CASE REPORT

A novel homozygous CERS3 frameshift mutation causing autosomal recessive congenital ichthyosis type 9: A case report

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ABSTRACT

Autosomal recessive congenital ichthyosis (ARCI) is a collection of uncommon keratinization disorders marked by widespread scaling and erythema from birth. CERS3 variants lead to ARCI type 9 (ARCI9) by interfering with ceramide biosynthesis and the formation of the epidermal barrier. We present a 25-year-old male, born as a collodion baby to consanguineous parents, who exhibited lifelong diffuse, plate-like scaling accompanied by mild ectropion. Histopathology revealed compact orthokeratosis accompanied by mild acanthosis. Genetic analysis identified a novel homozygous frameshift variant in CERS3 (NM_001292029.2:c.437del; p.[Ala146Valfs*9]), deemed likely pathogenic according to ACMG criteria. Parental carrier testing was recommended but has not yet been conducted. This case broadens the mutational spectrum of CERS3-related ichthyosis and underscores the necessity of amalgamating clinical, histological and molecular findings for accurate diagnosis. Genetic confirmation facilitates precise counselling, cascade testing and an enhanced comprehension of ceramide pathway deficiencies in ARCI. (www.actabiomedica.it)

Key words: autosomal recessive, ichthyosis, CERS3 mutation, ceramide synthase 3, genetic dermatology

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Introduction

Autosomal recessive congenital ichthyosis (ARCI) is a rare, lifelong collection of inherited keratinization disorders that cause scaling and variable redness all over the body from birth (1). The global incidence is estimated at one in 200,000–300,000 live births, underscoring the rarity of the disorder and the importance of international data sharing (1,2). Pathogenic variants in more than a dozen genes, such as TGM1, ABCA12, NIPAL4, ALOX12B and CERS3, interfere with the processing of lipids in the epidermis and the formation of barriers (2,3). Mutations in CERS3 characterise ARCI type 9 (ARCI9; OMIM 615276) and constitute approximately 4% of ARCI cases (4). The CERS3 gene encodes ceramide synthase 3 (CerS3), an enzyme that catalyses the acylation of sphingoid bases with very-long-chain fatty acids (C26–C34) to produce ω-O-acyl-ceramides, the lipids that anchor corneocytes and preserve skin barrier integrity (5,6). Loss-of-function variants eliminate CerS3 activity, resulting in significant depletion of ultra-long-chain ceramides and the inability to form an effective barrier (5–7). Clinically, affected neonates are frequently born as collodion babies and subsequently exhibit persistent, plate-like hyperkeratosis, xerosis and palmoplantar hyperlinearity, while the flexures remain relatively unaffected (4–6). Due to the overlap with other ARCI subtypes, molecular confirmation through targeted next-generation sequencing or whole-exome sequencing is crucial for precise classification, prognostication and genetic counselling (4,8). To date, fewer than 50 cases of CERS3 mutations have been reported, highlighting the rarity of this genotype.

Case report

A 25-year-old male presented with a history of lifelong generalised scaling. The patient was born at term after a normal pregnancy and found to be wrapped in a tight collodion membrane that came off within the first few weeks of life. During the neonatal period, there was temporary erythema, ectropion and eclabium, but no systemic illness. His parents were second-degree relatives, and there was no known familial history of analogous dermatological conditions. The patient experienced chronic xerosis and thick, plate-like brown scales on the trunk and extremities during infancy and adolescence, while the flexural areas were relatively spared. The skin on the face was shiny and red, and there was still some mild ectropion. There was no palmoplantar keratoderma, nail dystrophy or mucosal involvement. He had previously undergone intermittent courses of oral retinoids, which were halted due to the presence of lentigines. Daily emollients and 10% urea cream helped keep things under control for a long time. On examination, the patient had diffuse brown, plate-like scales on the trunk and limbs (Figure 1).

