Impacts of *FcγRIIB* and *FcγRIIIA G*ene Polymorphisms on Systemic Lupus Erythematous Disease Activity Index

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Research note

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Abstract

Objective: Systemic lupus erythematous (SLE) disease is a chronic autoimmune disease with unknown etiology that can involve different organs. Polymorphisms in Fcγ receptors have been identified as genetic factors in susceptibility to SLE. This study was aimed to investigate effects of two single nucleotide polymorphisms (SNPs) within *FcγRIIB* and *FcγRIIIA* genes on systemic lupus erythematous disease activity index (SLEDAI) in an Iranian population.

Results: Our findings indicated TT and GG genotypes were the common genotypes of FcγRIIB and FcγRIIIA SNPs in SLE patients, respectively. There were no significant differences in genotype and allele frequencies of FcγRIIB and FcγRIIIA SNPs in SLE and healthy subjects. However, the frequencies of genotypes and alleles of FcγRIIB and FcγRIIIA SNPs were significantly associated with some clinical manifestations used to determine SLEDAI ($P<0.001$-0.5).

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with unknown etiology described by the lack of immunological tolerance to self-antigens, atypical T-and B-cell reactions with the production of antibodies against self-antigens (1-4). Genetic, environmental, and hormonal factors play important roles in disease susceptibility (5). Genetic variations in the genes involved in immune functions contribute to the development of autoimmune disorders (1). Thus, immune receptor genes such as *fragment crystallizable (Fc) receptor (FcR)* and *programmed cell death 1 (PDCD1)* have always been candidate genes in polymorphism studies (6, 7).

FcRs on the leukocytes bind to the FC region of antibodies and enhance some functions, including the phagocytosis of antibody-antigen complexes and generation of signals regulating cell activities (8). Fc gamma receptor (FCγR) is the most important FcR for phagocytosis of opsonized antigens. Based on its hybrid desire, it is divided into three groups (FcγRI or CD64, FcγRII or CD32, and FcγRIII or CD16), which each of them exerts different functions (9, 10). The genes coding *FcγRII (CD32)* and *FcγRIII (CD16)* are located on chromosome 1q23.3 (11). Several genome-wide screens have shown that single nucleotide polymorphism (SNP) as a genetic variation can impair and/or change the normal functions of FcγRs and thereby results in the development of autoimmunity such as rheumatoid arthritis and SLE (12). Some reports have indicated that SLE patients suffered from the reduced expressions of FcγRII and FcγRIII (13). Furthermore, it is reported that the reduced expression of FcγRIIIA has a protective effect on lupus-susceptible mice through inhibiting the progression of lupus nephritis (14). FcγRIIB, unlike FcγRIIC and FcγRIIA, exerts immunosuppressive impacts on some immune cells such as monocytes and B cells. FcγRIIB binding to its ligand (FC region of IgG) produces an inhibitory signal leading to reduction in cell activation (15). Genetic variation in *FcγRII* gene may contribute to SLE susceptibility in some populations (16). Until now, several studies have been performed in different populations on the effects of FcγR polymorphisms, especially type IIA, IIB, and IIIA, and have showed that SNPs played indispensible roles in disease susceptibility and sickness period in autoimmune disorders such as SLE (17-21).

Regarding the fact that FcγR polymorphisms act as important risk factors in developing autoimmunity (22) and their roles in SLE development have not yet been identified in the Iranian population, this study was aimed to determine whether two SNPs (rs1050501 and rs396991) in *FcγRIIB* and *IIIA* genes may associate with systemic lupus erythematosus disease activity index (SLEDAI) in the Iranian population.

Methods

Study samples

The study populations comprised of 80 unrelated SLE patients and 95 sex-and age-matched healthy individuals without history of autoimmune disorders and cancers (Additional file 1: Table S1). The patients approved for SLE disease by the specialist based on the SLE American College of Rheumatology (ACR) classification criteria (23). Patients were interviewed by the specialist and disease activity index (DAI) was provided by a questionnaire according to SLEDAI-2K (30 days) guideline. The questionnaire contained 24 items, including seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident (CVA), vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcer, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia. There were eight scores (range: 0 to 8) for answering each item depending on symptom severities. Patients with more than 6 score were considered active. The researchers were blinded to patient information and contributed to this study without any costs. Participants were Persian ethnic and chosen from Isfahan province of Iran. The study was confirmed by the Ethics Committee of Isfahan University of Medical Sciences (ethic code: Ir.mui.rct.1396.3.668) and carried out based on the Helsinki declaration. Written informed consent was obtained from all subjects before entering the study.

