



Bronchiectasis and Recurrent Respiratory Infections with a *De Novo* *STAT1* Gain-of-Function Variant: First Case in Korea

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Bronchiectasis is a chronic disease characterized by airway infection and inflammation, leading to permanent dilation of the bronchi. Evaluation of underlying etiology is important in managing young bronchiectasis patients with recurrent infections caused by unusual pathogens. The signal transducer and activator of transcription 1 (*STAT1*) protein plays a key role in *STAT* signaling and immune system regulation. Heterozygotes for gain-of-function (GOF) alleles of the *STAT1* gene usually display autosomal dominant chronic mucocutaneous candidiasis (CMC) and a wide range of clinical features, such as bronchiectasis. Here, we report on a patient with CMC and bronchiectasis with various types of infections who carried a pathogenic variant of the *STAT1* gene. The 24-year-old female presented with recurrent respiratory bacterial and nontuberculous mycobacterial infections complicated by severe bronchiectasis and CMC. Whole-exome sequencing revealed a c.800C>T (p.Ala267Val) heterozygous mutation in the *STAT1* gene. Further analysis by Sanger sequencing of *STAT1* from the patient and her parents revealed the patient had a *de novo* occurrence of the variant. This is the first report of a Korean patient with a GOF pathogenic variant in *STAT1*. Physicians should be aware of the existence of this variant as a genetic factor associated with CMC and bronchiectasis complicated by recurrent infection.

Key Words: Bronchiectasis, chronic mucocutaneous candidiasis, gain-of-function mutation, nontuberculous mycobacteria, *STAT1* transcription factor

INTRODUCTION

Bronchiectasis is a chronic respiratory disease characterized by airway infection and inflammation, leading to permanent

dilation of the bronchi.¹⁻³ Bronchiectasis may be a consequence of structural lung damage caused by prior respiratory infection or systemic disorders associated with genetic defects, such as cystic fibrosis. Thus, evaluating causative or correctable un-

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derlying factors is important in the management of patients with respiratory infections complicated by bronchiectasis.⁴

The signal transducer and activator of transcription 1 (STAT1) plays an important role in STAT signaling and immune system regulation.⁵ In heterozygotes for gain-of-function (GOF) alleles in the *STAT1* gene, chronic mucocutaneous candidiasis (CMC) is common, whereas loss-of-function variants in *STAT1* give rise to a broad range of diseases, including bacterial, viral, or nontuberculous mycobacterial (NTM) infection.⁶⁻⁸ In addition, recent studies have demonstrated an association between *STAT1* GOF variants and a broader range of clinical phenotypes, including bronchiectasis and respiratory infections.⁹⁻¹³ Here, we report the first case of a young Korean female with a *de novo* *STAT1* GOF pathogenic variant who presented with recurrent respiratory bacterial and NTM infection complicated by CMC and severe bronchiectasis.

CASE REPORT

This case report was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2018-07-140). Patient information was anonymized and de-identified, and informed consent was waived. Our patient experienced repeated episodes of pneumonia commencing in childhood, with bronchiectasis first documented at the age of 12 years. She has no history of tuberculosis. When the patient was 18 years old, she had pneumonia caused by *Pseudomonas aeruginosa*. At the age of 23 years, the patient started to suffer from NTM lung disease caused by macrolide-susceptible *Mycobacterium massiliense*; the patient responded poorly to antibiotic treatment, including clarithromycin, rifampin, ethambutol, and intravenous amikacin, for 10 months at another hospital and was transferred to our hospital.

The patients had oral thrush, as well as cutaneous candidiasis of nasal skin (Fig. 1A) and onychomycosis of a fingernail (Fig. 1B), with the diagnoses confirmed by the observation of fungal hyphae on periodic acid-Schiff staining on biopsy specimens. A chest computed tomography scan revealed bilateral severe bronchiectasis and bronchiolitis in both lungs (Fig. 1C). Sputum examinations revealed multiple positive cultures for *P. aeruginosa* and *M. massiliense*, and the *M. massiliense* isolate was still susceptible to macrolide. The patient was treated for CMC with itraconazole. Multidrug antibiotic therapy consisting of amikacin, azithromycin, clofazimine, and linezolid was administered for *M. massiliense* lung disease.

