



# Chronic mucocutaneous Candidiasis caused by a novel *STAT1* mutation: a report of 4 patients

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## ABSTRACT

**Background:** Chronic mucocutaneous Candidiasis (CMCC) is characterized by recurrent or persistent fungal infections of the skin, nails, and oral and genital mucosae. There are several underlying genetic causes for CMCC, with mutations in Signal Transducer and Activator of Transcription-1 (STAT1) accounting for the majority of cases.

**Aim:** To broaden the genotypic spectrum of CMCC caused by *STAT1* mutations.

**Methods:** We evaluated a young patient and her family with CMCC. Immune workup and targeted gene sequencing were performed.

**Results:** The proband presented at 7 years of age with persistent oral thrush. Immune evaluation revealed her cellular and humoral immunity to be within normal range. Given that her family history was significant for oral lesions in father, siblings, and paternal family members, *STAT1* gene sequencing was performed. A novel heterozygous missense c.G799A, predicting a p. Ala267Thr amino acid change within the coiled-coil domain, was identified in our patient and 3 of her family members.

**Conclusion:** Gain-of-function mutations in *STAT1* have been associated with a variety of phenotypes, ranging from isolated CMCC to severe fatal combined immunodeficiency, mycobacterial infections, autoimmune disorders, as well as malignancy and aneurysms. Here, we describe a novel *STAT1* mutation, c.G799A, resulting in a very mild phenotype of isolated CMCC in 4 members of one kindred.

**Statement of novelty:** We describe 4 patients with a mild phenotype of CMCC caused by a novel *STAT1* heterozygous mutation.

## Introduction

Chronic mucocutaneous Candidiasis (CMCC) is a group of disorders characterized by susceptibility to Candidal infection of the skin, nails, and mucous membranes. The range of genetic etiologies underlying CMCC is broad, including defects in Autoimmune Regulator (*AIRE*), IL-17 pathway members (*IL17RA*, *IL17RC*, *IL17F*), Dectin-1, Caspase Recruitment Domain Family Member 9 (*CARD9*), Signal Transducer and Activator of Transcription (*STAT1*), and *STAT3* (Tangye et al. 2020).

STAT1 is a key transcription factor mediating signaling of various cytokines, notably interferons (IFN), playing roles in cell homeostasis, stress response, and defense against intracellular pathogens. Its activation is dependent upon initial phosphorylation in the cytoplasm by tyrosine kinases, of the Janus-kinase (JAK) family, formation of dimerization, and translocation to the nucleus, where it binds to promoters to impact transcription (Zheng et al. 2015). In response to IFN- $\gamma$  stimulation, STAT1 forms homodimers (known as gamma-activating factor, GAF) or heterodimers with STAT3 that bind to gamma-activating sequence (GAS)

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in gene promoters. In response to IFN- $\alpha$  or IFN- $\beta$  stimulation, STAT1 forms a heterotrimer with STAT2 and IFN-regulatory factor 9 (IRF9), also known as IFN-stimulated gene factor 3 (ISGF3) which binds to interferon-stimulated response element (ISRE) in gene promoters (Gough et al. 2008).

The clinical spectrum associated with *STAT1* GOF is broad, ranging from mild infections to life-threatening bacterial, viral and opportunistic infections, CMCC, endocrinopathies, variable autoimmune manifestations and gradually declining lymphocyte number and function (van de Veerdonk et al. 2011; Sharfe et al. 2014; Toubiana et al. 2016). Complications such as bronchiectasis (Toubiana et al. 2016; Breuer et al. 2017), intracranial aneurysms (Toubiana et al. 2016) and squamous cell carcinoma (Koo et al. 2017) have also been reported.

Herein, we report on 4 family members with a novel *STAT1* mutation, resulting in a mild phenotype of isolated CMCC.

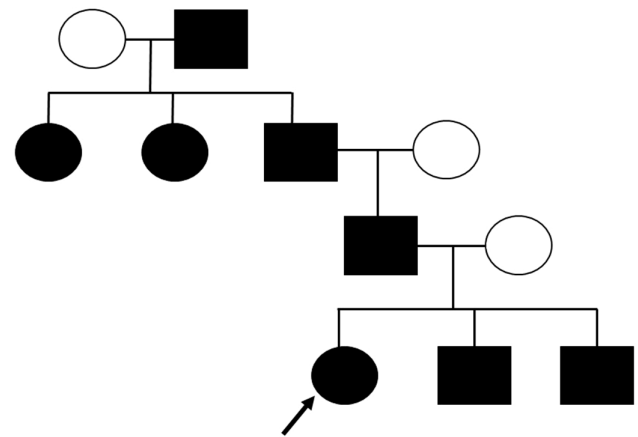
## Case presentation

### Proband

A 7-year-old female was referred to the Immunology clinic for persistent oral thrush involving her tongue, buccal mucosa, and hard palate, starting at 4 years of age. She was diagnosed with CMCC confirmed by positive swabs and oral biopsy. She did not experience dysphagia or odynophagia, nor involvement of the nails, skin, or vaginal mucosa. There was no history of invasive fungal infections or other systemic infections, and no features suggestive of endocrinopathy. Review of past medical history demonstrated that she had been born at term to nonconsanguineous parents of English descent following a normal pregnancy and uncomplicated delivery. She had undergone an eye surgery for correction of strabismus at early childhood. She had been otherwise well and developed normally. Family history was significant for similar oral lesions in her 2 younger male twin siblings and father, all of whom were healthy apart from CMCC. Other paternal family members (great grandfather and great aunts) also had a history of oral fungal infections (Figure 1).

