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Pathology analysis of tonsils and exome analysis of Japanese patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome

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Abstract

Background : Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is an autoinflammatory disease of unknown etiology. In recent years, variants of several genes that are known to cause other autoinflammatory diseases have been identified in patients with PFAPA.

Objective : To obtain detailed genetic, pathological, and clinical information on Japanese PFAPA patients towards establishing effective therapeutic strategies.

Methods : Six patients (3 boys and 3 girls) between the ages of 1 and 15, who were diagnosed as having PFAPA syndrome were included in the study. All patients were subjected to exome analysis using Next-Generation Sequencer. Blood laboratory data and clinical symptoms were compared with the genomic exome data. Pathological analysis was performed on tonsil samples from 5 additional PFAPA patients.

Results : Five rare variants were found, and each variant was found in 2 patients. A comparison of their clinical findings demonstrated that patients with rare *VPS8* variants had a family history of PFAPA. Colchicine was effective for patients with *MYCL* variants who had no *MEFV* variant. Patients with each variant showed no obvious difference in their laboratory findings. No common haplotypes of previously reported genes were associated with PFAPA. Tingible body macrophages and bacterial colonization were found in the tonsils of the patients.

Conclusion : *VPS8*, which plays an important role in phagocytosis, may be the causative gene for some PFAPA patients with a family history. Further studies using the same individual are required to confirm the association of genes involved in phagocytosis with the pathophysiology of PFAPA.

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA) was proposed by Marshall et al. in 1987 as a syndrome involving repeated fever attacks with aphthous ulcers, pharyngitis, and cervical lymphadenitis as the main symptoms[1]. The involvement of cytokine dysregulation has been suggested, but its detailed pathophysiology has remained unknown to date. At least 28% of patients with PFAPA have been reported to have a family history[2]. However, PFAPA has previously nonhereditary, and a causative gene has not been identified in patients of familial clusters. Recently, variants of the *NLRP3* gene were found in 26%, and variants of the *MEFV* gene were found in 65% of PFAPA patients, but the frequencies were not compared with a control group[3]. Furthermore, there were no descriptions of rare variants in those reports. In addition, a variant of the *CARD8* gene, which encodes a protein that suppresses the activity of caspase-1, resulted

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in higher expression levels of the CARD8 protein in patients with PFAPA than in healthy controls[4]. These data suggest that PFAPA might be caused by variants of a common gene, at least in some patients. In this study, we analyzed the genetic background of Japanese patients with PFAPA by using exome analysis, to clarify their genetic backgrounds. Tonsillectomy is performed in most older patients who are resistant to the treatment medications for PFAPA, and the efficacy is estimated to be more than 90%[5]. Therefore, we also performed pathological analysis of tonsil specimens of PFAPA patients.

Materials and methods

Six patients (3 boys and 3 girls) between the ages of 1 and 15, who visited our department between 2016 and 2018 and were clinically diagnosed as having PFAPA were analyzed. The diagnosis of PFAPA was based on the diagnostic criteria of Thomas[6]. The characteristics of the patients who underwent exome analysis are shown in Table 1. Exome analysis was performed on 6 patients after obtaining their written consent. Whole exome sequencing analysis was performed with Ion Ampliseq Exome kit ver. 3, and sequenced using Ion Proton sequencer. Torrent Suite (reference : hg19, default parameter) and ANNOVAR were used for the analysis. The coverage was more than 50× on the platform. The ensuing vcf file was then annotated using wAnnovar, and bioinformatic analyses were performed[7]. To evaluate the frequency of each variant, the gnomAD database was searched, and *in silico* analysis of each missense variant was performed using the website Varsome.com. All variants were then prioritized using PubMed Fetcher and Genie online software, interrogating PubMed with the list of genes coming out from our analysis and the already reported immunological diseases[8][9]. All the genes and their variants were manually inspected by loading all the reads as a custom track on the UCSC genome browser, and then confirming their presence and their frequency on gnome of ToMMo, HGVD, ToMMo, 1,000 g, and gnomAD databases. Variants were filtered using a minor allele frequency threshold of less than 0.005 (0.5%). The patients' laboratory data and clinical symptoms were compared with their genomic data.

