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CASE REPORT

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STAT1 gain-of-function and chronic demodicosis

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Abstract

Heterozygous *STAT1* gain-of-function (GOF) mutations result in a combined form of immunodeficiency which is the most common genetic cause of chronic mucocutaneous candidiasis (CMC). We present a pedigree with a GOF mutation in *STAT1*, manifesting with chronic demodicosis in the form of a facial papulopustular eruption, blepharitis, and chalazion. So far, demodicosis has been described in only one family with *STAT1*-GOF mutation. We suggest that chronic demodicosis is an under-recognized feature of the immune dysregulation disorder caused by *STAT1* gain-of-function mutations.

KEYWORDS
blepharitis, demodicosis, gain-of-function mutation, papulopustular rosacea, *STAT1*

1 | INTRODUCTION

Heterozygous *STAT1* gain-of-function (GOF) mutations result in combined immunodeficiency which is the most common genetic cause of chronic mucocutaneous candidiasis (CMC).[1,2] These mutations affect the coiled-coil domain or DNA-binding domain of *STAT1* and increase STAT1 phosphorylation resulting in activation of STAT1-dependent cytokines: interferon α/β/γ, interleukin (IL)-27, and STAT3-dependent IL-6 and IL-21.[3,4] Affected patients show a defective Th17 response with lower production of IL-17 and IL-22, crucial cytokines for host defense against Candida infection.[5] In addition, patients suffer from a variety of clinical features, including recurrent bacterial infections affecting respiratory tract and skin, mostly due to *Staphylococcus aureus*, cutaneous viral infections, invasive fungal infections, mycobacterial disease, autoimmune manifestations, cerebral aneurysms, and cancers.[2] Papulopustular rosacea due to *Demodex folliculorum* has been described as a possible additional clinical feature of *STAT1*-GOF mutations in only a single family.[6] We present a family with four affected individuals, carrying a heterozygous *STAT1*-GOF mutation, manifesting a rosacea-like demodicosis, thus highlighting demodicosis as an additional cutaneous finding in *STAT1*-GOF disorder.

2 | PATIENTS AND RESULTS

A 14-year-old girl (Patient II-1, Figure 1A) and her 12-year-old sister (Patient II-2, Figure 1A) presented with a similar facial rash, which appeared at age 5 and 6 years, respectively. Patient II-1 had been suffering from oral candidiasis since birth, and esophageal candidiasis was diagnosed at age 10 years. She was treated with doxycycline, and later with isotretinoin, for the facial rash, without improvement. Physical examination revealed numerous erythematous papules and pustules over her face (Figure 1B,C) and a dystrophic first left fingernail (Figure 1D). Smear for fungi from the fingernail was positive for hyphae. A smear taken from facial skin showed 17 *Demodex* mites. A skin biopsy from the facial rash revealed acute superficial and deep folliculitis, with acute and chronic perifollicular infiltrates, with the presence of *Demodex*.

Patient II-2 suffered from chronic blepharitis, recurrent chalazion, and aphthous stomatitis. Her physical examination was remarkable for a similar, but milder, facial eruption as her sister (Figure 1E). In addition, the patient had scaly erythema of the eyelids and erythematous scaly patches over the neck, consistent with eczema (Figure 1F). Facial smear was positive for *Demodex*.

Both sisters were treated with ivermectin 1% cream for their facial rash for 12 weeks with marked improvement. A repeat smear for *Demodex* was negative.