### Investigations

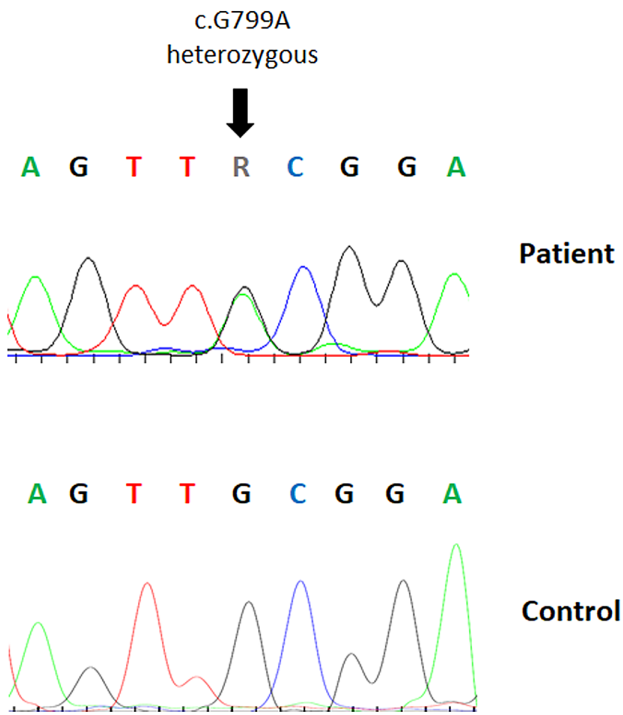
A full immunological laboratory assessment, including complete blood-count and differential,



**Table 1: Laboratory evaluation of proband at 7 years of age.**

	Value	Reference range
WBC (× 10 <sup>9</sup> /L)	8.9	4.3–11
Hemoglobin (g/L)	133	107–134
Platelets (× 10 <sup>9</sup> /L)	326	150–370
Neutrophils (× 10 <sup>9</sup> /L)	5.14	1.5–8
Lymphocytes (× 10 <sup>9</sup> /L)	2.84	1.5–7
Eosinophils (× 10 <sup>9</sup> /L)	0.15	0.02–0.05
Monocytes (× 10 <sup>9</sup> /L)	0.69	0.05–0.08
Basophils (× 10 <sup>9</sup> /L)	0.10	0.00–0.02
CD3+ (cells/μL)	2099	700–4200
CD3+/CD4+ (cells/μL)	1122	300–2000
CD3+/CD8+ (cells/μL)	786	300–1800
CD19+ (cells/μL)	424	200–1600
NK (cells/μL)	370	120–480
PHA stimulation index	390	>50% of control or >300
IgG (g/L)	11	5.4–13.6
IgM (g/L)	1	0.4–1.5
IgA (g/L)	2.6	0.3–1.5
Anti-tetanus Ab (IU/mL)	0.57	>0.1
Anti-Measles, Mumps, Varicella specific IgG	All non- reactive	—
Anti-rubella specific IgG	Reactive	—
TSH (mIU/L)	1.57	0.73–4.34
Free T4 (pmol/L)	12.5	11.4–17.6
PTH (ng/L)	53	16–63

We herein report on multiple members of one kindred, found to have a heterozygous *STAT1* gene mutation causing chronic oral Candidiasis. In this family, the onset of CMCC was in early childhood, and all affected members presented with a mild disease phenotype. The mutation, c.G799A, predicts an amino acid change A267T in the coiled-coil domain of *STAT1*, a domain involved in protein-protein interactions which plays a key role in the dimerization of *STAT1* and nuclear *STAT1* dephosphorylation (Levy and Darnell 2002). It is the most commonly affected domain implicated in *STAT1* GOF, with the 267 residue (and in particular the A267V mutation) being the most common mutation identified in large *STAT1* GOF cohorts (Toubiana et al. 2016). Clinical manifestations seen in patients with the A267V mutation have included CMCC, bacterial and viral infections, atopy, thyroid dysfunction, bronchiectasis, aneurysms, and squamous cell carcinoma. Notably, some of the more severe disease manifestations, such as malignancy, typically developed in adulthood between the third and fifth decade of life (Toubiana et al. 2016).



**Figure 2:** Electropherogram demonstrating the c.G799A missense variant in *STAT1*. The heterozygous variant was identified in the patient (upper panel), as well as her siblings and father, using targeted gene sequencing. The control sequence is shown in the lower panel.

The current report expands the genotypic spectrum of *STAT1* GOF, and supports the notion of genetic testing for an underlying immunodeficiency in patients and families with CMCC. While the patients in the current report have displayed mild disease to date, we suggest that regular and life-long follow up should be performed in all cases of *STAT1* GOF, screening periodically not only for changes in immune function, but also for late-onset disease manifestations, such as malignancies. Further studies looking into establishing genotype-phenotype correlation for *STAT1* GOF, are warranted and may help determine which mutations predispose patients to severe or life-threatening complications.

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