**News Release**

**Title**

**Variants in *MEFV*, a gene associated with familial Mediterranean fever, are a predisposing factor for generalized pustular psoriasis**

**Key Points**

- **Generalized pustular psoriasis (GPP) is a disease targeted for clinical investigation under the "Research Project on Overcoming Intractable Diseases" of the Ministry of Health, Labor and Welfare of Japan.**
- **Gene and statistical analyses of 24 Japanese patients with GPP found high allele frequencies of two *MEFV* variants.**
- **Our findings suggest that *MEFV* variants are associated with the development of GPP.**
- **Therapies targeting inflammatory pathways related to *MEFV* may be a promising therapeutic strategy for GPP patients with *MEFV* variants.**

**Summary**

Prof. Masashi Akiyama, Dr. Takenori Yoshikawa (first author) and Dr. Takuya Takeichi (corresponding author) of the Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura, MD, PhD) have proposed that *MEFV* variants are a predisposing factor for generalized pustular psoriasis (GPP).

GPP is characterized by erythema and sterile pustules on the whole body with fever (Figure 1). Severe complications can lead to death. GPP patients are found worldwide. GPP has been designated in Japan as an intractable disease, and severe GPP patients who were able to receive public subsidies for medical expenses numbered approximately 2,000 in the year 2021 (Report on Public Health Administration and Services FY2021; Ministry of Health, Labour and Welfare of Japan) . Including the first report on *IL36RN*, in 2011, six genes have been reported as being associated with GPP, and studies on the pathogenic mechanisms of GPP are gradually progressing. However, other disease-associated genes have been sought, because some GPP patients do not have variants in any of the genes reported to be associated with GPP.

We performed next-generation sequencing using genomic DNA samples from 24 Japanese patients with GPP. We found higher allele frequencies of two *MEFV* variants, p.Arg202Gln and p.Ser503Cys, in these patients than in the general control subjects. *MEFV* products are known to control inflammatory

pathways associated with pyrin inflammasomes, and due to certain *MEFV* variants, neutrophils eventually migrate to tissues and active inflammation.
Our study of *MEFV* in GPP patients revealed that approximately 21% carried the p.Arg202Gln variant and 13% carried the p.Ser503Cys variant (Figure 2). Therapies targeting inflammatory pathways related to *MEFV* may be a promising therapeutic strategy for GPP patients with *MEFV* variants.
The results of this research have been published in the *Journal of the American Academy of Dermatology* (published online on December 19th, 2023 in advance of print publication).

**Research Background**

Psoriasis is a chronic inflammatory skin disease. GPP, a psoriasis subtype, is targeted for clinical investigation under the "Research Project on Overcoming Intractable Diseases" of the Ministry of Health, Labor and Welfare of Japan. GPP has been designated as an intractable disease, and severe GPP patients who were able to receive public subsidies for medical expenses numbered approximately 2,000 in the year 2021 (Report on Public Health Administration and Services FY2021; Ministry of Health, Labour and Welfare of Japan) . GPP often develops in one's childhood and thirties. It is characterized by multiple erythematous lesions and sterile pustules over the whole body, with fever (Figure 1), and it recurs repeatedly over the course of many years. GPP is sometimes complicated with systemic inflammation, mucosal symptoms, and arthritis, and severe complications can lead to death. Histopathologically, GPP is characterized by pustules with numerous neutrophils, mainly in the epidermis. Since 2011, when *IL36RN* was first reported, six genes have been reported as associated with the disease: *IL36RN, CARD14, AP1S3, SERPINA3, MPO,* and *BTN3A3*. Studies on the pathology are gradually progressing. However, other disease-associated genes have been sought, because some GPP patients do not have variants in any of these reported genes.
*MEFV* products control inflammatory pathways associated with pyrin inflammasomes. In familial Mediterranean fever, certain *MEFV* variants cause neutrophils to eventually migrate to tissues and activate inflammation.