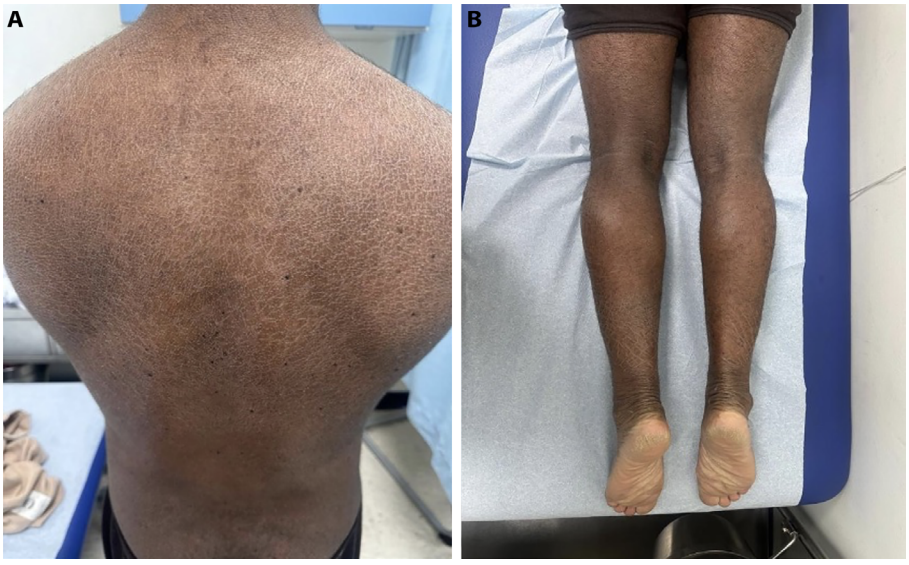

Figure 1. Back (Figure 1A) and lower limb (Figure 1B) diffuse xerosis with brown plate-like scaling.

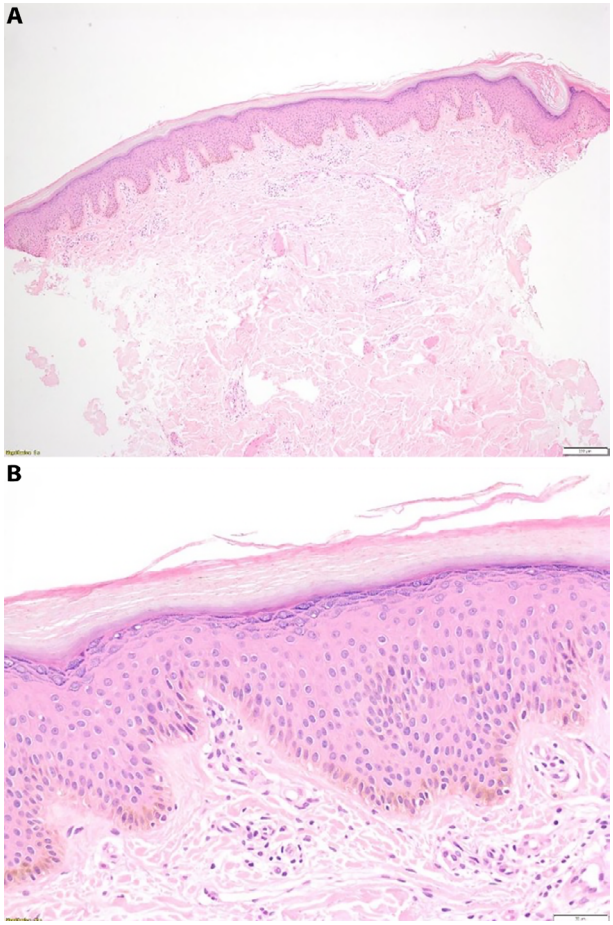

Figure 2. (A) There is compact hyperkeratosis with mild psoriasiform hyperplasia of the epidermis (H&E; 4x). (B) Higher magnification shows compact orthokeratosis with normal granular cell layer, mild acanthosis and a mild superficial dermal perivascular lymphocytic infiltration (H&E; 20x).

