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# Killer Cell Immunoglobulin-Like Receptor (KIR) Genotype Distribution in Familial Mediterranean Fever (FMF) Patients

Authors' Contribution:  
Study Design A  
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Manuscript Preparation E  
Literature Search F  
Funds Collection G

**BDEF 1 Ertugrul Erken**  
**BCD 2 Ozlem Goruroglu Ozturk**  
**BD 3 Ozlem Kudas**  
**B 3 Didem Arslan Tas**  
**B 4 Ahmet Demirtas**  
**D 2 Filiz Kibar**  
**B 3 Suzan Dinkci**  
**AF 3 Eren Erken**

1 Department of Nephrology, Gaziosmanpasa University, Faculty of Medicine, Tokat, Turkey  
2 Central Laboratory, Cukurova University, Faculty of Medicine, Balcali Hospital, Adana, Turkey  
3 Department of Rheumatology/Immunology, Cukurova University, Faculty of Medicine, Adana, Turkey  
4 Department of Internal Medicine, Gaziosmanpasa University, Faculty of Medicine, Tokat, Turkey

**Corresponding Author:** Ertuğrul Erken, e-mail: ertugrulerken@hotmail.com  
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**Background:** Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease predominantly affecting Mediterranean populations. The gene associated with FMF is the MEFV gene, which encodes for a protein called pyrin. Mutations of pyrin lead to uncontrolled attacks of inflammation, and subclinical inflammation continues during attack-free intervals. Killer cell immunoglobulin-like receptor (KIR) genes encode HLA class I receptors expressed by NK cells. The aim this study was to look for immunogenetic determinants in the pathogenesis of FMF and find out if KIR are related to susceptibility to disease or complications like renal amyloidosis.

**Material/Methods:** One hundred and five patients with FMF and 100 healthy individuals were involved in the study. Isolated DNA from peripheral blood was amplified by sequence specific PCR probes and analyzed by Luminex for KIR genotypes. Fisher Exact test was used to evaluate the variation of KIR gene distribution.

**Results:** All patients and healthy controls expressed the framework genes. An activator KIR gene, KIR2DS2, was significantly more frequent in FMF patients ( $p=0.036$ ). Renal amyloidosis and presence of arthritis were not associated with KIR genes and genotype. KIR3DL1 gene was more common in patients with high serum CRP ( $p=0.016$ ).

**Conclusions:** According to our findings, we suggest that presence of KIR2DS2, which is an activator gene for NK cell functions, might be related to the autoinflammation in FMF. The potential effect of KIR genes on amyloidosis and other clinical features requires studies with larger sample sizes.

**MeSH Keywords:** Amyloidosis • Familial Mediterranean Fever • Genotype • Killer Cells, Natural • Receptors, KIR

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## Background

Familial Mediterranean fever (FMF) is an autosomal recessive, autoinflammatory disease predominantly affecting populations of Mediterranean origin. The clinical picture is characterized by recurrent episodes of inflammation and serositis causing fever, peritonitis, pleuritis, and arthritis [1,2]. The gene associated with FMF is the Mediterranean fever gene (MEFV) located on chromosome 16, which encodes for a protein called pyrin. Mutations of pyrin protein lead to uncontrolled attacks of inflammation, while subclinical inflammation continues during attack-free intervals [1,3,4]. The most devastating complication of FMF is renal amyloidosis, leading to nephrotic syndrome and chronic renal failure. Lifelong use of colchicine provides complete remission or marked reduction of the inflammatory attacks and prevents amyloidosis. If not treated, type AA amyloidosis can cause multi-organ dysfunctions because of the systemic spread [1].

We know that some MEFV mutations may affect the clinical manifestations of FMF. M694V is associated with disease severity and especially amyloidosis [5,6]. Other genes, such as the SAA1 (serum amyloid A1) and the MICA (major histocompatibility chain related gene A), also might influence the clinical picture [5,7]. Some patients with FMF do not experience inflammatory attacks, and present with nephrotic syndrome due to amyloidosis, which is called phenotype 2 disease [5,8]. This leads us to wonder if there is more to the pathophysiology of FMF other than being a classical autosomal recessive disease, and to look for the role of innate immunity in this autoinflammatory disease.

