

Familial Mediterranean Fever Mutation Analysis in Pediatric Patients With Inflammatory Bowel Disease: A Multicenter Study

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ABSTRACT

Background: The aim of the study was to evaluate familial Mediterranean fever (FMF) mutation analysis in pediatric patients with inflammatory bowel disease (IBD). The relation between MEFV mutations and chronic inflammatory diseases has been reported previously.

Methods: Children with IBD (334 ulcerative colitis (UC), 224 Crohn's disease (CD), 39 indeterminate colitis (IC)) were tested for FMF mutations in this multicenter study. The distribution of mutations according to disease type, histopathological findings, and disease activity indexes was determined.

Results: A total of 597 children (mean age: 10.8 ± 4.6 years, M/F: 1.05) with IBD were included in the study. In this study, 41.9% of the patients had FMF mutations. E148Q was the most common mutation in UC and CD, and M694V in IC (30.5%, 34.5%, 47.1%, respectively). There was a significant difference in terms of endoscopic and histopathological findings according to mutation types (homozygous/heterozygous) in patients with UC ($P < .05$).

There was a statistically significant difference between colonoscopy findings in patients with or without mutations ($P = .031$, $P = .045$, respectively). The patients with UC who had mutations had lower Pediatric Ulcerative Colitis Activity Index (PUCAI) scores than the patients without mutations ($P = .007$).

Conclusion: Although FMF mutations are unrelated to CD patients, but observed in UC patients with low PUCAI scores, it was established that mutations do not have a high impact on inflammatory response and clinical outcome of the disease.

Keywords: Children, familial Mediterranean fever, MEFV, mutation analysis, inflammatory bowel disease

INTRODUCTION

Familial Mediterranean fever (FMF) and inflammatory bowel diseases (IBD) are 1 of the most common autoimmune-inflammatory diseases characterized by recurrent inflammatory episodes sharing similar symptoms.

FMF is an autosomal recessive disorder caused by mutations in the Mediterranean fever gene (MEFV), first identified in 1997 by French FMF Consortium¹ encoded on the short arm of chromosome 16. MEFV gene encodes the pyrin protein, which has a regulatory effect in the inflammasome-related innate immune response.²⁻⁸ Also NOD2/CARD15 gene related to Crohn's disease (CD) is localized on chromosome 16.²⁻⁴ The products of both the MEFV and NOD2/CARD15 genes are structurally similar.²

The relation between MEFV mutations and chronic inflammatory diseases such as CD, rheumatoid arthritis, Henoch-Schonlein purpura, polyarteritis nodosa, chronic arthritis, systemic lupus erythematosus has been reported previously.⁵⁻²³ FMF is more common in people of certain ethnic backgrounds, such as Sephardic Jews, Turks, Arabs, and Armenians. Thus, the aim of this study was to evaluate FMF mutation analysis in Turkish pediatric patients with IBD and define its impact on the clinical course of the disease.

MATERIALS AND METHODS

This was a multicenter study conducted by the Turkish IBD Study Group including 37 institutions in Turkey. Children with IBD diagnosed according to clinical, serological, endoscopic, and histopathological criteria and

followed up between 2000 and 2012 at clinics of pediatric gastroenterology were evaluated retrospectively.

The endoscopic examinations and biopsies were performed at the initial diagnosis. All of the patients were tested for common FMF mutations (M694V, M680I, E148Q, R202Q, A744S, V726A, and others). The blood samples drawn into EDTA were collected from all of the patients and DNA was isolated from peripheral blood lymphocytes by PCR. The distribution of mutations according to disease type, histopathological findings, and disease activity indexes was determined.

Pediatric Crohn Disease Activity Index (PCDAI) was used for patients with CD at diagnosis.^{24,25} The score was determined from items, which included subjective reporting of the degree of abdominal pain, stool pattern, and general well-being; presence of extraintestinal manifestations, such as fever, arthritis, rash, and uveitis; physical examination findings; weight and height; and hematocrit, erythrocyte sedimentation rate, and serum albumin.

