Neurological Sciences (2019) 40:2383–2389
https://doi.org/10.1007/s10072-019-04000-4

ORIGINAL ARTICLE

Association between interleukin-4 and interleukin-10 single nucleotide polymorphisms and multiple sclerosis among Iraqi patients

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Received: 6 April 2018 / Accepted: 27 June 2019 / Published online: 1 July 2019

Abstract

Multiple sclerosis (MS) is a neurodegenerative autoimmune disease, in which cytokines play a prominent role. Among these cytokines are interleukin-4 (IL-4) and IL-10, which have been demonstrated to be involved in immunopathogenesis of the disease. The present case-control study inspected the association between seven single nucleotide polymorphisms (SNPs) of *IL4* (*IL4*$_{-1098}$: rs2243248, *IL4*$_{-590}$: rs2243250, and *IL4*$_{-33}$: rs2070874), *IL4RA* (*IL4RA*$_{+1902}$: rs1801275), and *IL10* (*IL10*$_{-1082}$: rs1800896, *IL10*$_{-819}$: rs1800871, and *IL10*$_{-592}$: rs1800872) genes and MS in Iraqi patients. Sixty-eight clinically definite relapsing-remitting MS Iraqi patients and 158 age- and gender-matched healthy control subjects were enrolled in the study. The SNPs were detected by the PCR-SSP (polymerase chain reaction-sequence specific primer) method. Results revealed that only *IL4*$_{-1098}$, *IL4*$_{-590}$, *IL4*$_{-33}$, and *IL10*$_{-592}$ SNP allele and/or genotype frequencies showed a significant variation between MS patients and control. At the haplotype level, the estimated frequency of TCC (*IL4*$_{-1098}$-*IL4*$_{-590}$-*IL4*$_{-33}$) and GCC (*IL10*$_{-1082}$-*IL10*$_{-819}$-*IL10*$_{-592}$) haplotypes was significantly increased in patients compared to control (TCC: 63.2 *vs*. 48.0%; odds ratio = 2.81; 95% confidence interval = 1.86–4.25; pc = 5.0×10^{-6}; GCC 39.0 vs. 22.2%; odds ratio = 2.24; 95% confidence interval = 1.45–3.46; pc = 0.002). In conclusion, *IL4* and *IL10* genes harbor important SNPs that may confer MS susceptibility. In addition, their role in reducing the risk of disease is also suggested. However, the susceptibility of the investigated role can be better evaluated in terms of haplotype frequencies.

Keywords Relapsing-remitting multiple sclerosis · IL-4 · IL-10 · Polymorphism · Haplotype

Introduction

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) due to chronic immune-mediated inflammatory responses. Pathologically, it is characterized by perivascular mononuclear cell infiltrates, demyelination, axonal loss, and gliosis that consequence in the formation of multiple plaques in the brain and spinal cord [1]. As MS is an autoimmune disease, interactions between genetic and environmental factors are required to initiate the autoimmune mechanism (i.e., immunopathogenesis) that leads to axon demyelination and disease manifestation [2]. A breakage in the blood-brain barrier (BBB) and trafficking of myelin-basic protein (MBP) autoreactive T cells from the peripheral blood to the CNS is required to initiate MS immunopathogenesis [3]. However, recent evidences that have been based on experimental and clinical findings suggest that inflammatory mediators play an important role in MS pathogenesis and among these mediators are cytokines [4].

Cytokines are low molecular weight glycoprotein molecules that are produced by immune cells and considered as messengers between these cells and influence both innate and adaptive immune responses. They act synergistically or antagonistically and can function in autocrine, paracrine, or endocrine fashion. By attaching to their cognate receptors on certain cell, cytokines promote cell signaling for subsequent biochemical changes that lead to express or suppress cytokine genes and their transcription factors [5]. However, cytokines

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are under genetic control, and investigations have disclosed that single nucleotide polymorphisms (SNPs) of cytokine genes can impact serum level of cytokines and are positively or negatively associated with different autoimmune diseases including MS [6]. Therefore, such subject has attracted many researchers to investigate the association of cytokine SNPs and the disease susceptibility in addition to their impact on cytokine production. Furthermore, their frequency variations at the population level have been suggested to be one of the most important biomarkers for MS susceptibility, progression, and severity [7]. Among these cytokines are interleukin-4 (IL-4) and IL-10, which have not been investigated in Iraqi MS patients.

