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Clinical and Laboratory Parameters of Autoinflammatory Disorders in Single Tertiary Care Center

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ABSTRACT

Autoinflammatory diseases (AIDs) are disorders with an inborn error of innate immunity, characterized by recurrent episodes of fever and inflammatory attacks. The spectrum of AIDs is expanding, but there are no standardized clinical criteria for the diagnosis of the patients. This study aims at establishing the first autoinflammatory registry of an Iranian population focusing on the clinical and laboratory features that may help clinicians for a better understanding and diagnosis of these disorders.

Clinical and laboratory characteristics of patients who were clinically and or genetically diagnosed with AIDs were collected for 15 years. The updated version of classification criteria from the Eurofever Registry was used for the clinical diagnosis.

Twenty-eight patients (16 males and 12 females) with a mean±SD age of 28.03±14.49 years (from 2 to 68 years) entered this study. About 29% were genetically diagnosed. Familial Mediterranean fever (FMF) was the most common diagnosis of the patients. Fever duration episodes were between 1-10 days. Some of the clinical manifestations from the most to the least common were as follows: arthralgia and arthritis (80%), myalgia (76%), coughs and shortness of breath (68%), fatigue (60%), abdominal pain (56%), increased erythrocyte sedimentation rate(ESR) (48%), and splenomegaly (24%).

Here, we presented the most common clinical manifestations of Iranian AIDs who have registered in our AID registry which would be a useful guide for managing the same patients and also designing the future studies.

Keywords: Cryopyrin-associated periodic syndromes; Familial Mediterranean fever; Hereditary autoinflammatory diseases

INTRODUCTION

The term autoinflammatory diseases (AIDs), also called periodic fever syndromes, describes an emerging family of distinct hereditable disorders associated with recurrent episodes of fever and severe inflammation affecting the skin, joints, gut, and eyes. Abnormally elevated inflammation in AIDsis due to the deregulation

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of cells and molecules of the innate immune system with a significant host genetic predisposition. It is important to note that this new category of diseases is a group of clinical disorders other than autoimmune diseases.[1,2]

AIDs have been recently classified as primary immunodeficiency.[3] AIDs include a broad number of monogenic disorders such as familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), mevalonate kinase deficiency (MKD), tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS), and multifactorial disorders such as Behçet's, Stills disease, and Blau syndrome.[4] The main difference between these disorders with autoimmune diseases is that neither autoantigens nor autoantibodies are involved in their pathophysiology.[5] However, the majority of clinical manifestations of these disorders are similar to rheumatologic diseases such as arthralgia and arthritis, skin rash, myalgia, and ophthalmologic problems. Therefore, clinicians may have difficulties in differentiating between these disorders. Due to the rarity of these diseases and the fact that they are still under research worldwide and as a limited number of studies are available, providing a registry of AIDs is the main required step to have access to the patients' samples for the long-term, conduct basic research, make novel findings, recognize and confirm biomarkers, discover novel genes, and improve new therapeutic strategies. Therefore, in this study, we introduced a registry for AIDs patients to highlight the most common manifestations of AIDs in a population of Iranian origin that can be used as evidence-based clinical criteria for the diagnosis.

MATERIALS AND METHODS

Study Group

We directed a cross-sectional study. Data extracted from patients' registery were recorded in the first Iranian registry for AIDs. This registry was established in 2018 and suspected individuals referred from immunology clinics and Immunology Research Centers affiliated with Isfahan University of Medical Sciences were registered.[6] Exclusion criteria were patients with positive autoantibodies known for autoimmune disorders, individuals who were suspected of Immunodeficiency disorders, and those who did not provide consent to participate in the study. After having been fully informed about the purpose of the study, all the participants provided both verbal and written consent to participate in the study. The Ethics Committee of Isfahan University of Medical Sciences approved the study design ethics Committee code IR.MUI.MED.REC.1397.283. A clinical immunologist blinded to the study made the diagnosis for all the participants. To diagnose patients with FMF, the immunologist used either Tel Hashomer criteria or the updated version of classification criteria from the Eurofever registry. To diagnose the other subgroups of AIDs, the diagnostic criteria of the Eurofever registry were used.[7] It is of particular significance that both the afore-mentioned diagnostic criteria are valid for this reason. Demirkaya and his colleagues have shown that Tel Hashomer criteria have the highest specificity for the diagnosis of FMF.[8] In this study, we have used the gene panel of primary immunodeficiency patients based on 407 genes proposed in the International Union of Immunological Societies (IUIS) 2019. Whole exome sequencing (WES) was done in some of the patients and then the identified mutations by WES were confirmed by Sanger sequencing. Then, genetic analysis was performed for other first-degree relatives by Sanger sequencing and their information was collected.