Pediatric Ulcerative Colitis Activity Index (PUCAI) was used for patients with ulcerative colitis (UC) at diagnosis.²⁶ It was determined by items including abdominal pain, rectal bleeding, stool consistency of most stools, number of stools per day, nocturnal stools, and activity level.

5-ASA (5-aminosalicylic acid) was used in patients with mild UC, both 5-ASA and oral steroids in patients with moderate UC and 5-ASA, intravenous steroids, and azathioprine in severe UC. Rectal 5-ASA and rectal steroids were used in patients with proctocolitis.

5-ASA and modulen formula was used in patients with mild CD, 5-ASA, modulen formula and oral steroids in moderate CD, and 5-ASA, modulen formula, intravenous steroids, and azathioprine in severe CD. Steroids were reduced gradually before stopping in patients with moderate and severe disease and then immunosuppressant therapy was initiated.

PUCAI and PCDAI scores <10 denotes remission.²⁴⁻²⁶

Statistical Analysis

Statistical analysis were performed using the SPSS for Windows 15.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean, standard deviation, median, and minimum-maximum if appropriate. Statistical comparisons were made using the chi-square test for independent groups. The analysis was conducted using Mann-Whitney *U* test for comparison of 2 independent groups and the Kruskal-Wallis test for more than 2 groups. A value of $P < .05$ was considered statistically significant.

Ethics

Informed consent was taken from all of the parents before the endoscopy and the other procedures. The study was conducted in accordance with the principles

of the Declaration of Helsinki. The study protocol was approved by Ege University Ethics Committee (October 12, 2011, No: 11-7/2).

RESULTS

The mean age of 597 patients was 10.8 ± 4.6 (range 2-18 years) and the male:female ratio was 1.05. In this study, 334 patients were diagnosed with UC, 224 CD, and 39 indeterminate colitis (IC). In this study, 41.9% of the patients with IBD (39.2% of UC patients, 44% of CD patients, and 50% of IC patients) had MEFV mutations. The mean follow-up time was 3-5 years. The demographic and clinical characteristics of patients with IBD according to MEFV mutation carriage are shown in Table 1.

Heterozygous E148Q was the most common mutation in UC and CD, and M694V in IC (30.5%, 34.5%, 47.1%, respectively). The distribution of MEFV genotypes according to disease types are as; M694V 15.3%, M680I 8.5%, E148Q 30.5%, R202Q 28%, A744S 2.5%, V726A 6.8% in patients with UC, M694V 26.2%, E148Q 34.5%, R202Q 32.1%, V726A 2.4% in patients with CD and M694V 47.1%, E148Q 17.6%, R202Q 17.6%, V726A 11.8% in patients with IC.

The colonoscopy findings in patients with mutations according to disease types are shown in Tables 2, 3, and 4.

Table 1. The Demographic and Clinical Characteristics of Patients With IBD According to MEFV Mutation Carriage

	Patients With MEFV Mutations (n = 250)	Patients Without MEFV Mutations (n = 347)	P
Age (years; median)	10.5 ± 4.9	10.5 ± 4.7	.81
Gender (male/female)	131/119	164/183	.21
IBD type (n)			
UC	131 (52.4%)	203 (58.5%)	.23
CD	99 (39.6%)	125 (36%)	
IC	20 (8%)	19 (5.5%)	
Median PCDAI (median, range)	38.5 ± 18.9	40.5 ± 16	.24
Median PUCAI (median, range)	43.1 ± 19.8	49.4 ± 18.8	.007
Extraintestinal disease	58 (24%)	42 (12.5%)	.001
Perianal disease	60 (24%)	93 (26.8%)	.20
MEFV mutations			
Homozygous mutation	50 (25.5%)		
Heterozygous mutation	146 (74.5%)		
Not mentioned	23 (2.5%)		

IBD, inflammatory bowel disease; MEFV, Mediterranean fever gene; PCDAI, pediatric Crohn's disease activity index; PUCAI, pediatric ulcerative colitis activity index.

