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ORIGINAL ARTICLE

A functional microRNA binding site variant in *IL-23R* gene in systemic lupus erythematosus and rheumatoid arthritis: is there any correlation?

Samira Alesaeidi[1] · Saeed Esmaeili Dizghandi[2] · Goli Siri[3] · Meysam Mosallaei[4,5] · Taiebe Kenarangi[5] · Tahereh Ghorashi[2] · Mohsen Soosanabadi[2,6,7]

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Abstract

Background IL-23 receptor (IL-23R) dysregulation has been shown to have critical roles in pathogenesis of different autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) via suppression of regulatory T cells (Tregs) as well as differentiation, expansion, and survival of T helper 17 (Th17) cells, followed by upregulation of interleukin 17 (IL-17). Here, we assessed the association of a functional microRNAs (miRNAs)-related single nucleotide polymorphism (miR-SNPs: rs10889677) in *IL-23R*, which was correlated with its overexpression and increased risk for SLE and RA in the Iranian population.

Methods Genotype and allele distribution of rs10889677 variant were investigated in 105 RA patients, 100 SLE cases and 105 healthy controls via polymerase chain reaction– restriction fragment length polymorphism (PCR–RFLP) method.

Results Our findings suggested that AA genotype, but not AC genotype, was associated with increased risk of RA (AA vs. CC; OR: 3.27; 95%CI [1.467–7.551]). The allele A was more frequent in RA group compared to controls (A allele vs. C allele; OR: 1.92; 95%CI [1.282–2.894]). This common variant was not significantly correlated with SLE risk in our population ($P > 0.05$). However, stratification analysis indicated that RA patients with AA genotype show higher serum concentration levels of C-reactive protein (CRP) (P: 0.008). No obvious correlation was noticed between different genotypes in SLE cases, except for a slight difference in terms of oral ulcer manifestation incidence (P: 0.038).

Conclusion This study suggests a significant relationship between rs10889677 variant in *IL-23R* with increased risk of RA and some clinical features in RA and SLE patients.

Keywords Systemic lupus erythematosus · Rheumatoid arthritis · *IL-23R* gene · Variant

All authors were involved in whole work and the manuscript has been seen and approved by all the authors.

✉ Mohsen Soosanabadi
m_soosanabadi@yahoo.com

1 Rheumatology and Internal Medicine, Rheumatology Research Center, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran

2 Department of Medical Genetics, Semnan University of Medical Sciences, Semnan, Iran

3 Department of Internal Medicine, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran

4 Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

5 Student Research Committee, Faculty of Statistics, University of Social Welfare and Rehabilitation Science, Tehran, Iran

6 Abnormal Uterine Bleeding Research Center, Semnan University of Medical Sciences, Semnan, Iran

7 Department of Medical Genetics and Abnormal Uterine Bleeding Research Center, Semnan University of Medical Sciences, Semnan, Iran

Introduction

Interleukin 23 (IL-23) and its receptor (IL-23R) are required for suppression of regulatory T cells (Tregs) and differentiation of naïve T cells into T helper 17 (Th17) cells. They are involved in expansion and survival of these cells and promote production of interleukin 17 (IL-17), consequently initiating inflammation by producing proinflammatory cytokines [1, 2]. High levels of IL-17 release accompanied by extreme production of Th17 cells are critical in pathogenesis of different autoimmune and inflammatory diseases [3, 4]. Numerous reports have demonstrated the overexpression of IL-23R in various autoimmune diseases including psoriatic arthritis (PsA) [5, 6], ankylosing spondylitis (AS) [7], Hashimoto's thyroiditis (HT) [8], inflammatory bowel disease (IBD) [9] and particularly in systemic lupus erythematosus (SLE) [10, 11] and rheumatoid arthritis (RA) [12, 13].

SLE and RA are known as two common chronic multisystem autoimmune diseases sharing multiple clinical manifestations and immunological features with multifactorial nature and moderate to high overlap in genetic etiology [14]. In this respect, multiple genome-wide association studies (GWAS) have uncovered numerous significant loci and single nucleotide polymorphisms (SNPs) associated with RA and SLE risk and revealed some shared genetic components between these diseases [15, 16].