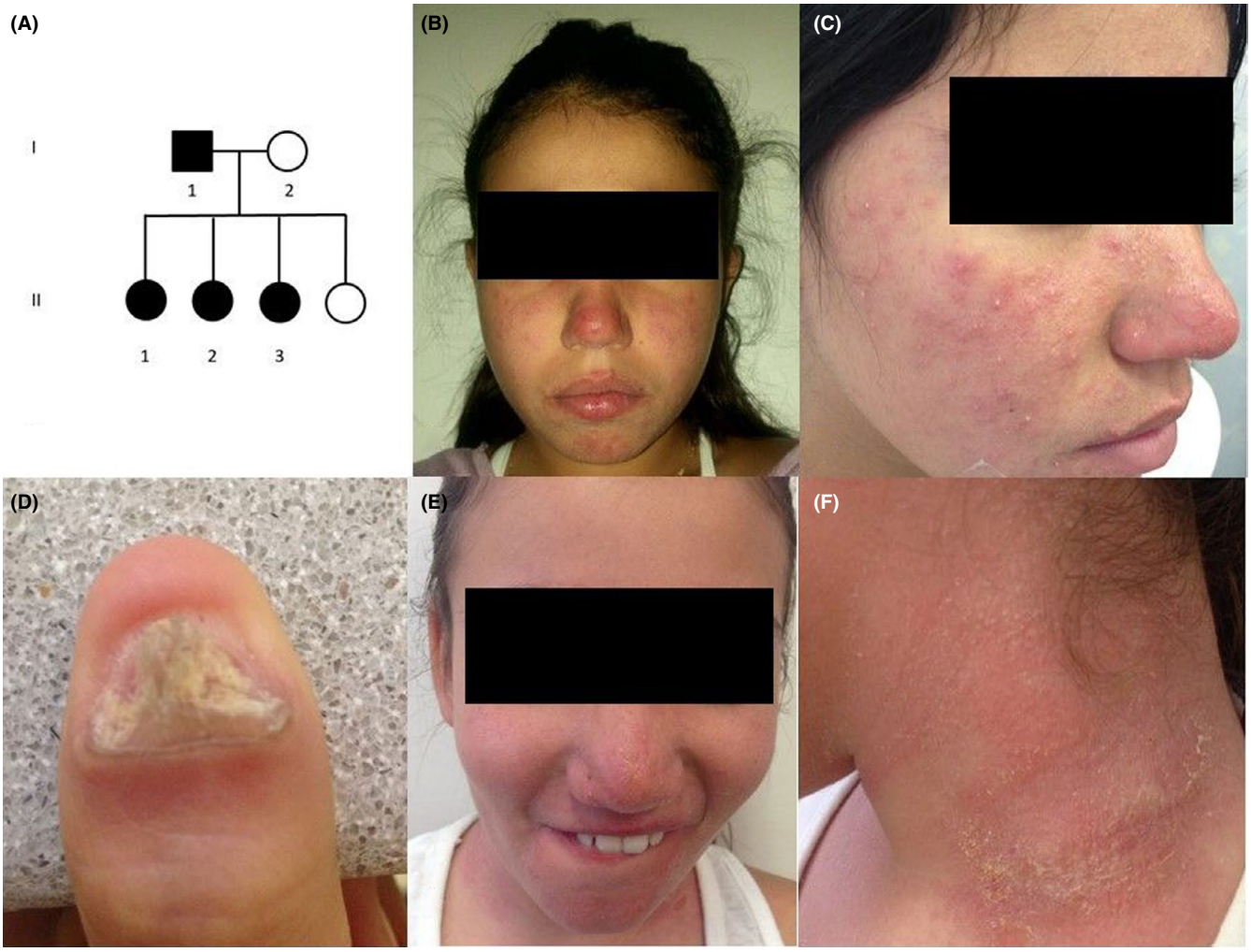

FIGURE 1 Pedigree and clinical features of affected members with *STAT1* gain-of-function mutation. A, Pedigree, affected individuals are marked black. B, C, Facial erythematous papulopustular eruption, more pronounced on the convex surfaces of the face in patient II-1. D, Dystrophic first left fingernail in patient II-1. E, Mild nasal erythematous papulopustular eruption in patient II-2. F, A scaly eczematous erythematous plaque over the neck of patient II-2

Their father (Patient I-1, Figure 1A), a 44-year-old male, suffered from diffuse tinea corporis and onychomycosis. At age 22, he was treated for active pulmonary tuberculosis. He had had recurrent episodes of oral and esophageal candidiasis and aphthous stomatitis since childhood, as well as chronic blepharitis and chalazia. He had been treated with various topical agents, doxycycline and underwent several surgical procedures for chalazia. Ophthalmological examination revealed scales over the eyelashes, shedding of eyelashes, and trichiasis with demonstration of *Demodex* by slit-lamp examination.

Patient II-3 (Figure 1A), a 5-year-old girl, the third daughter of patient I-1, also suffered from recurrent oral candidiasis, blepharitis, and chalazion.

