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CASE REPORT

A case of autosomal recessive congenital ichthyosis with a novel mutation identified in the *TGM1* gene by whole exome sequencing

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ABSTRACT

Background: The "autosomal recessive congenital ichthyosis (ARCI)" refers to a group of rare, heterogeneous, and non-syndromic disorders of keratinization, represented as abnormal scales over the entire body and attributable to defective epidermal keratinocyte differentiation and lipid metabolism. ARCI is caused by mutations in a wide variety of genes, including *ABCA12, ALOX12B, ALOXE3, CYP4F22, NIPAL4, TGM1, CERS3, PNPLA1, CASP14, SDR9C7*, and *SULT2B1*. The most common cause of ARCI is a *TGM1* gene mutation, which is strongly associated with a collodion membrane at birth.

Case presentation: A 15-year-old male patient presented with extensive scaling over the entire body since birth. His history revealed that he was born ash-colored in a membrane, kept in an incubator for one month, and clinically diagnosed with ichthyosis at birth. The patient, who had undergone no previous genetic testing, was subjected to whole exome sequencing with the preliminary diagnosis of autosomal recessive/X-linked recessive congenital ichthyosis. The analysis identified a homozygous c.1020delG change in the *TGM1* gene in the form of a frameshift mutation that is classified as pathogenic according to the American College of Medical Genetics criteria.

Conclusion: Next-generation sequencing technologies employing whole-exome sequencing enable the sequencing of all protein-coding DNA regions in a single run.

Keywords: Congenital, ichthyosis, TGM1, whole exome sequencing.

Introduction

The term "autosomal recessive congenital ichthyosis (ARCI)" refers to a group of rare, heterogeneous, and non-syndromic disorders of keratinization (1), taking the form primarily of abnormal scales over the entire body and attributable to defective epidermal keratinocyte differentiation and lipid metabolism (1). The reported prevalence of ARCI in the United States is 1:200,000-300,000, although it is more common in other countries, such as Norway (1:91,000) (2).

ARCI is caused by mutations in a wide variety of genes, including *ABCA12, ALOX12B, ALOXE3, CYP4F22, NIPAL4, TGM1, CERS3, PNPLA1, CASP14, SDR9C7*, and *SULT2B1* (3). Most of these identified genes are involved in the synthesis of the enzymes and transporters involved in the production, transport, and/or assembly of components of the stratum corneum (4).

The most common cause of ARCI is a *TGM1* gene mutation, which is strongly associated with a collodion membrane at birth (1). This case report aimed to present a pediatric case of ARCI with a novel homozygous mutation identified in the *TGM1* gene by whole exome sequencing (WES).

Case Presentation

A 15-year-old male patient presented with extensive scaling over the entire body since birth. The patient's

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history revealed that he was born ash-colored in a membrane, kept in an incubator for one month, and clinically diagnosed with ichthyosis at birth. The patient had taken various doses of acitretin intermittently since birth.

The patient's history involved no additional disease. According to the patient family history, he was born to non-consanguineous healthy parents from the same village and had no family member with a similar disease (Figure 1).

A dermatological examination revealed thick diffuse brown adherent scaly lesions over the entire body that was more prominent in the flexural areas and on the face (Figure 2).

Ectropion of the conjunctiva, teeth discoloration, and heat intolerance were also detected (Figure 3).

The patient had not undergone any previous genetic testing and was subjected to WES with the preliminary diagnosis of "autosomal recessive/X-linked recessive congenital ichthyosis." WES aims to identify the nucleotide size of the protein-coding regions (exons) and their flanking intronic regions in ~21,000 genes of the human genome and to identify disease-causing changes in these regions. The exon represents 2% of the human genome, but contains approximately 85% of disease-causing mutations. The diagnostic yield of WES ranges from 10% to 50%, depending on the clinical characteristics of the population tested, the year of testing, and the analytical strategy.