The pathology of the tonsils was investigated in 5 additional patients (2 boys and 3 girls) aged 3 to 16 years who showed frequent fever episodes despite taking oral medicines. These additional patients were also clinically diagnosed as having PFAPA based on the diagnostic criteria of Thomas[6]. Symptoms disappeared in all patients after tonsillectomy (Table 2).

Results

Exome analysis identified 5 rare gene variants (in

Table 1. Characteristics of the PFAPA patients in whom exome analysis was performed

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age of onset (years)	15	2	1	2	2	1
Sex	Female	Female	Female	Male	Male	Male
Past history	Not remarkable	Not remarkable	Not remarkable	Not remarkable	Kawasaki disease, ITP, febrile seizures	Febrile seizures
Family history	None	None	None	Positive (father)	Positive (brother)	Positive (sister)
WBC (/μL)	7,400	11,700	11,800	8,400	15,100	22,200
Neutrophils (%)	78.5	71.7	70.7	34.6	60.8	82.8
CRP (mg/dL)	1.51	7.3	6.6	0.5	3.0	1.97
ESR (mm/hr)	11	37	27	26	35	—
IL-6 (pg/mL)	11	27.6	15.0	—	17.5	14.4
SAA (μg/mL)	283	760	326	38.6	181	928
IgD (mg/dL)	≤ 0.6	33.1	0.9	2.1	1.9	0.6
CH50 (U/mL)	48	55.0	69.0	—	57.0	—
Cimetidine	Not effective	Effective	Effective	Unknown	Effective	Not effective
Steroids	Effective	—	Effective	—	—	Effective
NSAIDs	—	Not effective	—	—	—	—
Colchicine	Effective	Effective for abdominal pain	Effective	Unknown	—	—
Tonsillectomy	—	—	—	—	—	Effective

ITP : Idiopathic thrombocytopenic purpura

Table 2. Characteristics of the PFAPA patients in whom tonsillectomy was performed

	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age of onset (years)	10	3	1	3	5
Sex	Male	Female	Female	Male	Female
Past history	OMA	OMA, sinusitis	OMA, sinusitis	Bronchial asthma	Not remarkable
Family history	Negative	Negative	Negative	Unknown	Positive (mother)
Response to therapy					
Cimetidine	Not effective	Unknown	Partially effective	Not effective	Partially effective
Tonsil pathology					
Chronic active tonsillitis with lymphoid hyperplasia	+	+	+	+	+
Bacterial colonization	+	−	−	+	−
Tingible body macrophages	−	+	+	+	−

OMA : acute otitis media

MYCL, *VPS8*, *NUP54*, *PCDHA8*, and *LRIT2*), and all 5 gene variants were found in 2 of the patients. In addition, multiple rare variants were found in 4 patients. Of these identified genes, only *VPS8* was identified to be significantly associated with PFAPA using PolyPhen-2 predict scores, regardless of tolerated SIFT scores (Table 3). There was no common significant haplotype of genes previously reported to be associated with PFAPA (*MEFV*, *NRLP3*, *SPAG7*, *NOD2*, *TNFRSF1A*, *ALPK1*, and *IL12A*), as shown in Table 4. In our haplotype analysis, 1 patient showed a rare variation in the 5′ UTR of *NOD2*.

Regarding the clinical findings, both patients with rare *VPS8* gene variants had a family history of PFAPA. Patients with the *PCDHA8* variant had joint pain and abdominal pain. Colchicine was effective for patients with *MYCL* variants, although the patients showed no variations in *MEFV*, which are known to correlate with Familial Mediterranean fever (FMF). Patients with each variant showed no obvious differences in their laboratory findings and clinical symptoms.

All analyzed tonsils (n = 5) obtained by tonsillectomy demonstrated characteristics of chronic active tonsillitis with lymphoid hyperplasia, accompanied with bacterial colonization in 2 of the 5 tonsils, and tingible body macrophages together with neutrophil infiltration in 3 of the 5 tonsils (Fig. 1, Table 2). The colonizing bacteria was suspected to be *Actinomycetes* in 1 tonsil.

