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The importance of M694V mutation in systemic lupus erythematosus; implications for its role in neutrophil extracellular traps associated renal involvement

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is characterized by multisystem organ involvement. Enhanced neutrophil extracellular traps (NETs) formation and release as well as impaired clearance of NETs have been reported in SLE patients. Renal involvement is common in SLE which might be through deposition of immune complexes within the kidneys. M694V mutation is one of the hot spots of Mediterranean fever gene (MEFV). MEFV mutations have been previously reported in a number of auto-inflammatory and autoimmune diseases in Iranian patients.

Objectives: This case-control study was aimed to evaluate the potential influences of M694V gene mutation in SLE disease and in development of renal involvement.

Patients and Methods: Genotyping of 130 patients and 116 healthy controls was done for M694V mutation (rs61752717, c.2080A>G) using amplification refractory mutation system- polymerase chain reaction (ARMS-PCR) method.

Results: Significant differences in the alleles and genotypes frequencies of M694V mutation between SLE patients and ethnically matched healthy controls were detected in this study (9.9% versus 2.4% $P=0.000$, OR [odds ratio] = 4.277, CI = 2.213-8.265). Furthermore a significant difference of renal involvement between M694V mutation carriers versus non-carriers (8.5% versus 10.4%, $P=0.017$, OR = 2.149, CI = 1.135- 4.072).

Conclusions: The association between M694V mutation and SLE susceptibility was observed. Additionally, renal involvement was significant in SLE patients compared to controls. This finding probably is developed through NET-associated Dnase1 inhibition and maybe amyloidosis. This study may help to explain the nature of the inflammatory state in mutation carriers and assist to an accurate understanding of how it influences SLE pathogenesis.

Original Article

Implication for health policy/practice/research/medical education:
The association between M694V mutation and systemic lupus erythematosus (SLE) susceptibility and renal involvement in SLE patients probably can be developed through enhanced neutrophil extracellular traps (NETs) -associated Dnase1 inhibition and it might be amyloidosis. The results may assist to an accurate understanding of how it influences SLE pathogenesis.

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1. Background

Systemic lupus erythematosus (SLE) is a disease with heterogeneous involvement and mostly affects female subjects (1). Around 23% to 60% of SLE patients presented with renal involvement caused by inflammation which consequently leads to deposition of the glomerular immune complex. The clinical manifestations of renal disease occur in around half of the SLE patients. The

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most evidences for renal involvement appear within the first 6 to 36 months of diagnosis (2,3).

Positive antinuclear antibodies (ANAs), elevated anti-DNA, low complement levels and renal manifestations often indicate active lupus, particularly lupus nephritis. Nephritis relapse is a strong predictor of progression to end-stage renal disease (ESRD) (4).

SLE patients have disruptions in their innate immunity that could play a critical role in initiation and prolongation of the disease (5). In course of infections, neutrophils release neutrophil extracellular traps (NETs) which this process is known as NETosis and results in cell death. In SLE, NETosis occurs after neutrophil priming and activation respectively by type I interferon and cytokines (IL-1β, IL-8, IL-17 and TNF) and autoantibodies (6,7). Enhanced NET formation and impaired clearance may lead to immunogenicity in SLE by induction of the modified autoantigens externalization, such as synthesis of type I interferon, stimulation of the inflammasome, and activation of the complement system pathways (8). This can result to the release of more cytokines which further stimulate NETosis. Excess NETosis can potentially cause organ damage (9).

Mediterranean fever gene (*MEFV*) mutations develop the familial Mediterranean fever (FMF), an autosomal recessive disease. *MEFV* gene consists of 10 exons and is located on chromosome 16p13.3 (10). This gene encodes marenostrin/pyrin protein and has a vital role in the inflammatory responses (11). From *MEFV* gene mutations, the *M694V* mutation (c.2080A>G) in exon10 is the most common and disease-causing variation that has been presented in all studied groups (12,13). *M694V* mutation leads to the loss of inhibitory effects of the C-terminal B30.2 domain of pyrin protein on caspase-1 and other components of the inflammasome (14).

The most serious problem of FMF is the development of kidney amyloidosis that is highly associated with the M694V substitution (15) and results in renal insufficiency leading to ESRD (16).

The possible relation between FMF and SLE has been reported previously. In spite of the differences, numerous same pathogenic mechanisms are shared between these two disorders. Additionally, they have the same clinical conditions, like renal involvement (17,18). Releasing of the NETs along with IL-1β was observed in the course of disease attacks in both of diseases (19). Additionally, some cases of SLE with AA amyloidosis have been reported previously. In SLE cases, deposition of amyloid fibrils has been observed in some organs including gastrointestinal tract, heart, skin, and mostly in kidney which causes insufficiency of renal function (20,21).

Further scientific information on the role of innate immunity in SLE pathogenesis including the role of the pyrin domain on the inflammasomes activation makes the possible effect of MEFV mutation on SLE manifestations (22).

