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MEFV Gene Mutation Analysis in Children with Immunoglobulin A Vasculitis and Its Effects on Clinical Manifestations: A Big Series from a Tertiary Center

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Abstract

Aim: Immunoglobulin A vasculitis (IgAV) is the most common vasculitis of childhood, but its pathogenesis is largely unknown, despite evidence pointing to various environmental and genetic factors. We investigated the frequency of *MEFV* gene mutations that are considered in the pathogenesis and their effect on the clinical features of patients with IgAV.

Methods: The study included 244 children diagnosed with IgAV, who underwent *MEFV* gene analyses. We recorded the demographic and clinical characteristics of the patients, along with their laboratory results. We grouped the patients based on the presence of MEFV gene mutations and MEFV variants.

Results: At least one *MEFV* mutation was detected in 89 (36.5%) patients, with E148Q being the most common (n=31, 34.8%). Age at diagnosis and the frequency of hematuria and recurrence were significantly greater among patients with *MEFV* mutations (p=0.043, p=0.008, and p=0.009, respectively). Serum IgA levels were significantly higher in patients with the M694V mutation (p=0.040).

Conclusion: The presence of *MEFV* mutations, particularly E148Q and M694V, could be associated with the development and clinical course of IgA vasculitis.

Keywords: Children, hematuria, IgA vasculitis, *MEFV* gene, recurrence

Introduction

Immunoglobulin A vasculitis (IgAV), characterized by IgA and immune complex deposition in small vessels, is the most common vasculitis worldwide (1). The primary clinical manifestations of the disease include non-thrombocytopenic palpable purpura, joint gastrointestinal (GI) tract involvement, and renal involvement (2). The etiopathogenesis of IgAV remains unclear, and genetic and environmental factors are thought to contribute to the disease (3). Nonetheless, various recent publications have focused on genetic factors, exemplified by the demonstration of the roles of polymorphisms in genes encoding cytokines and cell adhesion molecules (4-6).

Familial Mediterranean Fever (FMF) is an autoinflammatory disorder characterized by recurrent attacks of fever and serositis. It is caused by mutations in the Mediterranean Fever (*MEFV*) gene that encode pyrin, a protein involved in apoptosis, inflammation, and the secretion of cytokines (7,8). Researchers have identified over 350 mutations in the *MEFV* gene. M694V, M694I, M680I, V726A, and E148Q are the most frequently detected mutations in patients with FMF in Turkey (9,10).

Researchers mentioned that FMF may co-exist with various inflammatory diseases, including IgAV, juvenile idiopathic arthritis, Behcet's disease, inflammatory bowel disease, and polyarteritis nodosa. It has been

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established in the literature that *MEFV* gene mutations lead to an uncontrollable inflammatory reaction (11-13). Immunoglobulin A vasculitis was reported as the most common coexisting vasculitis with FMF. It has been speculated that IgAV patients with *MEFV* gene mutations have greater clinical severity and worse laboratory findings due to an exaggerated inflammatory response (11,14,15). However, the available literature on this topic is limited because of the investigation of only a few common mutations.

In the present study, we aimed to investigate the frequency of *MEFV* gene mutations in children with IgAV and to assess potential relationships between these mutations and the clinical course and laboratory findings.

Methods

Compliance with Ethical Standards

Ethical approval was obtained from the Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2023/0059, date: 25.01.2023) before the experiment was started, and the experiment was conducted in accordance with the principles set forth in the Helsinki Declaration. Written informed consent was obtained from the legal guardians of the children.

Study Design and Population

The present study was a retrospective, cross-sectional study that was performed in a single tertiary healthcare institution from January 2005 to December 2021. Five hundred eighteen children aged 18 years who were admitted (and followed for at least 6 months) to the pediatric and pediatric rheumatology departments with the diagnosis of IgAV were assessed for inclusion in the study. Immunoglobulin A vasculitis diagnosis was made according to the consensus criteria put forth by the European League Against Rheumatism and the Pediatric Rheumatology European Society (EULAR/PRINTO/PRES 2010) (16).

Among these 518 children, we excluded subjects diagnosed with FMF before the onset of IgAV as well as those with additional chronic diseases (comorbidities), insufficient follow-up duration (<6 months), unperformed *MEFV* gene analyses, and incomplete data. A total of 244 children diagnosed with IgAV were included in the analyses. Criteria for inclusion and exclusion in the study are shown in Figure 1.