Discussion

Various symptoms occur during a regular febrile flare in PFAPA, accompanied with an increase in the levels of inflammatory markers, which is similar to other autoinflammatory disorders with a genetic basis.

Table 3. Results of exome analysis

Rare variant model	
Exon splice variants found in all patients	43,050
-Segmental duplication	39,457
Nonsynonymous, frameshift variant	18,667
Allele frequency < 0.5% (HGVD, ToMMo, 1,000 g, gnomAD)	2,554
-Inhouse	1,784
Common variants	9
Remainder	5

Gene	Function	AA change	HGVD 20160412	ToMM 20180219	PolyPhen 2 HVAR	PolyPhen 2 HDIV	SIFT	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
MYCL	Exonic	NM_005376 : exon2 : c.C695T : p.P232L	0.003162	0.0019	0.093	0.004	0.027	Hetero		Hetero			
VPS8	**Exonic**	**NM_001349292 : exon35 : c.C2942T : p.A981V**	0.002267	0.0023	0.455*	0.446	0.167					**Hetero**	**Hetero**
NUP54	Exonic	NM_017426 : exon6 : c.A749T : p.N250I	.	.	.		.				Hetero		Hetero
PCDHA8	Exonic	NM_018911 : exon1 : c.G28A : p.G10R	.	0.0039	0.149	0.09	0.242	Hetero	Hetero				
LRIT2	Exonic	NM_001284223 : exon4 : c.C1346T : p.P449L	0.001813	0.0031	0.201	0.256	0.01		Hetero			Hetero	

*represents “possible damaging”

Table 4. Polymorphisms of genes reported to be associated with PFAPA

Gene	avsnp150	Function	AA change	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
MEFV	rs224212	Intronic			TC		TC	CC	TC
NLRP3	rs3738447	Intronic		GA					
NLRP3	rs76255469	Intronic					GA*		
SPAG7	rs12451097	Intronic		AA	GA	AA		GA	AA
SPAG7	rs73343381	Intronic		AA					AA
NOD2	rs2076752	UTR5	NM_022162.3 : c.-59G>A						GA
NOD2	rs2076753	UTR5	NM_001293557.2 : c.-33G>T						GT
NOD2	rs1077861	Intronic		AT	AT				AT
TNFRSF1A	None								
ALPK1	None								
IL12A	None								

*coverage 32

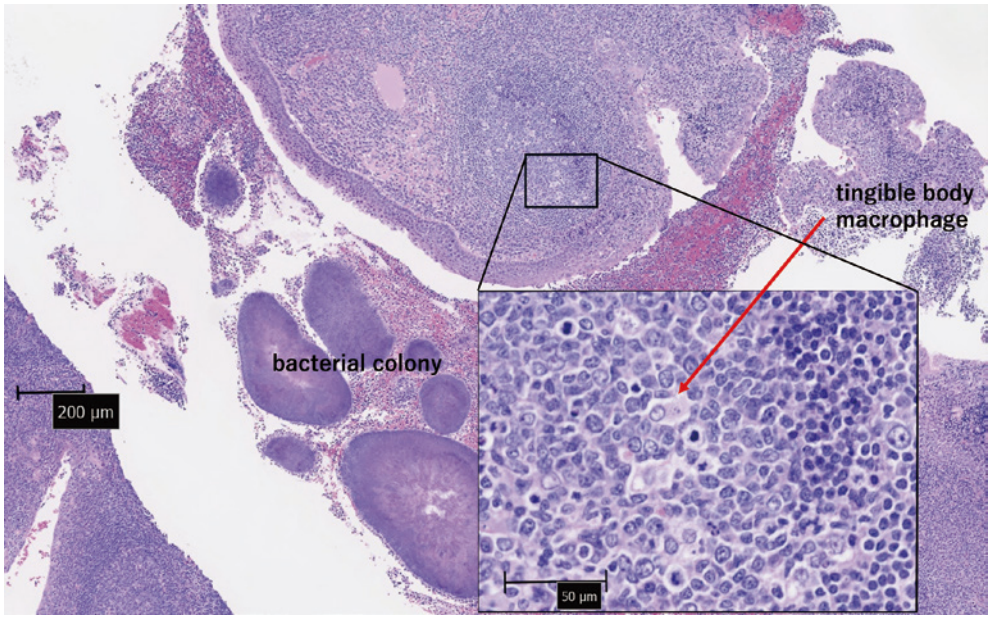

Fig. 1. Tingible body macrophages in a tonsil of a PFAPA patient, detected by Hemotoxylin and Eosin staining (The scale bars represent each length. An enlarged view is shown in the lower right.)
There are bacterial colonization and tingible body macrophages.