IL-4 is an anti-inflammatory cytokine that is mainly produced by T-helper 2 (Th2) cells [8]. Human *IL4* gene is located on chromosome 5 (5q31.1), and the promoter region harbors several polymorphic sites, of which $IL4_{-1098}$, $IL4_{-590}$, and $IL4_{-33}$ SNPs are frequently investigated [9]. Importantly, $IL4_{-590}$ SNP was concluded to be a functional one that increases the transcriptional level of *IL4* gene and genetically linked to $IL4_{-33}$, and both SNPs were associated with an exacerbation of MS [10]. A meta-analysis study performed by Li and co-workers on different autoimmune diseases showed that $IL4_{-590}$ *C* allele was significantly associated with MS risk [11]. Interestingly, a previous investigation also highlighted that −590 SNP *C* is a risk allele for MS, and the CC genotype was associated with a chronic course of MS in female patients [12]. It has been further demonstrated that $IL4_{-590}$ genotypes showed a significant variation between relapsing-remitting MS (RRMS) Iranian patients and healthy subjects [13]. The TT genotype of $IL4_{-33}$ SNP was also significantly increased in African-descendant MS patients as compared to Caucasian descendant of Brazilian MS patients; such finding may give an explanation for ethnicity-related MS susceptibility [14].

Another important studied cytokine is IL-10, which is a pleiotropic anti-inflammatory cytokine secreted mainly by Th2 and T regulatory (Treg) cells [15]. It is coded by a gene on chromosome 1 (1q31-1q32) with more than 20 SNPs in its promoter and non-coding regions have been described [16]. However, three SNPs ($IL10_{-1082}$, $IL10_{-819}$, and $IL10_{-592}$) are suggested to be functional polymorphisms that may alter transcription rate of *IL10* gene [9]. These SNPs have been investigated in MS, but conflicting results among different populations have been reported. For instance, a significantly increased frequency of CC genotype for both −819 and −592 SNPs in a sample of Bulgarian patients was demonstrated, and it was concluded that this genotype is involved in MS predisposition [17]. On the other hand, further studies showed no variation in allele or genotype frequencies of the three SNPs between MS patients and controls in different population groups [16, 18].

Currently, MS is increasingly recognized in Iraq, but there have been no overwhelming cytokine SNP data in Iraqi patients; therefore, the present case-control study aimed to inspect the association between SNPs of *IL4* ($IL4_{-1098}$: rs2243248, $IL4_{-590}$: rs2243250, and $IL4_{-33}$: rs2070874), *IL4RA* ($IL4RA_{+1902}$: rs1801275), and *IL10* ($IL10_{-1082}$: rs1800896, $IL10_{-819}$: rs1800871, and $IL10_{-592}$: rs1800872) genes and MS among Iraqi patients and to determine their risk effect.

Subjects and Methods

Patients and control

A case-control study was conducted during December 2013–March 2014 on 68 clinically definite RRMS Iraqi patients (age mean ± SE: 33.3 ± 2.3 years; 23 males and 45 females) and 158 ethnicity- (Iraqis), age- (32.7 ± 0.8 years), and gender (35 males and 123 females)-matched control subjects to determine the role of *IL4*, *IL4RA*, and *IL10* gene SNPs in MS predisposition. The study was approved by the Ethics Committee at Baghdad Medical Center (Iraqi Ministry of Health). The patients were referred to the Multiple Sclerosis Clinic at Baghdad Teaching Hospital for diagnosis and treatment. The diagnosis was made by the consultant medical staff at the clinic according to the revised McDonald criteria of 2010 [1].