$P < .05$ is statistically significant.

Table 2. The Distribution of the Patients According to Mutation Types

Mutations	Total		Homozygous		Heterozygous		Compound Heterozygous	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
M694V	48	21.4	36	58.1	12	7.7		
M680I	10	4.5	3	4.8	7	4.5		
E148Q	67	29.9	9	14.5	58	37.4		
R202Q	62	27.7	5	8.1	57	36.8		
A744S	3	1.3	2	3.2	1	0.6		
V726A	12	5.4	5	8.1	7	4.5		
Diğer	15	6.7	2	3.2	13	8.4		
M694 V/E148Q	3	1.3					3	42.9
R202Q/M694 V	4	1.8					4	57.1
Total	224	100	62	100	155	100	7	100

Moderate mucosal fragility was common in patients with MEFV mutations, whereas hemorrhagic ulcer was common in patients without mutations. There was a statistically significant difference between homozygous/heterozygous mutations and colonoscopy findings at cecum in patients with UC ($P=.045$), at ileum in patients with CD ($P=.008$) but no difference in patients with IC ($P > .05$) (Tables 2, 3, and 4).

When colonoscopy findings were examined according to mutation genotypes among patients with CD, the diffuse disease rate was lower in patients who had M694V mutation than the patients with other mutations (Table 3). The rate of normal colonoscopy in the ileum and cecum was low in patients with CD who had R202Q mutation.

There was a significant difference in terms of endoscopic and histopathological findings according to all of the mutation types (homozygous/heterozygous) in patients with UC ($P < .05$), whereas no significant difference was observed in patients with CD.

No significant difference was observed in terms of histopathological findings (increased plasma cell infiltration, basal plasmacytosis, cryptitis, pyloric metaplasia, paneth cell metaplasia, and granuloma) except crypt abscess ($P=.018$) at sigmoid colon in patients with UC and except crypt abscess ($P=.009$) and granuloma ($P=.002$) at caecum in patients with CD according to MEFV mutations ($P > .05$).

The patients with UC who had mutations had lower PUCAI scores than the patients without mutations

($P=.007$) (Table 1). No statistically significant difference was observed in terms of PCDAI between patients with CD whether they had mutations or not (Table 1). When the disease activity indexes were determined according to mutation genotypes among IBD patients, no significant differences were observed ($P > .05$).

No significant associations were established between remission and response to induction treatment and the presence of mutations, mutation types (homozygous/heterozygous), and genotypes ($P > .05$). FMF mutation analysis was performed after the diagnosis of IBD in all of the cases. IBD was not screened in the cases diagnosed as FMF.

DISCUSSION

There are a limited number of reports, mostly from Turkey which has studied the association between IBD and FMF in children, but none of those reports have included as many cases as in this multicentric study.^{2,3,9,13,14,16,23} The prevalence of FMF has been reported to be 1:1000 and the frequency of FMF mutation carrier state 20% in Turkey.¹² FMF accompanied 21.1% of the pediatric IBD patients in our country.³ None of the reports about pediatric IBD and FMF has studied the relation between MEFV genotypes and endoscopic findings. We also determined the disease activity indexes according to MEFV genotypes.

In this study, 41.9% of our patients with IBD (39.2% of UC patients, 44% of CD patients, and 50% of IC patients) had MEFV mutations. Uslu et al.³ have examined 33 children with IBD and found that 25.7% of the patients had MEFV mutations (32.1% of CD patients,

Table 3. The Distribution of Mutations According to Clinical Features of Patients With IBD