DNA extraction and SNP assessment

EDTA-treated blood samples (5 ml) were collected from participants. Genomic DNA was extracted from the leukocytes using a QIAamp DNA Mini kit (Qia gene, Germany) according to the manufacturer's instructions. The yield and purity of DNAs were determined by nano drop (BioTek, Epoch, USA) and quality of DNAs were evaluated by electrophoresis gel. Afterwards, two SNPs were investigated by the real-time polymerase chain reaction (PCR)/high-resolution melting (HRM) method. Each reaction for FcγIIB and IIIA SNPs were carried out in a 10μl mixture (Additional file 1: Table S2). PCR-HRM was done using Rotor Gene 6000 machine (Qiagen, Hilden, Germany). The machine was programmed as described previously (24). To determine SNPs, the melting curves were analyzed in the temperature range of 65 °C to 95 °C at the end of each run. All reactions were carried out in duplicate. Primer sequences were indicated in additional file 1: Table S3.

Statistical analysis

Data were analyzed using SPSS (v18; SPSS Inc. Chicago, IL, USA). Chi-square and Fisher's exact tests were used to evaluate the associations of genotype and allele frequencies with SLE susceptibility and SLEDAI. Bonferroni correction, as a post hoc analysis, was used to the pairwise comparisons with significance level of 0.017. P-value < 0.05 was statistically considered significant.

Results

Description of patients

In this study, the most frequent clinical manifestations among 80 SLE patients were rash, arthritis, and leucopenia, while the most common laboratory manifestations were anti-nuclear antibodies (100%), anti-ds DNA (97.5%) and low complement (83.75%). The clinical and laboratory characteristics of patients with SLE are shown in Table. 1.

Table. 1

The clinical and laboratory characteristics of patients with SLE.

The clinical and laboratory manifestations	Total (n=80)
Seizure	10 (12.5%)
Psychosis	4 (5%)
Rash	66 (82.5%)
Organic Brain Syndrome	2 (2.5%)
Visual disturbance	2 (2.5%)
Cranial nerve disorder	3 (3.75%)
Lupus headache	4 (5%)
CVA	0 (0.0%)
Vasculitis	2 (2.5%)
Myositis	4 (5%)
Urinary casts	6 (7.5%)
Hematuria	6 (7.5%)
Proteinuria	8 (10 %)
Pyuria	5 (6.25%)
Alopecia	2 (2.5%)
Pleurisy	4 (5%)
Precardia	7 (8.75%)
Low complement	59 (73.75%)
Increased DNA binding	25 (31.25%)
Fever	11 (13.755)
Thrombocytopenia	9 (11.25%)
Leukopenia	27 (26.25%)

Associations of genotype and allele frequencies of FcγRIIB and FcγRIIIA with SLE susceptibility

Our data revealed that there were no significant differences in FcγRIIB genotype frequencies between patient and control groups (Table. 2). Allelic analysis indicated that C and T allele frequencies of FcγRIIB in patients did not significantly differ from those of control group (Table. 2).

Table. 2

The genotypes and allele frequencies of FcγRIIB (rs1050501) and FcγRIIIA (rs396991) SNPs in patient and control groups.

Positions	Genotype and allele frequencies	Patients 2n= 160		Controls 2n = 190	OR (95% CI)	P value
Rs1050501	CC	25	(31.25%)	28 (29.47%)		0.64
	CT	30	(37.5%)	36 (37.89%)		
	TT	75	(46.8%)	31 (32.63%)		
	C	85	(53.2%)	92 (48.43%)	0.93 (0.61-1.43)	0.77
	T	38	(47.5%)	98 (51.57%)		
Rs396991	TT	25	(31.25%)	42 (44.21%)		0.73
	TG	17	(21.25%)	35 (36.84%)		
	GG	101 (63.1%)		18 (18.94%)		
	T	59	(36.9%)	119 (62.63%)	1.02 (0.66-1.57)	0.92
	G	25	(31.25%)	71 (37.36%)		

Values are indicated as count (percent).

The significance level was considered as $P < 0.05$.

