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ORIGINAL ARTICLE

Utility of a targeted next-generation sequencing-based genetic screening panel in patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome

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ABSTRACT

Objectives: This study aims to investigate a genetic panel in patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome and examine its performance for an accurate differential diagnosis.

Patients and methods: Between January 2021 and January 2022, a total of 104 children with PFAPA syndrome (63 males, 41 females; mean age: 4.8±2.3 years; range, 1.2 to 8.9 years) were retrospectively analyzed. Next-generation sequencing test was performed using a custom QIAGEN- QIAseq™ Targeted DNA Panel which includes six genes namely *ELANE, LPIN2, MEFV, MVK, NLRP3*, and *TNFRSF1A*.

Results: Of 104 patients, 38 (36.5%) had variants in the genetic panel. The most common variants were found in the *MEFV* gene (n=35, 33.6%), the most frequent genotype was E148Q heterozygosity (n=16). Four and two patients were eventually diagnosed with Familial Mediterranean fever (FMF) and hyperimmunoglobulin D syndrome (HIDS), since they had confirmative biallelic pathogenic in the *MEFV* and *MVK* genes, respectively.

Conclusion: A genetic panel, including *MEFV* and *MVK* genes, may be useful in patients, clinically resembling PFAPA, since they may have HIDS or FMF, but lack typical features of the exact disease. Nonetheless, we believe that distinct genetic panels should be developed for different populations.

Keywords: Adenitis syndrome, aphthous stomatitis, familial Mediterranean fever, MEFV, mevalonate kinase deficiency, periodic fever, pharyngitis.

Autoinflammatory diseases (AIDs) comprise a variety of disorders mainly characterized by systemic inflammation and organ-specific manifestations, resulting from the alterations in the innate immune system. There are several genes, of which the alterations have been linked to distinct AIDs, named monogenic AIDs. Periodic fever is one of the most common manifestations of monogenic AIDs, including familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS) or mevalonate kinase deficiency (MKD), cryopyrin-associated periodic syndrome (CAPS).[1]

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA) is one of the most common periodic fever syndromes; however, although several susceptibility genes have been proposed, an identifiable monogenic cause could not explain the entire disease to date. It usually starts before five years of age and is characterized by the regular attacks of fever, accompanied by

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pharyngitis and sometimes oral aphthous ulcers and cervical lymphadenopathy. Although the fever attacks are devastating and interrupt the daily well-being, they are always self-limiting and do not affect physical growth.[2,3]

Fever, pharyngitis, oral aphthous ulcers and cervical lymphadenopathy can be also seen in MKD, TRAPS, CAPS, and cyclic neutropenia, of which the latter is a hematological disorder, characterized by recurrent neutropenia caused by mutations in *ELANE* gene.[1,4] Moreover, although characteristic signs of Majeed syndrome due to *LPIN2* mutations are chronic bone changes, it usually presents with recurrent fever and musculoskeletal pain in early childhood. Within disease progression, recurrent osteomyelitis and neutrophilic dermatosis lead to differentiation from PFAPA.[5,6] Therefore, due to these overlapping features between periodic fever syndromes, and the absence of a definite tool for PFAPA diagnosis, several patients with monogenic diseases may be misdiagnosed with PFAPA.

In the present study, we aimed to investigate six genes related to periodic fever in children, clinically compatible with PFAPA, and to determine the performance and necessity of a genetic panel for an accurate differential diagnosis of children with PFAPA.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Adana City Training and Research Hospital, Department of Pediatric Rheumatology between January 2021 and January 2022. A total of 104 children with PFAPA syndrome (63 males, 41 females; mean age: 4.8±2.3 years; range, 1.2 to 8.9 years) were included. The diagnosis of PFAPA was made by a single pediatric rheumatologist and all patients fulfilled both the modified Marshall criteria and EUROFEVER.[2,7] We attempted to examine whether we misdiagnosed some patients with monogenic causes as PFAPA in the clinical practice. This genetic panel is currently available in our center and, therefore, we routinely perform this genetic analysis in patients compatible with PFAPA. Patients with suggesting features for other AIDs, immunodeficiencies, and neutropenia during an inflammatory attack were excluded. Clinical and demographic data were retrieved from the medical files of the patients.

