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# **Chronic mucocutaneous candidiasis due to signal transducer and activator of transcription 1 mutation in a Saudi patient: a case report**

Abdullah Alakeel, Khalid Nabil Nagshabandi, Abdulaziz Alsalhi

Department of Dermatology, College of Medicine, King Saud University and King Saud University Medical City, Riyadh, Saudi Arabia

**Correspondence:** Khalid Nabil Nagshabandi, Department of Dermatology, College of Medicine, King Saud University and King Saud University Medical City, Riyadh, Saudi Arabia.

E-mail: khaloed23@gmail.com

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## Abstract

Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency condition caused by a genetic abnormality that increases the risk of recurrent and persistent skin, nail and mucous membrane infections with *Candida* species, typically *Candida albicans*. Signal transducer and activator of transcription 1 (*STAT 1*) gene mutation is a genetic trigger that causes CMC, which increases the risk of infections, multisystem disorders and cancer susceptibility. We describe the first case of a Saudi female patient with clinical features of CMC with an underlying (*STAT 1*) gene mutation.

## Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare primary immunodeficiency condition caused by a genetic abnormality that increases the risk of recurrent and persistent skin, nail and mucous membrane infections with *Candida* species, mainly *Candida albicans*.<sup>1</sup> In patients with T-cell deficiencies, CMC is associated with multiple infections and autoimmune diseases.<sup>2</sup> Among those suffering from autosomal dominant (AD) hyper-immunoglobulin E (IgE) syndrome (AD-HIES), CMC is one of the most prevalent infections.<sup>3</sup> Heterozygous Signal transducer and activator of transcription 1 (*STAT1*) mutations were identified as a cause of CMC in 2011.<sup>4</sup> Since then, about half of CMC patients have been linked to *STAT1 gain-of-function (GOF)* mutations caused by defective *STAT1* dephosphorylation.<sup>5</sup> Autosomal dominant (*STAT 1*) gene mutation is considered the most prevalent genetic cause of CMC.<sup>6</sup> It raises the risk of cutaneous fungal candidiasis, invasive bacterial, viral, and mycobacterial infections, autoimmune diseases, respiratory and gastrointestinal problems. Additionally, these patients have a higher lifetime chance of acquiring oral, esophageal and brain squamous cell carcinomas, as well as potentially fatal cerebral and extracerebral aneurysms.<sup>1</sup> It has been demonstrated in recent years that CMC is caused by a number of abnormalities that compromise interleukin-17-mediated immunity.<sup>7</sup> Up to this date, nearly 105 *STAT 1 GOF* mutations have been found in over 400 patients globally, with 65 of them being recurrent.<sup>8</sup>

To the best of our knowledge, *STAT 1 GOF* induced CMC has not been reported previously in the literature on a patient in Saudi Arabia. Herein, we report a case of an eight-year-old Saudi female patient with clinical features of CMC with an underlying (*STAT 1 GOF*) gene mutation and *31C deficiency*.

## Case Report

An 8-year-old Saudi female, documented case of hypothyroidism receiving a daily dose of levothyroxine at 62.5 mg, presented to the dermatology outpatient clinic with exacerbation of lesions affecting the fingers, palms, nails, and right toe. The onset of these lesions occurred at the age of

three, progressively worsening over the intervening years. The patient has a history of persistent mucocutaneous fungal infections, notably recurrent oral thrush unresponsive to topical antifungal treatments since 18 months of age. A comprehensive review of her medical history yielded no evidence of recurrent respiratory infections, cough, dysphagia, weight loss, chronic diarrhea, or skin abscess. There is no known family history of autoimmune disorders or similar conditions. Upon cutaneous examination, pronounced thickening and hyperkeratotic plaques with a yellowish configuration over an erythematous background were observed on the thumb and index fingers of both hands, extending to a portion of the right palm. This presentation was further accompanied by fingernail dystrophy, subungual hyperkeratosis, and yellowish distortion on the nails of both thumbs and index fingers (Figure 1), as well as the right toenail (Figure 2). Additionally, the patient exhibited an active oral thrush (Figure 3). Fungal culture and histopathological examination of samples obtained from the hard palate confirmed the presence of *Candida albicans*. Nail clip scrapings demonstrated fungal hyphae, with positive staining for fungal pseudohyphae with periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS), consistent with onychomycosis. Considering the clinical manifestations, a diagnosis of Chronic Mucocutaneous Candidiasis (CMC) syndrome was favored. Subsequent referral to medical genetics for Whole Exome Sequencing (WES) identified an autosomal dominant *STAT 1 gene gain-of-function defect (STAT 1 GOF mutation)* associated with a 31C immunodeficiency — a variant not previously reported in a CMC patient in Saudi Arabia. Treatment involved a combination of oral systemic itraconazole and topical miconazole, resulting in a substantial clinical remission of the fungal infection (Figure 4).