Exome sequencing of DNA extracted from peripheral blood of patient I-1 revealed a heterozygous missense mutation in *STAT1* (c.821G > A, R274Q). The mutation, located in the coiled-coil domain of STAT1 (Figure 2), was previously reported to result in GOF of STAT1.[3] Sanger sequencing confirmed the presence of the mutation

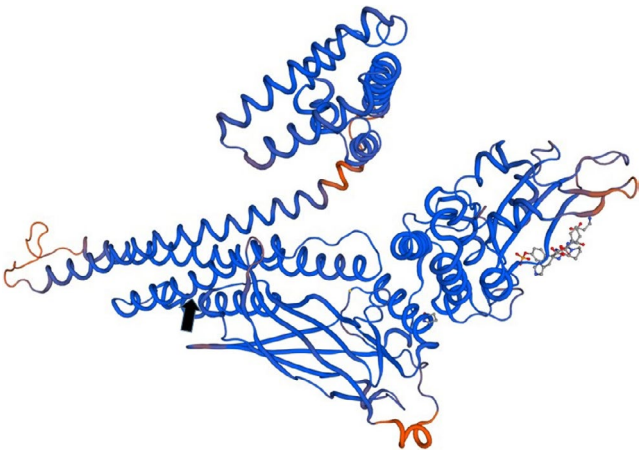

FIGURE 2 A structural model of chain A of STAT1 protein, showing the location of the substituted amino acid. A structural model of chain A of STAT1 protein was prepared using https://swissmodel.expasy.org. Arginine at position 274 of STAT1 is marked by an arrow. The mutation, R274Q, is located in the coiled-coil domain of STAT1

in a heterozygous state in patients I-1, II-1, II-2, and II-3 and was not present in the mother (I-2, Figure 1A).

3 | DISCUSSION

Demodex is a spindle-shaped mite which is normally present in the pilosebaceous follicles of adults, and its presence usually has no consequences.[7-9] In healthy children, *Demodex* is rarely found, probably due to the lower sebum production.[10]

Demodicosis is classified into primary and secondary forms. Primary demodicosis occurs in healthy adults and has several presentations: (a) spinulate demodicosis, involving pilosebaceous follicles without visible inflammation; (b) papulopustular demodicosis with marked inflammation affecting perioral and periorbital areas of the face; (c) ocular demodicosis, manifesting as chronic blepharitis, chalazia or keratoconjunctivitis; and (d) auricular demodicosis, characterized by external otitis or myringitis. The papulopustular variant of rosacea is believed to be a form of demodicosis, and its response to topical ivermectin supports this notion.[11] Secondary demodicosis is associated with systemic or local immunosuppression.[8] Cases of secondary demodicosis in children have been reported in severely immunocompromised conditions.[10] Topical calcineurin inhibitors[12] and corticosteroids[13] have also been associated with secondary demodicosis.

The pathogenesis of demodicosis is only partially understood. An immune defect against *Demodex* is believed to enable proliferation of the mite, which penetrates the dermis and activates Toll-like receptor 2 (TLR2), leading to inflammation.[9,14]

Demodicosis has been described previously in only one family with *STAT1*-GOF mutation.[6] A clinical review of 274 patients with *STAT1*-GOF mutations described various dermatological findings, including CMC, dermatophytosis, molluscum contagiosum, warts, herpes zoster, and herpes simplex, cutaneous bacterial infections and eczema. Facial demodicosis was not reported in this extensive clinical review. However, blepharitis and recurrent conjunctivitis/keratitis were noted in 15 and 39 patients, respectively, without mention of its etiology. *Demodex* is believed to be an important etiological factor in the pathogenesis of recurrent blepharitis and chalazion,[15] and therefore, it is likely that *Demodex* is the cause for the increased tendency to develop these ocular complications. In the family presented here patients suffered from both facial demodicosis and recurrent blepharitis and chalazion, suggesting that indeed demodicosis is the cause for the ophthalmological findings.

The exact mechanism causing demodicosis in patients with *STAT1*-GOF mutations is unknown. We hypothesize that the immunodeficiency state related to *STAT1*-GOF enables *Demodex* mites to proliferate and activate TLR2, resulting in the inflammatory lesions affecting facial skin and eyelids.

We believe demodicosis, manifesting as a facial papulopustular eruption, blepharitis, and chalazion, is an unrecognized feature of the immune dysregulation disorder caused by *STAT1*-GOF mutations.

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