Family clusters of PFAPA are rarely observed. It was first reported in 1987 by Marshall et al., that 2 out of the 12 patients were siblings[1]. However, their causative gene has remained unknown to date.

There are some reports regarding the involvement of other inflammasome-associated genes in PFAPA. Asna Ashari et al. analyzed the associations of PFAPA with variations in several genes, such as *MEFV*, *NLRP*, *TNFRSF1A*, *CARD15/NOD2*, and *MVK*. They demonstrated that a single gene was not found to be associated with PFAPA, and that the disease might have a multifactorial or polygenic basis, in which an environmental trigger can provoke inflammasome activation and activate PFAPA flares[10]. Celiksoy et al. analyzed 64 patients with PFAPA, and reported that heterozygous or compound heterozygous variants of the *MEFV* gene were found in 42 (66%) patients. They concluded that most patients presenting with PFAPA are heterozygous for *MEFV* gene variants. However, no significant differences in clinical or laboratory findings were observed between PFAPA patients with and without *MEFV* gene variants[3]. Cheung et al. performed next-generation sequencing on 82 unrelated PFAPA patients, and identified a frameshift variant in the *CARD8* gene (CARD8-FS). They compared the frequency of CARD8-FS carriers in their PFAPA cohort (13.9%) with a healthy local population (3.2%)[11]. In the present study, we could not find any similar gene variants to those that have been reported in autoinflammatory diseases, except for the common variants of *MEFV* in Japanese controls.

Some other genes have been reported to be associated

with PFAPA. Sangiorgi et al. performed a similar exome analysis to ours and found only 1 variant i.e., c.2770T>C p.(S924P), in the *ALPK1* gene in affected family members. The *ALPK1* gene is expressed in various tissues, and its protein is an intracellular kinase activated by the bacterial ADP-heptose bisphosphate, which phosphorylates and activates. Sequencing analysis of 13 additional sporadic patients and 10 familial PFAPA patients identified 2 additional heterozygous missense variants, namely c.1024G>C p.(D342H) and c.710C>T p.(T237M), in 2 sporadic patients[12]. Manthiram et al. reported that the *IL12A* (rs17753641) variant is strongly associated with PFAPA, Behçet's disease, and recurrent aphthous stomatitis in European-American cohorts and a Turkish cohort[13]. Bens et al. also found *SPAG7* as a candidate gene for PFAPA by cloning followed by long insert size paired-end sequencing of a *de novo* chromosomal translocation, t(10 ; 17)(q11.2 ; p13), in a patient with typical PFAPA syndrome lacking any variations in genes associated with other periodic fever syndromes. The SPAG7 protein has been functionally linked to antiviral and inflammatory responses. Sequence analyses of *SPAG7* in other patients with PFAPA have pointed to genetic heterogeneity or alternative mechanisms of SPAG7 deregulation, such as somatic or epigenetic changes[14]. In the present study, we did not identify any previously reported variants of *ALPK1* and *SPAG7*, or SNPs in *IL12A* in the patients.

