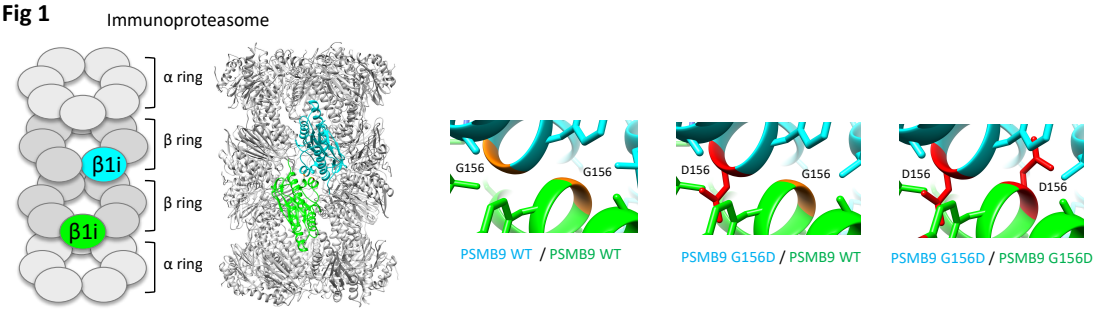
Fig 1



PSMB9 gene encodes β1i subunit

News Release

Successful treatment of a novel type Ⅰ interferonopathy due to a *de novo PSMB9* gene mutation with a Janus kinase inhibitor

Key Points

- A *de novo* heterozygous missense mutation (p.G156D) in *PSMB9* causes a novel type I interferonopathy.
- Tofacitinib, a JAK inhibitor, was effective in treating severe pulmonary hypertension in a patient. JAK inhibitors may be effective for treating patients with type I interferonopathy in which the JAK-STAT signaling pathway is overactivated.

Summary

A research group led by Professor Yoshiyuki Takahashi of the Department of Pediatrics, Nagoya University Graduate School of Medicine; Lecturer Hideki Muramatsu and Assistant Professors Nozomu Kawashima and Shinsuke Kataoka of the Department of Pediatrics, Nagoya University Hospital has discovered a novel type I interferonopathy caused by a *de novo* heterozygous missense mutation in *PSMB9* and clarified the pathogenesis of the disease.

Type I interferonopathy is a type of autoinflammatory syndrome in which genetic abnormalities in the proteasomal degradation pathway lead to overactivation of the JAK-STAT signaling pathway involved in interferon α secretion, thereby resulting in characteristic findings such as bilateral basal ganglia calcification, chilblain-like rashes, and liver dysfunction. In this study, we conducted a comprehensive genetic and functional analysis of a patient with severe type I interferonopathy without known gene mutations and found that *PSMB9* p.G156D heterozygous mutation was the cause of the disease. Our results suggest that JAK inhibitor and allogeneic hematopoietic stem cell

transplantation are effective therapeutic strategies for type I interferonopathy caused by *PSMB9* mutation.

Research Background

Type I interferonopathies are a recently established subgroup of autoinflammatory diseases caused by mutations in genes associated with proteasome degradation or cytoplasmic RNA and DNA sensing pathways. Typical type I interferonopathies include Aicardi–Goutières syndrome (AGS), STING-associated vasculopathy with onset in infancy (SAVI), and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. The clinical findings that are common to most of type I interferonopathies include bilateral basal ganglia calcification, chilblain-like rashes, and liver dysfunction. Moreover, early-onset encephalopathy in AGS and pulmonary hypertension in SAVI are known as characteristic findings of each disease. The JAK-STAT signaling pathway, which is involved in interferon α, is overactivated in type I interferonopathy, and the efficacy of JAK inhibitors has been reported in *in vitro* experiments and anecdotal case reports.

Research Results

We conducted whole exome sequencing to explore the causative gene in the patient who were diagnosed with type I interferonopathy based on elevated interferon α levels in serum and spinal fluid, presenting with fever, bilateral basal ganglia calcification, chilblain-like rashes, liver dysfunction, and pulmonary hypertension at age 1 month. Although the patient did not have any previously reported causative gene mutation, he did have a *de novo* heterozygous missense mutation (p.G156D) in *PSMB9*, which encodes the β1i subunit of the immunoproteasome.

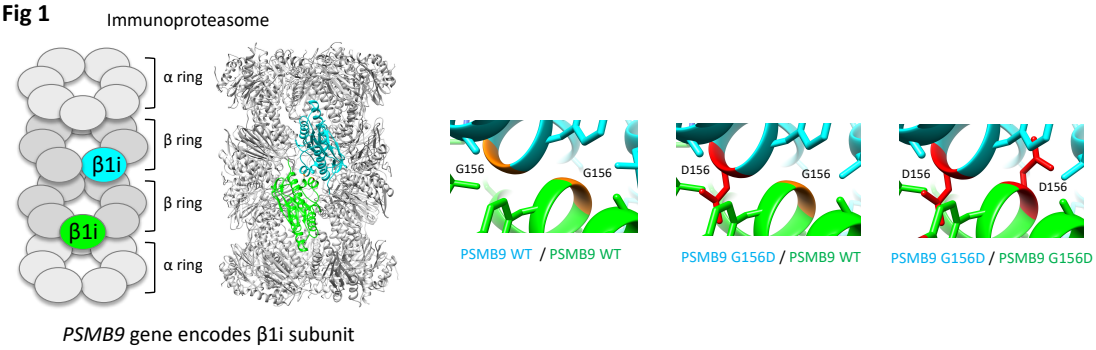
To examine whether the *PSMB9* p.G156D mutation found in the patient caused the disease, we conducted functional analysis using patient-derived lymphoblastoid cell line (LCL) and LCL derived from healthy parents. Our findings revealed that proteasome function was significantly diminished in the patient-derived LCL and the overexpression of *PSMB9* p.G156D in the father-derived LCL also significantly diminished the proteasome function. We then performed immunoblotting and immunoprecipitation using anti-PSMB9 and anti-ubiquitin antibodies, which revealed enhanced ubiquitination of PSMB9 protein in patient-derived LCL compared to that in healthy control-derived LCL. This result suggested the enhanced ubiquitination of PSMB9 protein in the patient, which resulted in proteasome degradation.