	Total		Homozygous*		Heterozygous*		Compound Heterozygous*		P
	N=224		n=62 (27.7%)		n=155 (69.2%)		n=7 (3.1%)		
	n	%	n	%	n	%	n	%	
Age (years)									
≤5	44	19.6	13	21.0	29	18.7	2	28.6	.776
>5	180	80.4	49	79.0	126	81.3	5	71.4	
Gender									
Male	116	51.8	35	56.5	76	49.0	5	71.4	.363
Female	108	48.2	27	43.5	79	51.0	2	28.6	
Consanguinity	44	21.1	10	17.2	33	22.9	1	14.3	.606
Family history of IBD except parents	9	4.7	5	8.9	4	3.1	0	0	
FMF mutation	219	97.8	62	100	155	100	2	28.6	.247
Perianal disease									
Abscess	7	3.1	2	3.2	5	3.2	0	0	1.000
Fissure	9	4.0	4	6.5	4	2.6	1	14.3	.094
Fistula	4	1.8	0	0	4	2.6	0	0	.632
Skin Tag	2	0.9	0	0	2	1.3	0	0	1.000
Diagnosis									
Ulcerative colitis	122	54.5	32	51.6	86	55.5	4	57.1	.933
Crohn disease	85	37.9	24	38.7	58	37.4	3	42.9	
Indeterminate colitis	17	7.6	6	9.7	11	7.1	0	0	
PUCAI	44.2 ± 20.3		42.5 ± 18.4		43.6 ± 20.7		67.5 ± 16.6		.090
PCDAI	37.4 ± 17.1		41.0 ± 14.1		35.9 ± 17.5		40.3 ± 30.2		.344
Crohn Disease									
Distribution									
Localized	48	57.1	17	70.8	30	52.6	1	33.3	.215
Disseminated	36	42.9	7	29.2	27	47.4	2	66.7	
Colonoscopy Rectum									
Mucosal hyperemia, diffuse aphthous lesions	19	23.8	4	17.4	15	27.3	0	0	.838
Ulceration and stricture	2	2.5	0	0	2	3.6	0	0	
Fistula	2	2.5	0	0	2	3.6	0	0	
>5 aphthous lesion	6	7.5	3	13.0	3	5.5	0	0	
<5 aphthous lesion	9	11.3	3	13.0	6	10.9	0	0	
Normal	42	52.5	13	56.5	27	49.1	2	100	
Sigmoid									
Mucosal hyperemia, diffuse aphthous lesions	17	21.3	3	13.0	14	25.5	0	0	.881

	Total		Homozygous*		Heterozygous*		Compound Heterozygous*		P
	N=224		n=62 (27.7%)		n=155 (69.2%)		n=7 (3.1%)		
	n	%	n	%	n	%	n	%	
Fistula	1	1.3	0	0	1	1.8	0	0	
>5 aphthous lesion	6	7.5	2	8.7	4	7.3	0	0	
<5 aphthous lesion	12	15.0	4	17.4	8	14.5	0	0	
Normal	44	55.0	14	60.9	28	50.9	2	100	
Left colon									
Mucosal hyperemia, diffuse aphthous lesions	14	18.4	1	4.5	13	25.0	0	0	.84
Ulceration and stricture	3	3.9	0	0	3	5.8	0	0	
>5 aphthous lesion	4	5.3	2	9.1	2	3.8	0	0	
<5 aphthous lesion	11	14.5	3	13.6	8	15.4	0	0	
Normal	44	57.9	16	72.7	26	50.0	2	100	
Right colon									
Mucosal hyperemia, diffuse aphthous lesions	11	15.1	2	9.1	9	18.4	0	0	.585
Fistula	1	1.4	1	4.5	0	0	0	0	
>5 aphthous lesion	9	12.3	4	18.2	5	10.2	0	0	
<5 aphthous lesion	14	19.2	3	13.6	11	22.4	0	0	
Normal	38	52.1	12	54.5	24	49.0	2	100	
Cecum									
Mucosal hyperemia, diffuse aphthous lesions	14	19.4	6	27.3	8	16.7	0	0	.796
Ulceration and stricture	3	4.2	1	4.5	2	4.2	0	0	
>5 aphthous lesion	7	9.7	3	13.6	4	8.3	0	0	
<5 aphthous lesion	20	27.8	5	22.7	15	31.3	0	0	
Normal	28	38.9	7	31.8	19	39.6	2	100	
Ileum									
Mucosal hyperemia, diffuse aphthous lesions	16	25.4	6	30.0	10	24.4	0	0	.426
Ulceration and stricture	15	23.8	3	15.0	11	26.8	1	50.0	
>5 aphthous lesion	2	3.2	2	10.0	0	0	0	0	
<5 aphthous lesion	15	23.8	5	25.0	10	24.4	0	0	
Normal	15	23.8	4	20.0	10	24.4	1	50.0	
Ulcerative colitis									
Distribution									
E1	16	13.3	2	6.3	14	16.7	0	0	.057
E2	31	25.8	4	12.5	26	31.0	1	25.0	
E3	73	60.8	26	81.3	44	52.4	3	75.0	