Data Collection

Clinical and laboratory characteristics of the participants were collected through their files, questionnaires, and previous medical interviews. These data include detailed demographic information, age at the time of disease diagnosis, disease course manifestation, ahe duration of attacks, atypical symptoms, history of atopy and autoimmune disorders, parental consanguinity, family history of autoinflammatory or immunodeficiency disorder, laboratory and imaging studies as well as complications, and response to treatment. Data were collected in the Excel spreadsheet and converted for analysis by the SPSS version 16. The average maximum and minimum values were used for quantitative variables. Analysis of variance was utilized to compare quantitative variables for more than 2 groups. Pearson's chi-square test was used to compare nominal/ordinal variables among groups. A *p*-value lower than 0.05 was considered statistically significant. We evaluated the prevalence of each symptom and compared the characteristics of participants with the same diagnosis in one table.

RESULTS

The clinical and laboratory data of 28 patients with AID were evaluated. The classification of the registered

patients was according to the IUIS2018. Most of the patients had Fars ethnicity. Twelve patients were female. The male to female ratio was 1.33. Their median age at the last visit was 28.03±14.49 years old (ranging between 2 and 68 years). Their age at the time of disease onset was 18.70±14.09 years old and ranged from 15 days to 58 years. Age at disease onset was not seen to be significantly different between men (19.31±9.03) and women (26.94±17.61) (p=0.19). Ten out of 28 were diagnosed genetically. FMF was the most common diagnosis. It was genetically diagnosed in 5 patients with mutations in the Mediterranean fever (MEFV) *gene*.

One patient had a mutation in the *PSTPIP*1 gene with a clinical diagnosis of Pyogenic arthritis, pyodermagangrenosum, and acne (PAPA) syndrome. One patient had a mutation in the *NLRP12* gene and a clinical diagnosis was consistent with Familial cold autoinflammatory syndrome-2 *(*FCAS2*)*. Another patienthada mutation in the *NOD2* gene and clinical manifestation of Blau syndrome and other patients were classified under undefined periodic fevers until their genetic analysis results were ready. The mean and standard deviation (SD) of the duration of attacks among participants was 3.53±2.80 days. The frequency of attacks per year was distributed widely and ranged from 3 to 48 times (14.18±9.93). Clinical and laboratory characteristics of patients are described in Table 1.

In our study, using the Tel-Hashomer criteria, we diagnosed 6 FMF patients. Five of them were associated with a mutation in the *MEFV* gene. The demographic and clinical characteristics of these patients are compared in Table 2. Cases 1 and 2 were brothers and homozygote for *M694I* mutation. They also had another asymptomatic brother with the same mutation and their mother (case 3) was heterozygote for M694I mutation. Case 4 was homozygote for E148Q mutation and case 5 was compound heterozygote for M680I/R761H mutations.

Clinical manifestations of genetically diagnosed patients other than FMF are also shown in Table 3.

Table 1. Clinical and laboratory characteristics of patients suspected of Autoinflammatory disorders.