Natural killer (NK) cells are cytotoxic lymphocytes that participate in innate immunity. In addition to their cytotoxic response, these cells produce cytokines to assist the adaptive immune response [9]. The cytotoxicity of NK cells is controlled by surface molecules that are either activator or inhibitor receptors. Killer cell immunoglobulin-like receptors (KIR) are the regulatory receptors expressed on NK cells and CD8 lymphocytes. KIRs determine target cells by HLA class I molecules to help provide selectivity to cellular cytotoxicity [10–12]. The KIR genes have remarkable allelic polymorphism. This polymorphic variation may affect the immune response of the NK cell by altering HLA selectivity and ligand affinity [10,13,14].

KIRs are immunoglobulin receptors encoded on chromosome 19q13.4 in the leukocyte receptor complex. Sixteen genes are present in the KIR gene cluster [9,10,15]; 6 of these genes (3DS1, 2DS1–5) encode receptors triggering activation and 7 of them (3DL1–3, 2DL1–3, 2DL5) encode receptors triggering inhibition of the immune response. Another member of this cluster, 2DL4, may either activate or inhibit the immune response. The last 2 KIR genes, 2DP1 and 3DP1, are pseudogenes that do not encode the surface receptors [10,15].

Activation of innate immunity might be related to pathogenesis of FMF since there is an incomplete penetrance of the disease. Therefore, the genetic variation of the KIRs might be associated with FMF. The aim of the current study is to define immunogenetic determinants in the pathogenesis of FMF and determine if KIRs are related to susceptibility to disease or complications such as renal amyloidosis.

## Material and Methods

### Study group selection and samples

The study groups were 105 nonconsanguineous Turkish patients with FMF (56 female, 49 male; mean age: 29.8 years) diagnosed by the Departments of Nephrology at Gaziosmanpasa University Faculty of Medicine in Tokat and Rheumatology/Immunology at Cukurova University in Adana; and 100 age- and sex-matched, nonrelated, healthy volunteers (53 female, 47 male; mean age: 29.4) from the same ethnic background. FMF patients were diagnosed according to the Tel Hashomer clinical criteria and MEFV mutations were identified by exon sequencing [1,3,16]. The control group never experienced clinical features of FMF and had no family history for autoinflammatory diseases. Therefore, they were not tested for MEFV mutations.

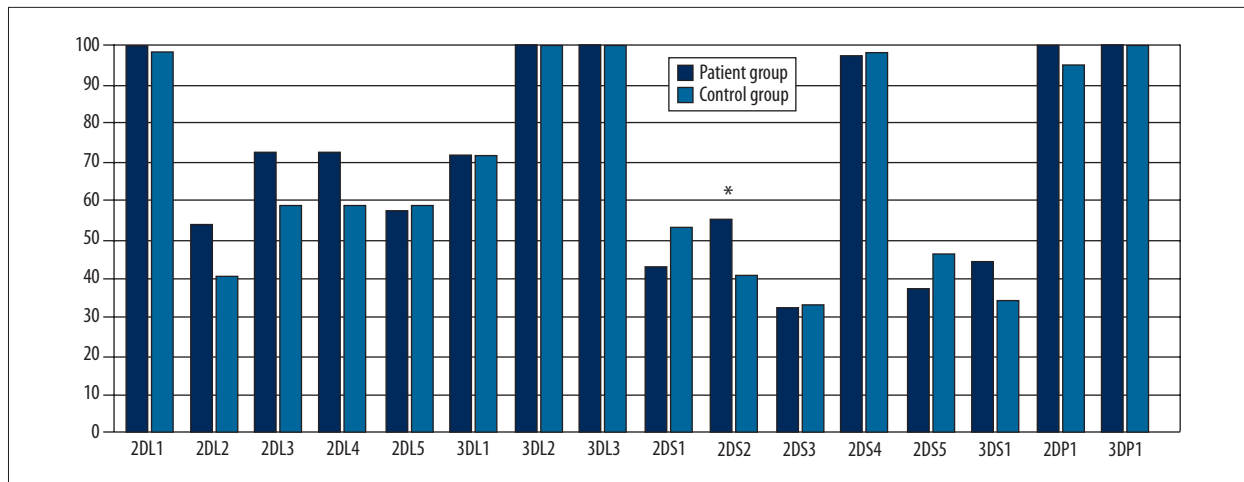
With the informed consent of all participants, the study was permitted by the Ethics Review Board at Gaziosmanpasa University Faculty of Medicine. Then, 5 milliliters of peripheral blood was obtained from all subjects for KIR genotyping. All FMF patients were attack-free and without active infection at the time of sample collection. Nine of them had renal amyloidosis confirmed by biopsy.

