Dermatology Practical & Conceptual

From Misdiagnosis to Molecular Insight: Lessons from Two ARCI Siblings Initially Treated as Netherton Syndrome

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Key words: Hidradenoma papilliferum, Vulva, Mammary-like gland adenoma

Citation: Yan S, Gan YT, Liu YW, Li YX, Song Q. From Misdiagnosis to Molecular Insight: Lessons from Two ARCI Siblings Initially Treated as Netherton Syndrome. *Dermatol Pract Concept*. 2026;16(1):6235. DOI: https://doi.org/10.5826/dpc.1601a6235

Accepted: August 21, 2025; **Published:** January 2026

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Autosomal recessive congenital ichthyosis (ARCI) comprises a group of rare keratinization disorders characterized by generalized scaling and variable erythroderma [1]. Mutations in *ALOXE3*, which encodes a lipoxygenase involved in skin barrier formation, have been associated with a spectrum of ARCI phenotypes, from mild scaling to lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE) [1,2]. Phenotypic overlap with other inflammatory dermatoses, particularly Netherton syndrome (NS), can lead to diagnostic delays. NS is classically associated with ichthyosis linearis circumflexa, trichorrhexis invaginata, and atopic diathesis, but incomplete forms may resemble ARCI [3].

Case Presentation

We report two brothers with novel compound heterozygous *ALOXE3* mutations. The elder sibling presented at birth with generalized xerosis, which progressed to serpiginous ichthyotic plaques, erythroderma, palmoplantar hyperkeratosis (Figure 1), and eosinophilia. His symptoms worsened after a SARS-CoV-2 infection and during dry seasons. Initially misdiagnosed with NS, he received dupilumab, secukinumab, and baricitinib over nine months without meaningful improvement. Topical anakinra led to transient lymphadenopathy. Systemic corticosteroids (prednisone 15 mg/day) later produced significant clinical relief, allowing tapering and maintenance on topical agents.

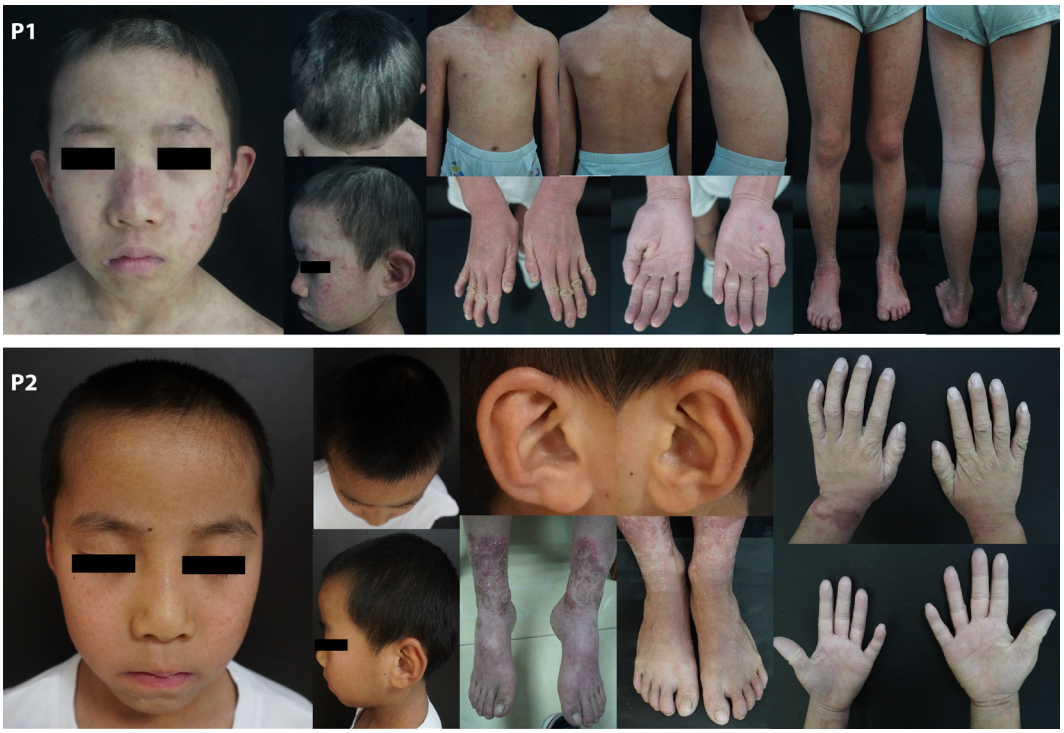

Figure 1. Clinical features of two brothers with autosomal recessive congenital ichthyosis (ARCI) carrying ALOXE3 mutations. P1: The elder brother presented with xerosis cutis, serpiginous ichthyosiform lesions on the trunk and limbs, erythroderma with ichthyosiform scaling on the hands and feet consistent with a CIE (congenital ichthyosiform erythroderma)-like phenotype, palmoplantar hyperkeratosis, and brachydactyly of the fifth fingers. P2: The younger brother showed milder serpiginous ichthyosiform lesions on the hands and feet, typical kinking of the auricles, brachydactyly, and palmoplantar findings.

