MEFV and SAA1 genotype associations with clinical features of familial Mediterranean fever and amyloidosis in Armenia

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ABSTRACT

Objective. *Familial Mediterranean fever (FMF) is a hereditary periodic disease characterised by recurrent attacks of fever and serositis. The most devastating complication of FMF is amyloidosis (AA) affecting mainly the kidneys.*

Aim of the study is to search for correlations between the MEFV genotype and the SAA polymorphisms with the clinical manifestations of FMF and the occurrence of amyloidosis in a large cohort of Armenian patients.

Methods. *Information about the MEFV mutations, SAA polymorphisms and FMF clinical features, were obtained for 1017 FMF patients, from the database of the Center of Medical Genetics in Yerevan. For identifying probable correlation between the MEFV and SAA genotype and clinical features of FMF, regression logistic analyses were conducted between the genotype and phenotype of the patients.*

Results. *Patients homozygous for M694V were highly associated with all the clinical features of FMF and its complications – proteinuria and amyloidosis. None of the SAA1 polymorphisms had any correlation with FMF clinical features. However, homozygosis for SAA1 α/α polymorphism was associated with proteinuria and amyloidosis whereas carrying the β/β polymorphism was found to be protective for amyloidosis.*

Conclusion. *The SAA1 α allele is strongly associated with amyloidosis in FMF patients. This observation is valid in inflammatory diseases other than FMF too. SAA1 polymorphism has no effect on the clinical features of FMF. M694V homozygosis is highly associated withal typical features of FMF and with amyloidosis. FMF course in Armenia is similar to that in Middle Eastern countries where FMF disease is common.*

Introduction

Familial Mediterranean fever (FMF) is a hereditary periodic disease mainly characterised by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like skin lesions (1, 2). The disease is relatively common among Armenians, Turks, non-Ashkenazi Jews and Arabs. The most devastating complication of FMF is the development of secondary amyloidosis (AA) affecting mainly the kidneys. In the past, two types of amyloidosis presentations have been described (3). The first was amyloidosis which appears many years after recurrent typical attacks of FMF (phenotype I). In the other presentation amyloidosis was the first or the only manifestation of FMF with no previous typical features of the disease (phenotype II). Today some authors doubt the presence of type II FMF since in those who present only with amyloidosis, thorough questioning and better anamnesis reveal typical FMF manifestations which were forgotten, overlooked or were related to other diseases rather than to FMF (4).

Colchicine is the drug of choice for FMF since 1972 (5, 6). It can prevent the attacks of FMF and may fend off the development of secondary amyloidosis. In 1997 two groups of investigators identified the gene associated with FMF (MEFV) (7, 8). Since then, more than 300 mutations have been discovered some of which are clearly responsible for the disease. Over the years many studies searched for correlations between the mutations carried by the FMF patients and their clinical manifestations. Many of them found that the M694V mutation, especially in the homozygous state, has been associated with more severe FMF with early disease onset, frequent attacks and common involvement of the joints (arthritis) (9-12). However, two studies from Turkey did not support this view (13, 14).

Table I. Correlation between MEFV genotypes and clinical features in FMF patients.

		Fever	Abdom.	Thorac	Arthralg	Arthritis	Mialgia	Hepat	Spleen	Erysi	Protein	Amyl
M694V/M694V	OR	**2.629**	**1.805**	**2.703**	**1.784**	**4.417**	**2.115**	**4.013**	**4.425**	**2.959**	**3.629**	**2.601**
	p	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.021**	**0.000**	**0.002**
M694V/-	OR	0.862	0.534	0.391	1.022	0.916	0.867	-	-	0.719	0.334	0.260
	p	0.547	0.007	0.003	0.928	0.796	0.622	-	-	0.749	0.113	0.154
M694V/V726A	OR	**2.343**	**2.919**	**2.339**	1.155	0.047	1.397	1.470	0.667	0.556	1.213	**2.433**
	p	**0.002**	**0.000**	**0.000**	0.496	0.471	0.155	0.279	0.317	0.566	0.622	**0.019**
M694V/M680I	OR	**3.491**	1.682	**2.204**	1.497	0.638	-	0.919	0.656	-	0.995	1.638
	p	**0.002**	0.093	**0.003**	0.128	0.303	-	0.874	0.422	-	0.997	0.358
M694V/E148Q	OR	1.759	0.564	2.117	1.373	2.167	1.300	2.017	1.452	-	0.997	1.593
	p	0.378	0.266	0.142	0.542	0.180	0.655	0.352	0.625	-	0.998	0.654
M680I/M680I	OR	0.692	0.663	1.502	2.530	1.777	0.294	2.389	1.720	-	1.165	1.862
	p	0.017	0.010	0.476	0.094	0.380	0.212	0.549	0.480	-	0.884	0.548
M694V/R761H	OR	2.647	1.839	0.955	0.621	1.614	1.432	-	-	-	-	3.813
	p	0.187	0.345	0.939	0.419	0.463	0.545	-	-	-	-	0.065
V726A/M680I	OR	1.484	**2.166**	1.527	0.817	0.109	0.952	1.402	0.771	1.162	0.544	0.420
	p	0.238	**0.027**	0.147	0.499	0.029	0.887	0.486	0.624	0.885	0.399	0.381
V726A/V726A	OR	0.526	0.923	0.261	0.664	1.037	0.623	0.676	-	3.227	0.731	1.168
	p	0.151	0.866	0.053	0.403	0.954	0.450	0.703	-	0.241	0.760	0.881
V726A/-	OR	0.608	0.555	0.382	-	0.207	0.763	0.464	0.516	1.074	1.078	0.388
	p	0.074	0.033	0.013	-	0.030	0.449	0.282	0.264	0.945	0.888	0.336