Data Collection and Disease Definitions

The patients' demographic, clinical, and laboratory data were recorded from their medical records. In all patients, symptoms, signs, and organ involvement, such as the skin, GI tract, joints, kidneys, testicles, and central nervous system, were recorded on admission and during follow-up. Cutaneous findings consisted of characteristic palpable purpura and subcutaneous edema. Gastrointestinal manifestations included vomiting, abdominal pain, invagination, and GI bleeding-defined as melena, hematochezia, or occult blood in the stool. Involvement of more than one joint but fewer than five joints was considered to demonstrate the presence of oligoarthritis. All patients were followed up for a minimum period of 6 months for renal involvement. Hematuria was defined as the presence of >5 red blood cells per high-power field in a urine examination. Mild proteinuria was defined as a spot urine protein-to-creatinine ratio of 0.2 mg/mg, whereas nephrotic proteinuria was defined in patients with a ratio of >3-3.5 mg/mg or those with absolute levels of >40 mg/m^2/h. Renal biopsy was performed in selected cases when patients presented with nephrotic-range proteinuria, persistent proteinuria of 4-40 mg/m^2/h for more than 3 months, and/or renal impairment. Skin biopsies were performed on selected IgAV patients with atypical rashes.

Patient Management

Treatment modalities, including hydration, non-steroidal anti-inflammatory drugs (NSAIDs), and the need for corticosteroid therapy and colchicine, were recorded. Treatment was planned according to existing symptoms; we routinely prescribed bed rest and NSAIDs for arthralgia and mild abdominal discomfort. Systemic steroid treatment was reserved for severe GI involvement, including severe abdominal pain, GI bleeding (GIS), progressive renal disease, and scrotal edema.

Biochemistry and Genetic Analyses

White blood cell (WBC) and platelet (PLT) count (10^9/L), hemoglobin (Hb) level (g/dL), C-reactive protein (CRP) (mg/dL), Westergren erythrocyte sedimentation rate (ESR) (mm/hr), stool blood analysis, and other laboratory parameters such as anti-streptolysin O (ASO), C3 and C4 complement levels, and serum IGA levels were determined by standard laboratory methods at the time of diagnosis. Leukocytosis was defined if the WBC count was ≥10,000/mm^3. Thrombocytopenia was accepted as a PLT level of <150,000. Elevated levels of CRP, ESR, ASO, C3, and C4 were defined as >5 mg/dL, >15 mm/h, >200 IU/mL, >170 mg/dL, and >44 mg/dL, respectively. Blood cultures, hepatitis B, hepatitis C, or human immunodeficiency virus infection serology were only performed when deemed necessary by the attending physician. Disease-related complications included the development of hypertension, invagination, and convulsions. The recurrence of disease was recorded in the medical files of the patients. Recurrence was defined as disease activation after a period of at least 3 months without signs or symptoms.