We also performed immunoblotting for phosphorylated STAT1 to elucidate the relationship between elevated interferon α levels and the JAK-STAT signaling pathway in the patient.

When measured continuously after the external application of interferon stimulation, the level of phosphorylated STAT1 in the healthy control-derived LCL increased temporarily and then returned to a steady state, whereas the level of phosphorylated STAT1 in the patient-derived LCL remained elevated. Moreover, it was confirmed that the addition of a JAK inhibitor to the patient-derived LCL under external interferon stimulation conditions inhibited STAT1 phosphorylation.

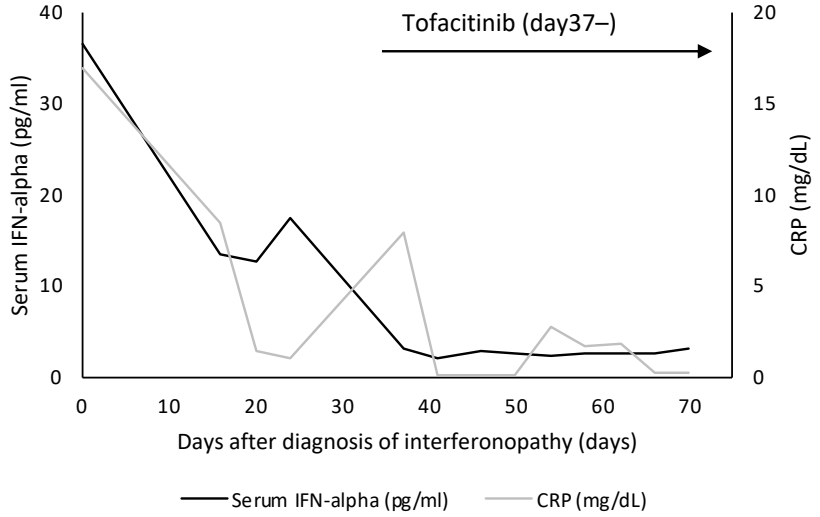
The results of these functional analyses suggest that the PSMB9 p.G156D mutant protein promotes proteasome degradation and suppresses the function of the normal PSMB9 protein. In our patient, we believed that it was a novel type I interferonopathy caused by *PSMB9* p.G156D mutation (Fig. 1).

Fig 1



The patient's clinical course was complicated by severe pulmonary hypertension, requiring management with extracorporeal membrane oxygenation (ECMO), but the administration of tofacitinib, a JAK inhibitor, reduced the level of serum interferon α, which is believed to reflect disease activity (Fig. 2), and the patient was successfully weaned from ECMO. At the age of 7 months, umbilical cord blood transplantation was performed for curative therapy, and currently, more than 2 years have elapsed since the transplantation. However, even after discontinuation of tofacitinib, the patient has progressed without a relapse of type I interferonopathy. This case suggests that JAK inhibitor and hematopoietic stem cell transplantation are effective in the treatment of severe type I interferonopathy.

Fig 2



Research Summary and Future Perspective

This case study has shown that (1) *PSMB9* mutation may be the cause of type I interferonopathy associated with pulmonary hypertension and (2) JAK inhibitor may be effective in treating type I interferonopathy caused by *PSMB9* p.G156D mutation. We anticipate that clinical trials for patients with type I interferonopathy would be conducted in the future to widen the therapeutic indications for JAK inhibitors.

Publication

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Successful treatment of a novel type I interferonopathy due to a *de novo PSMB9* gene mutation with a Janus kinase inhibitor

Shinsuke Kataoka[1], Nozomu Kawashima[1], Yusuke Okuno[2], Hideki Muramatsu[1], Shunsuke Miwata[1], Kotaro Narita[1], Motoharu Hamada[1], Norihiro Murakami[1], Rieko Taniguchi[1], Daisuke Ichikawa[1], Hironobu Kitazawa[1], Kyogo Suzuki[1], Eri Nishikawa[1], Atsushi Narita[1], Nobuhiro Nishio[1,3], Hidenori Yamamoto[1], Yoshie Fukasawa[1], Taichi Kato[1], Hiroyuki Yamamoto[1], Jun Natsume[1], Seiji Kojima[1], Ichizo Nishino[4], Takeshi Taketani[5], Hidenori Ohnishi[6], Yoshiyuki Takahashi[1]

[1]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

[2]Medical Genomics Center, Nagoya University Hospital, Nagoya, Japan
[3]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan
[4]Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan
[5]Department of Pediatrics, Shimane University Faculty of Medicine, Shimane, Japan
[6]Department of Pediatrics, Gifu University Graduate School of Medicine, Gifu, Japan

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