The empty squares mean no patients with this combination.

In addition, other studies looked for predisposing factors for the development of amyloidosis in FMF patients. Types of MEFV mutations, gender of the patients, their family history and country of origin were all investigated and found to have an effect on the occurrence of this FMF complication (15). In addition, 2 genes, namely *SAA1* (serum amyloid A type 1) and *MICA* have also been investigated in FMF patients and were found to have an effect on amyloidosis and on the course of the disease, respectively (16, 17). The genotype α/α of the *SAA1* gene was found to be associated with a sevenfold increase in the incidence of renal amyloidosis, especially in patients homozygous for M694V (16). The Major Histocompatibility Complex (MHC) class-I-chain-related gene A (MICA) alleles A4 and A9 were associated with a diminished attack frequency and an earlier age of onset, respectively, notably in patients homozygous for M694V (18). Association between the SAA1 gene polymorphism and the clinical features of FMF have not been studied. The purpose of the present study was to search for a correlation between the *MEFV* genotype and the SAA polymorphisms together with the clinical manifestations of FMF as well as with the occurrence of amyloidosis in a large cohort of Armenian patients from the Center of Medical Genetics and Primary Health Care in Yerevan.

Methods

The main study group was composed of 1017 patients from our cohort of about 26,000 FMF patients in the Center of Medical Genetics and Primary Health Care in Yerevan, Armenia (19). They were selected consecutively due to the availability of concomitant data on their MEFV and SAA1 genotype analysis. The reasons for checking this SAA1 genotype were: suspicion of amyloidosis (for which the FMF patient also underwent a renal biopsy), proteinuria of above 150mg/24/hours but with no renal biopsy, and a specific request by the family physicians of the FMF patients.

Information about the MEFV mutations, SAA polymorphisms, clinical symptoms, gender, age of onset of FMF, age at diagnosis and treatment with colchicine etc., were all derived from the database of our Centre.

Blood samples were drawn from all the patients on EDTA, and DNA was extracted from leucocytes by standard technique (20). Twelve mutations previously detected in the Armenian population were screened (M694V, M694I, V726A, M680I, E148Q, E167D, R761H, P369S, A744S, F479L, I692del, K695R) as previously described (21). *SAA1* gene polymorphisms were also tested in the FMF patients. The DNA fragment including the *SAA1* gene polymorphisms was amplified using the Saa1F (5'-GCCAATTACATCG-GCTCAG-3') and Saa1R (5'- TGGC-CAAAGAATCTCTGGAT-3') primers. The 3 polymorphisms of the SAA1 gene were determined with 2 restriction enzymes, BanI and BclI. that allowed the identification of the amino acids at positions 52 and 57, respectively (22). Valine/Alanine, Alanine/Valine and Alanine/Alanine amino acids at positions 52/57 defined respectively the alpha, beta and gamma *SAA1* alleles. This method for SAA analysis was applied in the first 382 patients out of 1017. The rest of the patients were tested by FMF and SAA1 StripAssay (Vienna-Lab) according to the manufacturer's manuals. Informed consent was obtained from all the patients studied.

Statistical analysis

The data were transferred from the database to SPSS Statistics 22.0 software for further analysis. Descriptive statistics were used to characterise study participants. Categorical variables were described using frequencies and percentages. For identifying the crude associations between the MEFV and SAA genes and clinical features of FMF, bivariate logistic regression analysis was conducted. After the bi-variate logistic regression analysis, the multiple logistic regression analysis was performed and the variables with $p<0.25$ level of association with the outcome in the bivariate analysis were included in the multivariate analysis. Multiple logistic regression analysis was repeated several times with different sets of variables until only the variables with statistically significant p-values ($p<0.05$) remained in the model. Results of p-value less than 0.05 were considered as statistically significant.