Variables	Number of patients (28)	Percent (%)
Gender		
Female	12	42.86
Male	16	57.14
Past Medical and Family History		
PFS in family history	11	39.30
Appendectomy/Cholecystectomy history	7	25
Parental consanguinity	13	46.43
Death for unknown reason in the family	2	7.14
Findings		
Fever	25	82.30
Abdominal pain	18	64.30
Chest pain	13	46.43
Headache	14	50
Gastrointestinal symptoms*	13	46.43
Upper and lower respiratory symptoms+	20	71.43
Joint involvement	20	71.43
Skin lesions#	19	67.90
Conjunctivitis	6	21.43
Ophthalmologic problems^	6	21.43
Aphthous stomatitis	17	60.71
Exudative/Erythematous Pharyngitis	16	57.14
Lymphadenopathy	11	39.30
Fatigue	25	82.30

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Myalgia	22	78.60
Hepatomegaly/Splenomegaly	8	28.60
Laboratory data		
Anemia	11	39.30
Increased acute phase reactant	22	78.60
Abnormal liver function test	7	25
Leukocytosis	13	46.43
Fatty liver	8	28.60
Active urinary sedimentation	7	25
Response to colchicine		
Complete	13	46.43
Partial	6	21.43
No response	9	32.14

* Nausea, vomiting and diarrhea+Cough, postnasal drip and shortness of breath # Folliculitis, urticarial rash, severe nodular acne, maculopapular rash, erythema nodosum and pyodermagangrenosum^Decreased vision, uveitis, and glaucoma

Table 2. Clinical and laboratory characteristics of familial Mediterranean fever (FMF) patients

Cases	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
Type of mutation	Homozygote	Homozygote	Heterozygote	Homozygote	Compound heterozygote	No mutation in *MEFV* gene
Genetic mutation	M694I/M694I	M694I/M694I	M694I/Wild type	E148Q/E148Q	M680I/R761H	Mutation in *TROVE2*
Age at last visit	27	34	58	22	18	12
Gender (F/M)	M	M	F	M	M	M
Age at onset (years)	26	25	40	20	2.5	6
Fever	+	+	+	+	+	+
Fever duration(days)	1-3	1-3	1-3	2-3	1-3	3-7
Fever frequency	Every 15 days	Every 15-30 days	Every 60 days	Every 30 days	Every 60 days	Every 15 days
Symptoms of allergy	+	+	+	+	+	+
Fatigue	+	+	+	_	+	+
Myalgia	+	+	+-	_	+	+
Conjunctivitis	_	_		_	_	+
Headache	+	+	+	_	+	-
Abdominal pain	+	+	+	+	+	+
Chest pain	+	+	+	_	+	-
Joint involvement	Arthralgia, hand, and foot	Arthralgia	Arthralgia	Destructive arthritis in Wrist, knee	_	Arthralgia
Skin lesions	_	_	-	Acne, soft tissue abscess	Dermatitis, Dry skin	Urticarial rash
Ophthalmologic involvement	_	_	-	_	_	_
Pharyngitis	_	+	-	_	+	+
Aphthous stomatitis	_	_	-	_	+	+
Upper and/or lower respiratory symptoms	SOB+	cough	cough	_	SOB, cough	Otitis media, PND*
Gastrointestinal symptoms (Nausea/Vomiting/Diarrhea)	_	_	-	_	D (sometimes)	+ (N/V)
Sensorineural hearing loss	_	_	-	_	_	_
Visual loss	_	_	-	_	_	_
Neurologic problems	_	_	Ataxia	_	Neuropathy (one episode)	_
History of appendectomy	_	_	+	_	+	_

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Positive family history	+	+	+	+	_	+
Consanguineous parents	+	+	-	+	_	+
Lymphadenopathy	_	_	-	+	_	_
Splenomegaly	Splenomegaly	Splenectomy due to accident	_	Hepatosplenomegaly	Splenomegaly	_
Other data	_	Increased TG, orchitis	Epigastric pain	Recurrent abscess in the soft tissue of the leg	Death with unknown reason in Family Polyneuropathy in his father	Scoliosis
Anemia	Not mentioned	_	-	+	_	+
Acute phase reactant	+ (ESR, CRP, Ferritin, WBC)	+ (ESR, CRP, WBC, PLT)	+(ESR)	+ (ESR, CRP, PLT, Ferritin, WBC)	_	_
Eosinophilia	_	_	-	_	_	+
Fatty liver/ elevated LFT	Fatty G 1/Increase in ALT	WNR/ Increase in AST	Fatty G 1/Increase in ALT and AST	WNR/WNR	_/_	_
Urine analysis	WNR	WNR	WNR	Trace proteinuria	WNR	WNR
Response to colchicine	+	+	+	+	+	+

+ Shortness of breath * Postnasal drip, LFT; liver function test, ALT; Alanine transaminase, AST; Aspartate transaminase, V; Vomiting, N; Nausea, D; Diarrhea, WNR; Within Normal Range, CRP; c-reactive protein, PLT: platelet, G; Grade, ESR; Erythrocyte sedimentation rate

Table 3. Clinical description of Non-familial Mediterranean fever (FMF) cases.