Genetic analysis

Genomic deoxyribonucleic acid (DNA) extraction and targeted next-generation sequencing was performed. The genomic DNA of the patient was extracted from peripheral blood sample using QIAGEN QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's protocol. The DNA integrity was confirmed using the Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA USA). Next-Generation Sequencing test was performed using a custom QIAGEN- QIAseq™ Targeted DNA Panel includes six genes namely *ELANE*, *LPIN2*, *MEFV*, *MVK*, *NLRP3*, and *TNFRSF1A*. The test platform examined >95% of the target gene with a sensitivity more than 99%. The test platform screened >95% of the target gene with greater than 99% sensitivity. The variants which passed through the filters were analyzed with QIAGEN Clinical Insight (QCI) software according to the pathogenicity scores, in-silico prediction tools, and genotype-phenotype correlation.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The normality distribution was performed using the Kolmogorov-Smirnov test. Data were compared between the two groups of patients according to the presence of a significant alteration in the genetic panel by chi-square, parametric Student t-test, and non-parametric Mann-Whitney U test, where appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the patients are presented in Table 1. The median fever duration was 4 (range, 2 to 7) days and fever attacks occurred with a median duration of 30 (range, 10 to 60) days.

Table 1. Demographic and clinical features of patients

Variables	n	%	Mean±SD	Median	Range
Current age (year)			4.8±2.3		
Sex Female	41	39.4			
Age at diagnosis (year)			4.0±1.7		
Age at symptom onset (month)				8	1-48
Recurrent fever	104	100			
Pharyngitis	103	99			
Oral aphthous ulcers	37	35.6			
Cervical lymphadenopathy	31	29.8			
Abdominal pain	46	44.2			
Arthralgia	18	17.3			
Diarrhea	2	1.9			
Rash (maculopapular)	1	1			

SD: Standard deviation.

The genetic results of the patients are summarized in Table 2. Of 104 patients, 38 (36.5%) had variants in the genetic panel. Four patients had variants in two genes. The most common variants were found in the *MEFV* gene (n=35, 33.6%) and the most frequent genotype was E148Q heterozygosity (n=16). Eleven patients had mutations in exon 10, of which four was homozygous or compound heterozygous. Two

Table 2. Results of the next-generation sequencing panel for periodic fever syndromes: frequency and pathogenicity of the genetic alterations

Gene/transcript	Alteration	Frequency (n)	Pathogenicity
MEFV (NM_000243)	E148Q/wt	19	Uncertain significance
	E148Q/R761H	1	Uncertain significance/pathogenic
	R314H	1	Uncertain significance
	N256Rfs*70/wt	1	Likely pathogenic
	T267I/wt	1	Likely pathogenic
	P369S/wt	1	Uncertain significance
	M680I/M680I	1	Pathogenic
	M680I/V726A	1	Pathogenic
	M694V/M694V	2	Pathogenic
	M694V/wt	1	Pathogenic
	K695R/wt	2	Likely pathogenic
	V726A/wt	3	Pathogenic
	A744S/wt	1	Uncertain significance
MVK (NM_000431)	V377I/V377I		Pathogenic
	V377I/G140Rfs*47		Pathogenic
NLRP3 (NM_001079821)	V198M/wt	1	Uncertain significance
LPIN2 (NM_014646)	D383V/wt	1	Uncertain significance
	Y235C/wt	1	Uncertain significance
ELANE (NM_001972.4)	S90L/wt	1	Uncertain significance
	E250K/wt	1	Uncertain significance

patients (4.4 and 4.7-year-old) had M694V homozygosity, one had M680I homozygosity (7-year-old) and another had M680I/V726A compound heterozygosity (5.5-year-old).

Two patients were eventually diagnosed with HIDS/MKD since they had confirmative biallelic pathogenic in the *MVK* gene. The first MKD patient, a seven-year-old girl, did suffer from recurrent fever attacks lasting three to six days every three to four weeks since the third month of her life. Fever attacks were usually accompanied by pharyngitis, oral aphthous ulcers, cervical lymphadenopathy, and abdominal pain, besides, her father and uncle had similar fever episodes during their early childhood. She had compound V377I/Gly140fs mutation in the *MVK* gene, whereas her parents were found heterozygous for these mutations in family screening. Another MKD patient, a six-year-old boy, had the similar fever attacks since three months of age and had homozygote V377I mutation in *MVK* gene. Both patients did not have skin rash or diarrhea during these attacks, thereby resembling the PFAPA phenotype.

