A GAIN-OF-FUNCTION MUTATION OF STAT1: A NOVEL GENETIC FACTOR CONTRIBUTING TO CHRONIC MUCOCUTANEOUS CANDIDIASIS

NARGES ESLAMI1,2, MARZIEH TAVAKOL3, MEHRNAZ MESDAGHI2, MOHAMMAD GHAREGOZLOU4, JEAN-LAURENT CASANOVA5,6,7,8,9, ANNE PUEL5,6,7, SATOSHI OKADA5,9, SABA ARSHI1, MOHAMMAD HASSAN BEMANIAN1, MORTEZA FALLAHPOUR1, RASOOL MOLATUREF1,10, FARHAD SEIF11, SAMANEH ZOGHI12,13,14, NIMA REZAEI12,13,15 and MOHAMMAD NABAVI1*

1Department of Allergy and Clinical Immunology, Rasool-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
2Department of Allergy and Clinical Immunology, Moﬁd Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3Department of Allergy and Clinical Immunology, Shahid Bahonar Hospital, Alborz University of Medical Sciences, Karaj, Iran
4Department of Allergy and Immunology, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
5St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA
6Laboratory of Human Genetics of Infectious Diseases, Necker Branch, French National Institute of Health and Medical Research (INSERM), Paris, France
7Imagine Institute, Paris Descartes University, Paris, France
8Pediatric Hematology-Immunology Unit, AP-HP, Necker Hospital for Sick Children, Paris, France
9Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan
10Department of Allergy and Clinical Immunology, Bu Ali Children’s Hospital, Ardabil University of Medical Sciences, Ardabil, Iran
11Department Immunology, School Medicine, Iran University of Medical Sciences, Tehran, Iran
12Research Center for Immunodeﬁciencies, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
13Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
14Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Vienna, Austria

*Corresponding author; E-mail: mnabavi44@yahoo.com
Heterozygous gain-of-function (GOF) mutations in the signal transducer and activator of transcription 1 (STAT1) have increasingly been identified as a genetic cause of autosomal-dominant (AD) chronic mucocutaneous candidiasis (CMC). In this article, we describe a 33-year-old man who experienced chronic refractory candidiasis, recurrent otitis media, and pneumonia resulting in bronchiectasis, severe oral and esophageal candidiasis with strictures associated with hypothyroidism and immune hemolytic anemia. His son also suffered from persistent candidiasis, chronic diarrhea, poor weight gain, and pneumonia that resulted in his demise because of sepsis. The immunological workup showed that an inverse CD4/CD8 ratio and serum immunoglobulins were all within normal ranges. The laboratory data revealed failure in response to Candida lymphocyte transformation test. In addition, by Sanger sequencing method, we found a heterozygous mutation, Thr385Met (T385M), located in the DNA-binding domain of STAT1, which was previously shown to be GOF. These findings illustrate the broad and variable clinical phenotype of heterozygous STAT1 GOF mutations. However, more clinical information and phenotype–genotype studies are required to define the clinical phenotype caused by AD STAT1 GOF.

Keywords: gain-of-function mutations in STAT1, chronic mucocutaneous candidiasis

Introduction

Chronic mucocutaneous candidiasis (CMC) is characterized by persistent or recurrent Candida infections of the skin, nails, and mucosal membranes, which may poorly respond to antifungal treatment or relapse upon discontinuation of treatment [1]. It is often associated with a variety of infectious diseases as well as autoimmune or endocrine disorders such as hypothyroidism [2]. CMC is frequent in immunodeficiencies affecting T cell number and/or function, associated with various infectious and/or autoimmune manifestations [1, 2]. Patients with syndromic CMC and primary immunodeficiencies have been displaying impaired interleukin (IL) 17 immunity [1]. IL-17-mediated immunity has recently been recognized as crucial in the human mucocutaneous defense against Candida [1–6]. The mutations selectively abolishing IL-17-mediated immunity are linked to pathogenesis of CMC [4–6]. CMC is a prominent feature of autosomal-dominant (AD) hyper immunoglobulin E (IgE) syndrome [7, 8], autosomal-recessive (AR) autoimmune polyendocrinopathy candidiasis with ectodermal dystrophy syndrome [9–11].
AR Caspase Recruitment Domain-containing protein 9 deficiency with invasive fungal infection [12, 13], and Mendelian susceptibility to mycobacterial disease (MSMD) with AR IL-12p40 or IL-12Rβ1 deficiency [7, 14, 15]. CMC can also be found as one of the main clinical presentations or the only clinical presentation in patients without any of the previously mentioned underlying causes of CMC disease (CMCD) [16, 17]. AD heterozygous gain-of-function (GOF) mutations in the signal transducer and activator of transcription 1 (STAT1) are the most common genetic etiology of CMC disease which impaires the development of IL-17-producing T cells [18–24]. STAT1 mutations cause a wide spectrum of diseases, ranging from severe intracellular bacterial and viral infections (biallelic loss-of-function mutations) to MSMD (monoaallelic loss-of-function mutations) and CMC with other infectious and/or autoimmune manifestations (monoaallelic GOF mutations) [18, 22, 25]. Most of these mutations affect the coiled-coil domain or DNA-binding domain (DBD) of STAT1. They increase STAT1 phosphorylation and cellular responses to STAT1-dependant cytokines, such as interferon (IFN)-α/β, IFN-γ, IL-27, and STAT3-dependent IL-6 and IL-21 [5, 18, 26]. In parallel, they inhibit the development of IL-17-producing T cells [5, 18, 26, 27]. Autoimmunity probably results from stronger IFN-α/β signaling as it is a frequent adverse effect of treatment with recombinant IFN-α or IFN-β. In addition, some autoimmunity signs in patients treated with IFN-α (e.g., thyroiditis) [20, 28].

