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CASE REPORT

Atopic Dermatitis with Ichthyosis, Recurrent Fungal and Viral Infections: A Case of Concurrent *FLG* and Multiple Immune-Related Gene Mutations

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Abstract: Atopic dermatitis (AD) is frequently associated with epidermal barrier dysfunction and may be complicated by recurrent infections. We report a 31-year-old Han Chinese woman with lifelong ichthyosis vulgaris and severe AD, complicated by recurrent vaginal Nakaseomyces glabratus (*N. glabrata*) infection and herpes simplex virus type 1 (HSV-1) reactivation. Antifungal susceptibility testing demonstrated reduced susceptibility to multiple azole agents. Whole-exome sequencing identified a heterozygous *FLG* frameshift mutation (c.3321delA) together with heterozygous variants in *TNFRSF13B, MPO*, and *DOCK8*, all confirmed by Sanger sequencing. At follow-up, mucocutaneous infections improved, while cutaneous manifestations persisted under topical management. This case highlights the potential combined contribution of epidermal barrier defects and immune-related gene variants to complex atopic disease with recurrent infections.

Keywords: atopic dermatitis, ichthyosis, *FLG* mutation, DOCK 8 deficiency, recurrent infection, immunodeficiency

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by epidermal barrier dysfunction and immune dysregulation. Ichthyosis vulgaris, the most common inherited disorder of keratinization, frequently coexists with AD and is most often caused by loss-of-function mutations in the *FLG* gene. Filaggrin deficiency compromises barrier integrity and predisposes affected individuals to eczema and cutaneous infections. Certain *FLG* mutations are population specific. Notably, c.3321delA is the most common *FLG* mutation reported in Chinese patients with AD.

In some patients, AD with ichthyosis is further complicated by recurrent mucocutaneous infections, suggesting an additional contribution of immune dysfunction. Variants in immune-related genes have been implicated in increased susceptibility to fungal and viral infections, but their combined impact with epidermal barrier defects remains incompletely characterized.

We report a case of severe AD with ichthyosis vulgaris complicated by recurrent *Nakaseomyces glabrata* (*N. glabrata*) and herpes simplex virus type 1 (HSV-1) infections, in which whole-exome sequencing identified a pathogenic *FLG* frameshift mutation together with additional immune-related gene variants.

Case Presentation

A 31-year-old Han Chinese woman presented with a lifelong history of dry, scaly skin and recurrent eczematous dermatitis. She had been diagnosed with ichthyosis in infancy and developed clinical features of AD, including persistent pruritus and flexural eczema, during early childhood. Over the past 6 years, she experienced recurrent vaginal infections with *N. glabrata* and recurrent HSV-1 infections.

Initially, *N. glabrata* showed sensitivity to fluconazole and wild-type susceptibility to itraconazole, amphotericin B, and voriconazole, though flucytosine lacked interpretive breakpoints. However, after 9 months of antifungal therapy—

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including oral itraconazole for 3 months, oral fluconazole for 6 months, and topical application of nystatin suppositories and clotrimazole ointment—the clinical response was poor. Following the Clinical and Laboratory Standards Institute (CLSI) guidelines using the broth microdilution method, antifungal susceptibility testing subsequently demonstrated increased fluconazole minimum inhibitory concentration (MIC) to 32 μg/mL, an elevated epidemiological cutoff value (ECV) for itraconazole (> 4 μg/mL), amphotericin B (> 2 μg/mL), and non-wild-type status for voriconazole (MIC 0.5 μg/mL). Following a 3-month course of boric acid vaginal gel, vaginal microecological examination showed no detectable spores or hyphae. Nonetheless, intermittent recurrences of *N. glabrata* were observed, for which boric acid gel continued to provide effective control. She was referred to our hospital for additional treatment for AD.

Physical examination revealed generalized xerosis, ichthyotic scaling (Figure 1) —most prominently on the hands and feet — and eczematous lesions with excoriations. Isolated discoid eczematous plaques were noted on the pretibial areas