## Discussion

The diagnosis of chronic mucocutaneous candidiasis (CMC) was made in our patient based on the clinical features of recurrent and persistent oral candida thrush, cutaneous fungal infections and hypothyroidism. Genes such as *STAT 1*, *STAT 3*, *IL-17 F*, *AIRE*, *IL-17RA*, *TRAF3IP2*, *Dectin*, *CARD 9*, *IL-12 Rβ1*, *ROR ηT*, and *TYK2* have been linked to genetic variants that increase the risk of developing CMC.<sup>8,9</sup> Nearly 50% of CMC patients have been shown to have a *STAT 1* mutation, which is followed by an *AIRE* deficit. Though the prevalence of genetic mutation in different ethnicities is variable.<sup>5</sup>

Autosomal dominant *STAT 1* mutations can be sporadic or familial. It predominantly manifests as mucocutaneous candidiasis typically as a result of the organism *Candida albicans*.<sup>11</sup> Our patient had mucosal *C. albicans* infection and associated onychomycosis. According to Toubiana et al. and Van FL et al, a high proportion of patients with *STAT 1 GOF* mutations also have autoimmune disorders.<sup>1</sup> Hypothyroidism, type 1 diabetes mellitus, systemic lupus erythematosus illness, vasculitis and skin

disorders such as vitiligo and psoriasis being the most commonly reported autoimmune conditions.<sup>1,4</sup> Which explains the coexistence of chronic hypothyroidism and CMC in our patient.

There have been reported a variety of *STAT 1 GOF* mutations that result in increased production of IFN-gamma, IFN-alpha/beta, and IL-27, which in turn causes an inadequate Th-17 response. These mutations are caused by poor nuclear dephosphorylation which are confirmed by functional immunological assay.<sup>1,12</sup> Our case, based on the whole exome genetic testing, identified a *STAT 1 GOF* mutation with heterozygous substitution of c.1154C>T (p.Thr385Met) as DNA variant type. Following the American College of Medical Genetics and Genomics (ACMG) guidelines, the detected variant was classified as *pathogenic* based on the collected evidence. Backed by functional studies the variant is associated with autoimmune enteropathy and endocrinopathy, susceptibility to chronic infections syndrome, chronic diarrheal disease, combined immunodeficiency and immunodeficiency 31B.<sup>13,14</sup> Vasilev T et al. reported a case of autoimmune monogenic diabetes, multiple endocrinopathies and other autoimmune phenomena in combination with immune deficiency, cystic fibrosis-like lung disease and APECED-like syndrome due to *STAT1 GOF* gene mutation with pathogenic variant of c.1154C>T, p.(Thr385Met).<sup>15</sup> This complex clinical presentation observed in patients with *STAT1* mutation underscores the comprehensive involvement of this gene in autoimmune, hematopoietic, gastrointestinal, and pulmonary systems.

P.(Thr385Met) DNA variant type has been reported previously in cases of CMC induced *STAT 1 GOF* mutation, one of which had early esophageal candidiasis that resulted in stricture formations and recurrent HSV infection.<sup>16,17</sup> Fortunately, our patient has not progressed to internal organ compromise.

This case underscores the significance of genetic investigations in elucidating the underlying immunodeficiency contributing to chronic mucocutaneous fungal infections, thereby informing targeted therapeutic interventions. Since there was no family history of overt CMC, it was likely a sporadic event of disease in our patient. Currently, the management of CMC is predominantly symptomatic, commonly employing long-term combined systemic and topical antifungal medications as first-line treatment. Nevertheless, immunoglobulin (IG) infusion, JAK/STAT inhibitors, G-CSF and GM-CSF, hematopoietic stem cell transplantation and other therapy options are also available.<sup>6</sup>

## **Conclusions**

Chronic mucocutaneous candidiasis (CMC) is an uncommon primary immunodeficiency disorder triggered by multiple gene defects. *STAT1* gene mutations produce a wide range of clinical features, including potentially fatal consequences including cerebral aneurysm and tumor susceptibility. Early identification of the genetic subset using Whole Exome Sequencing (WES) will aid in early screening,

counseling, and treatment of CMC, as well as improving outcomes and minimizing long-term sequelae in such patients.