One of the patients, a seven-year-old girl, suffering from recurrent fever and pharyngitis attacks since one year of age had a heterozygous missense variant of uncertain significance (VUS), c.748G>A (p.Glu250Lys, E250K) in *ELANE* gene (NM_001972.4) and a heterozygote E148Q mutation in *MEFV* gene. She had no other complaints, such as abdominal pain, arthralgia, lymphadenopathy, or oral aphthous ulcers. Another patient had a heterozygote S90L mutation in the *ELANE* gene, which could not explain the fever attacks, since neutropenia could not be encountered in laboratory studies.

One patient had both a heterozygous V726A mutation in the *MEFV* gene and a missense VUS, c.592G>A (p.Val198Met, V198M) in the *NLRP3* gene. This four-year-old patient had no urticarial skin rash and fever attacks started after his first birthday with three to four days duration accompanied by oral aphthous ulcers and pharyngitis and his attacks were colchicine responsive.

Two further patients had heterozygote missense c.1148A>T (p.Asp383Val, D383V) and c.704A>G (p.Tyr235Cys, Y235C) variants in the *LPIN2* gene, which were previously classified as VUS. These patients had no typical findings of Majeed syndrome.

No variants in the *TNFRSF1A* gene could be identified in the genetic analysis of the

Table 3. Comparison of demographic and clinical properties of children with PFAPA syndrome, grouped according to the presence of underlying genetic alteration

	Patients with a gene mutation (n=38)					Patients lacking a gene mutation (n=66)					
Variables	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Sex Female	19	50				22	33.3				0.101
Current age (year)			4.7±2.2					4.8±2.31			0.520
Age at diagnosis (year)			4.2±1.9					4.0.±1.6			0.367
Age at symptom onset (month)				8.5	1-48				8	2-36	0.882
Attack duration (days)			3.8±1.2					4.0±1.1			0.181
Attack period (days)			28±7.9					26.4±8.3			0.290
Pharyngitis	37	97.4				66	100				0.365
Oral aphthous ulcers	14	36.8				23	34.8				0.835
Cervical lymphadenopathy	10	26.3				21	31.8				0.658
Abdominal pain	19	50				27	40.9				0.416
Arthralgia	5	13.2				13	19.7				0.436
Diarrhea	2	5.3				0	0				0.131
Rash (maculopapular)	1	1.5				0	0				0.635

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis; SD: Standard deviation; P values below 0.05 are statistically significant.

Table 4. Comparison of demographic and clinical properties of children with PFAPA syndrome, grouped according to the presence of exon 10 mutations in *MEFV* gene

	Patients with exon 10 mutations in *MEFV* gene (n=12)					Patients lacking exon 10 mutations in *MEFV* gene (n=90)					
Variables	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Sex Female	5	41.7				35	38.9				0.544
Current age (year)			4.5±1.9					4.8±2.3			0.647
Age at diagnosis (year)			4.0±1.6					4.0±1.7			0.983
Age at symptom onset (month)				10	2-48				8.5	1-36	0.094
Attack duration (day)			3.4±1.1					4.0±1.1			0.095
Attack period (day)			32.5±10.7					26.4±7.6			0.083
Pharyngitis	12	100				89	98.9				0.882
Oral aphthous ulcers	3	25				32	35.6				0.354
Cervical lymphadenopathy	2	16.7				27	30				0.277
Abdominal pain	4	33.3				40	44.4				0.342
Arthralgia	3	25				14	15.6				0.319
Diarrhea	0	0				1	1.1				0.882
Rash (maculopapular)	0	0				1	1.1				0.882

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis; MEFV: Mediterrenean Fever; SD: Standard deviation; Patients eventually diagnosed as having Mevalonate kinase deficiency were excluded; P values below 0.05 are statistically significant.

patients. Demographic and clinical features did not statistically differ between the patients regarding the presence of a positive-genetic result or not (Table 3). Furthermore, after excluding MKD cases, we compared the data according to the presence of exon 10 mutations in the *MEFV* gene. We again could not find any statistically significant difference in demographic and clinical parameters between the groups (Table 4).

Tonsillectomy was performed in 23 (23.5%) patients and 22 of them (91.7%) had a favorable response to the procedure. Colchicine was initiated in 37 (76.9%) patients, of which 30 (76.9%) responded well to the treatment. The remaining patients were given non-steroidal anti-inflammatory drugs or systemic corticosteroids during fever attacks due to the refusal of the aforementioned treatment approaches.