### KIR genotype

DNA from the venous-EDTA blood sample of all subjects was extracted by a DNA isolation kit (QIAamp DNA blood mini kit, cat no: 51104, QIAGEN Vertriebs GmbH, Vienna, Austria). Genotyping of KIR genes were performed by the multiplex KIR-SSO kit which is a product of Tepnel Lifecodes Corporation – Immucor, Inc. (Ref: 545110, Connecticut, USA). The product includes locus-specific oligonucleotide probes coupled with color coded microspheres (Luminex Corp.) and 2 PCRs to amplify the KIR exons. Each sample was amplified with PCR and hybridized with SSO probes. Hybridized sample plates were placed in Luminex for analysis.

### Prediction of haplotype and genotype

Allel frequencies of KIR haplotypes group A and group B were taken from data pool (<http://www.allelefrequencies.net>) [17]. Individuals having the characteristic gene content of group A



**Figure 1.** Distribution of KIR gene frequencies of patient and control groups (\*:  $p=0.036$ ).

haplotypes (KIR2DL1, 2DL3, 2DL4, 2DP1, 3DP1, 3DL1, 3DL2, 3DL3 and 2DS4) were considered as AA genotype. If any gene among KIR2DL2, 2DL5, 2DS1, 2DS2, 2DS3, 2DS5, and 3DS1 were present, the individual was considered to be B haplotype (genotype Bx) [17].

### Statistical Analysis

Each KIR gene that is present in any subject is counted directly and the percentage of each KIR gene was calculated for the patient and the control groups. Data were analyzed using statistical software Minitab Version 17. Fisher's exact test was used to analyze the results for categorical variables and p values less than 0.05 were accepted as statistically significant.

## Results

### KIR gene and genotype distribution in FMF patients and healthy controls

The framework genes (KIR2DL4, 3DL2, 3DL3, and 3DP1) were present in all patients and controls. Additionally, a pseudogene, KIR2DP1, was present in all of the patients and in 95% of the controls. The frequencies of activator KIR genes except KIR2DS4 were lower than 58%, while the inhibitory genes KIR2DL1 and 3DL1 were more frequent in all samples (>71%) (Figure 1).

Thirty-eight different genotypes were found in 105 patients with FMF. Among the patients, 23.8% had AA genotypes (AA1, AA156, AA180), which consist of only 1 activating gene, 2DS4. The others demonstrated more than 1 activator gene defined as Bx genotype. Seven patients (6%) had all of the 16 KIR genes, which is called genotype Bx6, while 20 different genotypes were seen only once. Other genotypes that were seen contained 8 to 15 KIR genes (Figure 2).