Cases	Age(years)	Sex	Clinical symptoms	Abnormal labs	Type of mutation	Type of peptide change
7	34	F	Starts with decreased visual acuity at 14 years of age due to toxoplasma optic neuritis, Episodes of fever lasting 4-7 days accompanied by recurrent upper and lower infections, urticarial rash on legs, abdominal pain and bloody diarrhea, body pain, arthralgia and myalgia, chest pain, skin lesions, mouth ulcers, and history of pulmonary emboli	High CRP, leukocytosis, colonoscopy consistent with ulcerative colitis	*NOD2 (G1321A Variant)*	(E441K)
8	14	M	Episodes of fever and diarrhea, seizure and delay in developmental milestones, abdominal pain, recurrent upper and lower respiratory tract infections, mouth ulcers, urticarial with cold exposure, sensorineural hearing loss, and ADHD	Anemia, leukocytosis, Selective IgA deficiency decreased CD4,3, 8 Fatty liver	*NLRP12*	(I579fs)
9	30	M	Episodes of attacks with 1-15 days duration manifesting with fever, myalgia and body pain, arthralgia, headache, vomiting, diarrhea, recurrent pharyngitis, cervical lymphadenopathy, cough and chest pain, negative family history	High ESR, CRP, PLT, Fatty liver	*PSTPIP1*	(D384G)

ESR; Erythrocyte sedimentation rate, CRP; c-reactive protein, PLT: platelet, ADHD; attention-deficit/hyperactivitydisorder

DISCUSSION

A total number of 1395 primary immunodeficiency disorder (PID) patients were enrolled in the current

update of the Iranian PID registry (IPIDR) from 31 medical centers in different cities in Iran, and in our study, we used the data of 28 patients of Isfahan medical center that their immunologic, genetic and clinical data were complete.[9]

In our study, we evaluated the prevalence of each clinical symptom and sign in our patients. Participants' age at the disease onset, particularly in those with FMF, was widely distributed and ranged from 2.5 to 58 years following another study. This study also mentioned that 90% of affected patients become symptomatic by the age of 20.[10] We suggested that the discrepancy in the literature data could be because some patients might demonstrate the symptoms earlier in life, but they might be misdiagnosed or mistaken with a variety of diseases with similar clinical features.

All of the genetically diagnosed patients were males and there was a male preponderance in the study population. Consistent with our data, a Turkish study with almost 3000 participants showed a male: female ratio of 1.2:1.[11] Procopio and his colleagues explained that gender discrepancy among FMF patients could be the consequence of modifying gene hormonal factors which, in turn, results in a disease with milder clinical manifestations in females, and as a consequence, diagnosis at a later stage in life.[10] Although we failed to find any significant differences between the ages of men and women, we hypothesized that it could be due to the small sample size.

We found that fever, fatigue, and myalgia are the most common complaints among the patients, followed by joint involvement and respiratory symptoms. Our results were comparable to another study that was done on 339 patients with FMF and the outcome was the same for fever.[8] Although uncommon, afebrile attacks have also been reported.[12] In one study done on pediatric patients, fever, abdominal pain, and arthralgia have been observed to be the most common presenting signs.[13] Additionally, this study showed that, regardless of ethnicity, fever and abdominal pain were present in more than 90% of patients, followed by joint pain.[10]