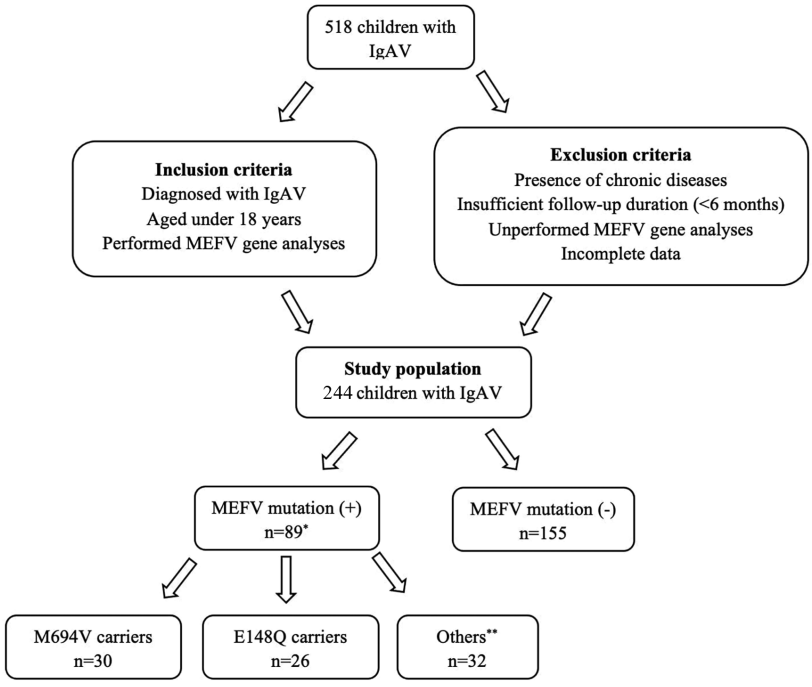

Figure 1. Criteria for inclusion and exclusion and subgroups of the study
**One patient had both E148Q and M694V mutation and was not included in the comparison analyses, **Others: R202Q, K695R, P369S, V726A, M680I, R761H*
IgAV: Immunoglobulin A vasculitis

All patients in the cohort were analyzed for sequence variants in exons 2, 3, 5, and 10 of the *MEFV* gene. For the main comparative analyses, the study population was divided into two main groups: "*MEFV* mutation carriers" (patients with mutations in at least one allele; heterozygous, homozygous, and compound heterozygous) and "non-carriers". Carrier patients were divided into three further subgroups according to their carrier status: p. M694V carriers, E148Q carriers, and "other mutation" carriers (Figure 1). We compared the demographic, clinical, and laboratory findings between the groups.

Statistical Analysis

All analyses were performed using the SPSS 23.0 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers (n) and percentages, whereas continuous variables were summarized as mean with standard deviation or as median with minimum and maximum where appropriate. Chi-square tests were used to compare categorical variables between groups. The normality of the distribution for continuous variables was tested using the Kolmogorov-Smirnov test (Lilliefors correction). For continuous variables that had a normal distribution, two-group comparisons were performed using the Independent Samples t-test (variances were assessed according to Levene's test, and p-values were determined according to those results). For >2-group comparisons, we used ANOVA. In the absence of a normal distribution, we used the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis test for >2-group comparisons. For the pairwise corrections of the ANOVA and Kruskal-Wallis tests, we used the Bonferroni correction, given that statistical assumptions were fulfilled. The statistical level of significance for all tests was defined as a p-value of <0.05. For power analysis, the G-Power 3.1.9.7 program was used. The power of the study was found to be 0.98.

Results

A total of 244 of the 518 children with IgAV were included in the analyses. Table 1 summarizes the demographic, clinical, and laboratory characteristics of patients with IgAV.

Distribution of *MEFV* Mutations in Patients with IgAV

At least one *MEFV* mutation was detected in 89 (36.5%) of the 244 patients with IgAV included in the study. Most were heterozygous mutations (n=71, 79.8%). E148Q was the most common mutation (n=31, 34.8%) among all *MEFV* mutations. One patient had both E148Q and M694V mutations and was not included in the comparison analyses to avoid errors in interpretations. The genotype distribution of the patients is depicted in Table 2.