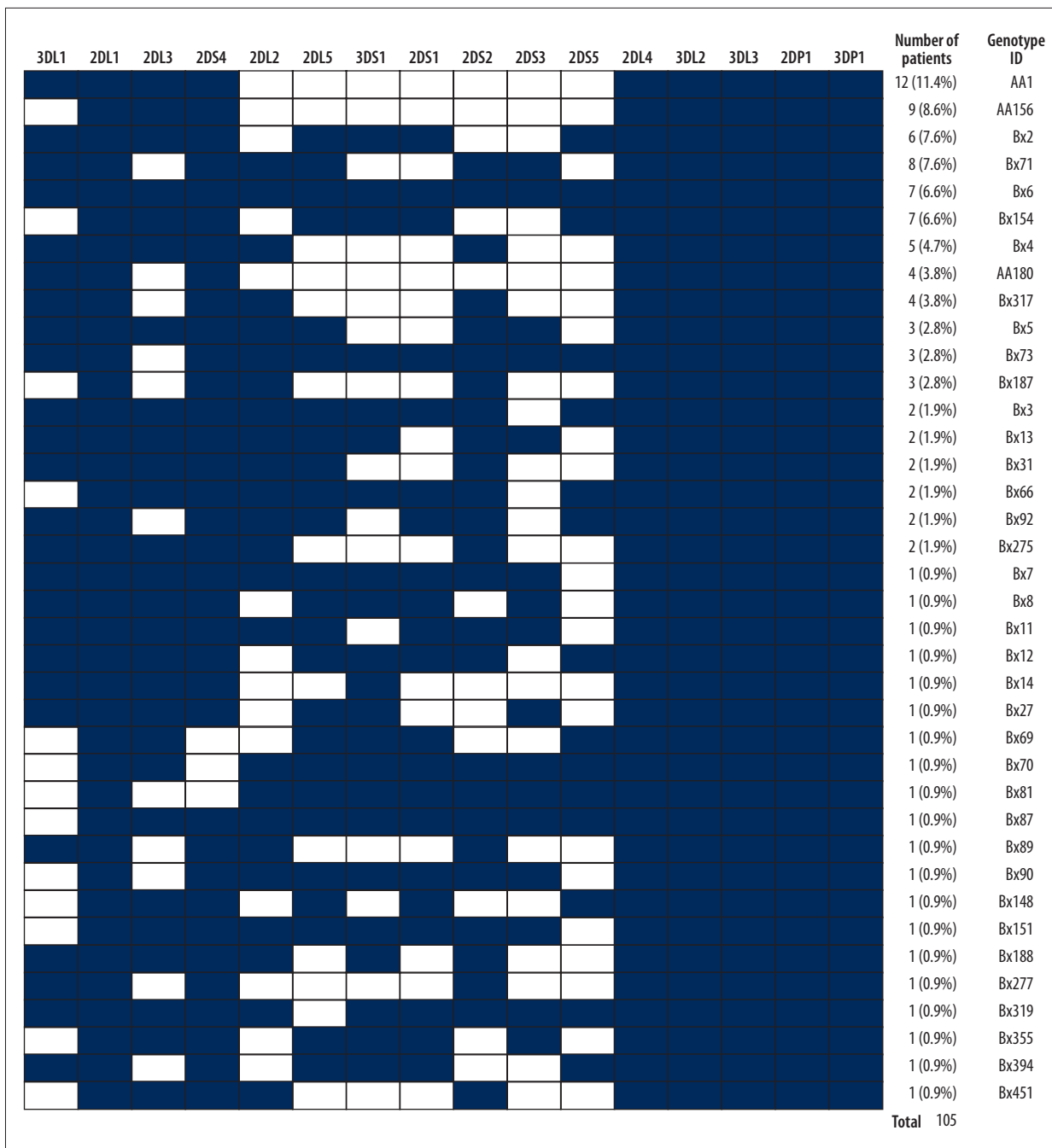
### Relationship of KIR genes with FMF

Frequencies of 16 KIR genes were compared between FMF patients and healthy controls using Fisher's exact test (Table 1). KIR2DS2 gene was significantly more common in the patients compared to the controls ( $p=0.036$ ). The rate of AA and Bx genotypes were not different in both groups ( $p>0.05$ ) (Figure 2).

### Distribution of KIR genes/genotypes of FMF patients with different clinical features

Distribution of individual KIR genes/genotypes was evaluated in FMF patients with and without amyloidosis and arthritis. Additionally, relationship between individual KIR genes/genotypes and the age of disease onset, serum C-Reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and MEFV mutations (M694V and R202Q) were evaluated. There were no statistically significant differences between KIR gene frequencies and the rate of AA and Bx genotypes of patients with ( $n=9$ )/without amyloidosis ( $n=96$ ) groups and with ( $n=53$ )/without arthritis ( $n=52$ ) groups ( $p>0.05$ ) (Table 2). Among our patients, 43.8% had high CRP levels (>0.8 mg/dl). When we compared KIR gene frequencies of FMF patients with high serum CRP levels to those with low serum CRP levels, we found that KIR3DL1 genes were more common in patients with high serum CRP. A statistically significant difference was found between these 2 groups ( $p=0.016$ ) (Figure 3).

As we compared KIR gene frequencies of patients who were carrying M694V and R202Q mutations with patients who were not carrying these mutations, we could not find any relationship between KIR gene polymorphism and those mutations. Additionally, the KIR genes and genotype were not associated with ESR and age of disease onset. MEFV mutations of 105 FMF patients are shown in Table 3.



**Figure 2.** KIR genotype profiles of patients with FMF. Thirty-eight genotypes were observed. Genotypes are differentiated from each other by the presence (blue box) and absence (white box) of 16 KIR genes. Genotype ID refers to genotype classification according to *www.allelefrequencys.net*.