MicroRNA (miRNA) -related single nucleotide polymorphisms (miR-SNPs) are considered as interesting class of functional polymorphisms with gene-regulatory potential [17, 18]. MiR-SNPs residing in putative miRNA binding sites at 3´untranslated regions (3´UTRs) of genes may interactively affect gene expression through direct disruption of miRNAs binding sites. They can also influence the secondary structure of 3'UTR and thermodynamic characteristics of binding sites, which subsequently lead to modification of the target genes' expression via altering the binding capacity of miRNAs [17, 19, 20]. Considering the importance of *IL-23R* in immune system function and its dysregulation implicated in SLE and RA pathogenesis, it is reasonably predicted that miR-SNPs in *IL-23R* may be associated with modulation of susceptibility to these diseases.

The SNP rs10889677)A > C(, a functional *IL-23R* variant is located at 3'UTR sequence and lead to loss of its binding sites for let-7e and let-7f miRNAs, consequently overexpression of *IL-23R* [21, 22]. Besides, rs10889677 has been reported to be correlated with different diseases, from various malignancies [23, 24] to autoimmune diseases [25–27].

Here, we assessed the association of SNP rs10889677 with SLE and RA in the Iranian population. Additionally, we evaluated the connection between this functional *IL-23R* variant and some clinical features and laboratory parameters described in these diseases.

Materials and methods

SNP selection approach

By investigating the dbSNP database (https://www.ncbi.nlm.nih.gov/snp/), we considered SNPs located at 3'UTR region of *IL-23R*. Then, we chose variants with a minor allele frequency (MAF) more than or equal to 5%. Subsequently, based on our literature review on previous functional studies and in silico analyses in miRNASNP-v3 (http://bioinfo.life.hust.edu.cn/miRNASNP#!/) [28] and miRdSNP (http://mirdsnp.ccr.buffalo.edu/) databases [29], we reached to one SNP; rs10889677 located within the confirmed miRNAs Let-7e and Let-7f binding sites or in the vicinity of multiple predicted miRNA response elements (MREs). The details of criteria used in this study and the number of SNPs found in each level have been previously described by Mosallaei et al. [23].

Sample collection

We conducted a case-control study to evaluate the correlation between rs10889677 polymorphism and the risk of SLE and RA occurrence, as well as its association with some clinical characteristics of these diseases. A total of 205 unrelated subjects including 105 RA and 100 SLE patients were selected from the patients referred to the rheumatology division of Alzahra hospitals, Isfahan, Iran according to 2019 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) diagnostic criteria [30]. All the participants were from Iranian ethnicity and 105 individuals collected in control group had no signs and symptoms of any autoimmune diseases, with no family history of immunological or autoimmune disorders. This study was approved by the Research Ethics Committee of Semnan University of Medical Sciences (approved number: IR.SEMUMS.REC.1400.337). Demographic data, clinical presentations, and laboratory results were recorded for each participant using a structured questionnaire and laboratory reports (Tables. 1 and 2). Venous whole blood samples were obtained in a 5 ml EDTA tube and stored at −20°C until further analysis.

Genotyping of polymorphism and statistics:

Genomic DNA was isolated from whole blood samples by GeNet Bio DNA extraction Kit (GeNetBio, Korea) based on the manufacturer's protocol. The quality and quantity of the extracted DNA samples were consequently evaluated by electrophoresis and spectrophotometric analysis.

The polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method was used to

Table 1 Clinical characteristics of patients (SLE and RA) and control subjects participated in the study

Characteristics	Controls	SLE	P_{Controls} vs. SLE	RA	P_{Controls} vs. RA
Total number	105	100		105	
Age (mean ± SD)	45.48 ± 12.88	43.18 ± 13.57	0.214	47.52 ± 10.53	0.211
Gender n (%)					
Male	29(27.6%)	22(22%)	0.420	30 (28.6%)	0.878
Female	76(72.4%)	78(78%)		75(71.4%)	
Age of onset (mean ± SD)	--	26.05 ± 10.91	--	41.45 ± 10.49	--
BMI (mean ± SD)	24.04 ± 3.33	25.75 ± 2.35	< 0.001*	26.21 ± 2.40	< 0.001*
SBP (mean ± SD)	120.71 ± 9.96	125.61 ± 15.72	0.008*	123.38 ± 12.49	0.089
DBP (mean ± SD)	78.76 ± 8.31	82.45 ± 5.96	< 0.001*	78.90 ± 7.75	0.898
Positive family history n (%)	0	20(20%)	--	19 (18.1%)	--
Neurological symptoms n (%)	0	24(24%)		--	--
Skin manifestations n (%)	0	65(65%)		--	--
Hematological manifestations n (%)	0	49(49%)		--	--
Oral ulcers n (%)	0	76(76%)		--	--
Arthritis n (%)	0	86(86%)		105	--
Renal involvement n (%)	0	45(45%)		--	--

* P value < 0.05. BMI: Body mass index; SD: Standard deviation; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 2 Laboratory findings of patients (SLE and RA) and control individuals

	Controls (105)	SLE (100)	P_{Controls} vs. SLE	RA (105)	P_{Controls} vs. RA
ESR (mm/h)	15.48 ± 7.08	42.13 ± 22.83	< 0.001*	36.76 ± 22.73	< 0.001*
CRP (mg/l)	4.51 ± 2.83	16.7500 ± 9.68	< 0.001*	16.29 ± 13.59	< 0.001*
White blood cell (10^9/1)	6.49 ± 1.39	6.87 ± 1.78	0.092	7.42 ± 2.03	< 0.001*
Hemoglobin	14.29 ± 1.61	11.84 ± 1.36	< 0.001*	12.46 ± 1.05	< 0.001*
PLT(10^9/1)	248.49 ± 68.59	228.36 ± 63.23	0.030*	264.81 ± 68.59	0.09
Creatinine (mg/dL)	0.85 ± 0.17	1.10 ± 0.35	< 0.001*	1.00 ± 0.18	< 0.001*
BUN	16.15 ± 4.15	19.81 ± 12.22	0.004*	17.37 ± 4.75	0.049*
FBS	92.11 ± 22.48	89.78 ± 13.06	0.368	95.84 ± 15.40	0.162
HDL	50.74 ± 11.40	51.08 ± 8.89	0.814	49.47 ± 7.59	0.345
LDL	107.93 ± 32.63	103.62 ± 26.18	0.299	109.84 ± 28.40	0.651
TG	153.37 ± 54.64	157.93 ± 47.07	0.524	167.24 ± 44.81	0.045*
AntidsDNA (IU/ml)	10.64 ± 4.32	203.40 ± 178.65	< 0.001*	--	--
C3 level (mg/dl)	140.98 ± 35.43	47.27 ± 32.37	< 0.001*	--	--
C4 level (mg/dl)	19.84 ± 5.61	10.20 ± 7.02	< 0.001*	--	--

* P value < 0.05. SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; SD: Standard deviation; ESR: Erythrocyte sedimentation rate; CRP: Creactive protein; BUN: Blood urea nitrogen; PLT: Platelet; HDL: Highdensity lipoprotein; LDL: Lowdensity lipoprotein; TG: Triglyceride; FBS: Fasting blood sugar; C3: Complement component 3; C4: Complement component 4; dsDNA: Doublestranded DNA

genotype the rs10889677 variant. First, we performed a PCR for amplification of the sequence flanking the target variant (amplicon size; 249bp). Details of PCR methodology and the used primer sets have been previously described [23]. RFLP was carried out using the MnlI restriction endonuclease enzyme overnight at 37°C. The restriction enzyme was deactivated at 80°C for 30min and the digestion products were subsequently investigated on 2% agarose gel. A single 189bp fragment were indicative of CC homozygous genotype, a single 249bp fragment displayed the presence of AA homozygous and two fragments of 249 and 189bp indicated the presence of AC heterozygous (Fig. 1). Eventually, we randomly selected and sent some samples for direct Sanger sequencing in order to confirm the RFLP results.