(Continued)

	Total		Homozygous*		Heterozygous*		Compound Heterozygous*		P
	N=224		n=62 (27.7%)		n=155 (69.2%)		n=7 (3.1%)		
	n	%	n	%	n	%	n	%	
Colonoscopy Rektum									
Normal	8	6.3	2	5.7	6	6.9	0	0	.865
Mild mucosal fragility	10	7.9	2	5.7	8	9.2	0	0	
Moderate mucosal fragility	34	27.0	9	25.7	25	28.7	0	0	
Hemorrhagic ulcers	74	58.7	22	62.9	48	55.2	4	100	
Sigmoid									
Normal	8	6.6	1	3.0	7	8.2	0	0	.715
Mild mucosal fragility	13	10.7	2	6.1	11	12.9	0	0	
Moderate mucosal fragility	37	30.3	9	27.3	27	31.8	1	25.0	
Hemorrhagic ulcers	64	52.5	21	63.6	40	47.1	3	75.0	
Left colon									
Normal	15	12.8	2	6.1	12	15.0	1	25.0	.126
Mild mucosal fragility	13	11.1	3	9.1	10	12.5	0	0	
Moderate mucosal fragility	38	32.5	7	21.2	29	36.3	2	50.0	
Hemorrhagic ulcers	51	43.6	21	63.6	29	36.3	1	25.0	
Right colon									
Normal	31	30.4	5	16.7	25	36.8	1	25.0	.094
Mild mucosal fragility	11	10.8	5	16.7	6	8.8	0	0	
Moderate mucosal fragility	29	28.4	6	20.0	21	30.9	2	50.0	
Hemorrhagic ulcers	31	30.4	14	46.7	16	23.5	1	25.0	
Cecum									
Normal	44	46.3	9	33.3	34	53.1	1	25.0	.025
Mild mucosal fragility	15	15.8	2	7.4	12	18.8	1	25.0	
Moderate mucosal fragility	17	17.9	5	18.5	11	17.2	1	25.0	
Hemorrhagic ulcers	19	20.0	11	40.7	7	10.9	1	25.0	
Ileum									
Normal	61	80.3	14	73.7	44	83.0	3	75.0	.300
Mild mucosal fragility	5	6.6	2	10.5	3	5.7	0	0	
Moderate mucosal fragility	4	5.3	0	0	3	5.7	1	25.0	
Hemorrhagic ulcers	6	7.9	3	15.8	3	5.7	0	0	
Indeterminate colitis									
Sigmoid									
Mucosal hyperemia, diffuse aphthous lesions	1	7.7	1	33.3	0	0	-	-	.335

	Total		Homozygous*		Heterozygous*		Compound Heterozygous*		P
	N=224		n=62 (27.7%)		n=155 (69.2%)		n=7 (3.1%)		
	n	%	n	%	n	%	n	%	
<5 aphthous lesion	3	23.1	0	0	3	30	-	-	
Normal	9	69.2	2	66.7	7	70	-	-	
Left colon									
Mucosal hyperemia, diffuse aphthous lesions	1	7.7	1	33.3	0	0	-	-	.231
Normal	12	92.3	2	66.7	10	100	-	-	
Right colon									
>5 aphthous lesion	1	7.7	1	33.3	0	0	-	-	.231
Normal	12	92.3	2	66.7	10	100	-	-	
Ileum									
<5 aphthous lesion	2	15.4	0	0	2	20	-	-	1.000
Normal	11	84.6	3	100	8	80	-	-	

*The most common homozygous mutation M694V.