Further tests, including *CFTR* gene testing and quantitation of serum immunoglobulin (Ig) and alpha-1-antitrypsin, were performed to find the underlying etiology in this patient. However, we found no pathogenic variants of the *CFTR* gene, and the levels of serum IgG (1580 mg/dL), IgA (90 mg/dL), IgM (94 mg/dL), and alpha-1-antitrypsin (173.7 mg/dL) were normal. To rule out primary ciliary dyskinesia, electron microscopy of

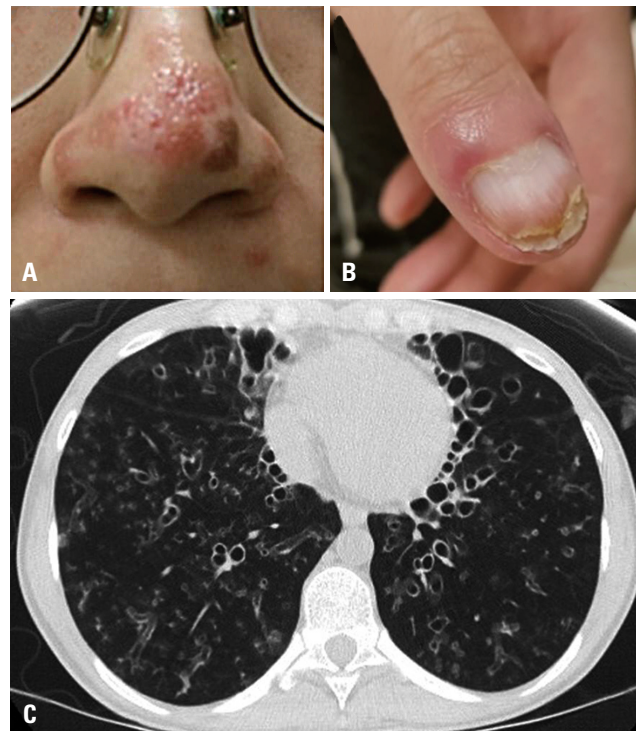


Fig. 1. Fungal infections and severe bronchiectasis in the 24-year-old female patient. (A) Cutaneous candidiasis of nasal skin. (B) Onychomycosis of a fingernail. (C) Bilateral bronchiectasis and bronchiolitis on chest computed tomography scan.

respiratory epithelial samples was performed, but showed normal cilia structures.

Due to uncertainty regarding the basic etiology, we performed whole-exome sequencing (WES), with the written informed consent of the patient, to identify genetic causes of the disease. Genomic DNA was extracted and captured with the Agilent SureSelect Human All Exon V5 Kit (Agilent Technologies, Santa Clara, CA, USA) and sequenced on the Illumina Next-Seq500 platform (Illumina Inc., San Diego, CA, USA). Raw sequence reads were processed and aligned to the hg19 human genome reference sequence. A mean coverage of 99.05× was achieved, and 95.4% of targeted bases were read >20 times by exome capture and sequencing. A total of 99028 variants were identified. After screening pneumonia-related or CMC-related genes, we identified a missense variant (NM_007315.3:c.800C>T, p.Ala267Val) in the coiled-coil domain of the *STAT1* gene (Fig. 2A). This variant was not reported in the Exome Aggregation Consortium (ExAC, <http://exac.broadinstitute.org>) nor in the Korean Reference Genome database (KRGDB, <http://152.99.75.168/KRGDB>). According to the 2015 guidelines from the American College of Medical Genetics and Genomics and the Association of Molecular Pathology,¹⁴ this p.Ala267Val variant can be categorized as a “pathogenic” variant based on the following factors: PS1, same amino acid change as a previously established pathogenic variant, and PS3, well-established functional studies support its damaging effect on the gene prod-