We found that patients with *VPS8* variants had a history of other immune response-associated disorders, and a family history (siblings) of PFAPA. Other genes that were previously reported to be associated with PFAPA were not identified in this study. Four other rare variants of *MYCL*, *NUP54*, *PCDHA8*, and *LRIT2* were detected in patients without a family history of PFAPA. *MYCL*, which is a proto-oncogene, is unlikely to be involved in the pathophysiology of PFAPA, as it is expressed mainly in the skin and pancreas. However, there have been many reports in recent years on the association between MYC and the activation of immune cells. Mycl1 supports the function of classical type I dendritic cells[15]. Colchicine also promotes antigen cross-presentation by murine dendritic cells[16]. Therefore, there is a possibility that *MYCL* is associated with the pathology of some PFAPA patients, because colchicine was effective in some patients. *NUP54*, which is expressed mainly in the bone marrow and testis, is a member of the nuclear pore complex, which is a large supramolecular assembly that spans the nuclear envelope and mediates molecular exchange between the nucleus and cytoplasm. *PCDHA8* is a member of the protocadherin alpha gene cluster, which is 1 of 3 related gene clusters that are tandemly located on chromosome 5, which demonstrate an unusual genomic organization similar to that of B-cell and T-cell receptor gene clusters, and most likely plays a crucial role in the establishment and function of specific cell-cell connections in the brain. Somatic variants of *LRIT2* have been detected in various cancers. These genes, except for *VPS8*, were unlikely to be associated with PFAPA according to their predicted scores from exome analysis in our present study. However, new immunological actions of these genes are currently being identified one after another. Therefore, the possibility of the association other periodic inflammatory diseases cannot be denied.

The detected SNP of *VPS8* (rs142178072) was a rare variant (in the East Asian genomeAD : 0.005019, ToMMO 2018 : 0.0023), and assumed as "Uncertain significant" by InterVar. VPS8 is a component of the class C core vacuole/endosome tethering (CORVET) complex, which takes extracellular substances into a cell and transports it to the Golgi apparatus and lysosome by endocytosis. Endocytosis begins with the formation of endocytic vesicles from the plasma membrane. Early endosomes fuse with each other and undergo changes in morphology, cargo, lipid composition, subcellular position, and intraluminal acidity. VPS8 is the effector subunit of the CORVET complex, which is required for homotypic fusion of early endosomes[17]. In particular, VPS8 is involved in the specialized recycling pathway needed to transport integrins from the early to recycling endosomes. Depletion of the CORVET-specific subunit of VPS8 inhibits homotypic fusion of early endosomes and impairs the conversion of early endosomes to late endosomes[18]. VPS8 is responsible for the endocytosis step of phagocytosis, and consequently regulates the production of cytokines in macrophages[19]. As the conservation score of exon 35 of *VPS8* was high, this exon, which includes the variant that we identified in this study, is a highly conserved region (Fig. 2). No family history was observed even in patients without *VPS8* variants. The *VPS8* gene is thought to be associated with the elimination of bacteria from the body. In addition, the overexpression of VPS8 has been reported to inhibit autophagosome clearance[20]. Pathological analysis of PFAPA patient tonsils showed the frequent presence of tingle body macrophages and bacterial colonization. The tingible body macrophage is a type of macrophage that is predominantly found in germinal centers, which contain many phagocytosed apoptotic cells in various states of degradation, referred to as tingible bodies of chromatin fragments. Treatments for PFAPA include tonsillectomy, a single dose of corticosteroids, and most recently, interleukin-1 blockers, such as anakinra, rilonacept, and canakinumab. Tonsillectomy remains the only permanent treatment[21]. Therefore, bacteria that escape the body's immunological reaction might