*The most common heterozygous mutation E148Q.

*The most common compound heterozygous mutation R202Q/M694 V.

IBD, inflammatory bowel disease; PCDAI, pediatric Crohn's disease activity index; PUCAI, pediatric ulcerative colitis activity index.

P < .05 is statistically significant.

9.4% of UC patients). Salah et al.¹⁶ reported that 88.1% of the children with IBD (28% of UC patients, 73% of CD patients) had mutations and explained their high prevalence as ethnic differences, genetic heterogeneity, and small sample size.

In this study, E148Q was the most common mutation in patients with UC and CD, and M694V in patients with IC, in contrast with the other studies that M694V was the most common mutation detected in pediatric IBD patients.^{2,3,9,13,14,23} Only 1 study has reported E148Q as the most common mutation in adult IBD patients.⁸ Salah et al.¹⁶ studied 33 Egyptian children with IBD and found that V627A mutation was the most common one. Beser et al.^{2,14} also mentioned the high rate of K695R mutation (25%) in their patients with UC which has not been detected in previous studies.

We observed that there was a significant difference in terms of endoscopic and histopathological findings according to mutation types (homozygous/heterozygous) in patients with UC, but not in patients with CD. When the colonoscopy findings were examined according to mutation genotypes, the diffuse disease rate was found to be lower in CD patients who had M694V

mutation than the patients with other mutations, and no significant differences were obtained among patients with UC.

The impact of MEFV mutations on the clinical course of IBD is controversial. While some of the authors assessed no clinical difference between MEFV mutation carriers and noncarrier IBD patients,^{8,9,16} the others reported that the presence of MEFV mutations has shown to affect the disease activity and severity and may have an impact on the clinical course of the disease.⁶ Although Uslu et al.³ reported higher disease activity indexes, (PCDAI: median 40, range 32.5-60; PUCAI: median 47.5, range 35-65), was not statistically significant due to the small number of patients. While the patients with UC who had mutations had lower PUCAI scores than the patients without mutations, no significant difference was observed in terms of PCDAI between patients with CD whether they had mutations or not in our study. The disease activity indexes did not change according to mutation genotypes among IBD patients.

Fidder et al.⁶ found that extraintestinal disease and the strictures were more frequent among MEFV mutation carriers. Uslu et al.³ found no significant difference in