Table 1. Demographic, clinical and laboratory characteristics of 244 patients with IgA vasculitis	
Parameters	**Values**
Age at diagnosis (year) median (min.-max.)	7.60 (3-18)
Time from admission to final diagnosis (days) median (min.-max.)	5.0 (1-90)
Male sex (n, %)	137 (56.1)
Distribution of clinical features during follow-up (n, %)	
Gastrointestinal system involvement	125 (51.2)
Abdominal pain/angina	94 (38.5)
Fecal occult blood	71 (30.2)
Vomiting	18 (7.4)
Macroscopic bleeding (melena/hematochezia)	7 (2.9)
Invagination	4 (1.6)
Musculoskeletal system involvement	86 (35.3)
Arthralgia	36 (14.8)
Arthritis	55 (22.5)
Oligoarthritis	31 (12.7)
Myalgia	3 (1.2)
Subcutaneous edema	72 (29.5)
Renal involvement	49 (20.1)
Hematuria	31 (12.7)
Proteinuria	36 (14.8)
Mild proteinuria	26 (10.7)
Nephrotic range proteinuria	10 (4.1)
Hypertension	5 (2)
Testis involvement (in male patients, n=137)	13 (9.5)
Fever	7 (2.9)
CNS involvement (seizure, headache)	0
Medical treatments (n, %)	92 (37.7)
Only hydration	41 (16.8)
Hydration plus NSAIDs	38 (15.6)
Hydration plus steroid	52 (21.3)
Hydration + NSAIDs + steroid	10 (4.1)
Hydration + NSAIDs + pulse steroid	2 (0.8)
Colchicine treatment	5 (2.0)
Pneumatic reduction	1 (0.4)
Cytotoxic drugs	1 (0.4)
Renal biopsy	4 (1.6)
MPGN	4 (1.6)
Laboratory parameters	
WBC (10^9/L), median (min.-max.)	10.4 (2.3-36.9)
Leukocytosis (>10.000/uL), n%	124 (52.1)
Hb level (g/dL), Mean ± Standard deviation	12.11±1.12
PLT level (10^9/L), median (min.-max.)	334.0 (128-898)
Thrombocytopenia (n%)	3 (1.3)
CRP (mg/dL), median (min.-max.)	0.91 (0.01-23.2)
Elevated CRP (n, %)	31 (13.5)
ESR (mm/hr), median (min.-max.)	32.0 (1-111)
Elevated ESR (n, %)	150 (83.3)
ASO (IU/mL), median (min.-max.)	147.0 (10-1491)
Elevated ASO (IU/mL) (n, %)	22 (46.8)
C3 level (mg/dL), Mean ± Standard deviation	145.03±31.51
Elevated C3 (n, %)	17 (17.3)
C4 level (mg/dL), Mean ± Standard deviation	27.22±10.62
Elevated C4 (n, %)	4 (4.3)
Serum IgA (mg/dL), median (min.-max.)	213.0 (46-869)
Recurrence (n, %)	27 (11.1)

Min.-Max.: Minimum-maximum, NSAIDs: Non-steroidal anti-inflammatory drugs, MPGN: Membranous proliferative glomerular nephritis, WBC: White blood cell, PLT: Platelets, Thrombocytopenia <150.000 10^9/L, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ASO: Anti-streptolysin O, IgA: Immunoglobulin A

Comparison of Clinical Characteristics and Laboratory Findings Between *MEFV* Mutation Carriers and Non-Carrier Patients

Clinical and laboratory parameters were compared between *MEFV* mutation carriers and non-carrier patients with IgAV. Age at diagnosis, frequency of hematuria, and disease recurrence were significantly greater in *MEFV* mutation carrier patients than in non-carriers (p=0.043, p=0.008, p=0.009) respectively. Although patients with *MEFV* mutations had relatively higher WBC, CRP, and ESR levels, there was no statistically significant difference between the groups (Table 3).

Comparison of Demographic, Clinical, and Laboratory Findings of Patients with IgAV According to the Presence of *MEFV* Gene Variants

The relationship between the different *MEFV* gene variants (E148Q, M694V, and "others") and clinical characteristics is shown in Table 4. In terms of clinical characteristics, vomiting was more frequent in patients with mutations other than E148Q and M694V (p=0.026). None of the patients with E148Q and M694V mutations experienced vomiting. In terms of laboratory findings, only the serum IgA level was significantly higher in patients with the M694V mutation (p=0.040).

Discussion

Association of IgAV with *MEFV* Mutations and Their Variants

The association of vasculitis with FMF has been extensively reported in previous studies (11-13,17). The *MEFV* gene encodes the pyrine protein, which plays an essential role in inflammatory pathways by

Table 2. Distribution of *MEFV* mutations in 244 patients with IgAV	
Type of mutations	**n, %**
Non-carriers	155 (63.5)
***MEFV* mutation carriers**	89 (36.5)
E148Q	31 (34.8)
M694V	27 (30.3)
Others**	32 (36)
Homozygous mutations	**10 (11.2)**
M694V homozygote	4 (4.5)
R202Q homozygote	1 (1.1)
E148Q homozygote	5 (5.6)
Heterozygous mutations	**71 (79.8)**
E148Q heterozygote	23 (25.9)
M694V heterozygote	19 (21.4)
R202Q heterozygote	9 (10.1)
V726A heterozygote	8 (9.0)
M680I heterozygote	5 (5.6)
P369S heterozygote	3 (3.4)
K695R heterozygote	2 (2,2)
M694I heterozygote	1 (1.1)
R761h heterozygote	1 (1.1)
Compound heterozygous mutations	**8 (9.0)**
E148Q/M694V heterozygote	1 (1.1)
E148Q/P369S heterozygote	1 (1.1)
M680I/M694V heterozygote	1 (1.1)
M680I/V726A heterozygote	1 (1.1)
M694V/V726A heterozygote	1 (1.1)
P369S/R202Q heterozygote	1 (1.1)
R202Q/E148Q heterozygote	1 (1.1)
R202Q/M694V heterozygote	1 (1.1)