The analysis identified a homozygous c.1020delG change in the *TGM1* gene in the form of a frameshift mutation that is classified as pathogenic according to the American College of Medical Genetics criteria. The identified

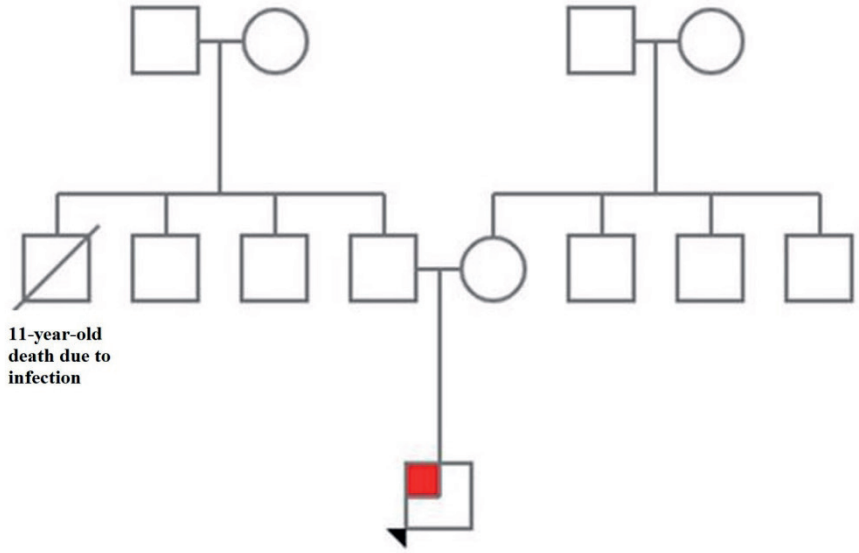

Figure 1. *The pedigree of the patient. The arrow indicates the proband.*

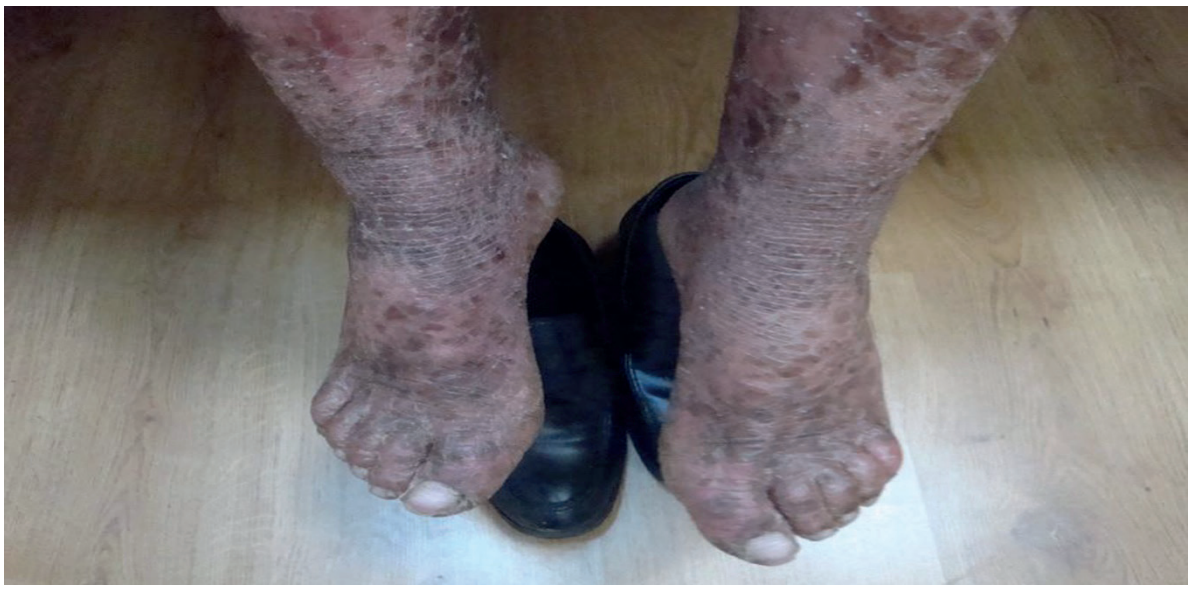

Figure 2. *Thick diffuse brown adherent scaly lesions over the entire body.*

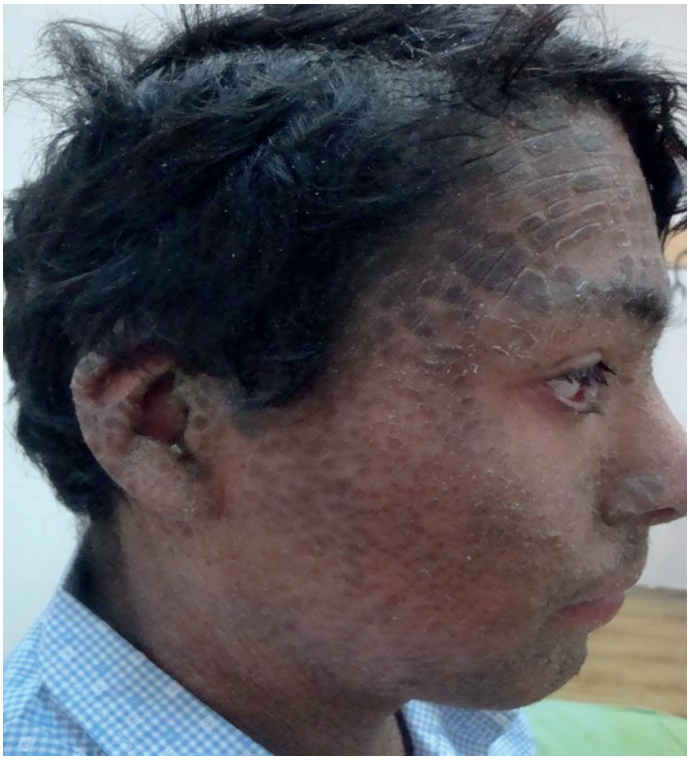

Figure 3. *Ectropion of the conjunctiva.*

change has not been previously reported in the literature and is a "novel" mutation.

Homozygous changes in the *TGM1* gene lead to "Congenital Ichthyosis Type 1" according to the Online Mendelian Inheritance in Man database. The reported findings for this disease included taut facial skin, ectropion, eclabium, skin findings collodion membrane at birth (reported in most patients), self-healing collodion baby (reported in some patients), large thick plate-like scales, fine white scales, erythroderma, hypohidrosis or anhidrosis, mild palmoplantar hyperkeratosis, dystrophic nails, alopecia (in some patients), and hypotrichosis (in some patients). The patient had phenotype-genotype concordance and a definitive diagnosis of "Congenital Ichthyosis Type 1" was made.

Discussion

ARCI is a heterogeneous group of disorders associated with congenital ichthyosis and without extracutaneous involvement. The most common phenotypes are lamellar ichthyosis and congenital ichthyosiform erythroderma, and it is often accompanied by palmoplantar keratoderma, ectropion, and anhidrosis. Severe heat intolerance and nail dystrophy are common in both types (1,5).