Cytokine genotyping

Genomic DNA was extracted from whole EDTA blood using Relia Prep™ Blood gDNA Miniprep System (Promega Corporation, USA). The cytokine CTS-PCR-SSP (Collaborative Transplant Study-Polymerase Chain Reaction-Sequence Specific Primer) Tray Kit (University Clinic, Heidelberg, Germany) was used to determine SNPs of *IL4*, *IL4RA*, and *IL10* genes. Some SNPs were in the promoter regions of *IL4* ($IL4_{-1098}$: rs2243248, $IL4_{-590}$: rs2243250, and $IL4_{-33}$: rs2070874) and *IL10* ($IL10_{-1082}$: rs1800896, $IL10_{-819}$: rs1800871, and $IL10_{-592}$: rs1800872) genes, while $IL4RA_{+1902}$ (rs1801275) SNP was in the translated regions of *IL4RA* gene. The PCR primers were designed by the Department of Transplantation Immunology, University Clinic at Heidelberg (Germany), according to the WHO International Nomenclature Committee of cytokines [19]. The optimized thermocycling conditions were initial denaturation at 94 °C for 2 min, followed by 10 cycles of denaturation (94 °C for 15 s), and annealing/extension (65 °C for 60 s). This was followed by 20 cycles of denaturation (94 °C for 15 s), annealing (61 °C for 50 s), and extension (72 °C for 30 s). Finally, the process hold was accomplished at 4 °C for 15 min. The amplified PCR products were electrophoresed on 2% agarose gel at 170 V for 25 min. The migrating bands were

visualized through a UV-transilluminator and the results were interpreted according to a manual supplied with the kit.

Statistical analysis

Pearson chi-square (χ^2) goodness-of-fit test was used to assess the significance of Hardy-Weinberg equilibrium (HWE). Allele frequency of SNPs was calculated by direct gene counting method. The association between an allele or a genotype and MS was given as odds ratio (OR) with its 95% confidence interval (95% CI). The significance of such association was assessed by two-tailed Fisher's exact probability (p value), which was subjected to Bonferroni correction (pc value). The WinPepi software version 11.23 was employed to carry out these calculations [20]. Haploview software version 4.2 was also used to construct three-locus haplotypes and their frequencies were estimated via the expectation-maximization method. A determination of linkage disequilibrium (LD) between loci located in each chromosome was also carried out [21]. The LD was assessed by disequilibrium coefficient (D′), logarithm of likelihood odds ratio (LOD), and correlation coefficient between loci (r^2).

Results

HWE analysis

Assessing HWE revealed that genotype frequencies of three SNPs were significantly deviated from the equilibrium. They were of *IL4*$_{-1098}$ (control), *IL4*$_{-33}$ (patients), and *IL10*$_{-819}$ (patients and control) SNPs (Table 1).