Flexures were spared, there was mild erythema on the face, along with fine scales and partial ectropion. There was clear diffuse xerosis. There were no significant findings on systemic examination. Two punch biopsies of the lesions were taken, and histopathological analysis demonstrated compact orthokeratosis with an intact granular layer, mild acanthosis and a superficial perivascular lymphocytic infiltrate (Figure 2).

Genetic testing using a next-generation sequencing panel (CentoSkin®, Centogene) detected a novel homozygous frameshift variant in CERS3 (NM_001292029.2: c.437del; p.[Ala146Valfs*9]), categorised as likely pathogenic according to ACMG/AMP guidelines. This finding validated our diagnosis of autosomal recessive congenital ichthyosis type 9 (ARCI9) (1–3), and to the best of our knowledge, this variant has not been previously reported in the literature. The patient's parents were counselled for carrier testing, but have yet to undergo the test. Furthermore, genetic counselling was provided to explain the risk of passing on genes and the benefits of cascade testing. At follow-up, the patient's condition was found to be stable on topical emollients and urea cream. He was advised to continue regular ophthalmology review for ectropion and dermatology follow-ups. Summary of Clinical, Histopathological and Genetic Findings (Table 1).

Table 1. Summary of clinical, histopathological and genetic findings.

Category	Key findings
Age/Sex	25-year-old male
Family background	Consanguineous parents (second-degree relatives); no affected siblings
Perinatal history	Born with collodion membrane; transient erythema, ectropion, and eclabium
Clinical features	Lifelong xerosis; diffuse brown plate-like scaling on trunk and limbs; mild facial erythema and ectropion; sparing of flexures
Histopathology	Compact orthokeratosis, normal granular layer, mild acanthosis, superficial perivascular lymphocytic infiltrate
Genetic findings	*CERS3* (NM_001292029.2): c.437del; p.(Ala146Valfs*9), homozygous frameshift variant; classified *likely pathogenic* (ACMG)
Diagnosis	Autosomal recessive congenital ichthyosis type 9 (ARCI9)
Management	Emollients and 10% urea cream; ophthalmologic follow-up
Genetic counselling	Parental carrier testing advised but not yet performed

Discussion

Cases of CERS3-related autosomal recessive congenital ichthyosis (ARCI) are uncommon and characterised by the classic triad of collodion membrane at birth, persistent lamellar/plate-like scaling and xerosis; palmoplantar hyperlinearity is prevalent (1,4,5). Previous series and individual case reports indicate that CERS3 variants may manifest as missense, nonsense or splice-site

alterations that diminish or eliminate the functionality of ceramide synthase-3, consequently depleting ultra-long-chain ω-O-acyl-ceramides and hindering the assembly of the stratum corneum barrier (5,6). Clinically, the phenotype of our patient closely corresponds with prior descriptions (1,4), reinforcing a stable genotype–phenotype correlation for loss-of-function alleles. The homozygous frameshift variant identified here, CERS3 NM_001292029.2:c.437del (p.Ala146Valfs*9), is predicted to introduce a premature stop codon and either truncate CerS3 or trigger nonsense-mediated mRNA decay, producing a loss-of-function effect analogous to previously reported pathogenic alleles (5,6). This molecular diagnosis has direct clinical significance: it validates autosomal recessive inheritance, facilitates precise recurrence risk counselling and emphasises targeted family (cascade) carrier testing—particularly critical in consanguineous lineages where carrier frequency and recurrence risk are elevated (4,3). Lastly, recording new pathogenic variants adds to the CERS3 mutational catalogue and helps with diagnostic panels and future functional or therapeutic studies (3,6).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contributions: HA: conceptualization, review and editing. TSA: original draft preparation, letrurte reivew. MA: conceptualization and pathology review. AANA: review and editing. SA: validation and review.

Ethics Approval and Consent to Participate: The work was undertaken according to the provisions of the Declaration of Helsinki. The involved subject gave informed consent to participate and patient anonymity has been constantly preserved. Written informed consent was obtained from the patient for publication of the case details and accompanying images. Ethical committee approval was obtained on Tuesday, September 16, 2025. IRB number: IRB-2025-01-0559

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Declaration on the use of AI: The authors confirm that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

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