In contrast, the younger sibling showed milder scaling limited to the hands and feet, auricular kinking (Figure 1), and normal growth. He was managed conservatively with emollients and topical corticosteroids. Genetic testing in both patients identified compound heterozygous *ALOXE3* nonsense variants (Figure 2), none previously reported. This confirmed diagnosis of ARCI and prompted discontinuation of inappropriate immunomodulators.

Conclusions

This familial case illustrates how ARCI may phenotypically mimic NS, especially when early-onset scaling and atopic features are present. Although the elder brother lacked trichorrhexis invaginata and had only mildly elevated IgE, clinical features led to an NS diagnosis and empirical biological therapy. Similar pitfalls are reported in the literature, underscoring the importance of genetic confirmation before initiating targeted treatment [3,4]. Truncating *ALOXE3* mutations are frequently linked to moderate-to-severe disease, yet significant intrafamilial variation exists [1,2,5]. Environmental triggers, including infection and allergen exposure, may modulate phenotype [6]. The four mutations identified here expand the mutational spectrum of *ALOXE3*. New diagnostic techniques, such as mRNA testing from hair roots, may offer less invasive tools for early molecular confirmation in pediatric patients [4].

This case highlights the diagnostic challenges posed by ARCI's phenotypic overlap with NS. Empirical use of biologics in the absence of molecular confirmation can delay effective care and increase costs. Early genetic testing is essential to avoid misdiagnosis, guide appropriate treatment, and inform family counseling.

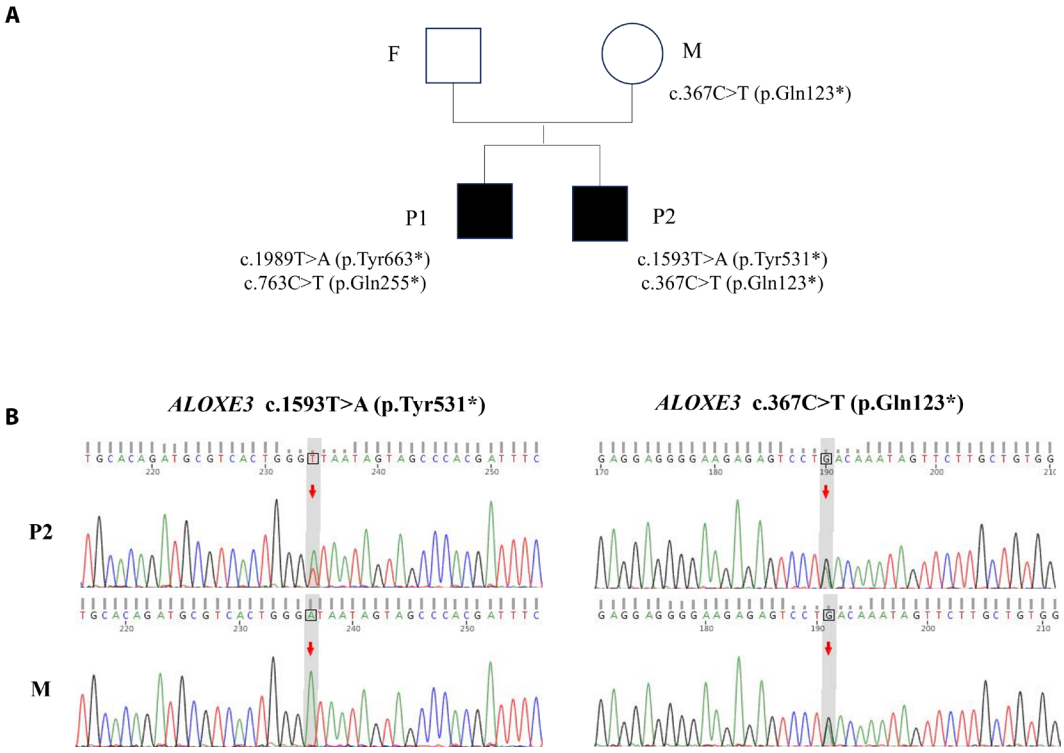

Figure 2. Genetic findings in the affected family. A) Pedigree of the family showing autosomal recessive inheritance of *ALOXE3* mutations. Both affected siblings (P1 and P2) are compound heterozygotes, while their mother is asymptomatic carriers. B) Sanger sequencing of the younger brother (P2) revealed two pathogenic variants in the *ALOXE3* gene: c.1593T>A (p.Tyr531*) and c.367C>T (p.Gln123*), confirming a compound heterozygous state.

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