Table 4. The comparison of homozygous M694V with the other mutations

	Homozygous M694V		Heterozygous M694V		Compound Heterozygous		Other Homozygous		P
	n=36		n=12		n=7		n=26		
	n	%	n	%	n	%	n	%	
Age (years)									
≤ 5	10	27.8	4	33.3	2	28.6	3	11.5	.281
>5	26	72.2	8	66.7	5	71.4	23	88.5	
Gender									
Male	22	61.1	7	58.3	5	71.4	13	50.0	.726
Female	14	38.9	5	41.7	2	28.6	13	50.0	
Consanguinity	7	21.2	1	8.3	1	14.3	3	12.0	.769
Family history of IBD except parents	4	11.8	1	8.3	0	0	1	4.5	.918
Perianal disease	36	100	12	100	2	28.6	26	100	<.001
Abse	2	5.6	1	8.3	0	0,0	0	0	.543
Fissure	4	11.1	1	8.3	1	14.3	0	0	.217
Fistula	0	0	0	0	0	0	0	0	
Skin Tag	0	0	0	0	0	0	0	0	
Diagnosis									
Ulcerative colitis	15	41.7	3	25.0	4	57.1	17	65.4	.102
Crohn disease	15	41.7	7	58.3	3	42.9	9	34,6	
Indeterminate colitis	6	16.7	2	16.7	0	0	0	0	
PUCAI	39.5 ± 18.2		55.0 ± 7.1		67.5 ± 16.6				.064
PCDAI	40.3 ± 11.7		27.5 ± 11.9		40.3 ± 30.2				.088
Crohn Disease									
Distribution									
Localized	10	6.7	6	85.7	1	33.3	7	77.8	.392
Disseminated	5	33.3	1	14.3	2	66.7	2	22.2	
Colonoscopy Rectum									
Mucosal hyperemia, diffuse aphthous lesions	3	21.4	1	14.3	0	0	1	11.1	.976
Ulceration and stricture	0	0	1	14.3	0	0	0	0	
Fistula	0	0	0	0	0	0	0	0	
>5 aphthous lesion	2	14.3	0	0	0	0	1	11.1	
<5 aphthous lesion	2	14.3	1	14.3	0	0	1	11.1	
Normal	7	50.0	4	57.1	2	100	6	66.7	
Sigmoid									
Mucosal hyperemia, diffuse aphthous lesions	3	21.4	0	0	0	0	0	0	.131
Fistula	0	0	0	0	0	0	0	0	
>5 aphthous lesion	0	0	1	14.3	0	0	2	22.2	
<5 aphthous lesion	4	28.6	3	42.9	0	0	0	0	

	Homozygous M694V		Heterozygous M694V		Compound Heterozygous		Other Homozygous		P
	n=36		n=12		n=7		n=26		
	n	%	n	%	n	%	n	%	
Normal	7	50.0	3	42.9	2	100	7	77.8	
Left colon									
Mucosal hyperemia, diffuse aphthous lesions	1	7.7	0	0	0	0	0	0	.726
Ulceration and stricture	0	0	0	0	0	0	0	0	
>5 aphthous lesion	1	7.7	0	0	0	0	1	11.1	
<5 aphthous lesion	2	15.4	3	50.0	0	0	1	11.1	
Normal	9	69.2	3	50.0	2	100	7	77.8	
Right colon									
Mucosal hyperemia, diffuse aphthous lesions	1	7.7	0	0	0	0	1	11.1	.834
Fistula	1	7.7	0	0	0	0	0	0	
>5 aphthous lesion	3	23.1	0	0	0	0	1	11.1	
<5 aphthous lesion	2	15.4	3	50.0	0	0	1	11.1	
Normal	6	46.2	3	50.0	2	100	6	66.7	
Cecum									
Mucosal hyperemia, diffuse aphthous lesions	4	30.8	0	0	0	0	2	22.2	.432
Ulceration and stricture	0	0	0	0	0	0	1	11.1	
>5 aphthous lesion	2	15.4	0	0	0	0	1	11.1	
<5 aphthous lesion	2	15.4	4	66.7	0	0	3	33.3	
Normal	5	38.5	2	33.3	2	100	2	22.2	
Ileum									
Mucosal hyperemia, diffuse aphthous lesions	4	36.4	1	16.7	0	0	2	22.2	.864
Ulceration and stricture	1	9.1	1	16.7	1	50.0	2	22.2	
>5 aphthous lesion	2	18.2	0	0	0	0	0	0	
<5 aphthous lesion	2	18.2	3	50.0	0	0	3	33.3	
Normal	2	18.2	1	16.7	1	50.0	2	22.2	
Ulcerative colitis									
Distribution									
E1	1	6.7	0	0	0	0	1	5.9	.739
E2	3	20.0	0	0	1	25.0	1	5.9	
E3	11	73.3	3	100	3	75.0	15	88.2	
Colonoscopy Rektum									
Normal	0	0	1	33.3	0	0	2	11.8	.398
Mild mucosal fragility	2	11.1	0	0	0	0	0	0	
Moderate mucosal fragility	5	27.8	0	0	0	0	4	23.5	
Hemorrhagic ulcers	11	61.1	2	66.7	4	100	11	64.7	
Sigmoid									