Among our genetically diagnosed FMF patients, two had the homozygous mutation for M694I and were brothers. Their mother was heterozygote for M694I that was reported to have multiple abdominal surgeries. Interestingly, a study has shown that patients with this type of mutation were more likely to later be complicated by the peritoneal adhesions.[14] In addition, in a study of the Japanese population, peritonitis was reported in 93% of patients with M694I/Wild type mutation.[15] Data from another study have shown an increased frequency of the *MEFV* gene mutations in individuals with primary dysmenorrhea.[16] Additionally, abdominal attacks of FMF may increase the unnecessary abdominal surgeries in these patients.[17]Another important aspect of this gene mutation (M694I/M694I) is its strong association with the development of amyloidosis and a favorable response to the colchicine therapy that is in agreement with our data.[15,18]

In a survey with 1620 FMF patients, the *MEFV* gene mutation was not found in 889 patients. The author explained that the absence of mutation in the analysis or the presence of symptomatic patients with heterozygote mutation may be due to unrecognized rare mutations in these individuals.[19] Although some studies claimed that E148Q mutation is either of unknown significance or may cause disease with low penetrance,[13,14,20,21] our homozygous case for this mutation showed clinical manifestations, in particular, destructive joint disease. Interestingly, one report from Japan described a patient with a destructive hip injury whose genetic analysis revealed the same genetic mutation.[22] In contrast to our data, previous investigations have shown an association between *M694V* mutation and destructive arthritis.[23]There were also other reports showing heterogeneity of clinical manifestations among patients with E148Q mutation. One study compared the presentation of 30 patients homozygous for this mutation with other *MEFV* variants and indicated that 50% of individuals homozygous for this mutation had moderate to severe forms of the disease. However, the disease tended to manifest later and was less severe when compared to other variants using symptom severity indexes.[24] In addition, one study suggested that pyrin E148Q mutation could be a potential risk factor for multiple sclerosis (MS). This study indicated that the E148Q substitution co-segregated with MS in three multiplex families with MS.[25] In another report, a patient carrying the heterozygous mutation for E148Q showed clinical and laboratory manifestation of glomerulonephritis. This report mentioned that patients carrying this mutation usually show heterogeneous clinical manifestations.[26] Taken together, this data points to the unknown effect of this genetic mutation, however, another explanation for these findings could be the role

of unrecognized genetic modifiers that change the expression of this gene.[27]

Among our approved FMF patients, the *MEFV* gene analysis failed to find any mutation in case 6, but one mutation was found in the *TROVE2* gene. Additionally, the colchicine trial resulted in remarkable symptom improvement in this patient. The *TROVE2* gene is responsible for encoding Ro60, a protein also known as SS-A.[28] Autoantibodies to Ro60 ribonucleoprotein are clinically important in the pathogenesis of rheumatic diseases such as systemic lupus erythematosus (SLE) as well as Sjogren's syndrome.[29] Another report demonstrated that mice lacking Ro protein developed symptoms consistent with the lupus-like syndrome.[30] It is worth mentioning that autoimmune disorders including SLE were exclusion criteria in our study. Whether this mutation is an accidental finding or an important piece of the puzzle in autoinflammatory disorders remains to be discovered. Studies were reporting no mutation in patients suspected of FMF.[31,32] On the other hand, some studies showed that more than one mutation can be present in one patient.[31,33] It was also suggested that only 60% of individuals suspected of having FMF would show the known mutations in the genetic analysis and 28% do not show any known genetic mutation in the analysis.[26] Possible explanations for the *MEFV* mutation-negative FMF include epigenetic changes of the *MEFV* gene such as DNA methylation or histone modification, the interaction between gene modifiers and environmental factors as well as unknown mutations in other genes causing a similar disease.[32]In a study on PID associated with common variable immunodeficiency (CVID) and autoimmunity**,** it was shown that in most cases, no correlation between genotype and phenotype was observed, for example, the patient with signs of CVID had a mutation in the mevalonate kinase (*MVK*) gene in Hyper immunoglobulin D syndrome (HIDS).[34] Finally, although studies were showing some genotype and phenotype correlations, individuals with the same mutation may show different phenotypic presentations.[35] These data further delineated the importance of non-genetic factors in the pathogenesis of this disorder.