### Discussion

NK cell-mediated cytotoxicity is regulated by surface receptors that can either be inhibitors or activators [9,15]. Two types of receptors provide the NK cells with target selectivity by interacting with HLA class I molecules. C-type lectin-like receptors (CD94/NK62 heterodimers) bind to the HLA-E and some

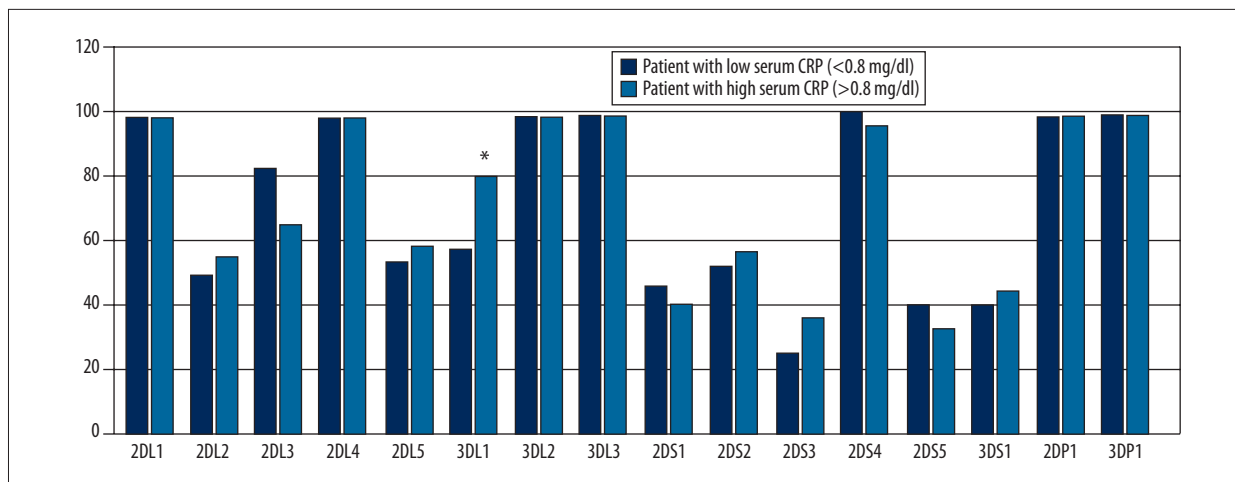
peptides derived from other HLA class I molecules, while the KIRs are immunoglobulin-like receptors which can recognize polymorphic HLA-A, -B, or -C determinants [12,14,18,19]. Alternations in KIR expression on the NK cells can be related to the development of some malignancies, as well as autoimmune and inflammatory diseases [19–22]. Normally, inhibition and activation cycles of KIRs are kept in balance, but

**Table 1.** Frequencies of KIR genes in FMF patients (n=105) and healthy controls (n=100). Statistically significant genes are indicated are boldface.

	Gene	Patients		Controls		P value
		Number	%	Number	%	
Inhibitory KIRs	2DL1	105	100.0	98	98.0	0.237
	2DL2	56	53.3	40	40.0	0.069
	2DL3	76	72.4	58	58.0	0.055
	2DL4	105	100.0	100	100.0	1.000
	2DL5	60	57.1	58	58.0	1.000
	3DL1	75	71.4	71	71.0	1.000
	3DL2	105	100.0	100	100.0	1.000
	3DL3	105	100.0	100	100.0	1.000
	Activating KIRs	2DS1	45	42.9	53	53.0
<b>2DS2</b>		58	55.2	40	40.0	<b>0.036</b>
2DS3		34	32.4	33	33.0	1.000
2DS4		102	97.1	98	98.0	1.000
2DS5		39	37.1	46	46.0	0.206
3DS1		46	43.8	34	34.0	0.156
Pseudogenes	2DP1	105	100.0	95	95.0	0.114
	3DP1	105	100.0	100	100.0	1.000

**Table 2.** Comparison of the frequencies of KIR genes in FMF patients with (n=9)/without (n=96) amyloidosis and with (n=53)/without (n=52) arthritis.