## References

1. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, Ouachée-Chardin M, Fouyssac F, Girisha KM, Etzioni A, Van Montfrans J, Camcioglu Y, Kerns LA, Belohradsky B, Blanche S, Bousfiha A, Rodriguez-Gallego C, Meyts I, Kisand K, Reichenbach J, Renner ED, Rosenzweig S, Grimbacher B, van de Veerdonk FL, Traidl-Hoffmann C, Picard C, Marodi L, Morio T, Kobayashi M, Lilic D, Milner JD, Holland S, Casanova JL, Puel A; International STAT1 Gain-of-Function Study Group. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. *Blood*. 2016 Jun 23;127(25):3154-64. doi: 10.1182/blood-2015-11-679902. Epub 2016 Apr 25. PMID: 27114460; PMCID: PMC4920021.
2. Puel A, Cypowyj S, Maródi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol*. 2012 Dec;12(6):616-22. doi: 10.1097/ACI.0b013e328358cc0b. PMID: 23026768; PMCID: PMC3538358.
3. Chandesris MO, Melki I, Natividad A, Puel A, Fieschi C, Yun L, Thumerelle C, Oksenhendler E, Boutboul D, Thomas C, Hoarau C, Lebranchu Y, Stephan JL, Cazorla C, Aladjidi N, Micheau M, Tron F, Baruchel A, Barlogis V, Palenzuela G, Mathey C, Dominique S, Body G, Munzer M, Fouyssac F, Jaussaud R, Bader-Meunier B, Mahlaoui N, Blanche S, Debré M, Le Bourgeois M, Gandemer V, Lambert N, Grandin V, Ndaga S, Jacques C, Harre C, Forveille M, Alyanakian MA, Durandy A, Bodemer C, Suarez F, Hermine O, Lortholary O, Casanova JL, Fischer A, Picard C. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine (Baltimore)*. 2012 Jul;91(4):e1-e19. doi: 10.1097/MD.0b013e31825f95b9. PMID: 22751495; PMCID: PMC3680355.
4. van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CA, Kullberg BJ, van der Meer JW, Lilic D, Veltman JA, Netea MG. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011 Jul 7;365(1):54-61. doi: 10.1056/NEJMoa1100102. Epub 2011 Jun 29. PMID: 21714643.
5. Depner M, Fuchs S, Raabe J, Frede N, Glocker C, Doffinger R, Gkrania-Klotsas E, Kumararatne D, Atkinson TP, Schroeder HW Jr, Niehues T, Dücker G, Stray-Pedersen A,