Case 7 had a novel mutation in the*NOD2* gene. Gene mutation was also detected in her family members including her mother and her brother; however, none of the affected family members had shown the clinical manifestations of the disease. They had none of the afore-mentioned clinical characteristics. Additionally, our case showed some atypical manifestations which were not presented in previously reported cases with this disease. Saulsbury et al reported that Blau syndrome may not show full penetrance.[36] Although the majority of studies indicated that mutation in the *NOD2* gene is associated with Crohn's disease,[37]our case manifested with ulcerative colitis, which was following another study.[38]

The clinical manifestations of case 8 are explained in Table 3. This case was suspected of FCAS2. The interesting point about this case was its familial relationship with case 6. Which was suspected of FMF. We will describe these two cases and their family members in another report.

In our study, case 9 was diagnosed with PAPA syndrome; however, his clinical manifestation is more consistent with the diagnosis of FMF. PAPA syndrome usually develops in early childhood and manifests with aseptic inflammation of the skin and joints. Mutation in *PSTPIP1* is responsible for its pathogenesis. Mutated *PSTPIP1* leads to hyperphosphorylation of *PSTPIP1*, which increases its binding capacity to pyrin and subsequent over-activation of pyrin and increased interleukin-1 (IL-1) production. Overproduction of IL-1 and pyrin also plays role in the FMF pathophysiology that may explain the similarities between these two disorders.[39,40] In line with our study, another report described two siblings with frequent attacks of fever, aphthous stomatitis, abdominal pain, and other symptoms. Both of them had gene mutations of unknown significance in the *PSTPIP1* gene and one of them also showed a mutation in the *MEFV* gene.[40] Another interesting report demonstrated that this disorder tended to manifest with a wide variable expressivity even in one family with the same mutation.[41] There was also another report of a patient presenting with clinical manifestations of PAPA syndrome, showing no mutation in the genetic analysis.[42] Incomplete penetrance is also a common phenomenon in this disorder confirming the absence of clinical manifestation in our patient parents.[43] Finally, it is still unclear whether these manifestations were due to the novel mutation in the *PSTPIP1* gene or may be due to a similar pathophysiological pathway with FMF syndrome. It is suggested that considering the wide variety of presentations from case to case, the spectrum of PAPA syndrome may be more extensive than currently thought.[41,43,44]