IL4 and IL4RA SNPs

The three SNPs of *IL4* gene showed a significant variation between RRMS patients and control (Table 1). *IL4*$_{-1098}$ *T* allele (86.0 *vs.* 69.6%; OR = 2.69; 95% CI = 1.57–4.61; pc value = 0.001) and its homozygous genotype (73.5 vs. 53.2%; OR = 2.45; 95% CI = 1.32–4.54; pc value = 0.025) demonstrated a significant increased frequency in patients compared to control. Such increased frequencies were counteracted by a significantly decreased frequency of *G* allele and GG genotype. *IL4*$_{-590}$ is the second SNP, in which a significantly increased frequency of *C* allele was observed in patients (77.9 vs. 65.8%; OR = 1.83; 95% CI = 1.15–2.92; pc value = 0.05); however, at the level of genotype frequency, the differences were not significant. The CC genotype was an exception and maintained uncorrected significant increased frequency in patients (61.8 vs. 46.2%; OR = 1.88; 95% CI = 1.06–3.35; p = 0.04). The final SNP was *IL4*$_{-33}$, and its *C* allele (80.6 vs. 63.3%; OR = 2.41; 95% CI = 1.49–3.91; pc value = 0.001) and CC genotype (71.6 vs. 39.2%; OR = 3.91; 95% CI = 2.11–7.24; pc value = 5.0×10^{-5}) maintained a marked significant increased frequencies in patients. Equally important, the *IL4*$_{-33}$ CT genotype showed a significantly decreased frequency in patients compared to control (17.9 vs. 48.1; pc = 1.2×10^{-4}). At the haplotype level (*IL4*$_{-1098}$-*IL4*$_{-590}$-*IL4*$_{-33}$), the estimated frequency of TCC haplotype was significantly increased in patients compared to control (63.2 vs. 48.0%; OR = 2.81; 95% CI = 1.86–4.25; pc = 5.0×10^{-6}) (Table 2). For *IL4RA*$_{+1902}$ SNP, neither alleles nor genotype frequencies maintained a corrected significant variation between patients and control (Table 1).

IL10 SNPs

Among the three determined SNPs of *IL10* gene (*IL10*$_{-1082}$, *IL10*$_{-819}$, and *IL10*$_{-592}$), only *IL10*$_{-592}$ SNP showed a significant variation between MS patients and control (Table 1). The *C* allele frequency was significantly increased in patients (72.8 vs. 58.5; OR = 1.89; 1.22–2.93; pc = 0.02), while *A* allele frequency was significantly decreased (27.2 vs. 41.5%; pc = 0.02). The homozygous AA genotype also showed a significantly decreased frequency in patients (7.4 vs. 20.9; pc = 0.05). At the haplotype level (*IL10*$_{-1082}$-*IL10*$_{-819}$-*IL10*$_{-592}$), the estimated frequency of GCC haplotype was significantly increased in patients compared to control (39.0 *vs.* 22.2%; OR = 2.24; 95% CI = 1.45–3.46; pc = 0.002) (Table 2).

Linkage disequilibrium

There was a strong LD between the two SNP loci − 590 and − 33 of *IL4* (LOD = 9.05, D′ = 0.74, r^2 = 0.50). For *IL10* gene, three SNP pair combinations showed a strong LD; *IL0*$_{-1082}$-*IL10*$_{-592}$ (LOD = 7.0, D′ = 1.0, r^2 = 0.30), *IL10*$_{-819}$-*IL10*$_{-592}$ (LOD = 17.3, D′ = 1.0, r^2 = 0.60), and *IL10*$_{-1082}$-*IL10*$_{-819}$ (LOD = 7.5, D′ = 0.83, r^2 = 0.30) haplotypes (Fig. 1).

Discussion

The current study attempted to disclose the influence of genetic variation in seven anti-inflammatory cytokine gene SNPs (*IL4*$_{-1098}$, *IL4*$_{-590}$, *IL4*$_{-33}$, *IL4RA*$_{+1902}$, *IL10*$_{-1082}$, *IL10*$_{-819}$, and *IL10*$_{-592}$) on predisposition to MS. As a matter of fact, it is the first documentation of these SNPs in Iraqi RRMS patients, and the results highlighted significant positive associations between MS risk and *IL4* and *IL10* gene SNPs. In this context, the predisposing and protecting potential of *IL4*$_{-590}$ SNP is suggested in Iraqi MS patients. Several studies explored the involvement of such SNP in MS susceptibility and severity; however, the evidence has not been conclusive and the reported results were controversial [11, 14, 22]. Such controversy has led Zhang and colleagues to conduct a meta-analysis on five published case-control studies to

Table 1 Numbers and percentage frequencies of *IL4*, *IL4RA*, and *IL10* single nucleotide polymorphisms in multiple sclerosis patients and control.