*One patient had both E148Q and M694V mutation and was not included in the summary to avoid errors in interpretation. **R202Q, K695R, P369S, V726A, M680I, R761H, IgAV: Immunoglobulin A vasculitis

decreasing inflammation; hence, the mutated protein causes uncontrolled inflammation and predisposes to the occurrence of vasculitis (including IgAV) (12,18). Previous research indicates that if IgAV is diagnosed in a patient belonging to an ethnic/racial group in which FMF is frequent, physicians should assess the presence of FMF symptoms (19). It has been established that the prevalence of *MEFV* gene mutations in children with IgAV is higher than that in the general population, ranging from 21% to as high as 50.7%, and it has been shown that *MEFV* mutations can affect the clinical and laboratory findings of IgAV (14,20-26). In a previous study, Ozçakar et al. (20) reported that 27 out of 80 patients (34%) with IgAV had *MEFV* gene mutations. Additionally, in a recent study from Turkey, Acarı et al. (15) reported that *MEFV* gene mutations were found in 25 out of 47 (53%) patients with IgAV, and this rate was significantly higher than that in the general Turkish population (27,28). In another study from Israel, Gershoni-Baruch et al. (21) reported that 27% of 52 patients with IgAV had at least one *MEFV* mutation. In contrast, in a recent literature review, Yokoyama et al. (29) mentioned that only five patients with IgAV-carrier *MEFV* mutations appear in Japan. In the current study, we also found that the prevalence of *MEFV* mutations in IgAV patients was significantly higher (n=89, 36.5%) than in the normal population and mostly demonstrated a heterozygous nature (n=71, 79.8%). The high prevalence of mutations in our study might be due to ethnic or racial predisposition, but it could also be explained by the likelihood of parental consanguinity. However, data concerning consanguinity were not assessed.

Research assessing the associations between *MEFV* genetic variants and IgAV has described various findings (20,21). Ozçakar et al. (20) showed that the frequencies of M694V and E148Q mutations were 20% (16 out of 80 patients) and 3.8% (3 out of 80 patients), respectively, while they were reported as 3% and 12%, respectively, in the healthy Turkish population (28). Additionally, Acarı et al. (15) reported that M694V (25%, 12 out of 47 patients), R202Q (17%, 8 out of 47 patients), and E148Q (11%, 5 out of 47 patients) were the most common detectable variants in children with IgA (15). Thus, the authors concluded that the M694V mutation was a more important predisposing factor for IgAV development, which has been supported by other studies (20,22,30). However, in another study from Turkey, it was reported that while the frequency of the M694V mutation carrier in 76 patients with IgAV was 11.7%, the frequency of the E148Q mutation carrier was 9.1% in those patients (31). Another study found that 34.8% of Turkish children with IgAV had the E148Q mutation, which is a higher frequency than that of the general Turkish population (32). In a study from China, none of the IgAV patients were found to carry the M694V mutation (33). In our study, the E148Q mutation was the most common allele; however, the frequency of the M694V mutation was also similar, indicating consistency with most of the literature.

Clinical Significance of *MEFV* Mutations and Variants in Patients with IgAV

It was reported earlier that *MEFV* mutations affect the clinical and laboratory presentation of IgAV in populations in which FMF is common (20,22,25,33,34). However, studies comparing carriers and non-carriers of *MEFV* mutations have reported conflicting results. In some of those studies, it was found that there was no relationship between the presence of *MEFV* carriers and disease characteristics in analyses including laboratory parameters,