DISCUSSION

The pathogenesis of PFAPA is still controversial and suggested to have polygenic inheritance since no identifiable gene has been linked to the disease so far.[8] Given the periodicity, self-limiting nature of the disease, and the elevated levels of proinflammatory cytokines during inflammatory attacks, dysregulation of the innate immune system has been proposed in the pathogenesis of PFAPA.[9] Familial aggregation is another hallmark of the disease, since half of the patients with PFAPA have recurrent fever and tonsillectomy history among their parents and siblings.[10,11] A flowchart diagram regarding the diagnosis and treatment of the patients with PFAPA is shown in Figure 1.

Genetic studies and approaches have been performed to identify a specific gene for PFAPA; however, they cannot confirm a one-gene hypothesis. Therefore, it has been hypothesized that PFAPA may be a milder AID, resulting from some alterations in genes responsible for other AIDs.[12] This hypothesis has been examined in several studies investigating the role of *MEFV* mutations in PFAPA patients in FMF endemic regions. Yildiz et al.[13] from Türkiye showed that 59.9% of PFAPA patients had at least one *MEFV* mutation and the most common variants were M694V, E148Q, and V726A, in descending order. Another study from Iran

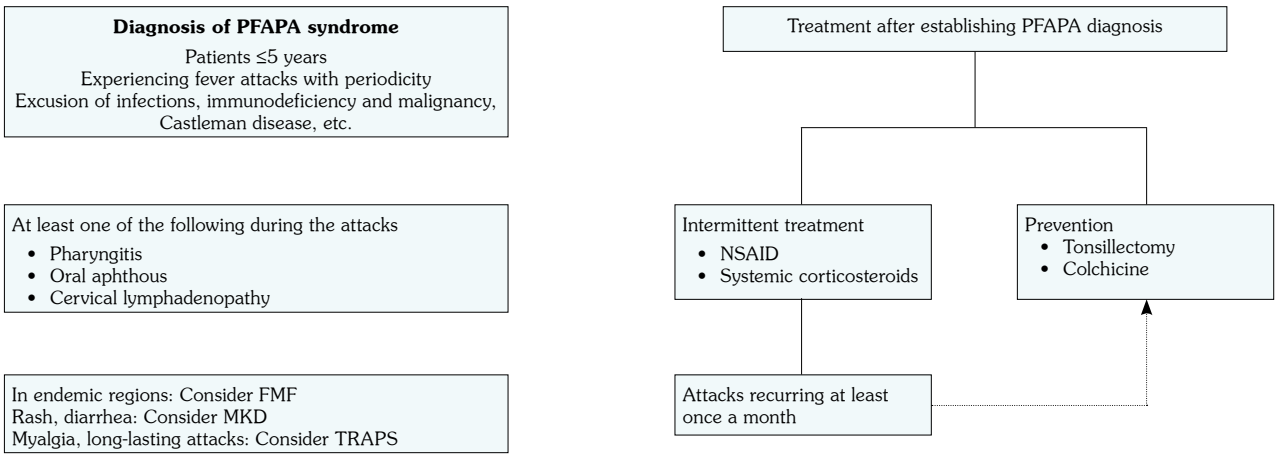

Figure 1. Flowchart diagram for the diagnosis and the treatment for patients with PFAPA.

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis; MEFV: Mediterrenean Fever; NSAIDs: Non-steroidal anti-inflammatory drugs; FMF: Familial Mediterranean fever; MKD: Mevalonate kinase deficiency; TRAPS: Tumor necrosis factor receptor-associated periodic fever syndrome.

found *MEFV* mutations in 38% of the PFAPA patients.[14] Similarly, we identified at least one *MEFV* mutation in 33.6% of PFAPA patients in our study. In the aforementioned study, the authors emphasized that the age at disease onset was higher, and the duration of attacks was shorter in patients with exon 10 mutations in the *MEFV* gene than in others, whereas the clinical symptoms and treatment responses were similar.[13] Again, disease characteristics did not significantly differ between the patients classified according to *MEFV* genotype in our study and we found older age at symptom onset and shorter attacks in patients with exon 10 mutations in the *MEFV* gene, although the difference was not statistically significant. These results confirm that the disease presentations and severity can be affected by other genetic or environmental factors rather than *MEFV* mutations alone.