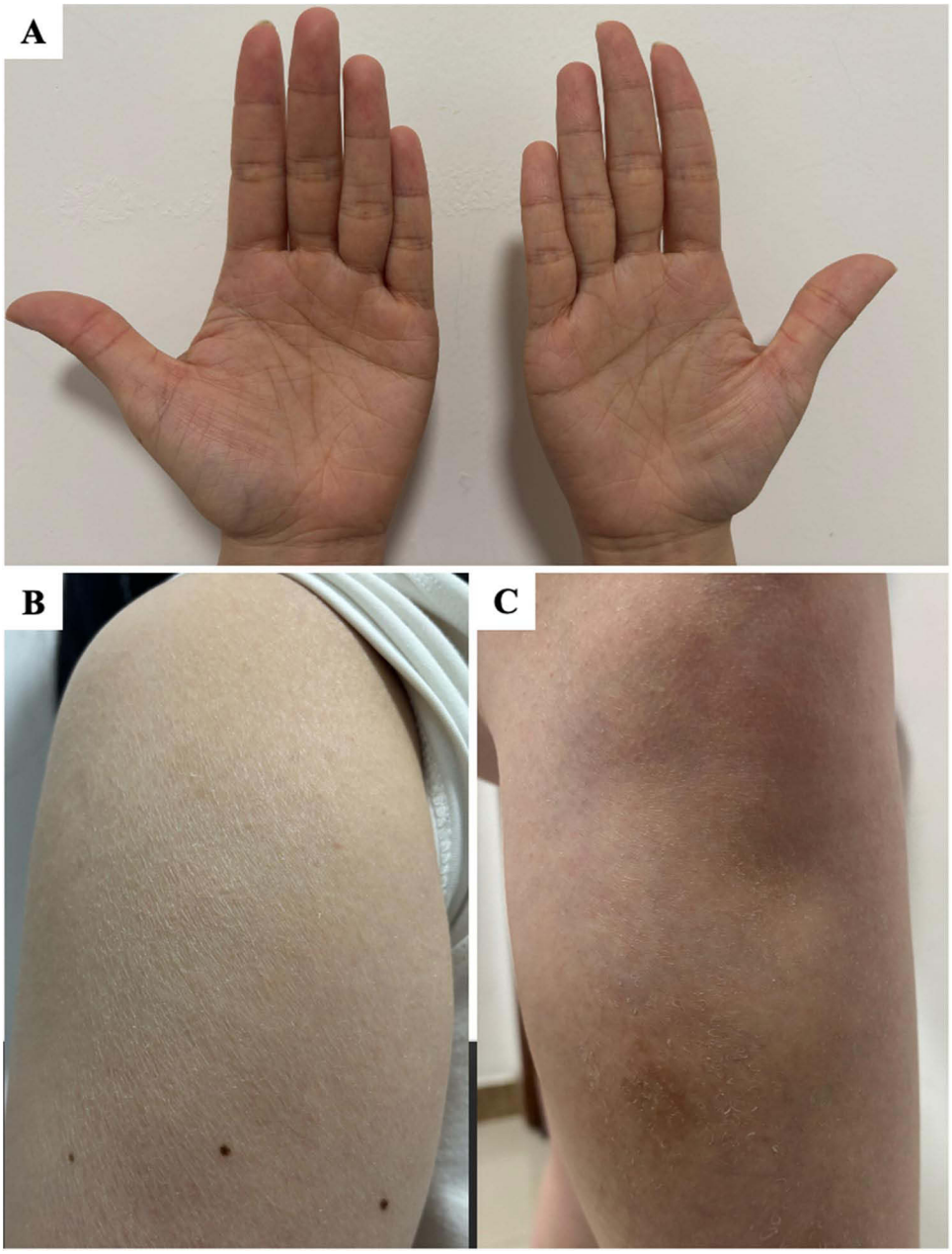

Figure 1 Clinical presentation of ichthyosis vulgaris in the patient. (**A**) Palmar view showing prominent hyperlinear palms, consistent with ichthyosis vulgaris. (**B**) Extensor aspect of the upper arm displaying fine scaling and xerosis. (**C**) Anterior aspect of the lower leg exhibiting diffuse scaling and dryness.