Table 3. Comparison of demographic and clinical features and laboratory findings of patients according to *MEFV* mutation carrier state			
Parameters	***MEFV* mutation (-) (n=155)**	***MEFV* mutation (+) (n=89)**	**p-value**
Age at diagnosis (year) median (min.-max.)	7 (3-15)	8 (3-18)	**0.043**^{*,s}
Time from admission to diagnosis (days) median (min.-max.)	4 (1-45)	6 (1-90)	0.633**
Male sex (n, %)	85 (62.0)	52 (38.0)	0.587***
Clinical features during follow-up (n, %)			
Fever	3 (42.9)	4 (57.1)	0.262***
Angioedema/subcutaneous edema	47 (65.3)	25 (34.7)	0.713***
Abdominal pain/angina	63 (67.0)	31 (37.0)	0.369***
Fecal occult blood	50 (70.4)	21 (29.6)	0.166***
Vomiting	14 (77.8)	4 (22.2)	0.192***
Macroscopic bleeding (melena/hematochezia)	3 (42.9)	4 (57.1)	0.262***
Invagination	3 (75)	1 (25)	1.00***
Arthralgia	22 (61.1)	14 (38.9)	0.745***
Arthritis	31 (56.4)	24 (43.6)	0.210***
Multiple arthritis (oligoarthritis)	18 (58.1)	13 (41.9)	0.499***
Myalgia	2 (66.7)	1 (33.3)	1.000***
Hematuria	13 (41.9)	18 (58.1)	**0.008**^{***,s}
Proteinuria	18 (50)	18 (50)	0.068***
Hypertension	2 (40)	3 (60)	0.358***
Testis involvement (in male patients, n=137)	7 (53.8)	6 (46.2)	0.557***
Medical treatments (n, %)			
Only hydration	25 (61.0)	16 (39.0)	0.349***
Hydration plus NSAIDs	21 (55.3)	17 (44.7)	
Need of steroid/pulse steroids	40 (59.7)	27 (40.3)	
Colchicine treatment	1 (20.0)	4 (80.0)	
Recurrence (n, %)	11 (40.7)	16 (59.3)	**0.009**^{***,s}
WBC (10^9/L), median (min.-max.)	10.1 (2.3-30.8)	11 (5.2-36.9)	0.728****
Hb level (g/dL), median (min.-max.)	12.1 (8.6- 15.3)	11.9 (9.8-14.9)	0.208*
PLT level (10^9/L), median (min.-max.)	345.5 (136-898)	322.5 (128-674)	0.404****
CRP (mg/dL), median (min.-max.)	0.90 (0.01-15)	1 (0.01-23.2)	0.233****
ESR (mm/hr), median (min.-max.)	31.5 (1-111)	35 (2-105)	0.056*
Elevated ESR (>15), n, %	94 (62.7)	56 (37.3)	0.240****
ASO (IU/mL) level, median (min.-max.)	165 (10-866)	147 (20-1491)	0.215****
C3 level (mg/dL), median (min.-max.)	149 (33-196)	145 (10-203)	0.645****
C4 level (mg/dL), median (min.-max.)	29.2 (3-55)	25.4 (3-64)	0.496*
Serum IgA mg/dL level, median (min.-max.)	204 (46-869)	216 (84-563)	0.483****

Min.-max.: minimum-maximum, WBC: White blood cells, PLT: Platelets, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ASO: Anti-streptolysin O, IgA: Immunoglobulin A, *Student's t-test, **One-Way ANOVA test, ***Chi-square test, ****Mann-Whitney U test, ^{s}Significant (p<0.05)

complications, outcomes, and treatment-related needs of patients (21,23,31,34,35). On the other hand, Ozçakar et al. (20) found that IgAV patients with *MEFV* carriers were younger and that *MEFV* mutations could affect clinical symptoms. Cakici et al. (14) demonstrated that arthritis, bowel angina, scrotal involvement, and recurrence were more common in patients with *MEFV* mutation positivity. In a study from Egypt, higher frequencies of arthritis, abdominal pain, GIS, hypertension, anemia, proteinuria, fecal occult blood, and recurrence were found in patients with *MEFV* mutations (36). Bayram et al. (22) reported that the frequency of scrotal involvement and WBC, ESR, CRP, and serum Ig levels were significantly higher in patients with *MEFV* mutations. Several other studies have shown significantly elevated acute phase reactants among mutation carriers (20,31,34).