2. Objectives

The idea of the current study came up with the aim of discovering the clinical significance of the *M694V* gene mutation in SLE patients. *MEFV* mutations have been studied before in a variety of auto-inflammatory and autoimmune diseases in Iranian patients. However, the role of these mutations in the susceptibility of SLE in Iranian population is not clear. This study was aimed to evaluate the potential influences of *M694V* gene mutation in SLE disease, particularly in development of renal involvement in Iranian SLE patients.

3. Patients and Methods

3.1. Study population

The present study included 130 SLE cases and 116 healthy controls. Of 130 SLE patients, 113 patients were female and 17 were male (female to male ratio of 7.53:1), thus, the majority of SLE patients were female. The mean age of patients was 22.31 ± 8.351 years and the mean duration of SLE was 4.85 ± 2.901 years. The patients met at least four criteria of American College of Rheumatology (ACR) for SLE disease (17). The study was established by the local ethics committee. All of the individuals joined in this study voluntarily and after clarification of the aim of the study informed consents were attained from all cases. The laboratory and clinical features of the patients were recorded using a standard form.

3.2. DNA extraction and mutation analysis

For each patient, DNA extraction was done from whole blood. Each DNA sample was genotyped for *M694V* (rs61752717, c.2080A>G) mutation using amplification refractory mutation system-polymerase chain reaction (PCR). Genotyping was done through four primers, forward outer: 5'TCCTGGGAGCCTGCAAGAC3' and reverse outer: 5'ACTGGACAGATAGTCAGAGG3', forward inner: 5'GCTACTGGGTGGTGATAAGGG3', reverse inner: 5'GACGCCTGGTACTCATTTTCCTTAAT3'. It was done in two separated PCR reaction, one comprised three primers of F inner, R outer and F outer (59°C) with PCR product of 328 and 235bp and other reaction consisted of three primers of R inner, F outer and R outer (62°C) with PCR products of 328 and 110 bp. Data analysis from these two PCR reactions led to identify the *M694V* carriers in all subjects. Sequencing of PCR products was carried out by automated DNA-sequencing.

3.3. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki and its later amendments; 2) informed consent was obtained; and 3) This study was allowed by the Ethics Committee of Shahid Beheshti University, Tehran, Iran (#D-200-2782).

3.4. Statistical analysis

Statistical analysis was carried out using SPSS version 22. Differences between the groups in separate variables were compared using a chi-square test (Pearson or Fisher's exact test was applied whenever needs), and odds ratios (OR) were given with 95% CIs. Results were given as a mean ± standard deviation (SD). Statistical significance was defined as $P<0.05$.

4. Results

One hundred thirteen (86.9 %) of patients (n = 130) were female. The mean age of total patients was 22.31 ± 8.351 years and the mean age of SLE onset was 17.14 ± 7.332 years. The mean age of lupus nephritis patients with positive ANA, elevated anti-DNA, low complements (C3 and C4) levels and renal manifestations was 21.35 ± 7.656. Their mean age of lupus nephritis onset was 15.88 ± 5.666 and the mean duration of their lupus nephritis was 5.47 ± 2.501. Patients in the SLE nephritis group were younger. The disease onset was around one year earlier and disease duration was a little higher compared to non-nephritis lupus patients. All subjects were genotyped for *M694V* gene variation. A significant association for allelic and genotypic frequency of the *M694V* mutation between SLE patients and controls was observed (9.9% vs. 2.4%, $P = 0.000$, OR = 4.277, CI = 2.213-8.265).

No mutations were identified in 91 of patients (70%), although we cannot ignore the probability that some of the patients had other mutations. The *M694V* mutation carriage rate in our SLE patients was 18.8%.

Renal involvements were more significant in *M694V* carriers than those in non-carriers (8.5% versus 10.4%, P=0.017, OR= 2.149, CI= 1.135- 4.072) (Table 1). There were no significant differences in other clinical manifestations and laboratory abnormalities between SLE patients and *M694V* mutation occurrence. Additionally, no significant difference of SLE onset in patients with *M694V* mutation (15.76 ± 7.60 versus 18.53 ± 7.15 years, carriers versus non-carriers, $P=0.084$) was observed.

5. Discussion

In this study, the frequency of the *M694V* gene variation in SLE patients was investigated. This mutation is the most important variation that has been reported previously in FMF patients. Therefore, further studies in other diseases helps to accurately explain the nature of the inflammatory state in *M694V* mutation carriers. Moreover, how it can influences SLE pathogenesis, along with other autoimmune disorders is remarkable. The *M694V* mutation carriage rate in our SLE patients was 18.8%. We found a statistically significant difference between SLE patients and matched healthy controls for allelic and genotypic frequencies ($P = 0.001$).

This result may be explained by the contribution of the methionine residue at the position 694 to the protein function. It is located in the binding site of the caspase-1 enzyme thus any substitution or deletion of this residue affects the inhibitory interaction between pyrin and caspase-1. *M694V* mutation alters suppression of caspase-1, dysregulates the function of the inflammasome, results to excessive production of interleukin (IL)-1β. This leads to influx of numerous neutrophils into the affected spots (23).