	Genes	Amyloidosis (-)		Amyloidosis (+)		P value	Arthritis (-)		Arthritis (+)		P value
		Number	%	Number	%		Number	%	Number	%	
Inhibitory KIRs	2DL1	96	100.0	9	100.0	1	52	100.0	53	100.0	1
	2DL2	50	52.1	6	66.7	0.498	27	51.9	29	54.7	0.846
	2DL3	68	70.8	8	88.9	0.439	37	71.2	39	73.6	0.830
	2DL4	96	100.0	9	100.0	1	52	100.0	53	100.0	1
	2DL5	55	57.3	5	55.6	1	30	57.7	30	56.6	1
	3DL1	71	74.0	4	44.4	0.115	39	75.0	36	67.0	0.518
	3DL2	96	100.0	9	100.0	1	52	100.0	53	100.0	1
	3DL3	96	100.0	9	100.0	1	52	100.0	53	100.0	1
Activating KIRs	2DS1	41	42.7	5	55.6	0.501	21	40.4	24	45.3	0.695
	2DS2	52	54.2	6	66.7	0.728	29	55.8	29	54.7	1
	2DS3	31	32.3	3	33.3	1	21	40.4	13	24.5	0.098
	2DS4	93	96.9	9	100.0	1	49	94.2	53	100.0	0.118
	2DS5	35	36.5	4	44.4	0.724	18	34.6	21	39.6	0.687
	3DS1	41	42.7	5	55.6	0.501	21	40.4	25	47.2	0.557
Pseudogenes	2DP1	96	100.0	9	100.0	1	52	100.0	53	100.0	1
	3DP1	96	100.0	9	100.0	1	52	100.0	53	100.0	1



**Figure 3.** Distribution of KIR gene frequencies with percentage of patients with low (<0.8 mg/dl) and high (>0.8 mg/dl) CRP levels. KIR3DL1, which is an inhibitor gene, was significantly more common in patients with high serum CRP levels (>0.8 mg/dl), (\*: p=0.016).

**Table 3.** MEFV genotype of 105 FMF patients. “Others” include E148Q and some rare MEFV mutations (S52N, A744S, R761H, V722M, L110P).

MEFV genotype			
Two alleles	Number	One allele	Number
M694V/M694V	17	M694V/-----	13
M680I/M680I	3	M680I/-----	4
R202Q/R202Q	1	V726A/-----	3
M694V/M680I	2	M694I/-----	3
M694V/V726A	2	R202Q/-----	14
M694V/R202Q	9	Others/-----	12
M680I/R202Q	2		
V726A/R202Q	2		
M694V/Others	3		
M680I/Others	2		
M726A/Others	3		
M694I/Others	2		
R202Q/Others	3		
Others/Others	5		

an increase in the activation of NK cells may result in proliferation and change the immune response [19]. Activator KIR genes bind to HLA determinants and enhance the activation of NK cells and CD8+ T cells, which leads to strengthened cellular cytotoxicity and increased cytokine production [9,19]. Genetic variations in the KIR gene family may also affect the immune response of the NK cell and contribute to the phenotype of inflammatory diseases like FMF. KIR genotype is quite variable among different ethnic groups [13,14].

In the current study we investigated the KIR gene frequencies and genotype in 105 unrelated Turkish FMF patients. This is the first study to demonstrate the KIR genes and genotype of Turkish patients with FMF and the first study to compare the KIR genes with the clinical features of FMF. We found KIR2DS2 to be more frequent in our FMF patients compared to in healthy controls (p=0.036). Since it is an activator gene, we think that the presence of KIR2DS2 might be associated with susceptibility to FMF. Another possibility is that KIR2DS2 might be involved in the pathogenesis of FMF.



A previous study by Mahfouz et al. showed a higher prevalence of a pseudogene KIR 3DP1\*003 in 56 Lebanese FMF patients. In contrast to our data, KIR2DS2 was not increased in their results [14]. Not only did we have a larger group of FMF patients, but also the ethnicity was different. Therefore, we suggest the importance of KIR2DS2 in FMF for further research with on ethnic background.

Our study also aimed to search for possible relations between KIR genes and genotype with complications of FMF particularly renal amyloidosis. Type AA amyloidosis is the most important complication of FMF causing nephrotic syndrome and end-stage renal disease (ESRD). Amyloidosis might develop in a small subset of FMF patients even if they are treated with colchicine. This leads researchers to investigate other factors contributing to the susceptibility to disease and disease complications, like renal amyloidosis. We did not find any study about KIR genes and amyloidosis in our literature search.