SNP allele and genotype		MS patients ($N = 68$)		Control group ($N = 158$)		OR (95% CI)	*p* value	pc value
		N	%	*N*	%			
$IL4_{-1098}$	*T*	117	86.0	220	69.6	2.69 (1.57–4.61)	2.4×10^{-4}	0.001
(rs2243248)	*G*	19	14.0	96	30.4	0.37 (0.22–0.64)	2.4×10^{-4}	0.001
	TT	50	73.5	84	53.2	2.45 (1.32–4.54)	0.005	0.025
	TG	17	25.0	52	32.9	0.68 (0.36–1.29)	NS	NS
	GG	1	1.5	22	13.9	0.09 (0.01–0.69)	0.003	0.015
H-W *p* value		NS		0.005				
$IL4_{-590}$	*C*	106	77.9	208	65.8	1.83 (1.15–2.92)	0.01	0.05
(rs2243250)	*T*	30	22.1	108	34.2	0.55 (0.34–0.87)	0.01	0.05
	CC	42	61.8	73	46.2	1.88 (1.06–3.35)	0.04	NS
	CT	22	32.3	62	39.2	0.74 (0.41–1.34)	NS	NS
	TT	4	5.9	23	14.6	0.37 (0.12–1.10)	NS	NS
H-W *p* value		NS		NS				
$IL4_{-33}$	*C*	108	80.6	200	63.3	2.41 (1.49–3.91)	2.5×10^{-4}	0.001
(rs2070874)†	*T*	26	19.4	116	36.7	0.42 (0.26–0.67)	2.5×10^{-4}	0.001
	CC	48	71.6	62	39.2	3.91 (2.11–7.24)	1.0×10^{-5}	5.0×10^{-5}
	CT	12	17.9	76	48.1	0.24 (0.12–0.47)	2.3×10^{-5}	1.2×10^{-4}
	TT	7	10.5	20	12.7	0.80 (0.33–1.99)	NS	NS
H-W *p* value		5.0×10^{-4}		NS				
$IL4RA_{+1902}$	*G*	29	21.3	96	30.6	0.62 (0.38–0.99)	0.05	NS
(rs1801275)††	*A*	107	78.7	218	69.4	1.62 (1.01–2.61)	0.05	NS
	GG	5	7.4	16	10.2	0.70 (0.25–1.98)	NS	NS
	GA	19	27.9	64	40.8	0.56 (0.30–1.04)	NS	NS
	AA	44	64.7	77	49.0	1.90 (1.06–3.42)	0.04	NS
H-W *p* value		NS		NS				
$IL10_{-1082}$	*G*	60	44.1	119	37.7	1.31 (0.87–1.96)	NS	NS
(rs1800896)	*A*	76	55.9	197	62.3	0.77 (0.51–1.15)	NS	NS
	GG	12	17.7	27	17.1	1.04 (0.49–2.19)	NS	NS
	GA	36	52.9	65	41.1	1.61 (0.91–2.84)	NS	NS
	AA	20	29.4	66	41.8	0.58 (0.32–1.06)	NS	NS
H-W *p* value		NS		NS				
$IL10_{-819}$	*C*	86	63.2	186	59.2	1.18 (0.78–1.79)	NS	NS
(rs1800871)††	*T*	50	36.8	128	40.8	0.84 (0.56–1.28)	NS	NS
	CC	34	50.0	63	40.1	1.49 (0.84–2.64)	NS	NS
	CT	18	26.5	60	38.2	0.58 (0.31–1.09)	NS	NS
	TT	16	23.5	34	21.7	1.11 (0.57–2.18)	NS	NS
H-W *p* value		4.0×10^{-4}		0.009				
$IL10_{-592}$	*C*	99	72.8	185	58.5	1.89 (1.22–2.93)	0.004	0.02
(rs1800872)	*A*	37	27.2	131	41.5	0.53 (0.34–0.82)	0.004	0.02
	CC	36	52.9	60	38.0	1.84 (1.04–3.25)	0.04	NS
	CA	27	39.7	65	41.1	0.94 (0.53–1.68)	NS	NS
	AA	5	7.4	33	20.9	0.30 (0.11–0.80)	0.01	0.05
H-W *p* value		NS		NS				