IL-1β is involved in the excessive formation and release of NETs in systemic inflammatory response syndromes (24,25). It is suggested that NETs contributed to the pathogenesis of autoimmune and inflammatory disorders including SLE. NETs potentially represent a chief reservoir of autoantigens that cause activation of B-cell and dendritic cell and have a function in the proliferation of the inflammatory response (26). Increased NET release, NETosis, and impaired NET clearance were detected in SLE patients (27). Furthermore, we studied the effect of *M694V* occurrence on the lupus phenotype such as renal involvement. To the best of our knowledge, the relation of the *M694V* mutation and SLE phenotype has not been previously reported in Iranian population. Renal involvement developed in 30% of our patients that is in accordance with previous studies (3).

Table 1. Genotype and allele frequencies of *M694V* mutation in two subgroups of patients and control groups

		SLE patients, No. (%)	Healthy controls, No. (%)	*P* value	SLE nephritis	SLE mild	*P* value
Genotypes	AA	91 (70)	106 (91.4)	>0.001	22 (55)	69 (76.7)	>0.001
	AG	29 (22.3)	9 (7.8)		14 (35)	15 (16.7)	
	GG	10 (7.7)	1 (0.9)		4 (10)	6 (6.7)	
Alleles	G	49 (18.8)	12 (5.2)	>0.001	22 (27.5)	27 (15)	>0.001
	A	211 (81.2)	221 (94.8)		58 (72.5)	153 (85)	

We observed a statistically significant difference between *M694V* carriers and non-carriers in our SLE patients with renal involvement. Therefore, the *M694V* mutation is likely to be an important factor in developing renal involvement in SLE patients especially in lupus nephritis. (28). However, the modifying role of *M694V* mutation on the clinical manifestation of SLE is not supported by our results. This finding is in contrast to the study by Shinar et al (29). It may be explained by different frequency of alleles and genotypes and different penetration between populations. According to our observation, it could manifest itself in both homozygote and heterozygous states in patients with renal involvement. Our results are in agreement with the study of Deniz et al (30). They reported an association between exon 10 mutations of *MEFV* gene including M694V variation with lupus nephritis. Our findings may be partially explained by the excessive IL-1β production along with neutrophil activation which results to more profound inflammatory state associated with *M694V*. This condition may lead to overreaction to infections or to any other stimulus. This causes overwhelming of NET formation and release (31). NETs contain autoantibodies and C1q, which prevents DNase-I access to NETs and also degradation of chromatin (27).

Impairment of DNase I function leads to failure of dismantling NETs and cause to more IL-1β production (31,32). On the other hand, the inhibitory effect of DNase I on IL-1β production was altered through its inhibition (19). All of these consequences correlated with kidney involvement. The immune complexes may get deposited in the kidneys, leading to lupus nephritis. Moreover, NETs stimulate interferon-α release, which can directly damage tissues. It is also demonstrated to be associated with lupus nephritis (9,31). Finally, the uncontrolled inflammatory response leads to autoimmune-mediated renal involvement, which is due to *M694V* mutation in pyrin protein.

Furthermore, *M694V* is associated with amyloidosis or amyloid production in familial Mediterranean fever (33). The defective pyrin protein loses its direct or indirect anti-amyloid effect, leading to a deposition of amyloid fibrils (15). Moreover, mutations that cause an alteration in native peptides or inflammatory processes leads to abnormal protein folding that may develop amyloid fibril deposition (34).

Secondary amyloidosis (AA amyloidosis) was reported in certain autoimmune diseases, such as rheumatoid arthritis and dermatomyositis. Therefore, it would not be unexpected to occur in SLE (35). AA amyloidosis associated with SLE may affect several organ and tissues such as the kidney, gastrointestinal tract, liver, spleen, heart, lung, and bone marrow (36,37). AA amyloidosis may be associated with long-standing SLE (36). The development of renal involvement is a potentially lethal complication of SLE. Despite all of the challenges, advances in understanding the biological basis of SLE can suggest more effective approaches to patient care. Early diagnosis and prompt treatment decrease morbidity and mortality of the disease.

6. Conclusions

In conclusion, we found the *M694V* mutation could be an additional genetic susceptibility cause of SLE disease and development of renal involvement. Future studies focusing on the presence of the *M694V* mutation in SLE patients are required to provide more reliable and conclusive results.

Limitations of the study

This study should be considered as an initial finding. Therefore, larger proportion of patients in independent studies with a wider spectrum of MEFV variations is needed to define its exact role in this disease. Additionally, the frequency of alleles and genotypes may be different between populations. Hence, the association studies of *MEFV* gene with SLE disease in various populations can lead to more accurate understanding about the impact of this mutation on SLE susceptibility and help to develop new treatments.

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Author's contribution

SF proposed the idea of the study. FM participated in the design, laboratory working, analysis and writing the first draft. MRK read and revised the manuscript profoundly. All authors read the final version and its publication.

Conflicts of interest

The authors report no conflicts of interest.

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