Table 4. Comparison of demographic, clinical and laboratory finding of patients with IgAV according to presence of *MEFV* gene variants				
Parameters	**E148Q (n=30)**	**M694V (n=26)**	**Others* (n=32)**	**p-value**
Age at diagnosis (year), median (min.-max.)	8.75 (3-15)	8.2 (3-16)	7.7 (3-18)	0.501**
Time from admission to diagnosis (days) median (min.-max.)	6 (1-15)	5 (1-30)	5 (1-90)	0.867***
Male sex (n, %)	21 (70)	16 (61.5)	15 (46.9)	0.172****
Clinical features during follow-up (n, %)				
Fever	1 (3.3)	1 (3.8)	2 (6.3)	0.841****
Angioedema/subcutaneous edema	6 (20.0)	9 (34.6)	9 (28.1)	0.468****
Abdominal pain	7 (23.3)	12 (46.2)	12 (37.5)	0.193****
Fecal occult blood	6 (20.7)	6 (23.1)	9 (31.0)	0.637****
Vomiting	0	0	4 (12.5)	**0.026****,s
Macroscopic bleeding (melena/hematochezia)	1 (3.8)	1 (3.8)	2 (6.3)	0.841****
Invagination	1 (3.3)	0	0	0.376****
Arthralgia	4 (13.3)	5 (19.2)	5 (15.6)	0.833****
Arthritis	8 (26.7)	6 (23.1)	9 (28.1)	0.907****
Oligoarthritis	5 (16.7)	4 (15.4)	3 (9.4)	0.672****
Myalgia	1 (3.3)	0	0	0.376****
Hematuria	7 (23.3)	6 (23.1)	5 (15.6)	0.697****
Proteinuria	8 (26.7)	6 (23.1)	4 (12.5)	0.356****
Mild proteinuria	5 (62.5)	4 (66.7)	2 (50.0)	0.864****
Nephrotic range	3 (37.5)	2 (33.3)	2 (50.0)	
Hypertension	1 (3.3)	2 (7.7)	0	0.275****
Testis involvement (in male patients, n=137)	4 (19.0)	2 (12.5)	0	0.209****
Medical treatments (n, %)				
Only hydration	4 (25.0)	4 (25.0)	8 (50.0)	0.708****
Hydration plus NSAIDs	6 (35.3)	5 (29.4)	6 (35.3)	
Need of steroid/pulse steroid	9 (33.3)	9 (33.3)	9 (33.3)	
Colchicine treatment	2 (50.0)	2 (50.0)	0	
Recurrence (n, %)	4 (13.3)	5 (19.2)	7 (21.9)	0.675****
WBC (10^9/L), median (min.-max.)	10.85 (5.3-36.9)	10.1 (5.2-20.4)	11.25 (5.3-24.3)	0.760***
Hb level (g/dL), median (min.-max.)	11.6 (9.9-14.6)	11.65 (10-13.6)	12.2 (9.8-14.9)	0.276**
PLT level (10^9/L), median (min.-max.)	349.5 (223-674)	307 (128-620)	308 (215-565)	0.113**
CRP (mg/dL), median (min.-max.)	0.76 (0.1-7.99)	1.5 (0.01-23.2)	0.81 (0.01-12.8)	0.247***
ESR (mm/hr), median (min.-max.)	30 (15-91)	41 (13-105)	32 (2-103)	0.218***
Elevated ASO (IU/mL) (>200) (n, %)	1 (14.3)	1 (14.3)	5 (71.4)	0.813**
C3 level (mg/dL), median (min.-max.)	142.5 (10-193)	149.4 (69-203)	146 (98-173)	0.433***
C4 level (mg/dL), median (min.-max.)	24.5 (13-31)	23.4 (3-50)	29.8 (12-64)	0.343**
Serum IgA level (mg/dL), median (min.-max.)	413.5 (303-563)	210 (84-456)	212 (139-281)	**0.040***,s

IgAV: Immunoglobulin A vasculitis, min.-max.: minimum-maximum, *Others: R202Q, K695R, P369S, V726A, M680I, R761hNSAIDs: Non-steroidal anti-inflammatory drugs, WBC: White blood cell, PLT: Platelets, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ASO: Anti-streptolysin O, IgA: Immunoglobulin A, **One-Way ANOVA test, ***Kruskal-Wallis test, ****Chi-square test, sSignificant (p<0.05)