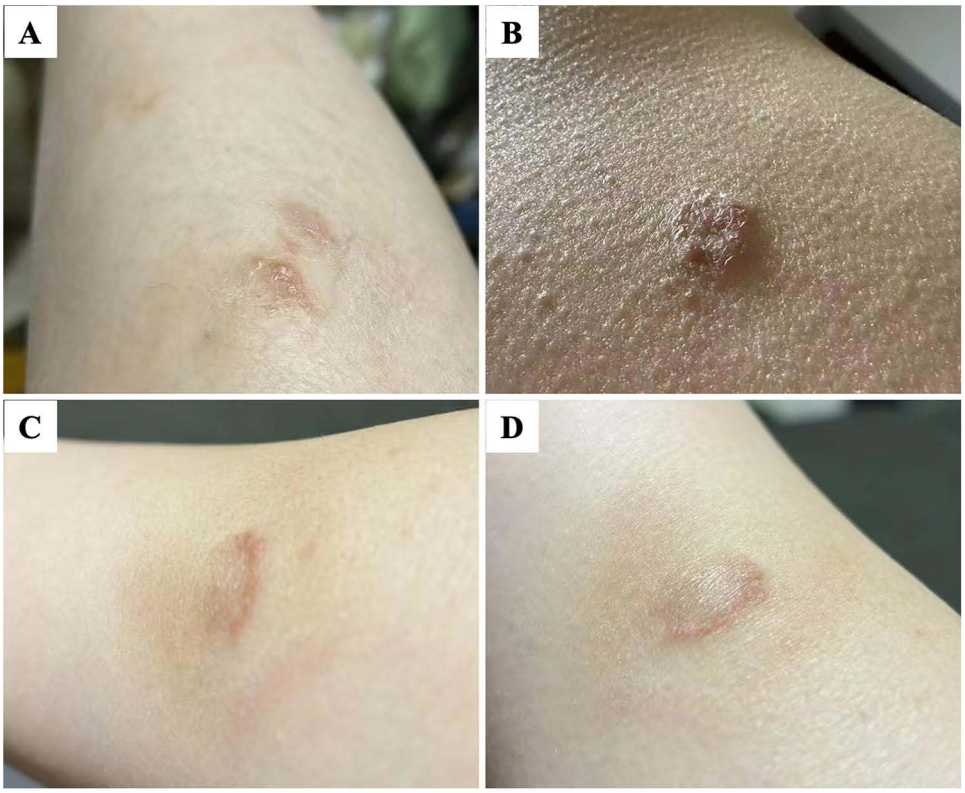

Figure 2 Clinical images of the patient's eczematous skin lesions. (**A**) Erythematous, scaly plaques with excoriations located on the pretibial area of the lower legs. (**B**) Discoid eczematous plaque with central clearing and peripheral scaling on the trunk. (**C** and **D**) Isolated discoid eczematous plaques with erythema and scaling observed on the upper arms.

of the lower legs and upper arms (Figure 2). The patient reported a history of allergic rhinitis and conjunctivitis but had no other underlying systemic diseases. Family history was notable for paternal diabetes mellitus. The patient's father has a history of ichthyosis vulgaris and atopic dermatitis but has not experienced recurrent infections. Her mother has no history of atopic disease, ichthyosis, or recurrent infections. Genetic testing was not performed in either parent, which limits segregation analysis of the identified variants.

Laboratory evaluations showed elevated serum IgE levels (283 IU/mL). However, eosinophil counts remained within normal limits. Flow cytometry analysis demonstrated normal counts and ratios of peripheral blood CD4+ and CD8+ T cells, and thyroid function tests were also within normal ranges. Vaginal swabs confirmed *N. glabrata* infection, and PCR assays detected HSV-1 DNA.

Given the severity of her disease, whole-exome sequencing was performed. The analysis identified the following pathogenic mutations (Table 1). The presence of these four mutations was validated by targeted PCR amplification and Sanger sequencing (Figure 3).

The combination of these genetic and clinical findings suggested a complex interplay between impaired barrier function and immune dysregulation.

At the most recent follow-up, conducted approximately six months prior to the submission of this manuscript, the patient exhibited persistent, scattered erythematous and scaly lesions. Typical ichthyotic changes remained evident on the lower extremities and both hands. Notably, mucocutaneous infections had improved, with no active episodes of candidiasis or herpes simplex virus infection at that time.

The patient's current management consists of regular use of emollients and intermittent application of topical crisaborole as needed for eczematous flares. For infection surveillance, periodic vaginal microbiome assessments are performed, with no recent detection of fungal overgrowth.