All statistical analyses were carried out by SPSS 25.0 (SPSS Statistics 25, Armonk, NY, IBM Corp.). Logistic regression analysis was performed to examine the association between alleles and genotypes in cases and controls and compute specific odds ratios (ORs), 95% confidential intervals (CIs), and P values. Mann–Whitney U-test and Pearson χ^2 test were used to analyze the data regarding demographics, clinical features, and laboratory findings. A threshold probability value of $P < 0.05$ was used to indicate statistical significance.

Results

The gender distribution of the participants was as follow: SLE patients; 78 females and 22 males, RA patients; 75 females and 30 males, and control individuals; 76 females and 29 males. The mean age of onset in SLE and RA groups

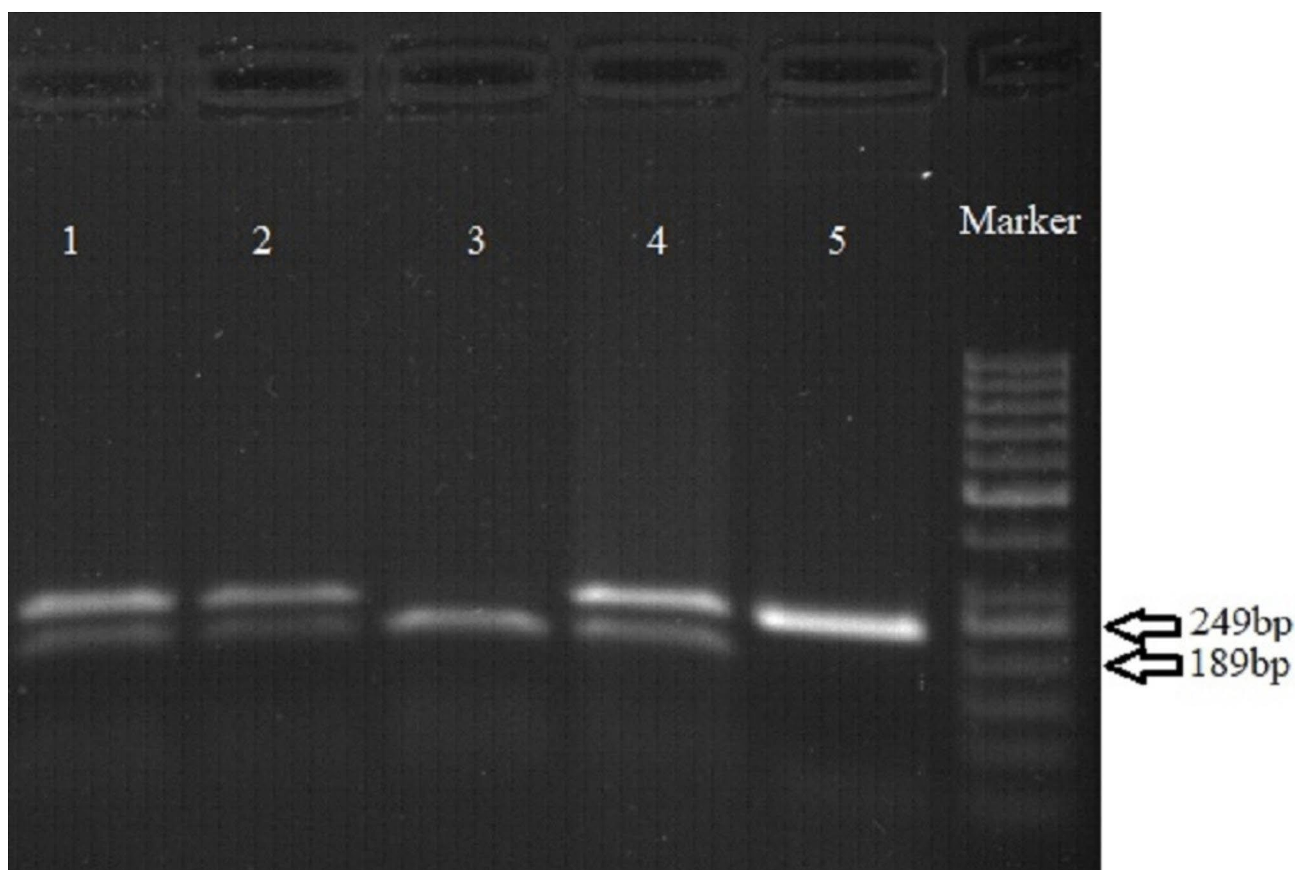

Fig. 1 Agarose gel electrophoresis analysis of restriction fragment length polymorphism-polymerase chain reaction (RFLP) products. Lines 1, 2 and 4 are AC genotype, 3 is CC genotype, and line 5 is AA genotype

was 26.05 ± 10.91 and 41.45 ± 10.49, respectively. There were insignificant differences between patients and control individuals in terms of gender and age at sampling, indicating the acceptable rate of matching ($P > 0.05$). Subjects in two patient groups showed obviously higher body mass index (BMI) compared with controls ($P < 0.001$). Factors related to blood pressure in SLE subjects were significantly different from volunteers in control group. In detail, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) in SLE patients were 125.61 ± 15.72 and 82.45 ± 5.96, respectively, while in non-SLE individuals were 120.71 ± 9.96 and 78.76 ± 8.31, respectively.

A 20 SLE patients (20%) and 19 RA patients (18.1%) showed family history of autoimmune diseases. The major phenotypes documented in SLE group were as follow: twenty-four patients (24%) with neurologic events, sixty-five patients (65%) with skin lesions, forty-nine cases (49%) with hematological disorders, seventy-six cases (76%) with oral lesions, eighty-six cases (86%) with arthritis, and forty-five cases (45%) with kidney disease. The demographic data and clinical features of patients and control individuals are provided in Table. 