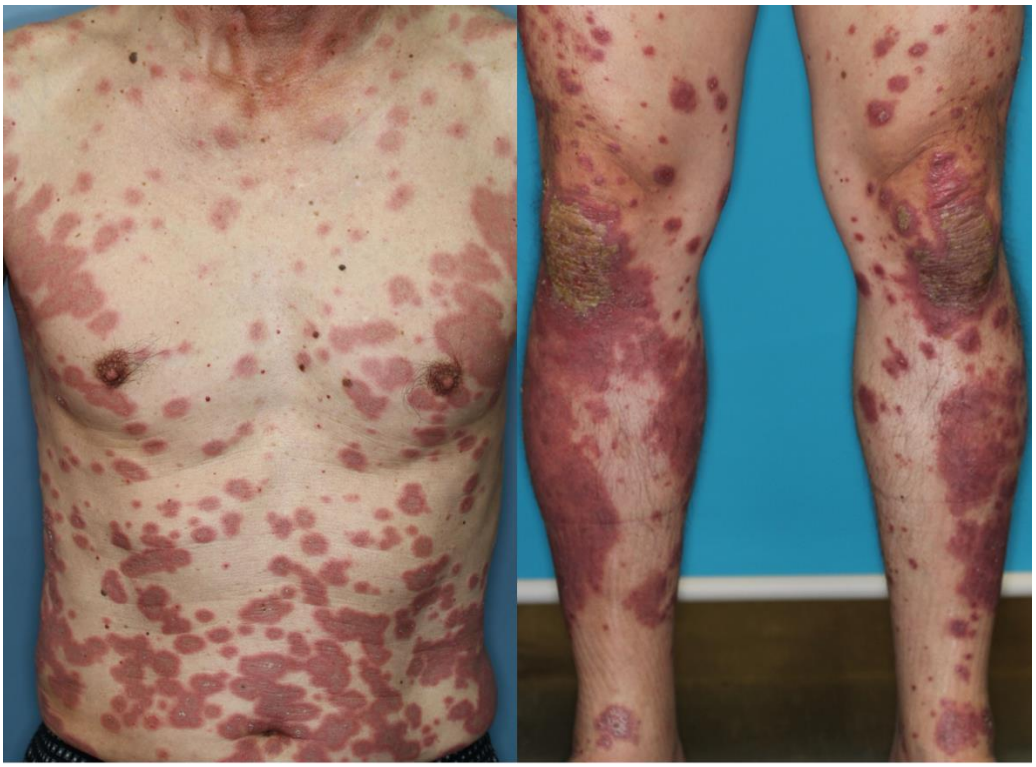

Figure 1

**Research Results**

We performed next-generation sequencing using genomic DNA samples from 24 Japanese patients with GPP. The allele frequencies of two *MEFV* variants, p.Arg202Gln and p.Ser503Cys, were higher in these patients than in the general control subjects. Our study of *MEFV* in GPP patients revealed that 20.8% carried the p.Arg202Gln variant and 12.5% carried the p.Ser503Cys variant (Figure 2).

In addition to those 24 GPP patients, we performed the same analysis on 10 patients with pustular skin diseases that typically show sterile pustules, such as acute generalized exanthematous pustulosis and acrodermatitis continua Hallopeau. We statistically analyzed the entire group of 34 patients (24 patients with GPP + 10 patients with pustular skin diseases other than GPP). We found the allele frequencies of the two *MEFV* variants described above also to be high. Our report is the first to find that *MEFV* variants are a predisposing factor for GPP. Additionally, our findings suggest that *MEFV* variants might be associated with pustular skin diseases other than GPP.