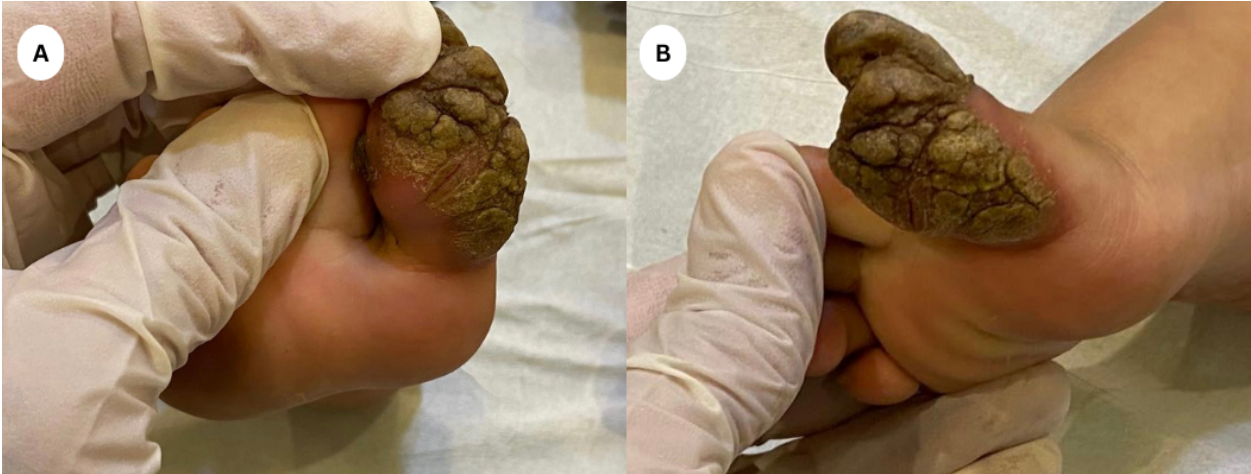
- Baumann U, Schmidt R, Franco JL, Orrego J, Ben-Shoshan M, McCusker C, Jacob CM, Carneiro-Sampaio M, Devlin LA, Edgar JD, Henderson P, Russell RK, Skytte AB, Seneviratne SL, Wanders J, Stauss H, Meyts I, Moens L, Jesenak M, Kobbe R, Borte S, Borte M, Wright DA, Hagin D, Torgerson TR, Grimbacher B. The Extended Clinical Phenotype of 26 Patients with Chronic Mucocutaneous Candidiasis due to Gain-of-Function Mutations in STAT1. *J Clin Immunol*. 2016 Jan;36(1):73-84. doi: 10.1007/s10875-015-0214-9. Epub 2015 Nov 25. PMID: 26604104; PMCID: PMC4718942.
6. Carey B, Lambourne J, Porter S, Hodgson T. Chronic mucocutaneous candidiasis due to gain-of-function mutation in STAT1. *Oral Dis*. 2019 Apr;25(3):684-692. doi: 10.1111/odi.12881. Epub 2018 Jun 8. PMID: 29702748.
  7. Boisson-Dupuis S, Kong XF, Okada S, Cypowyj S, Puel A, Abel L, Casanova JL. Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. *Curr Opin Immunol*. 2012 Aug;24(4):364-78. doi: 10.1016/j.coi.2012.04.011. Epub 2012 May 30. PMID: 22651901; PMCID: PMC3477860.
  8. Okada S, Asano T, Moriya K, Boisson-Dupuis S, Kobayashi M, Casanova JL, Puel A. Human STAT1 Gain-of-Function Heterozygous Mutations: Chronic Mucocutaneous Candidiasis and Type I Interferonopathy. *J Clin Immunol*. 2020 Nov;40(8):1065-1081. doi: 10.1007/s10875-020-00847-x. Epub 2020 Aug 27. PMID: 32852681; PMCID: PMC8561788.
  9. Humbert L, Cornu M, Proust-Lemoine E, Bayry J, Wemeau JL, Vantyghem MC, Sendid B. Chronic Mucocutaneous Candidiasis in Autoimmune Polyendocrine Syndrome Type 1. *Front Immunol*. 2018 Nov 19;9:2570. doi: 10.3389/fimmu.2018.02570. PMID: 30510552; PMCID: PMC6254185.
  10. Plantinga TS, Johnson MD, Scott WK, Joosten LA, van der Meer JW, Perfect JR, Kullberg BJ, Netea MG. Human genetic susceptibility to *Candida* infections. *Med Mycol*. 2012 Nov;50(8):785-94. doi: 10.3109/13693786.2012.690902. Epub 2012 Jun 4. PMID: 22662758; PMCID: PMC5826648.
  11. Milner JD, Holland SM. The cup runneth over: lessons from the ever-expanding pool of primary immunodeficiency diseases. *Nat Rev Immunol*. 2013 Sep;13(9):635-48. doi: 10.1038/nri3493. Epub 2013 Jul 26. PMID: 23887241.
  12. Depner M, Fuchs S, Raabe J, Frede N, Glocker C, Doffinger R, Gkrania-Klotsas E, Kumararatne D, Atkinson TP, Schroeder HW Jr, Niehues T, Dückers G, Stray-Pedersen A, Baumann U, Schmidt R, Franco JL, Orrego J, Ben-Shoshan M, McCusker C, Jacob CM, Carneiro-Sampaio M, Devlin LA, Edgar JD, Henderson P, Russell RK, Skytte AB, Seneviratne SL, Wanders J, Stauss H, Meyts I, Moens L, Jesenak M, Kobbe R, Borte S, Borte