This study presented the most common clinical manifestations of AIDs in the population of Iranian descent and it can be used as a guide for future studies as well as for clinicians who will encounter potential cases of these disorders.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Azizi G, Azarian SK, Nazeri S, Mosayebian A, Ghiasy S, Sadri G, et al. Monogenic Auto-inflammatory Syndromes: A Review of the Literature. Iran J AllergyAsthma Immunol. 2016;12(5):430-44.
2. de Jesus AA, Canna SW, Liu Y, Goldbach-Mansky R. Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling. Annu Rev Immunol. 2015;33(8):823-74.
3. Picard C, Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, Conley ME, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol. 2015;35(8):696-726.
4. Shwin KW, Lee C-CR, Goldbach-Mansky R. Dermatologic manifestations of monogenic autoinflammatory diseases. Dermatol Clin. 2017;35(1):21-38.
5. Moreira A, Torres B, Peruzzo J, Mota A, Eyerich K, Ring J. Skin symptoms as diagnostic clue for autoinflammatory diseases. An Bras Dermatol. 2017;92(1):72-80.
6. Montazerin SM, Sherkat R, Mosayebian A, Shahrooei M, Homayouni V, Najafi S, et al. Clinical and Laboratory Manifestations of Autoinflammatory Diseases: The Results from the First Iranian Registry. J Clin Immunol. 2019;39(4):S135-S6.
7. Federici S, Sormani MP, Ozen S, Lachmann HJ, Amaryan G, Woo P, et al. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. Ann Rheum Dis. 2015;74(5):799-805.
8. Demirkaya E, Saglam C, Turker T, Koné-Paut I, Woo P, Doglio M, et al. Performance of different diagnostic criteria for familial Mediterranean fever in children with periodic fevers: results from a multicenter international registry. J Rheumatol. 2016;43(1):154-60.
9. Abolhassani H, Kiaee F, Tavakol M, Chavoshzadeh Z, Mahdaviani SA, Momen T, et al. Fourth update on the Iranian national registry of primary immunodeficiencies: integration of molecular diagnosis. J Clin Immunol. 2018;38(7):816-32.
10. Procopio V, Manti S, Bianco G, Conti G, Romeo A, Maimone F, et al. Genotype-phenotype correlation in FMF patients: a “non classic” recessive autosomal or “atypical” dominant autosomal inheritance?. Gene. 2018;641(23):279-86.
11. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine. 2005;84(1):1-11.
12. Battal F, Silan F, Topaloğlu N, Aylanç H, Yıldırım Ş, Binnetoğlu FK, et al. The MEFV gene pathogenic variants and phenotype-genotype correlation in children with familial Mediterranean fever in the Çanakkale population. BJMG. 2016;19(2):23-8.
13. Kilic A, Varkal MA, Durmus MS, Yildiz I, Yıldırım ZNY, Turunc G, et al. Relationship between clinical findings and genetic mutations in patients with familial Mediterranean fever. Pediatr. Rheumatol. 2015;13(1):59.
14. Papa R, Doglio M, Lachmann HJ, Ozen S, Frenkel J, Simon A, et al. A web-based collection of genotype-phenotype associations in hereditary recurrent fevers from the Eurofever registry. Orphanet J Rare Dis. 2017;12(1):167.
15. Kishida D, Nakamura A, Yazaki M, Tsuchiya-Suzuki A, Matsuda M, Ikeda S-i. Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations. Arthritis Res Ther. 2014;16(5):439-43.
16. Erten S, Altunoglu A, Keskin H, Ceylan G, Dalgaci A, Uyanık G, et al. Increased frequency of MEFV gene mutations in patients with primary dysmenorrhea. Mod Rheumatol. 2013;23(5):959-62.
17. Kasifoglu T, Cansu DÜ, Korkmaz C. Frequency of abdominal surgery in patients with familial Mediterranean fever. Intern Med. 2009;48(7):523-6.
18. Ait-Idir D, Djerdjouri B, Bouldjennet F, Taha RZ, El-Shanti H, Sari-Hamidou R, et al. The M694I/M694I genotype: a genetic risk factor of AA-amyloidosis in a