1. Based on laboratory findings, SLE cases showed higher levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, blood urea nitrogen (BUN), and anti-dsDNA ($P < 0.05$) compared to individuals in the control group. However, the mean serum concentrations of hemoglobin, platelet count (PLT), complement component 3 (C3), and complement component 4 (C4) levels were expressively higher in the control group ($P < 0.05$). Details of serologic findings of all participants were documented in Table. 2.

Correlation between SNP rs10889677 and RA:

In RA subjects, significant association was found between AA genotype and the risk of disease development (P: 0.001). The frequency of AA, AC, and CC genotypes were 36.2%, 38.1%, and 25.7% in RA group and 16.2%, 45.7%, and 38.1%, in control individuals, respectively. However, combined genotype analysis established that there is no clear difference between individuals with AA + AC genotypes (dominant inheritance) and subjects with CC genotype in RA cases and control individuals (P: 0.075). In respect to allele distribution, A allele was more frequent in RA group compared to controls (P: 0.001). The frequency of A allele in case and control groups was 55.2% and 39%, respectively

Table 3 Associations of the genotypes and allele frequencies of *IL23R* polymorphism (rs10889677) with the risk of RA and SLE development

rs10889677	Patients (n = 205)	Controls (n = 105)	OR (95%CI)	*P* value
	RA (105)			
Genotype				
CC	27(25.7%)	40(38.1%)	Reference	---
AC	40 (38.1%)	48(45.7%)	1.33 (0.661–2.703)	0.412
AA	38(36.2%)	17(16.2%)	3.27 (1.467–7.551)	0.001*
Allele				
C	94(44.8%)	128(61%)	Reference	---
A	116(55.2%)	82(39%)	1.92 (1.282–2.894)	0.001*
Dominant inheritance				
CC	27(25.7%)	40(38.1%)	Reference	---
AC + AA	78(74.3%)	65(61.9%)	1.77 (0.948–3.352)	0.075
	SLE (100)			
Genotype				
CC	37(37%)	40(38.1%)	Reference	---
AC	38(38%)	48(45.7%)	0.85 (0.440–1.661)	0.640
AA	25(25%)	17(16.2%)	1.58 (0.695–3.667)	0.254
Allele				
C	112(56%)	128(61%)	Reference	---
A	88(44%)	82(39%)	1.22 (0.811–1.853)	0.317
Dominant inheritance				
CC	37(37%)	40(38.1%)	Reference	---
AC + AA	63(63%)	65(61.9%)	0.71 (0.399–1.289)	0.262