(Continued)

	Homozygous M694V		Heterozygous M694V		Compound Heterozygous		Other Homozygous		P
	n=36		n=12		n=7		n=26		
	n	%	n	%	n	%	n	%	
Normal	1	5.9	0	0	0	0	0	0	.570
Mild mucosal fragility	2	11.8	1	33.3	0	0	0	0	
Moderate mucosal fragility	5	29.4	0	0	1	25.0	4	25.0	
Hemorrhagic ulcers	9	52.9	2	66.7	3	75.0	12	75.0	
Left colon									
Normal	1	5.9	0	0	1	25.0	1	6.3	.251
Mild mucosal fragility	3	17.6	1	33.3	0	0	0	0	
Moderate mucosal fragility	4	23.5	0	0	2	50.0	3	18.8	
Hemorrhagic ulcers	9	52.9	2	66.7	1	25.0	12	75.0	
Right colon									
Normal	3	20.0	0	0	1	25.0	2	13.3	.316
Mild mucosal fragility	4	26.7	1	33.3	0	0	1	6.7	
Moderate mucosal fragility	4	26.7	0	0	2	50.0	2	13.3	
Hemorrhagic ulcers	4	26.7	2	66.7	1	25.0	10	66.7	
Cecum									
Normal	5	35.7	1	33.3	1	25.0	4	30.8	.707
Mild mucosal fragility	2	14.3	1	33.3	1	25.0	0	0	
Moderate mucosal fragility	3	21.4	0	0	1	25.0	2	15.4	
Hemorrhagic ulcers	4	28.6	1	33.3	1	25.0	7	53.8	
Ileum									
Normal	7	70.0	1	33.3	3	75.0	7	77.8	.527
Mild mucosal fragility	1	10.0	1	33.3	0	0	1	11.1	
Moderate mucosal fragility	0	0	0	0	1	25.0	0	0	
Hemorrhagic ulcers	2	20.0	1	33.3	0	0	1	11.1	
Indeterminate colitis									
Sigmoid									
Mucosal hyperemia, diffuse aphthous lesions	1	33.3	0	0,0					1.000
<5 aphthous lesion									
Normal	2	66.7	2	100					
Left colon									
Mucosal hyperemia, diffuse aphthous lesions	1	33.3	0	0					1.000
Normal	2	66.7	2	100					
Right colon									
>5 aphthous lesion	1	33.3	0	0					1.000
Normal	2	66.7	2	100					
Ileum									
<5 aphthous lesion	0	0	0	0					
Normal	3	100	2	100					

terms of extraintestinal disease whether the patients had mutations or not. Yurtcu et al.⁸ observed that extraintestinal disease frequencies were higher in patients without mutations. In concomitant with Fidler et al.⁶ we found that extraintestinal disease (arthritis, arthralgia, edema, erythema nodosum, myalgia, sacroiliitis, pyoderma gangrenosum, clubbing finger, numbness) was more common in patients with mutations.

There is a limited number of studies reporting the relation between response to treatment and accompanying FMF mutations in patients with IBD.³ In this study, no association was established between remission and response to induction treatment and the presence of mutations, mutation types (homozygous/heterozygous), and genotypes.

In conclusion, although colonoscopy findings were shown significantly higher at cecum in patients with UC and at ileum in patients with CD who had FMF mutations and low PUCAL scores were observed in UC patients with mutations, in concomitant with the previous studies it was established that mutations do not have a high impact on inflammatory response and clinical outcome of the disease, since the effect on treatment was not observed during follow-up as in our study. It is controversial if the routine molecular analysis of the MEFV gene is needed or not in patients with IBD, considering the economic burden and loss of time.

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