Table II. Association between SAA1 polymorphisms and clinical features of FMF patients (α/α; α/β; β/β; β/γ) in 1017 FMF patients*.

	α/α n=172		α/β n=482		β/β n=325		β/γ n=29	
Clinical features	OR	*p*-val	OR	*p*-val	OR	*p*-val	OR	*p*-val
Fever	1.155	0.438	0.990	0.940	0.933	0.634	1.150	0.740
Abdominalgia	1.071	0.701	0.935	0.612	1.180	0.253	0.523	0.081
Thoracalgia	0.911	0.616	0.856	0.260	1.216	0.178	1.478	0.312
Arthralgia	0.884	0.477	1.014	0.913	1.123	0.398	0.817	0.610
Arthritis	1.114	0.640	1.028	0.879	0.919	0.662	1.231	0.677
Mialgia	1.231	0.285	1.156	0.338	0.756	0.095	0.926	0.129
Hepatomegalia	1.679	0.067	1.152	0.559	0.679	0.165	-	-
Splenomegalia	1.204	0.492	1.025	0.906	0.933	0.764	0.328	0.252
Skin	-	-	0.986	0.978	1.915	0.178	2.170	0.449
Proteinuria	1.428	0.241	0.868	0.575	0.948	0.844	1.035	0.963
Amyloidosis	**6.057**	**0.000**	**0.504**	**0.034**	**0.324**	**0.008**	0.785	0.814

The group of patients with α / γ polymorphism was too small (nine) so they were not included in the analysis.

Table III. Association between age of onset and amyloidosis status.

Total n=973 Amyloidosis n=44		Age of onset <20	Age of onset 20 ≥
Amyloidosis	No	76.8%	23.2%
	Yes	92.0%	8%

*p-value = 0.075.

Table IV. Frequency of FMF attacks among patients with and without amyloidosis.

Total n=973 Amyloidosis n=44		Attack frequencies <1 in month	in month	>2 in month
Amyloidosis	No	20.9%	60.8%	18.3%
	Yes	4.7%	74.4%	20.9%

*p-value = 0.021.

Results

From our FMF cohort of 26,000 FMF patients, we selected 1017 that were tested for MEFV mutations and SAA1 polymorphisms. Out of these 1017 patients 44 had amyloidosis proven by renal biopsy, 68 had proteinuria above 150mg/24hours, and 871 had typical FMF who were sent to our centre for SAA1 testing by their family physicians although they did not have amyloidosis or proteinuria. The other 34 patients had a clinical diagnosis of FMF but no MEFV mutations (3.3%). The patients carried different combinations of MEFV mutations, as seen in Table I. Regarding SAA1 polymorphisms,172 patients carried the α/α polymorphism, 485 had α/β, 325 had β/β, 29 carried β/γ and 9 patients carried α/γ polymorphism (Table II).

Multiple logistic regression analysis was conducted in order to identify a correlation between the various clinical manifestations of the FMF patients and their MEFV mutations. Table I summarises the results and demonstrates that patients homozygous for M694V were highly associated with almost all the clinical features of FMF and its complications - proteinuria and amyloidosis. The rest of the genotype combinations were associated mainly with fever, peritonitis and pleuritis. If we choose an odd ratio (OR) over 1.0 with significant p-value (<0.05) we can see in bold numbers that in addition to M694V homozygosis, compound heterozygotes consisting of M694V and another mutation significantly correlated with fever, peritonitis and pleuritis (Table I).

Multiple logistic regression analysis was also conducted to identify whether the SAA1 gene polymorphisms are associated with certain clinical manifestations of FMF. Table II shows that none of the SAA1 polymorphisms had any statistically significant correlation with FMF clinical features. However, regarding the association with proteinuria and amyloidosis, it is clearly shown that homozygosis for α/α polymorphism carried a significant risk for these complications whereas carrying the β/β polymorphism was found to be protective for amyloidosis (OR=0.104, p=0.027) (Table II).

When we compared the 44 patients with amyloidosis to the 973 patients without amyloidosis – regarding disease severity as reflected by their age at disease onset and frequency of attacks – we found that the amyloidosis group displayed significantly worse disease (Tables III, IV).

