite.de/hpoweb/showterm?id=HP:0000118) was used to determine genes related to the ichthyosis for targeted NGS data analysis. Sanger sequencing was used to confirm a candidate pathogenic variant identified by whole exome sequencing in the proband and the family members.

Among identified variants in whole exome sequencing, a novel nonsense variant c.1243C>T (p.Gln415Ter) located at exon 11 of the *ST14* gene was most likely the cause of phenotype seen in the family. The result of whole exome sequencing was confirmed by Sanger sequencing (**Figure 2**). Both affected individuals were homozygous for the identified variant. The homozygous state of this variant was not observed in healthy members of this family.

Case Discussion

ST14 gene (OMIM No.: 606797) is located in the chromosome 11q24.3 region and composed of 19 exons encoding an 855-amino acid protein, named matriptase, a type II transmembrane serine protease [14, 15]. The variant c.1243C>T creates an early stop codon in the *ST14* gene and can affect matriptase functions. The predicted effect of this variant, co-segregation of this mutation with the disease in this family and the absence of it in any of the population/disease databases suggest that this condition is caused by the variant c.1243C>T in this family.

The *ST14* gene was first identified as the defective gene in ichthyosis by Basel-Vanagaite et al. in 2007 using homozygosity mapping in a consanguineous Arab family [16]. Since 2007, only eight mutations in the *ST14* gene have been reported. Seven of these eight mutations have been identified in consanguineous families, which can show the rarity of the mutations in this gene [16-21]. The nonsense mutation c.1243C>T found in this study is the ninth mutation identified in the *ST14* gene.

A mild phenotype was observed in the homozygous affected members of the family in this study. The skin, hair, and eyes were affected in the proband and his sister but no dental problems were detected in the patients. Clinical features of the patients in this family were similar to those noted in the previous studies [10, 15-21].

Conclusion

In summary, we report a novel variant in the *ST14* gene responsible for ichthyosis in an Iranian family. Further studies are needed to develop our knowledge about the spectrum of changes in this

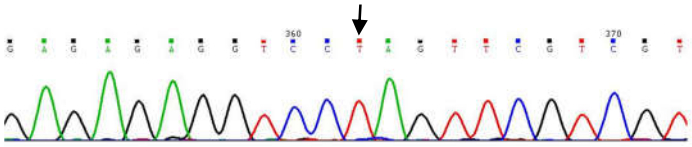

Figure 2*: Sequence chromatogram of the variant c.1243C>T identified in the affected members of the investigated family.*

gene and their effects on protein function and disease phenotype.

Potential conflicts of interest

The authors declare no conflicts of interests.

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