In addition, statistical analyses indicated that FcγRIIIA genotype frequencies were not significantly different from those of healthy individuals (Table. 2). As shown in Table. 2, no significant differences were observed between T and G alleles frequencies in patient and control groups. Other results indicated that T allele was the most frequent allele in two SNPs (Table. 2).

Correlations of FcγRIIB and FcγRIIIA with SLEDAI

To determine the associations of FcγRIIB and FcγRIIIA with SLEDAI, the relationships of genotype and allele frequencies of these SNPs with some clinical parameters, which were the most frequent clinical manifestations of SLE patients, were evaluated. Our data indicated that FcγRIIB genotype and allele frequencies were significantly associated with the frequencies of leucopenia, rash, mucosal ulcer, arthritis, thrombocytopenia in SLE patients (P <0.001-0.05, Table. 3). The results of multiple comparisons revealed that there were significant correlations between distribution frequencies of FcγRIIB CC, CT and TT genotypes versus (vs) other genotypes and these clinical factors used to determine SLEDAI (P <0.001-0.05, Table. 3).

Furthermore, other results of statistical analyses showed that the frequencies of some genotype and allele of FcγRIIIA played significant roles in determining SLEDAI. Similar to FcγRIIB, our results indicated that some genotype and allele frequencies of FcγRIIIA were significantly correlated to SLEDAI (P <0.001-0.05, Table. 5). The frequencies of FcγRIIIA TT, TG and GG genotypes vs other genotypes were significantly associated with SLEDAI (P <0.001-0.05, Table. 3).

Table. 3

The correlations of rs1050501 and rs396991 with some clinical manifestations used to SLEDAI

Positions	Genotype and allele frequencies	Rash		P value	Thrombocytopenia		P value	Leukopenia		P value	Ulcer		P value	Arthritis		P value
		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
Rs1050501	CC	7	18	0.001	16	9	<0.001	14	11	0.001	16	9	0.001	6	19	0.001
	CT	8	17	0.001	19	6	<0.001	17	8	0.001	16	9	0.001	9	16	0.001
	TT	14	16	0.08	21	9	<0.001	20	10	0.001	19	11	0.001	12	18	0.001
	C	22	53	0.02	51	24	0.001	45	30	0.03	48	27	0.03	21	54	0.001
	T	36	49		61	24		57	28		54	31		33	52	
Rs396991	TT	11	27	0.001	25	13	0.01	17	21	0.41	22	16	0.65	12	26	0.01
	TG	9	16	0.02	13	12	0.65	15	10	0.021	17	8	0.02	13	12	0.42
	GG	6	8	0.001	9	8	0.72	8	9	0.71	10	7	0.03	9	8	0.51
	T	31	70	0.001	63	38	0.01	49	52	0.08	61	40	0.051	37	64	0.03
	G	21	32		51	28		32	28		37	22		31	28	

Discussion

Numerous investigations stated that defects in genes related to the immune system can participate in the pathogenesis of autoimmune diseases such as SLE, but the roles of genetic agents have not clearly reported so far (25). Thus, this study investigated rs1050501 and rs396991 SNPs and their associations with SLEDAI in an Iranian population from Isfahan province.

FcγRs have key functions in the immune system through regulating the effector activates of antibodies. FcγRIIB with low-tendency and inhibitory function expresses on macrophages, B cells, granulocytes, and dendritic cells (DCs) (26). This receptor suppresses the stimulation of B cells and inhibits the development of autoimmunity. Some reports have shown that FcγRIIB SNP substitutes isoleucine with threonine at position 232 (T232I), leading to decreased suppressor activity and thereby enhances susceptibility to SLE (27).

In this case-control study, genotype frequencies of FcγRIIB SNP showed that TT genotype frequency was higher in patient than healthy group, although the difference was not statistically significant. This finding proposes a key question why there is an inconsistency between TT genotype and T allele frequency in patients with SLE. As mentioned previous, T allele frequency showed a reduction in patients compared to healthy subjects. Despite a tendency for increase of CC genotype in SLE patients, the differences of CC and CT genotype frequencies between patient and healthy groups were not statistically significant. The increased frequency of CC genotype in patients was consistent with the tendency for increase of C allele number. Our data revealed that although there were some changes in the frequencies of genotypes and