KIR genotypes and gene frequencies of our patients were not related to renal amyloidosis. All 9 patients with amyloidosis were Bx genotype; exhibiting 1 or more of the activator KIR genes, but there was no significant relation for KIR genotype and renal amyloidosis. FMF patients with amyloidosis also exhibited KIR2DS2 at a rate higher than the patients without amyloidosis (66.7% over 54%), but the difference was not significant. The effect of KIR2DS2 in predisposition to renal amyloidosis could be studied with a larger group of FMF patients with amyloidosis.

The acute-phase proteins CRP and SAA levels are elevated as a result of inflammation during febrile attacks in FMF patients. Although colchicine prophylaxis prevents febrile attacks in FMF, CRP and/or SAA levels may persist to be higher than normal in FMF patients during the attack-free period [23,24]. We did not measure SAA levels of the patients, but we measured serum CRP levels during attack-free periods. In patients with high serum CRP levels (>0.8 mg/dl), KIR3DL1, which is an inhibitor gene, was significantly more common ( $p=0.016$ ). Although CRP is not involved in effector-target cell-mediated recognition, it has been demonstrated that CRP is present on at least certain NK effectors, thus CRP or a molecule that co-caps with CRP is required for optimal NK cell function [25,26]. Our finding of inhibitor KIR3DL1 association with higher CRP in FMF patients may indicate some direct or indirect preventive role of KIRs in inflammation. It has been proposed that evolutionary pressures, such as pathogen-mediated immune evasion strategies, may drive KIR3DL1 diversification [27]. We can speculate that inhibitor KIR3DL1 might provide a selective advantage in FMF patients with high CRP to prevent hazardous effects of inflammation, such as increased cardiovascular risk or even renal amyloidosis. Further studies of CRP

measurements, as well as KIR gene studies, in larger FMF patient groups and healthy populations are needed to obtain a more precise conclusions.

Finally, we want to point out some other studies indicating activator KIR genes and inflammatory conditions. A recent study Zal et al. showed that CD4+ T cells exhibited increased KIR2DS2 and reduced KIR2DL3 expression in patients with end-stage renal disease compared to nondialysis-dependent chronic kidney disease patients. They suggested that immune activation through KIR expression might increase with progressive renal impairment and contribute to cardiovascular risk [28]. Studies by Yen et al. and Prakash et al. note that KIR2DS2 is related to rheumatoid arthritis (RA) [29,30]. The latter study, which indicates the enhancing role of activator gene KIR2DS2 for the immune response denotes that patients with RA positive for KIR2DS2 and KIR3DS1, showed risk associations [30].

Another activator gene, KIR2DS4, was found to be associated with acute rejection in renal transplant recipients by Kusnierczyk, and the relation was stronger for patients whose ESRD was caused by glomerulonephritis. Interestingly, KIR2DS5, which is also an activator, was found to be protective against acute rejection in the same study [31].

A meta-analysis provided evidence that KIR2DL1, KIR2DS4, KIR2DS5 and KIR3DS1 gene variations may contribute to susceptibility to ankylosing spondylitis [19]. The association with KIR2DL1 is interesting yet it is an inhibitory receptor for NK cell activities.

We could conceivably think that combinations of variations in activating, inhibitory, and pseudo KIR genes is crucial for some diseases. The pathogenesis of FMF and inflammatory diseases is not understood comprehensively. Genetic imbalance altering the innate immunity at the receptor level may be an accelerator for the disease process.

## Conclusions

KIR genes have many variations among different ethnic groups. These variations may cause a genetic imbalance and change the course of some diseases. In this study we found KIR2DS2 to be more frequent in 105 FMF patients, for the first time demonstrating the KIR genotype of Turkish patients with FMF. We suggest that the presence of KIR2DS2, which is an activator gene for NK cell functions, might be related to the autoinflammation in FMF. The association of KIR3DL1 with high CRP needs further investigation. None of the KIR genes was associated with common MEFV or age of disease onset. There was no significant difference between KIR gene frequencies and genotypes of the patients with renal amyloidosis. The potential

effect of KIR genes on predisposition to renal amyloidosis and other clinical features requires studies with larger sample sizes.

### Conflict of interest

The authors declare that they have no competing interests.

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### Compliance with ethical standards

Human blood samples were collected from the patients and healthy controls and the study was carried out with the informed consent from all participants.