Table 1 Summary of Genetic Variants Identified in the Patient

Category	*FLG*	*TNFRSF13B*	*MPO*	*DOCK8*
Nucleotide Change Protein Change	c.3321del p.G1109Efs*13	c.226G>A p.G76S	c.1805G>A p.W602*	c.5223+4A>G — (Intronic variant)
Variant Type	DEL Heterozygous frameshift mutation (rs200519781)	SNV Heterozygous missense mutation (rs146436713)	SNV Heterozygous nonsense mutation (rs555739612)	SNV Heterozygous intronic variant, potential splicing effect (rs117109271)
Functional Insight	Barrier dysfunction, associated with ichthyosis vulgaris and atopic dermatitis[1]	May impair B cell maturation,[2] related to CVID[3]	Reduced neutrophil antimicrobial function[4]	Potential splicing defect, immune dysregulation in HIES context[5]

Note: *Indicates a nonsense mutation, resulting in a premature stop codon and truncated protein.
Abbreviations: DEL, deletion; SNV, single nucleotide variant; CVID, common variable immunodeficiency; HIES, hyper-IgE syndrome.

Discussion

This case illustrates the intricate relationship between genetic mutations impairing both skin barrier function and immune regulation, resulting in severe AD, ichthyosis, and recurrent mucocutaneous infections.

FLG mutations tend to be population specific. S2554X and 3321delA mutations were prevalent mutations in Asians, including Japanese and Chinese ichthyosis vulgaris patients. In China, c.3321delA is reported as the most common *FLG* mutation among AD patients.[1] The *FLG* c.3321del (p.G1109Efs*13) frameshift mutation identified in this patient leads to a truncated filaggrin protein, significantly compromising epidermal barrier integrity, resulting in the development of AD and ichthyosis vulgaris.[2] Beyond the skin, *FLG* is also expressed in mucosal tissues including the oral cavity, esophagus, vagina, and cervix. Studies have shown that *FLG* mutations not only increase susceptibility to skin infections, but are