alleles between patients and control subjects, these differences were not statistically considerable and rs1050501 was not associated with SLE susceptibility. In contrast with these observations, Zhu et al. in a Meta-Analysis study concluded that C allele of rs1050501 can be effective in SLE susceptibility and disease progression (28). Furthermore, another study conducted by Pan et al. on 119 SLE patients from 95 nuclear families has indicated that C and T alleles of FcγRIIB were significantly associated with SLE and CT genotype was the most frequent genotype in SLE patients (29). Although rs1050501 did not influence SLE susceptibility in our study population, other statistical analyses indicated that genotype and allele frequencies of FcγRIIB could be considered as genetic factors for determining SLEDAI in Iranian SLE patients. We observed that the frequencies of FcγRIIB genotypes and alleles were significantly correlated to some clinical parameters used to determine SLEDAI.

FcγRIIIA gene is located on chromosome 1q23.3 and encodes for FcγRIIIA, a glycosylated heterogeneous form of FcγR (30, 31). This receptor expresses on some immune cells such as T and NK cells with low-tendency for immune complexes and interestingly interplays with IgG2 subclass (32, 33). It is stated that differences in genotypes and alleles of FcγRIIIA may be associated with autoimmunity (34). Other results of this study indicated that GG genotype of rs396991 polymorphism had higher frequency in patients than healthy subjects. However, this difference was not statistically significant. On the contrary, TT, GT genotype frequencies were lower in patients than control group. These findings were agreed with the increased frequency of T allele in healthy subjects compared to SLE patients. Our data demonstrated that the frequency of G allele was in contrast with GG genotype frequency of FcγRIIIA SNP. Similar to the data of FcγRIIB SNP, allele and genotype frequencies of FcγRIIIA SNP in patients were not significant different from those of control group. These observations are consistent with the results of a study conducted on SLE patients showing the differences in genotypes and alleles of FcγRIIIA SNP between SLE and healthy subjects were not statistically significant (35). Alansari et al. conducted a study on five SNPs in *FcγR* gene in three ethnic groups of SLE patients. The authors reported that genotype and allele frequencies of five SNPs in patients with SLE did not statistically differ from healthy subjects and subsequently concluded FcγR SNPs could not contribute to SLE susceptibility (36). However, there are some studies revealing FcγRIIB and FcγRIIIA SNPs may participate in SLE development (37). It is shown that 232TT genotype had an increased frequency in SLE patients compared to healthy subjects (38). Zhou et al. reported that the decreased expression of FcγRIIIA contributed to SLE severity, but no significant relationship was observed between FcγRIIIA expression level and SLEDAI (37). In contrast, we found that the frequencies of some genotypes and alleles of FcγRIIIA were significantly associated with SLEDAI. This discrepancy may attribute to ethnic and geographic differences, inter-study heterogeneity in the studied SNPs and alleles, and sample size used in different studies.

Overall, our study indicated that FcγRIIB and FcγRIIIA SNPs were associated with SLEDAI in the Iranian population.

Limitations

It should be noted that sample size may be a limitation of the study which may correlate to no correlations of these SNPs with SLE susceptibility. Therefore, more robust studies in different populations with larger sample size are needed to support our data and determine the effects of other *FcγR* SNPs in SLE development.

Abbreviations

SLE: Systemic lupus erythematosus; SNPs: single nucleotide polymorphisms; SLEDAI: systemic lupus erythematous disease activity index; FcγR: fragment crystallizable (Fc) receptor; PDCD1: programmed cell death 1; ACR: American College of Rheumatology; CVA: cerebrovascular accident; DC: dendritic cell.

Declarations

Ethics approval and consent to participate

This work was confirmed by the Ethics Committee of Isfahan University of Medical Sciences (ethic code: Ir.mui.rct.1396.3.668). Written informed consent to participate in the study was obtained from all subjects before entering the study.

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interest.

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Author contributions

Mansoor Karimifar and Khosro Akbari participated in the disease diagnosis, sample collections, and obtained funding for the work. Farshid Fathi and Reza ArefiNejad participated in the design of some experiments and statistical analysis of the data. Mohammad Moosaeepour carried out some of the experiments. Hossein Motedayyen participated in the study design and drafted the manuscript. The authors read and approved the final version of manuscript.

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Data availability

All data generated or analyzed during the study are included in this published article.

Consent to publish

Consent to publish the data was obtained from participants prior to entering the study.

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