*P value < 0.05, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus

and the frequency of C allele in RA subjects and RA-free group was 44.8% and 61%, respectively. The distributions of genotypes and allele frequencies are shown in Table. 3. According to genotype stratification analysis, there was significant difference between RA patients in terms of CRP levels (*P*: 0.008). Among RA patients, CRP level in individuals with AA, AC and CC genotypes were 21.55 ± 16.74, 12.33 ± 6.57, and 14.75 ± 14.45, respectively. There was not any difference in other evaluated factors of genotype classifications in RA cases (Table. 4).

Correlation between SNP rs10889677 and SLE:

Our analysis demonstrated that genotype and allele distribution in SLE subjects had no significant difference compared with controls ($P > 0.05$). The frequencies of AA, AC, and CC genotypes in SLE group were 25%, 38%, and 37%, respectively. The frequencies of A and C alleles in SLE patients were 44% and 56%, respectively (Table. 3). Besides, combined genotype analysis demonstrated that there was no statistically significant difference in dominant inheritance between SLE and controls (*P*: 0.262). Stratification analysis also revealed no obvious correlation between different genotypes in SLE cases except for a slight difference in terms of oral ulcer manifestation (*P*: 0.038). The results of whole stratification investigation are shown in Table. 4.

Discussion

Due to the role of IL-23R in pathogenesis of autoimmune diseases and its upregulation in induction of different autoimmune diseases and chronic inflammation, we intended to evaluate the effect of a genomic factor (rs10889677 variant) associated with dysregulation of *IL-23R* expression followed by modulation of susceptibility to SLE and RA diseases (Fig. 2). In the current study, we assessed the correlation between a functional miRSNP rs10889677 (A > C) in *IL-23R* and susceptibility to SLE, RA and other related aspects in Iranian population.

It was first shown that rs10889677 variant in 3'UTR region of *IL-23R* may lead to increased transcriptional and translational expression of *IL-23R* through disruption of miRNAs target site recognition which leads to the loss of binding capacity of two miRNAs including Let-7e and Let-7f [21]. Similarly, it was revealed that rs10889677 AA genotype leads to enhanced expression of *IL-23R* compared to CC and AC genotypes. Moreover, it was also demonstrated that individuals with rs10889677 A allele showed higher levels of in vivo Treg cells and lower levels of in vitro T-cells proliferation rates, compared to those with C allele. They confirmed that rs10889677 could decrease the binding affinity of miRNAs Let-7e and Let-7f and consequently downregulate the *IL-23R* expression [31].

In this study, we confirmed the association of AA genotype and A allele in rs10889677 with significantly increased risk of RA development in Iranian population ($OR_{\text{for AA genotype}}$: 3.27; 95%CI [1.467–7.551], $OR_{\text{for A allele}}$: 1.92; 95%CI [1.282–2.894]). Furthermore, our findings revealed significant differences between various genotypes in RA patients. Patients with AA genotype were shown to have higher levels of CRP, which was accordingly correlated with higher diseases activity [32].