- M, Wright DA, Hagin D, Torgerson TR, Grimbacher B. The Extended Clinical Phenotype of 26 Patients with Chronic Mucocutaneous Candidiasis due to Gain-of-Function Mutations in STAT1. *J Clin Immunol*. 2016 Jan;36(1):73-84. doi: 10.1007/s10875-015-0214-9. Epub 2015 Nov 25. PMID: 26604104; PMCID: PMC4718942.
13. <https://www.ncbi.nlm.nih.gov/clinvar/RCV000133515/>
  14. <https://www.ncbi.nlm.nih.gov/clinvar/RCV000698604/>
  15. <https://abstracts.eurospe.org/hrp/0094/hrp0094p2-109>
  16. Eren Akarcan S, Ulusoy Severcan E, Edeer Karaca N, Isik E, Aksu G, Migaud M, Evin Gurkan F, Azarsiz E, Puel A, Casanova JL, Kutukculer N. Gain-of-Function Mutations in *STAT1*: A Recently Defined Cause for Chronic Mucocutaneous Candidiasis Disease Mimicking Combined Immunodeficiencies. *Case Reports Immunol*. 2017;2017:2846928. doi: 10.1155/2017/2846928. Epub 2017 Nov 13. PMID: 29259832; PMCID: PMC5702932.
  17. Soltész B, Tóth B, Shabashova N, Bondarenko A, Okada S, Cypowyj S, Abhyankar A, Csorba G, Taskó S, Sarkadi AK, Méhes L, Rozsival P, Neumann D, Chernyshova L, Tulassay Z, Puel A, Casanova JL, Sediva A, Litzman J, Maródi L. New and recurrent gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis from Eastern and Central Europe. *J Med Genet*. 2013 Sep;50(9):567-78. doi: 10.1136/jmedgenet-2013-101570. Epub 2013 May 24. PMID: 23709754; PMCID: PMC3756505.





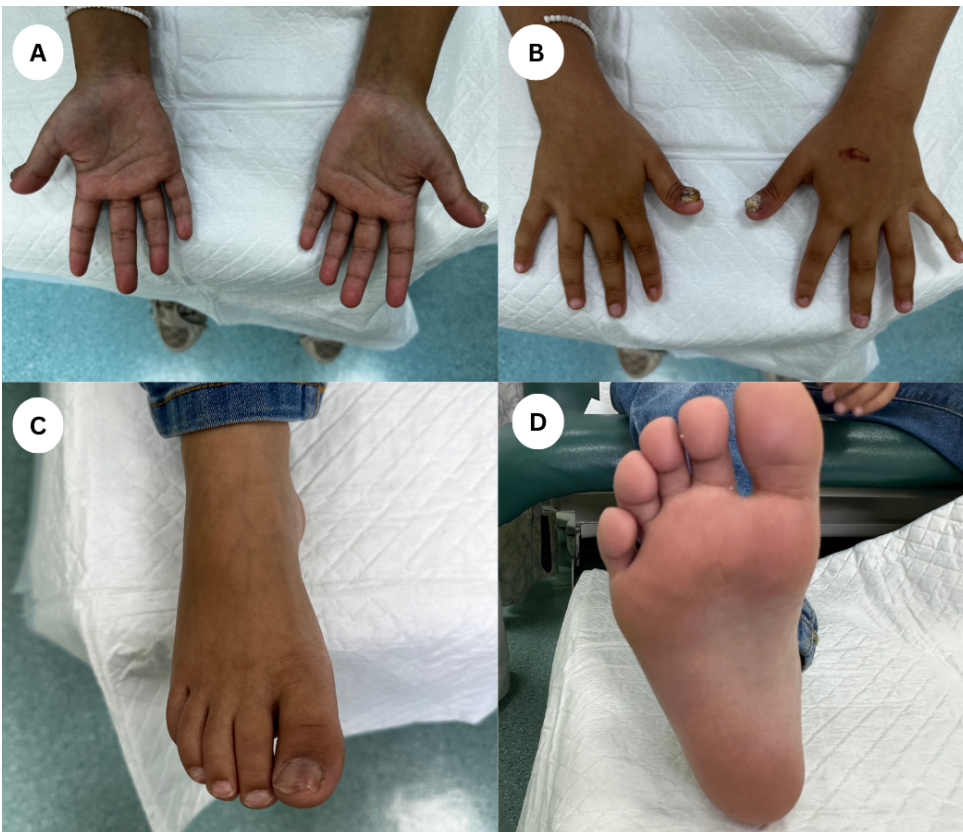
**Figure 1. (A, B) Severe thickening and plaques of hyperkeratosis with yellowish configuration over an erythematous background located over part of the right palm, index and middle finger, along with subungual hyperkeratosis and yellowish distortion of the nails of both thumbs and index fingers.**



**Figure 2. (A, B) Subungual hyperkeratosis and yellowish distortion of the right big toe.**



**Figure 3. Active oral thrush evident under wood's light with associated angular stomatitis.**



**Figure 4. (A, B, C, D) Marked improvement noticed after starting combined treatment with topical and systemic antifungal therapy with near-complete clinical remission.**