Another cohort from Slovenia investigated patients with PFAPA with a two-gene panel, including *MEFV* and *NLRP3*.[14] Contrary to the results from our country where FMF is more common, this study demonstrated E148Q and I591T heterozygosity in only two of 30 patients. Besides, they found several *NLRP3* variants in nine of 30 PFAPA patients. This difference could be explained by the lower frequency of *MEFV* alterations in European countries. We also believe that several distinct genes can stand out in the pathogenesis of PFAPA among distinct regions of the world. In the regions endemic to FMF, the differential diagnosis may be more challenging. The regularity of the fever attacks, and the upper respiratory system symptoms could lead to the PFAPA diagnosis.[15] Besides, some patients may exhibit PFAPA and FMF at the same time and, therefore, it is not surprising that clinicians perform *MEFV* gene analysis in most PFAPA patients in endemic regions. A recent review revealed the association between *MEFV* mutations and PFAPA and suggested that *MEFV* mutations might cause shorter fever duration, longer fever-free intervals, and lower doses of corticosteroid administration during attacks of PFAPA patients.[16] Moreover, a recent case report showed a PFAPA-like phenotype, responsive to both systemic steroids and colchicine treatment in a patient eventually diagnosed as having TRAPS.[17] The authors highlighted the presence of myalgia and the long duration of fever attacks were not usual for PFAPA and should lead to further evaluation of such patients.

One of the most insightful studies was performed by Di Gioia et al.,[11] which investigated a definite genetic cause of PFAPA in patients with family clustering. However, this study also failed to show a single responsible gene. Similar to our study, the authors showed I591T and E148Q heterozygosity in the *MEFV* gene of three patients from six families; however, these alterations could not be held responsible for the phenotype due to the absence in other affected family members. The same study tested the phenotypic effect of

V198M mutation in the *NLRP3* gene, which was previously linked to milder forms of CAPS patients in the literature.[18,19] This mutation was found in unaffected members of the family and absent in the affected proband.[11] Our patient with that mutation in *NLRP3* gene lacked the classical phenotype for CAPS, which led us ask whether this change can lead to a milder disease, however, this study confirmed its non-pathogenicity.

The genetically confirmed two MKD patients in our PFAPA cohort was remarkable that we misclassified these patients as PFAPA with the clinical criteria, since these patients had no skin rash, and distinct gastrointestinal symptoms, thereby resembling PFAPA. We emphasize that these diseases may sometimes phenotypically interfere with each other and early-onset cannot discriminate between these patients, since PFAPA may occur before the first birthday. Therefore, genetic analysis for HIDS or MKD should be performed before unnecessary and unsuccessful treatment protocols, such as colchicine or tonsillectomy.

A recent study revealed the final diagnosis of MKD in a patient previously diagnosed as FMF with heterozygote M694V mutation in the *MEFV* gene.[20] This report highlights the need for further genetic analysis in patients with one *MEFV* mutation and partial response to colchicine.

The two patients with M694V and one with M680I homozygosity patients were between four and seven years of age. Again, the presence of these FMF patients in our PFAPA cohort was insightful and we believe that the comorbidity of PFAPA and FMF may lead to PFAPA diagnosis before FMF onset, since symptoms of FMF may usually occur at later age. Most comprehensive cohort of PFAPA patients did not discriminate patients with homozygote *MEFV* mutations in contrast to our study; however, they found two patients with compound heterozygote mutations in the exon 10 of the *MEFV* gene.[21] These results also confirm our hypothesis.

The main limitation to this study is the lack of a control group, since we cannot compare the frequency of our results with the general population in the area where the study was performed. Besides, it is not a genome-wide study and, thus, the primary objective was not to determine the genetic basis of PFAPA. Indeed, we attempted to clarify whether we could classify some patients with monogenic AIDs, clinically compatible with PFAPA, and whether we could avoid misdiagnosis with a genetic panel, investigating genes responsible for the most common monogenic AIDs. We found two MKD and four further FMF patients with homozygote exon 10 mutations. Moreover, we found *MEFV* mutations in 33.6% of the PFAPA patients; however, we could not find any significant differences in demographic and clinical features between patients with or without *MEFV* mutations, either exon 10 mutations.

In conclusion, our study results suggest that some patients with MKD or FMF may be misdiagnosed as PFAPA without genetic analysis, since they may lack typical features for these disorders, or they may clinically overlap with PFAPA. However, we could not reveal any clinical parameters that led us to choose patients for further genetic evaluation. Further studies investigating a broad spectrum of genes for AIDs are needed to clarify whether the underdiagnosis is prominent and whether the genetic panel is cost-effective or not. We also highlight that our results cannot be generalized across the world, and reflects the necessity for our country; nonetheless, we believe that distinct genetic panels should be developed for different populations.

Ethics Committee Approval: The study protocol was approved by the Adana City Training and Research Hospital Institutional Local Ethics Committee (date: 16.12.2021, no: 95/1678). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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