Multiple previous studies have established the association of rs10889677 A allele with increased risk of various solid tumors, especially colorectal, breast and gastric cancers [23, 31]. To date, several studies were conducted on possible associations of rs10889677 with different autoimmune

Table 4 Associations of *IL23R* polymorphism (rs10889677) with various parameters in RA and SLE patients

Genotype group	CC	AC	AA	*P* value
RA (number)	**CC = 27**	**AC = 40**	**AA = 38**	
Age of onset	44.37 ± 12.45	40.37 ± 9.17	40.52 ± 10.16	0.248
ESR (mm/h)	36.62 ± 28.30	33.42 ± 19.27	40.36 ± 21.74	0.407
CRP (mg/l)	14.75 ± 14.45	12.33 ± 6.57	21.55 ± 16.74	0.008*
Creatinine (mg/dL)	1.00 ± 0.15	0.98 ± 0.18	1.03 ± 0.20	0.465
Hemoglobin (HB)	12.60 ± 1.27	12.34 ± 0.98	12.49 ± 0.95	0.594
BMI (mean ± SD)	26.43 ± 2.25	26.33 ± 2.48	25.93 ± 2.46	0.657
SLE (number)	**CC = 37**	**AC = 38**	**AA = 25**	
Age of onset	26.37 ± 11.06	25.55 ± 12.14	26.32 ± 8.91	0.939
ESR (mm/h)	37.21 ± 22.07	46.47 ± 20.31	42.80 ± 26.74	0.213
CRP (mg/l)	17.29 ± 7.70	16.81 ± 8.86	15.84 ± 13.26	0.846
C3 level (mg/dl)	42.88 ± 28.76	49.64 ± 35.34	50.18 ± 33.30	0.586
C4 level (mg/dl)	9.37 ± 5.81	10.47 ± 7.53	11.02 ± 7.95	0.637
Anti-dsDNA (IU/mL)	212.27 ± 178.10	213.06 ± 197.90	175.61 ± 150.42	0.672
Creatinine (mg/dL)	1.11 ± 0.40	1.07 ± 0.32	1.13 ± 0.32	0.819
Hemoglobin (HB)	11.96 ± 1.54	11.98 ± 1.26	11.45 ± 1.19	0.260
Neurological symptoms n (%)	9(24.3%)	11(28.9%)	4(16.0%)	0.499
Skin manifestations n (%)	27(73.0%)	22(57.9%)	16(64.0%)	0.389
Hematological manifestations n (%)	22(59.5%)	15(39.5%)	12(48.0%)	0.222
Oral ulcers n (%)	23(62.2%)	33(86.8%)	20(80.0%)	0.038*
Arthritis n (%)	33 (89.2%)	33(86.8%)	20(80.0%)	0.582
Renal involvement n (%)	16(43.2%)	18(47.4%)	11(44.0%)	0.931

Data are mean ± SD, or n (%). * *P* value < 0.05. SD: Standard deviation; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; ESR: Erythrocyte sedimentation rate; CRP:Creactive protein; C3: Complement component 3; C4: Complement component 4; dsDNA: Doublestranded DNA