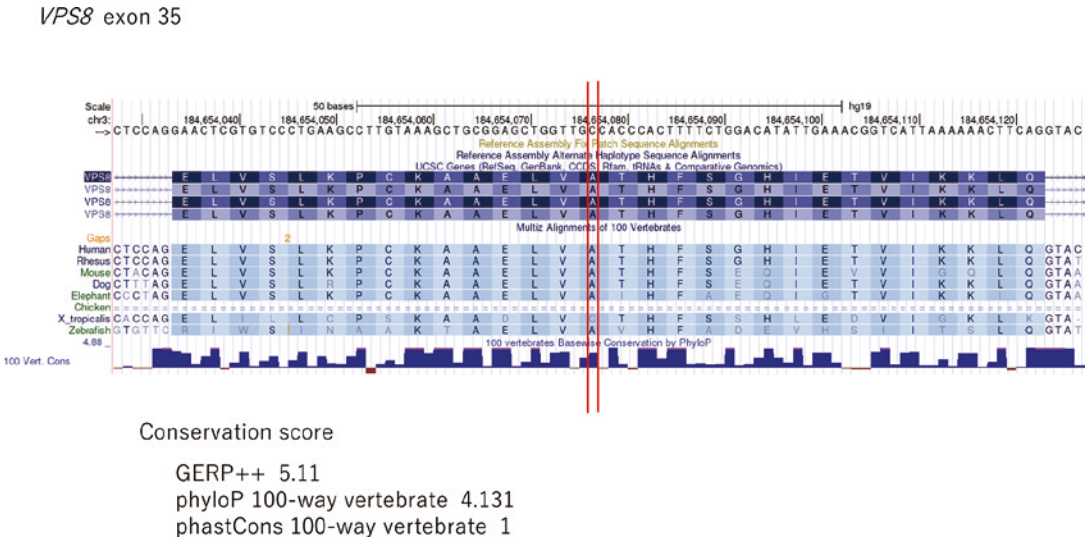

Fig. 2. Sequence conservation analysis of *VPS8* exon 35 : Exon 35 is highly conserved among many species.

cause refractory fever. Many types of bacteria survive in cells, such as *Streptococcus pyogenes* and *Chlamydia pneumoniae*. We found bacterial colonization in the tonsils of patients, which were surgically removed to cure PFAPA. Patients with intractable PFAPA are usually effectively cured after tonsillectomy. The *VPS8* gene is thought to be associated with phagocytosis in the body. Therefore, the tonsil might be the site of recurrent infection in such patients with intractable PFAPA, who do not have an adequate system of bacterial elimination. Therefore, the *VPS8* variant is suspected to correlate with PFAPA. However, these findings of the tonsils are not specific to patients with PFAPA, and hence further studies are needed to conclude the role of bacterial colonization in the pathophysiology of PFAPA.

Conclusion

VPS8, which plays an important role in phagocytosis, may be the causative gene for some cases of familial PFAPA. Further studies are required to confirm the association of genes involved in phagocytosis with the pathophysiology of PFAPA.

Compliance with ethical standards

The authors declare that they have no conflicts of interest to declare.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all participants included in this study.

Author contributions

KO and HK designed the study ; KO, SS, NA, and SN performed the experiments, and collected and analyzed the data ; KO wrote the manuscript ; TY and YK provided technical support and conceptual advice. All authors read and approved the final manuscript.

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PFAPA 症候群日本人患者における扁桃病理とエクソーム解析

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【要旨】背景：周期性発熱、アフタ性口内炎、咽頭炎、および腺炎（PFAPA）症候群は、病因が不明な自己炎症性疾患とされている。近年、他の自己炎症性疾患を引き起こすいくつかの遺伝子の変異が、PFAPA の症候群患者で確認されてきている。

目的：日本人 PFAPA 症候群患者に関する遺伝的背景を知り、病理学的、および臨床的情報を検討し、効果的な治療戦略を確立すること。

方法：PFAPA 症候群と診断された 1 歳から 15 歳までの 6 人の患者（男児 3 名、女児 3 名）をエクソーム解析の対象とし、血液検査データと臨床症状をエクソームデータと比較した。さらに、別の５例の患者において扁桃腺サンプルを病理学的に検討した。

結果：5 つのレアバリアントが同定され、各レアバリアントはおのおの 2 人の患者で同定された。臨床所見の比較では、*VPS8* 変異を持つ患者が PFAPA の家族歴を持っていた。コルヒチンは、*MEFV* 変異を持たない *MYCL* 変異の患者に効果的であった。各変異と検査所見に明らかな差はなかった。以前に報告のあった遺伝子のハプロタイプは今回対象患者では認められなかった。病理ではティンジブルボディマクロファージと細菌のコロニー形成が摘出扁桃に認められた。

結論：貪食機能おいて重要な役割を果たす *VPS8* 変異が家族歴のある PFAPA 患者の原因の可能性が示唆された。PFAPA の病態における實食機能の関与の結論にはさらに同一個人を対象とした研究が必要である。

〈キーワード〉 *VPS8*、*MEFV*、*MYCL*、細菌コロニー、colchicine