Altug et al. (34) showed that ESR and CRP levels were significantly higher in patients with the IgAV-carrier *MEFV* mutation. Additionally, they noted that GI and joint involvement and subcutaneous edema were more common in IgAV patients carrying the *MEFV* mutation. Prior research has revealed that physicians should be aware of the possibility of FMF in children with intussusceptions, lower hemoglobin, higher serum IgA, and elevated PLT count; however, the study could not identify any effects of the *MEFV* mutations on recurrence rate (25). Interestingly, Gershoni-Baruch et al. (21) found that the recurrence rate was twofold higher in patients

with two mutated alleles on *MEFV* compared with those without mutations, although statistical analyses were non-significant. On the other hand, in a recent study, Acarı et al. (15) found that disease relapse was significantly higher in IgA patients who were *MEFV* carriers than non-carriers. They also mentioned that Hb levels were lower and PLT count and CRP levels were higher in IgAV patients who had *MEFV* carriers (15). In comparison to prior studies, we found that mutation carriers were significantly older than non-carriers, and our results revealed that the presence of *MEFV* mutations was significantly associated with a higher frequency of hematuria and recurrence. White blood cell, CRP, and ESR levels were similar in carriers and non-carriers, similar to a previous report by Dogan et al. (31). Further studies are needed to determine the effects of *MEFV* mutations on the laboratory characteristics of patients with IgAV.

Regarding the variants (subgroup analysis) and their clinical effects, the M694V variant was found to be associated with the clinical and laboratory findings of patients with IgAV in a previous study from Turkey (22). Ozçakar et al. (20) demonstrated that the presence of edema, arthritis, and urogenital involvement was more common in patients with M694V mutations, although E148Q mutations had no clinical significance in patients with IgAV. In later years, Bayram et al. (22) found similar results to those of Ozçakar et al. (20) in their study. A study involving Chinese patients found that the E148Q variant was associated with the severity of disease, specifically with joint abnormalities; however, the researchers did not observe any significant effects of the E148Q variant on the analyzed laboratory parameters (IgA, CRP, C3, and C4) (33). In another study from Turkey, Cakici et al. (14) reported that although *MEFV* mutations were influential on the clinical characteristics of IgAV, variants of *MEFV* were not found to have any effect on the clinical course of IgAV. Acarı et al. (15) reported that scalp edema, elevated CRP levels, and disease recurrence were more common in patients with IgAV who were carriers of the *M694V* mutation. On the other hand, they mentioned that there was no significant relationship between the long-term prognosis of the disease and renal involvement or the presence of *MEFV* mutations (15). In our study, we could not find any significant results regarding the effect of the E148Q mutation in any clinical findings, but serum IgA levels were found to be significantly higher in patients with the E148Q variation, which is in contrast to the findings of the study from China. In addition, we found that vomiting was only present among patients with "other" mutations. However, this result needs further support in larger cohorts because of the limited patient counts in this study. The E148Q variant has been considered a genetic marker in some studies (33); however, to draw conclusions regarding this matter, the functional role(s) of the E148Q variant in IgAV should be elucidated.

Study Limitations

There are some limitations to our study. First, the lack of a prospective design is a major limitation of our study. Second, we only investigated 12 well-known *MEFV* variants instead of identifying all the variants. Finally, the clinical spectrum of IgAV is similar between isolated IgAV and FMF-associated IgAV; therefore, particularly in some cases, IgAV may be an initial symptom of FMF. Despite these limitations, the strength of our study is that it includes one of the largest numbers of patients among published studies to date. The potential for such a complex relationship between these conditions demonstrates the need for prospective studies including IgAV patients (with or without *MEFV* mutations) in which longitudinal analyses are performed in larger populations.

Conclusion

Our results showed that *MEFV* mutations (especially E148Q and M694V mutations) are more frequent in IgAV patients compared with the general population, and the presence of those mutations seems to have some effects on the clinical features of IgAV patients, as demonstrated by results concerning hematuria and recurrence. Therefore, patients with IgAV, especially older children, should be followed more carefully regarding FMF development. In addition, closer follow-up for hematuria and recurrence appears to be necessary for patients with IgAV who carry those mutations. However, the different results and clinical effects observed in other studies indicate the need for further research.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2023/0059, date: 25.01.2023).

Informed Consent: Written informed consent was obtained from the legal guardians of the children.

Authorship Contributions

Surgical and Medical Practices: S.Y., Z.K., M.E., Concept: S.Y., M.E., Design: S.Y., M.E., Data Collection or Processing: S.Y., Z.K., Analysis or Interpretation: O.O., Literature Search: S.Y., Z.K., Writing: S.Y., Z.K., M.E.

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