The presented patient had no nail dystrophy but had significant heat intolerance. Although lamellar ichthyosis and congenital ichthyosiform erythroderma were initially believed to be different types, there have been reports presenting cases with intermediate clinical manifestations, suggesting that the two conditions might be caused by mutations in the same gene. Moreover, different phenotypes might occur in patients with the same mutation, even within the same family (1). Patients are often born as collodion babies, and there is a risk of perinatal mortality in rare cases of harlequin ichthyosis (5). The presented patient was covered with a membrane at birth.

Diagnosis of non-syndromic ARCI is based on skin findings at birth and in infancy. A skin biopsy is not necessary to establish a diagnosis of ARCI (1). Massive orthokeratotic hyperkeratosis is observed in lamellar ichthyosis. The epidermis is acanthotic and sometimes has a psoriasis-like appearance, and the cell proliferation rate could be normal to slightly elevated. Patients with congenital ichthyosiform erythroderma, in turn, have focal or diffuse parakeratosis, a normal to thickened granular layer, less pronounced hyperkeratosis with more prominent acanthosis and an increased epidermal turnover (6). The presented case was clinically diagnosed in the neonatal period and no skin biopsy was performed.

Regardless of the diversity of mutations and phenotypic manifestations associated with ARCI, the condition is caused by mutations in the *TGM1* gene in 32%-68% of cases. *TGM1* mutations account for 55% of all ARCI cases in the United States, and to date, more than 115 mutations in the *TGM1* gene have been identified in patients from different racial and ethnic backgrounds including Caucasian American, Norwegian, Swedish, Finnish, German, Swiss, French, Italian, Dutch, Portuguese, Hispanic, Iranian, Tunisian, Moroccan, Egyptian, Afghan, Hungarian, African-American, Korean, Japanese, and South African (7).