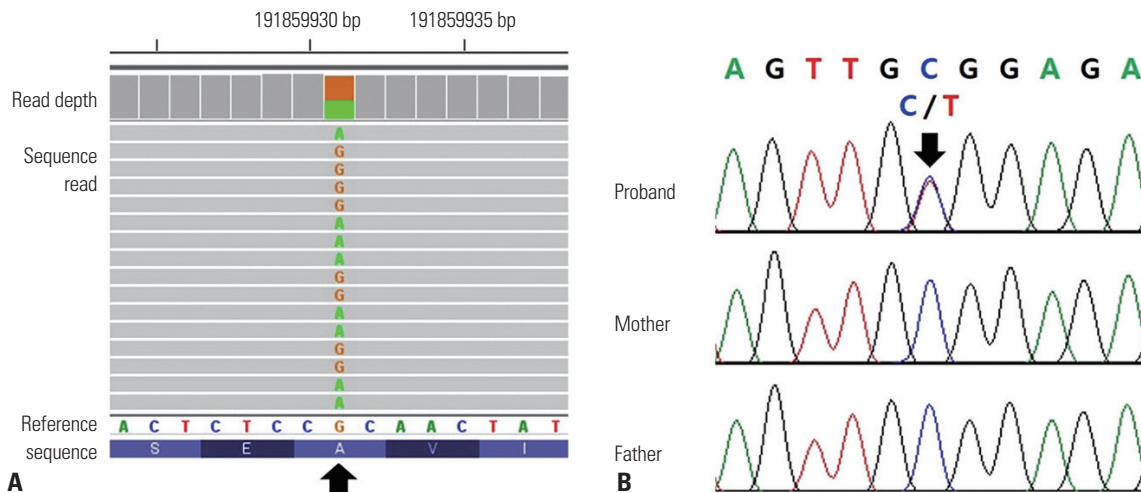


Fig. 2. Pathogenic *STAT1* variant identified in the 24-year-old female patient. (A) Integrative Genomics Viewer snapshot of the *STAT1* pathogenic variant (NM_007315.3:c.800C>T, p.Ala267Val) (arrow) identified by whole-exome sequencing. (B) Validation of the *STAT1* variant by Sanger sequencing. Chromatograms show the heterozygous variant in the proband (patient), indicated by the arrow, and the normal sequence in the unaffected parents.

uct.^{6,13-15} Sanger sequencing confirmed the heterozygous *STAT1* variant (NM_007315.3:c.800C>T, p.Ala267Val) in the patient, whereas her parents did not have the variant, indicating that the variant occurred *de novo* (Fig. 2B).

DISCUSSION

We present the first case of a Korean patient with a *de novo* *STAT1* GOF variant. She presented with recurrent respiratory infection by unusual pathogens complicated by severe bronchiectasis and CMC. GOF variants of the *STAT1* gene affect the coiled-coil domain of *STAT1*, increase *STAT1* phosphorylation by impairing nuclear dephosphorylation, and eventually can cause diminished numbers of interleukin-17-producing T cells.⁷ The heterozygous c.800C>T (p.Ala267Val) variant in *STAT1* identified in our patient was originally described as an autosomal dominant GOF pathogenic variant causing CMC. However, recent studies have demonstrated the potential association between these variants and more broad-ranging clinical phenotypes, including sinopulmonary disease and severe bronchiectasis.⁹⁻¹³ Although the underlying mechanisms remain elusive, it was suggested that degrees of impairment in B cells, especially class switched memory B cells, in patients with *STAT1* GOF variants might contribute to the phenotypic variation in sinopulmonary manifestation.¹³ *STAT1* GOF variants are also reported to be associated with various kinds of infectious disease, autoimmune disease, cerebral aneurysms, and cancer.^{9-13,15-18} Regarding these topics, Toubiana, et al.⁹ recently reported detailed clinical spectrums in 274 patients from 40 countries with *STAT1* GOF pathogenic variant: 98% of them had CMC, 37% had autoimmune manifestations, 21% had bronchiectasis, and 6% had mycobacterial infections, including tuberculosis and NTM infections.

In our case, diagnosis of underlying disease of bronchiectasis and recurrent infections led to the patient's and her parents' psychological stability and compliance to treatment, and it eventually suggested the possibility of application of targeted therapy, such as Janus kinase (JAK) family tyrosine kinase inhibitor, such as ruxolitinib, for disease control.¹⁹ Therefore, our case highlights the importance of a thorough evaluation of the underlying etiology in patients with bronchiectasis, particularly those with chronic recurrent infections by unusual pathogens.

In our case, we used WES to identify basic etiology and discovered the *STAT1* GOF variant. The diagnosis of *STAT1*-related disorders based on clinical features can be hampered since patients with autosomal dominant *STAT1* GOF variants often present broad clinical phenotypes. Therefore, patients with this rare genetic disease might undergo a futile and time-consuming process for a definitive diagnosis.¹³ WES can be a useful and cost-effective diagnostic tool, especially for patients with broad or unusual clinical presentation.

In summary, this report describes the first case of a Korean patient carrying a pathogenic variant of the *STAT1* gene, which likely resulted in the patient's recurrent respiratory bacterial and NTM infection complicated by severe bronchiectasis and CMC. Our report highlights the need for physicians to be aware of GOF pathogenic variants in the *STAT1* gene as a genetic factor associated with CMC and bronchiectasis complicated by infection by various pathogens.

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