Case Report

A 33-year-old male has been referred to our clinic with a history of recurrent oral thrush and productive cough soon after the birth. He was the eighth child of unrelated parents with seven healthy siblings. He had a history of chronic refractory candidiasis affecting different sites of his skin, mucous membranes, and nails since early childhood. He was diagnosed with hiatal hernia with remarkable gastroesophageal reflux at age of 11 months that required a surgical intervention. He also suffered from recurrent otitis media and otorrhea since early infancy that led to tympanomastoidectomy at the age of 12 years. Frequent episodes of pneumonia since his childhood resulted in multiple hospitalizations with development of clubbing, focal bronchiectasis, and partial pulmonary fibrosis (Figure 1). Prophylactic oral itraconazole administered with initial diagnosis of CMC at the age of 14 years resulted in partial control of oral candidiasis. He also suffered from recurrent aphthous stomatitis, chronic diarrhea, growth retardation, and delayed puberty. He was diagnosed with hypothyroidism at the age of 18 years and treated with thyroid hormone replacement. At the age of 21 years, he developed severe esophageal candidiasis with resultant strictures associated with dysphagia and

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odynophagia that led to multiple esophageal dilatations. When he was 27 years old, he experienced multiple episodes of acute immune hemolytic anemia with warm autoantibodies with positive Coombs’ test (Table I). High doses of prednisolone were not tolerated by the patient; hence intravenous immunoglobulins were begun and advised to be injected every month. His son also suffered from persistent whitish oral plaques, chronic diarrhea, poor weight gain, and pneumonia since birth, which resulted in his demise because of the sepsis at the sixth month of life. Azole-resistant *Candida albicans* was isolated from his oral lesions.

**Results**

Flow cytometry revealed an inverse CD4/CD8 ratio and his serum immunoglobulins were all within normal ranges (Table I). The laboratory data showed impaired lymphocyte proliferative response to *Candida* and Bacillus Calmette–Guérin antigens [impaired lymphocyte transformation test (LTT)] (Table I). Sputum analysis and culture for acid-fast bacilli were negative. In addition, on genetic study, we found that both of the patient and his son had a heterozygous DBD GOF mutation at *Thr385Met (T385M)* in the *STAT1* gene [29] (Figures 2 and 3).