Fischer et al. examined 520 families with ARCI and identified mutations in at least one of these genes in 78% of cases including *TGM1* in 32%, *NIPAL4* in 16%, *ALOX12B* in 12%, *CYP4F22* in 8%, *ALOXE3* in 5%,

and *ABCA12* in 5% (8). In a study of 250 ARCI patients of different origins, *TGM1* mutations were identified in 38%, *ALOXE3* mutations in 6.8%, and *ALOX12B* mutations in 6.8% of the cases (9).

The *TGM1* gene is located on chromosome 14q11.2 and has 15 exons (GenBank NM-00359.2). It encodes TGase 1 - one of the three TGase enzymes found in the epidermis (1). This enzyme participates in the formation of the cornified envelope by catalyzing the calcium-dependent cross-linking of various proteins, such as involucrin and loricrin, as well as proline-rich proteins. It also catalyzes the binding of alpha-hydroxy ceramides in the outer layer of the cornified envelope with proteins in the inner layer. Patients with *TGM1* mutations have no cornified envelope and reduced or zero TGase 1 activity. The altered function of the TGase-1 leads to the formation of defective intercellular lipid layers and impaired barrier function of the stratum corneum (7). In the presented case, a Homozygous Class 1 c.1020delG change was identified in the *TGM1* gene that has not been previously included in any variant database (ClinVar, 1000 Genomes, gnomeAD, etc.), and no such change has been reported in the literature. This change could thus be considered a "novel" mutation.

For more than 30 years, the optimum approach to genetic analysis has been Sanger sequencing, which involves analyzing the coding portion of the gene that is suspected to cause disease. This technique is expensive and time-consuming when compared to the next-generation techniques currently available (5). Next-generation sequencing technologies employing WES enable the sequencing of all protein-coding DNA regions in a single run. WES is most likely to reveal the molecular cause, and for most types of ichthyoses, it produces results with a diagnostic yield similar to that of single-gene testing. It also provides an excellent base from which to investigate the novel genes underlying these disorders in patients with hereditary ichthyosis (5), and one such investigation of the presented patient indeed revealed a novel gene mutation.

The current treatment approaches to ARCI are symptomatic and do not address the underlying cause, with the primary aim being to improve the patient's quality of life. Current treatment options include moisturizers, keratolytics, retinoids, vitamin D analogs, corticosteroids, and calcineurin inhibitors (7). Retinoids improve the condition of the patient's skin through their ability to reduce corneocyte adhesion, and hence to increase exfoliation, inhibit epithelial proliferation and help normalize the terminal differentiation of skin cells. In addition, retinoids could activate the production of epidermal enzymes that are impaired by the *TGM1* mutation (10). The presented patient was thus treated with low-dose (0.3 mg/kg) acitretin, moisturizers, and keratolytics. Gene and cell therapies are considered promising for the treatment of ARCI, with the goal being to restore the functional activity of altered proteins, although such approaches are still being researched (7).

When a patient is diagnosed with ichthyosis, appropriate genetic counseling should be provided to explain the nature of the disorder, the mode of inheritance, and the risk of future occurrence within the family (1). The presented patient was evaluated together with the medical genetics department, and the necessary counseling was provided. The identification of a homozygous variant in this family with non-consanguineous parents sets an example for potential consanguinity among people from the same village. When evaluating the family history of patients, a family "from the same village" should lead to the consideration of autosomal or X-linked recessive disorders. The chance of inheriting autosomal recessive disorders, as in the presented patient, is 25%, and the parents of the presented patient were duly informed. This patient group was given counseling on having a healthy child in terms of the respective gene by prenatal genetic testing.

Conclusion

The early diagnosis of genetic disorders such as congenital ichthyosis that affect both the individual and their families is important, along with the initiation of appropriate treatments. It is predicted that in the future, gene therapies would be a source of hope in the field of genetic skin disorders, which greatly affect the quality of life.

List of Abbreviations

ARCI Autosomal recessive congenital ichthyosis WES Whole exome sequencing

Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for publication

Due permission was obtained from the patient/parents/guardians of the patient to publish the case and the accompanying images.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author's contribution

The authors confirm their contribution to the article as follows: study conception and design: GG, ME; data collection: GG, ME, BG; analysis and interpretation of results: GG, ME, BG; and draft manuscript preparation: GG, ME. All authors reviewed the results and approved the final version of the manuscript.

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