Discussion

Familial Mediterranean fever is a clinically heterogeneous disease. The quite variable phenotypes among FMF patients have suggested specific muta-

tional effects as well as additional modifier genes that would affect the appearance of the different clinical signs of the disease and its main complication – amyloidosis. Our study shows that M694V homozygosis was associated with all the typical features of FMF, whereas patients with other combinations of mutations displayed only some of these clinical manifestations (Table I). These results are in accord with previous studies which showed that M694V homozygotes frequently present with arthritis and erysipelas-like erythema (10). On the other hand, we failed to show any correlation between the SAA1 genotype and the clinical features of FMF (Table II).

Serum amyloid A protein (SAA) is an acute phase reactant which increases considerably during inflammation and by proteolytic cleavage may become the major fibrillar protein deposited in secondary amyloidosis (23). Two isotypes, SAA1 and SAA2, with quite homologous sequences have been distinguished, and allelic forms of these isotypes have been identified (24). Thus the SAA gene was a natural potential candidate to be evaluated for its effect on the development of amyloidosis in FMF.

Over the years, additional genetic and non-genetic components have been reported to be associated with the risk of developing amyloidosis in FMF patients. Gender, family history for the presence of amyloidosis and country of origin were all implicated in increasing this risk (15).

Genotype-phenotype studies have tried to associate amyloidosis with specific combinations of MEFV mutations. The M694V mutation that has often been correlated with a severe FMF phenotype has also been correlated, especially in the homozygous state, with amyloidosis development (25, 26). Nevertheless, studies on Turkish families presenting FMF patients with amyloidosis failed to show correlation with the M694V mutation (13, 14). In later studies, also from Turkey, a significant increase in the number of patients homozygous for the M694V mutation was noted in the groups of FMF patients with amyloidosis ($p<0.001$), suggesting that this correlation is valid among various FMF populations (9).

In the present study, FMF onset occurred before age 20 in 70% of the patients without amyloidosis, whereas 30% developed the disease after age 20. In the group of patients with amyloidosis, 92% were younger than 20 years at FMF onset and only 8% were older ($p=0.075$ borderline significance) (Table III).

Regarding the relationship between FMF severity – as reflected by the attack frequency – and the development of amyloidosis, Table IV shows that in the amyloidosis group 20.9% of the patients had one or more attacks per week, 74.4% had one or more attacks per month and in 4.7% the frequency of attacks was less than once a month. Among the non-amyloidosis group, 18.3% had one or more attacks per week, 60.8% had them once a month or more and in 20.9% the frequency of the attacks was less than once a month ($p<0.05$). In the present study amyloidosis was more common among FMF patients homozygous for M694V mutation. Taken together, the age of FMF onset, frequency of the attacks and the carriage of M694V, it seems that amyloidosis development is clearly associated with more severe disease. These results further support previous reports from France, Turkey and Israel and show that the course and character of FMF and its complications are similar in patients from Armenia.

Amyloidosis, mainly the AA type, is one of the common diseases in nephrology clinics in Turkey and Armenia. AA type amyloidosis is a complication of various chronic infections or inflammatory diseases such as rheumatoid arthritis (RA), osteomyelitis, bronchiectasis and tuberculosis. The SAA1 allelic forms have been associated with the incidence of amyloidosis in different diseases and various populations. For example, a study from Turkey investigated the association of SAA1 gene polymorphisms and amyloidosis in different Behçet's disease (BD) patient groups: BD with amyloidosis (n=9), BD without amyloidosis (n=39), and healthy controls (n=63) (27). The SAA1 α/α genotype was significantly more common (78%) among patients with BD and amyloidosis. This may suggest that SAA1 α/α polymorphisms presents a risk factor for the development of amyloidosis also in BD. Similar results were reported in patients with RA who developed amyloidosis (28).

In the present study, our results show that the β/β and β/γ SAA1 genotypes were more frequent among the group without amyloidosis, whereas the α/α and the α/β genotypes were much more observed in patients with amyloidosis. These results are also in accord with previous publications from other countries (29). Thus, it seems that the β and γ alleles are protective against the development of amyloidosis in FMF patients.

The main limitation of the present study is its being retrospective and as such may suffer from the bias of lacking data. However, the fact that it confirms results published from other countries suggest that it is quite valid.

In summary, the present study confirms the association of the α allele with the development of amyloidosis in FMF patients. Since this was also shown in inflammatory diseases other than FMF, it seems to be a valid general observation. The present study also shows that SAA1 polymorphism has no effect on the clinical features of FMF. Moreover, it confirms the high association between M694V homozygosis and amyloidosis. It also supports the view that development of amyloidosis correlates with FMF disease severity. The results presented herein show that the course and patterns of FMF in Armenia are similar to those in Middle Eastern countries where FMF disease is common.

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