**Discussion**

According to previous reports, patients with *STAT1* GOF mutations are expected to have a broader immunological and infectious phenotype, given the role of STAT1 in multiple signaling pathways [18]. Several patients with *STAT1* GOF mutations possess not only CMC, but also severe viral and mycobacterial
infections and/or autoimmune diseases \[18, 21, 24\]. However, our case did not have any problems with severe viral or mycobacterial infection. Takezaki et al. \[19\] and Sharfe et al. \[23\] reported patients with the same T385M GOF STAT1 allele who had CMC, recurrent lower respiratory tract infections, bronchiectasis, and autoimmunities similar to the case described here. Moreover, this case had diaphragmatic hernia and esophageal dysmotility which seems to be a noteworthy feature of this syndrome as hypothesized by Uzel et al. \[22\] and Frans et al. \[30\].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amount</th>
<th>Unit</th>
<th>Normal range</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Immunoglobulin levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>1,022</td>
<td>mg/dl</td>
<td>767–1,590</td>
<td>Normal</td>
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<tr>
<td>IgA</td>
<td>346</td>
<td>mg/dl</td>
<td>61–356</td>
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</tr>
<tr>
<td>IgM</td>
<td>159</td>
<td>mg/dl</td>
<td>37–286</td>
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<tr>
<td>IgE</td>
<td>20</td>
<td>IU/ml</td>
<td>&lt;100</td>
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<tr>
<td>CD3+ T cell</td>
<td>66</td>
<td>%</td>
<td>55–82</td>
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<tr>
<td>CD4+ T cell</td>
<td>26</td>
<td>%</td>
<td>25–75</td>
<td>Lower limit normal</td>
</tr>
<tr>
<td>CD8+ T cell</td>
<td>41</td>
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<td>14–34</td>
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<td>CD56+ NK cell</td>
<td>6</td>
<td>%</td>
<td>6–31</td>
<td>Normal</td>
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<tr>
<td>CD19+ B cell</td>
<td>20</td>
<td>%</td>
<td>6–23</td>
<td>Normal</td>
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<tr>
<td>CD20+ B cell</td>
<td>19</td>
<td>%</td>
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</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBT</td>
<td>98</td>
<td>%</td>
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<tr>
<td>WBC</td>
<td>5.3 × 10^3</td>
<td>cells/μl</td>
<td>4.5–13.5 × 10^3</td>
<td>Normal</td>
</tr>
<tr>
<td>Hb</td>
<td>6.3</td>
<td>g/dl</td>
<td>12–15</td>
<td>Normal</td>
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<tr>
<td>PLT</td>
<td>199 × 10^3</td>
<td>cells/μl</td>
<td>140,000–440,000</td>
<td>Normal</td>
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<tr>
<td>Corrected retic</td>
<td>6.7</td>
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<td>0.5–2.5</td>
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<tr>
<td>Neutrophil</td>
<td>62</td>
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<tr>
<td>Lymphocyte</td>
<td>32</td>
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<td></td>
<td>Normal</td>
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<tr>
<td>Monocyte</td>
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<td>%</td>
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</tr>
<tr>
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<td>Negative</td>
<td></td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>Anti-IgG</td>
<td>Positive(+3)</td>
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<tr>
<td>Anti-C3d</td>
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<td>84</td>
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<td>90–180</td>
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</tr>
<tr>
<td>C4</td>
<td>40</td>
<td>mg/dl</td>
<td>10–40</td>
<td></td>
</tr>
<tr>
<td>CH50</td>
<td>94</td>
<td>%</td>
<td>&gt;90%</td>
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<tr>
<td>LTT BCG</td>
<td>&lt;0.75</td>
<td>RPI</td>
<td>0.75–1.65</td>
<td>Low</td>
</tr>
<tr>
<td>LTT Candida</td>
<td>&lt;0.75</td>
<td>RPI</td>
<td>0.75–1.65</td>
<td>Low</td>
</tr>
<tr>
<td>LTT PHA</td>
<td>0.85</td>
<td>RPI</td>
<td>0.75–1.65</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Note: NBT: nitro blue tetrazolium; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; RPI: Railway Performance Index; CH50: total hemolytic complement; PHA: phytohemagglutinin; LTT: lymphocyte transformation test.
Whether the gastrointestinal manifestations are all secondary to CMC or a primary manifestation of disturbed STAT1 signaling has yet to be determined [20, 22]. Soltész et al. [20] and Depner et al. [31] described patients carrying GOF

![Figure 2](image2.png)

**Figure 2.** Direct sequence analysis of STAT1 exon 14 in patient revealed base change of c.1153C > T resulting in p.T385M in STAT1

![Pedigree](image3.png)

**Figure 3.** The pedigree of the family

Whether the gastrointestinal manifestations are all secondary to CMC or a primary manifestation of disturbed STAT1 signaling has yet to be determined [20, 22]. Soltész et al. [20] and Depner et al. [31] described patients carrying GOF
mutations of STAT1 with developed multiple intracranial aneurysms, but our patient fortunately had no cerebral vascular complications.

Increased susceptibility to Fas activation in T385M T cells induces cell apoptosis which might contribute to the progressive decline in T cell numbers [23]. These findings show that some heterozygous aberrations of STAT1 can be associated with progressive combined immunodeficiency, accompanied by life-threatening severe infections. These infections increase with age, sometimes into their second decade of life, accompanied by variable autoimmune features [23]. This finding suggests that these STAT1 GOF mutations may ultimately be fatal due to overwhelming infections [19, 23, 32, 33]. However, we discuss here a patient with a relatively long life span.

These data suggest that heterozygous STAT1 GOF mutations underlie an unexpectedly broad clinical phenotype. More clinical information and phenotype–genotype studies are required to determine the clinical phenotype caused by AD GOF mutations of STAT1.

**Conflict of Interest**

The authors also declare that there is no conflict of interest.

**References**


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