group of Algerian patients with familial Mediterranean fever. Eur J Med Genet. 2017;60(3):149-53.
19. Dogan H, Bayrak OF, Emet M, Keles M, Gulluoglu S, Gul Z, et al. Familial Mediterranean fever gene mutations in north-eastern part of Anatolia with special respect to rare mutations. Gene. 2015;568(2):170-5.
20. Tchernitchko DO, Gérard-Blanluet M, Legendre M, Cazeneuve C, Grateau G, Amselem S. Intrafamilial segregation analysis of the p. E148Q MEFV allele in familial Mediterranean fever. Ann Rheum Dis. 2006;65(9):1154-7.
21. Ben-Chetrit E, Lerer I, Malamud E, Domingo C, Abeliovich D. The E148Q mutation in the MEFV gene: Is it a disease-causing mutation or a sequence variant?. Hum Mutat. 2000;15(4):385-6.
22. Migita K, Hisanaga S, Izumi Y, Kawahara C, Shigemitsu Y, Iwanaga N, et al. Protracted arthritis in a Japanese patient with familial Mediterranean fever. Mod Rheumatol. 2017;27(5):905-9.
23. Jarjour RA, Dodaki R. Arthritis patterns in familial Mediterranean fever patients and association with M694V mutation. Mol Biol Rep. 2011;38(3):2033-6.
24. Cekin N, Akyurek ME, Pinarbasi E, Ozen F. MEFV mutations and their relation to major clinical symptoms of Familial Mediterranean Fever. Gene. 2017;6269(24):9-13.
25. Kümpfel T, Gerdes L, Wacker T, Blaschek A, Havla J, Krumbholz M, et al. Familial Mediterranean fever-associated mutation pyrin E148Q as a potential risk factor for multiple sclerosis. Mult Scler. 2012;18(9):1229-38.
26. Rigante D, Federico G, Ferrara P, Maggiano N, Avallone L, Pugliese AL, et al. IgA nephropathy in an Italian child with familial Mediterranean fever. Pediatr Nephrol. 2005;20(11):1642-4.
27. Topaloglu R, Ozaltin F, Yilmaz E, Ozen S, Balci B, Besbas N, et al. E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever. Ann Rheum Dis. 2005;64(5):750-2.
28. Hung T, Pratt G, Sundararaman B, Townsend M, Chaivorapol C, Bhangale T, et al. The Ro60 autoantigen binds endogenous retroelements and regulates inflammatory gene expression. Science. 2015;350(6259):455-9.
29. Boccitto M, Wolin SL. Ro60 and Y RNAs: structure, functions, and roles in autoimmunity. Crit Rev Biochem Mol Biol. 2019;54(2):133-52.
30. Xue D, Shi H, Smith JD, Chen X, Noe DA, Cedervall T, et al. A lupus-like syndrome develops in mice lacking the Ro 60-kDa protein, a major lupus autoantigen. Proc Natl Acad Sci U S A. 2003;100(13):7503-8.
31. Coşku S, Kurtgöz S, Keskin E, Sönmez F, Bozkurt G. Frequency of mutations in Mediterranean fever gene, with gender and genotype–phenotype correlations in a Turkish population. J Genet. 2015;94(4):629-35.
32. Ben-Zvi I, Herskovizh C, Kukuy O, Kassel Y, Grossman C, Livneh A. Familial Mediterranean fever without MEFV mutations: a case–control study. Orphanet J Rare Dis. 2015;10(1):34-41.
33. Stella A, Cortellessa F, Scaccianoce G, Pivetta B, Settimo E, Portincasa P. Familial Mediterranean fever: breaking all the (genetic) rules. Rheumatology (Oxford). 2019;58(3):463-7.
34. Asgardoon MH, Azizi G, Yazdani R, Sohani M, Pashangzadeh S, Kalantari A, et al. Monogenic primary immunodeficiency disorder associated with common variable immunodeficiency and autoimmunity. Int Arch Allergy Immunol. 2020;181(9):706-14.
35. Erten S, Erzurum C, Altunoglu A. Three family members with familial Mediterranean fever carrying the M694V mutation showed different clinical presentations. Intern Med. 2012;51(13):1765-8.
36. Saulsbury FT, Wouters CH, Martin TM, Austin CR, Doyle TM, Goodwin KA, et al. Incomplete penetrance of the NOD2 E383K substitution among members of a pediatric granulomatous arthritis pedigree. Arthritis Rheum. 2009;60(6):1804-6.
37. Caso F, Galozzi P, Costa L, Sfriso P, Cantarini L, Punzi L. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD open. 2015;1(1):e000097.
38. Pugazhendhi S, Santhanam S, Venkataraman J, Creveaux I, Ramakrishna BS. NOD2 gene mutations associate weakly with ulcerative colitis but not with Crohn's disease in Indian patients with inflammatory bowel disease. Gene. 2013;512(2):309-13.
39. Shoham NG, Centola M, Mansfield E, Hull KM, Wood G, Wise CA, et al. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. PNAS. 2003;100(23):13501-6.
40. Maggio MC, Ceccherini I, Grossi A, Gattorno M, Corsello G. PAPA and FMF in two siblings: possible amplification of clinical presentation? A case report. Ital J Pediatr. 2019;45(1):111-9.
41. Schellevis MA, Stoffels M, Hoppenreijs EP, Bodar E, Simon A, van der Meer JW. Variable expression and

treatment of PAPA syndrome. Ann Rheum Dis. 2011;70(6):1168-70.

42. Hong J-B, Su Y-N, Chiu H-C. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome): report of a sporadic case without an identifiable mutation in the CD2BP1 gene. J Am Acad Dermatol. 2009;61(3):533-5.
43. Demidowich A, Freeman A, Kuhns D, Aksentijevich I, Gallin J, Turner M. Genotype, phenotype, and clinical course in five patients with pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. Arthritis Rheum. 2011;64(8):2022-7.
44. Lindwall E, Singla S, Davis WE, Quinet RJ, editors. Novel PSTPIP1 gene mutation in a patient with pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. Semin Arthritis Rheum; 2015: Elsevier.