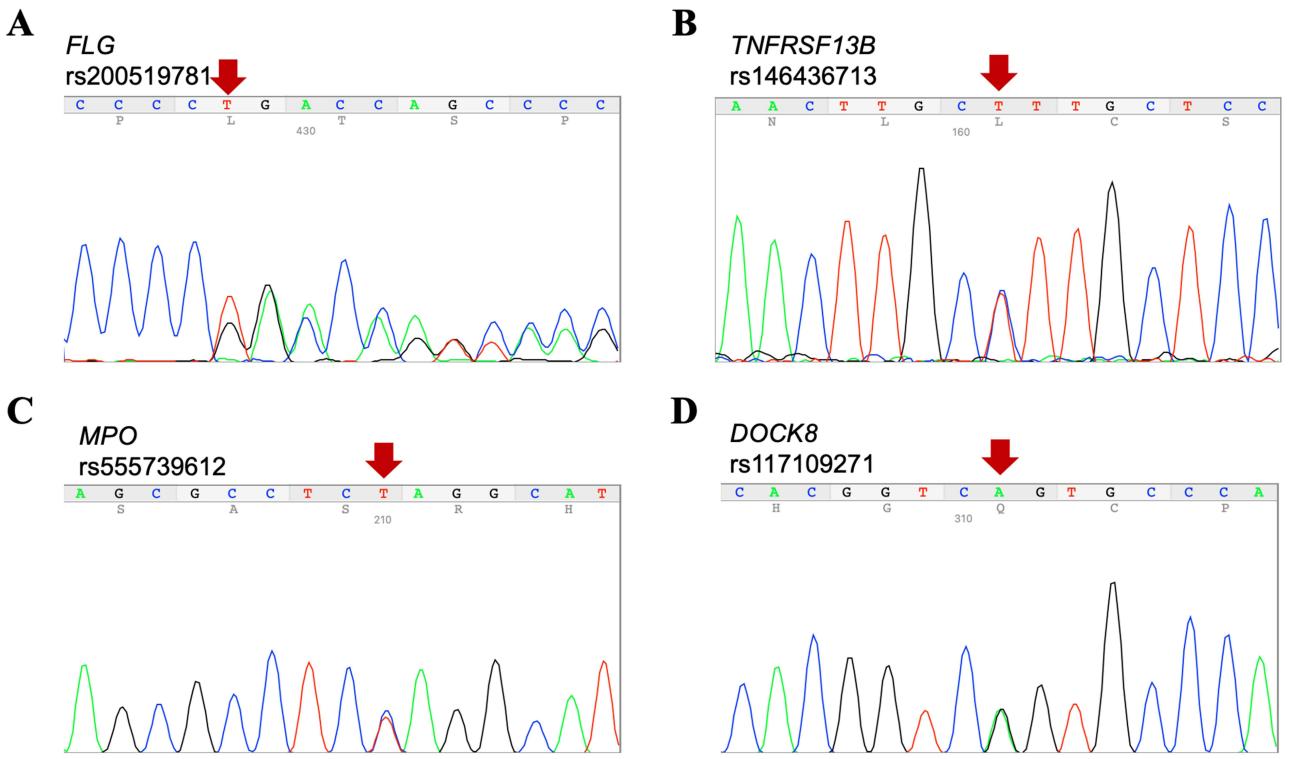

Figure 3 Sanger sequencing confirming four heterozygous mutations. (**A**) *FLG* c.3321delA (p.G1109Efs13). (**B**) *TNFRSF13B* c.226G>A (p.G76S). (**C**) *MPO* c.1805G>A (p.W602). (**D**) *DOCK8* c.5223+4A>G.

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also associated with a heightened risk of Human papillomavirus (HPV) infection and HPV-related malignancies. An analysis of 13,376 individuals revealed that carriers of *FLG* mutations had a significantly higher risk of HPV infection compared to wild-type individuals, with a hazard ratio of 2.1 (95% confidence interval: 1.2–3.7).[3] This suggests that the *FLG* mutation in this patient may be associated with her recurrent vaginal fungal infections and labial viral infections.

The multiple immune deficiency-related mutations of this patient may also contribute to her recurrent infections. The patient harbored a *TNFRSF13B* (c.226G>A, p.G76S) mutation, a gene encoding TACI, essential for B-cell maturation and immunoglobulin class switching.[4] *TNFRSF13B* variants have been implicated in Common Variable Immunodeficiency (CVID) and other immune-mediated pathologies.[5] Functional studies have demonstrated that such mutations can impair humoral immunity and exacerbate susceptibility to recurrent infections, including fungal pathogens.[6]

The *MPO* gene mutation (c.1805G>A, p.W602*) further complicates the immune landscape. *MPO* deficiency is linked to impaired neutrophil antimicrobial function, increasing vulnerability to fungal infections despite normal neutrophil counts.[7] Our patient's recurrent candidiasis could, in part, be attributed to this defect.

Additionally, the *DOCK8* (c.5223+4A>G) intronic variant, predicted to impact splicing, is noteworthy. *DOCK8* plays a pivotal role in immune synapse formation and lymphocyte function.[8] *DOCK8* deficiency typically manifests as autosomal recessive hyper-IgE syndrome (HIES) with severe viral and fungal infections.[9] Although our patient harbors a heterozygous mutation, it may contribute to her immunological phenotype, especially in the context of other genetic defects.

From a therapeutic perspective, this case raises important considerations about balancing anti-inflammatory treatment for AD with potential infection risks, particularly in patients with compromised immune function. While systemic immunosuppressants carry the risk of exacerbating infections, targeted biologic therapies, such as dupilumab, present a promising alternative. Recent case series have demonstrated that dupilumab not only improves severe AD but may also facilitate the resolution of secondary infections, including molluscum contagiosum.[10] Although concerns exist regarding the potential impact of Th2 pathway blockade on infection susceptibility, accumulating evidence supports the safety and efficacy of dupilumab in patients with complex immunological profiles, including those with HIES-like phenotypes.

Several limitations of this case should be acknowledged. First, the identified genetic variants were heterozygous, and although some have been previously associated with atopic dermatitis or skin barrier dysfunction, their individual pathogenic contributions remain uncertain. Second, as a single case report, the findings cannot be generalized to broader patient populations. Finally, long-term follow-up data were unavailable, limiting assessment of disease progression and long-term treatment outcomes. Future studies with larger cohorts and functional validation are needed to better clarify genotype–phenotype correlations in similar patients.

In summary, comprehensive genetic analysis in this patient has elucidated a multifactorial basis for her severe cutaneous and infectious manifestations. The convergence of barrier dysfunction and immune dysregulation underscores the need for precision medicine approaches. Personalized therapeutic strategies, incorporating targeted biologics like dupilumab and close monitoring, hold promise for improving outcomes in such complex cases.

Abbreviations

AD, atopic dermatitis; *FLG*, filaggrin; HSV-1, herpes simplex virus type 1; CVID, common variable immunodeficiency; *N. glabrata, Nakaseomyces glabratus*; HPV, Human papillomavirus.

Ethics Statement

The publications of images were included in the patient's consent for publication of the case. The Hospital Ethics Committees of the Peking University Third Hospital approved to publish the case details.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Acknowledgments

We thank the patient for providing consent to publish this case report.

Disclosure

The authors declare no conflicts of interest in this work.

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