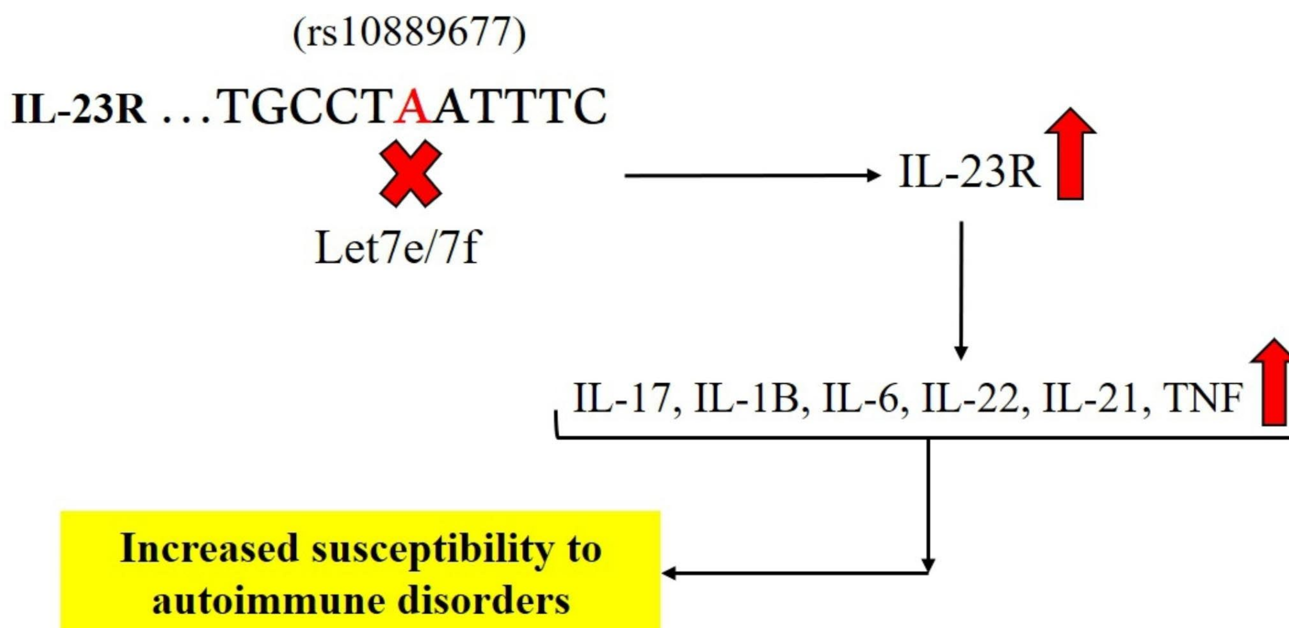

Fig. 2 Suggested mechanistic relationship of the miRNA Let7e/7f and rs10889677 variant in *IL-23R* 3'UTR region with the upregulation of *IL-23R* and subsequent autoimmune disease development via increased inflammatory cytokines production

diseases including IBD [33], juvenile idiopathic arthritis [34], AS [27, 35], Sjogren's syndrome [36], alopecia areata [25], psoriasis [37], vitiligo [38], systemic sclerosis (SSc) [26], rheumatic heart disease (RHD) [39], RA [26, 40, 41], and SLE [42–45]. In consistent with our findings, Soysal et al. [46] and Farago et al. (34), respectively in Turkish and Hungarian populations reported that AA genotype were shown to be more prevalent in RA patients. However, in contrast to our findings, it was shown that RA patients with CC genotype had higher concentrations of CRP and ESR [46]. Another study on Egyptian population revealed that, although rs10889677 was not correlated with RA risk,

patients with AA genotype was more frequent in those with deformities and positive rheumatoid factor (RF) [41]. On the other hand, in two different studies in Spanish and Polish populations, no significant correlations were found between this functional variants and RA risk and clinical characteristics [40, 47].

Our findings confirmed that rs10889677 variant was not correlated with SLE risk and there was not any obvious association between different rs10889677 genotypes and clinical characteristics of SLE, except for oral ulcer incidence (Tables 3 and 4). In line with our results, two studies in Chinese population and two research on Spanish and Hungarian populations indicated no relationships between SLE incidence and rs10889677 polymorphisms [43, 44, 48]. However, Azadeh et al. showed that A allele (AA+AC genotypes) was correlated with susceptibility to SLE development and presence of mucosal ulcers [45].

Considering the contrasting results of studies from various populations, it is conceivable that *IL-23R* locus (rs10889677) causes different impacts on RA and SLE pathogenesis in different ethnicities. This may emanate from the different impact of *IL-23R* and rs10889677 in pathogenesis of these diseases and existence of different genetic backgrounds of each population. However, the present study unveiled an important relationship between rs10889677 as a functional polymorphism in *IL-23R* and RA risk in Iranian population. Furthermore, our findings showed that this variant is associated with increased serum concentration of CRP, which is an indicator of disease activity in RA patients. We acknowledge that some possible boundaries in the statistical validity of the current study including small population size may hamper retrieving correct results, so further association studies in populations with larger sample sizes will help confirm the suggested correlations. Besides, in order to approve the role of rs10889677 on the expression of *IL-23R*, it will be better to evaluate the effect of this variant on the expression level of *IL-23R* in patients and cell lines.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This study was approved by the ethics committee of Semnan University of Medical Science.

Informed consent Informed consent was obtained from all subjects. Also, all authors agree to publish this manuscript in your valuable journal.

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