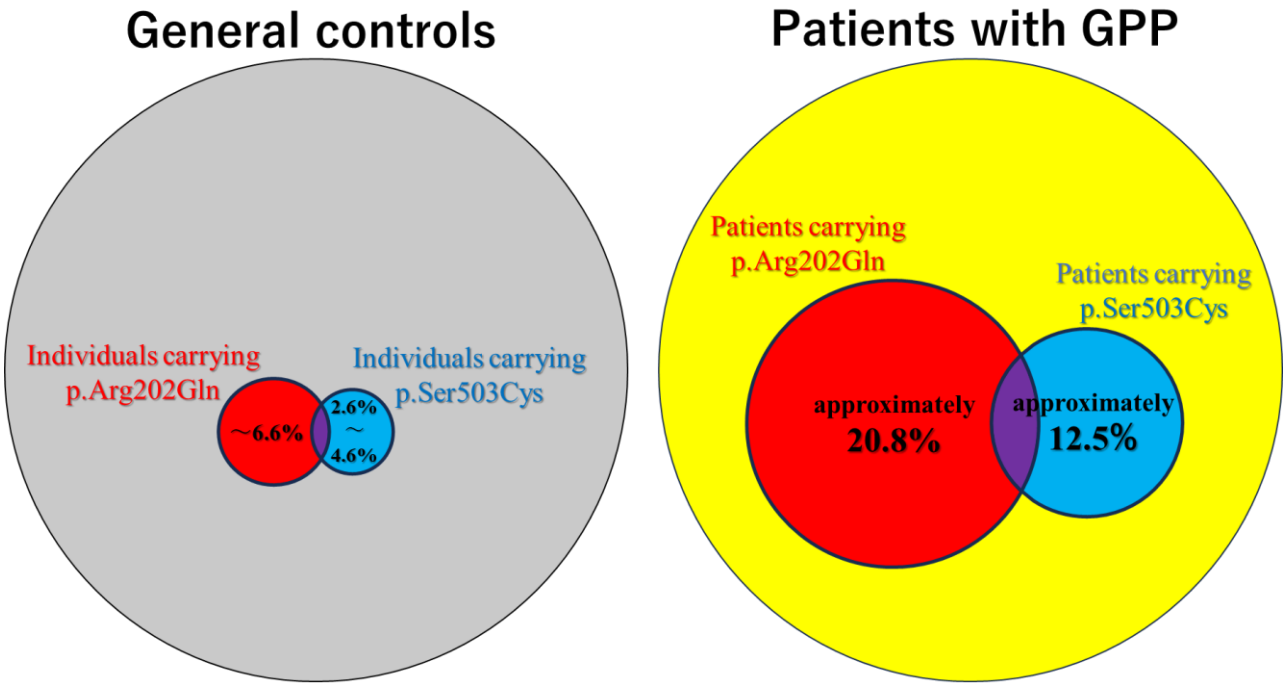


Figure 2

**Research Summary and Future Perspective**

Our study of *MEFV* in GPP patients revealed that approximately 21% carried the p.Arg202Gln variant and 13% carried the p.Ser503Cys variant (Figure 2). Therapies targeting inflammatory pathways related to *MEFV* may be a promising therapeutic strategy for GPP patients with *MEFV* variants.

**Publication**

Takenori Yoshikawa, Takuya Takeichi, Kazuki Nishida, Yumiko Kobayashi, Hozumi Sano, Akitaka Shibata, Haruka Koizumi, Reiko Tsutsumi, Ryo Fukaura, Masahiro Hayashi, Akiko Imanishi, Kenta Nakamura, Yasutomo Mikoshiba, Eisaku Ogawa, Shinya Sano, Manao Kinoshita, Takashi Okamoto, Reiko Kageyama, Yuko Sano, Sakae Kaneko, Jun Aoi, Toshihide Hara, Yaei Togawa, Mari Kishibe, Yuichi Yoshida, Hiroaki Yagi, Tetsuya Honda, Kazumitsu Sugiura, Shigetoshi Sano, Tamio Suzuki, Tomoo Ogi, Yoshinao Muro, and Masashi Akiyama

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Japanese ver.
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