SNP, single nucleotide polymorphism; *MS*, multiple sclerosis; *OR*, odds ratio; *CI*, confidence interval; *p*, probability; *pc*, corrected *p*; *H-W*, Hardy-Weinberg; *N*, Absolute number; %, percentage; *NS*, not significant (*p* value > 0.05)

† Number of patients, 67

†† Number of controls, 157

Table 2 The four most frequent estimated three-locus haplotypes for *IL4* and *IL10* single nucleotide polymorphisms in multiple sclerosis patients and controls.

Haplotype		MS patients		Control group		OR (95% CI)	*p* value	pc value
		N	%	*N*	%			
$IL4_{-1098}$-$IL4_{-590}$-$IL4_{-33}$	TCC	86	63.2	120	38.0	2.81 (1.86–4.25)	1.0×10^{-6}	5.0×10^{-6}
	TTT	19	14.0	49	15.6	0.88 (0.50–1.57)	NS	NS
	GCC	20	14.7	32	10.1	1.53 (0.84–2.78)	NS	NS
	TTC	7	5.1	12	3.8	1.37 (0.53–3.56)	NS	NS
	GCC	53	39.0	70	22.2	2.24 (1.45–3.46)	3.4×10^{-4}	0.002
$IL10_{-1082}$-$IL10_{-819}$-$IL10_{-592}$	ACC	31	22.8	75	23.7	0.95 (0.59–1.53)	NS	NS
	ATA	32	23.5	65	20.6	1.19 (0.74–1.92)	NS	NS
	ATC	12	8.8	28	8.9	1.0 (0.49–2.02)	NS	NS

MS, multiple sclerosis; *OR*, odds ratio; *CI*, confidence interval; *p*, probability; *pc*, corrected *p*; *N*, absolute number; %, percentage; *NS*, not significant (*p* value > 0.05)

assess a possible association between $IL4_{-590}$ SNP and MS in Caucasians [10]. The analysis declared that there was a significant association between the $IL4_{-590}$ and MS susceptibly under allele and dominant models. Furthermore, the protective potential of *T* allele was also suggested. The present study strongly confirms such findings, and the *T* allele showed a corrected significant decreased frequency in MS patients compared to control (22.1 vs. 34.2%; pc = 0.05).

With respect to $IL4_{-33}$ SNP, the results favored the predisposing effects of *C* allele and CC genotype in MS patients, while *T* allele and TT genotype may be considered as protective markers against the development of disease. These findings are supported by the results of Quirico-Santos et al. who also reported that $IL4_{-33}$ CC genotype had the highest frequency in Brazilian patients and control [14]. The TT genotype was also reported to be decreased in primary progressive versus RRMS patients in Northern Irish population [23]. However, in a more recent meta-analysis, it has been reported that there was no evidence of statistically significant association between $IL4_{-33}$ SNP and MS [24].

The third SNP that showed a significant variation between MS patients and control was $IL4_{-1098}$. Probably, such SNP has not been investigated in MS, but if the results are confirmed, its alleles and genotypes are suggested to have a role in MS susceptibility. In the neurodegenerative Alzheimer's disease, $IL4_{-1098}$ SNP has been investigated and it was associated with a decreased risk in Caucasian patients, while in Han Chinese patients, it was associated with an increased risk [25]. Therefore, $IL4_{-1098}$ SNP requires further investigations to determine its risk effects in MS and other neurological disorders.

For *IL10* SNPs, and in agreement with the present results, it has been demonstrated that there was no significant variation between Iranian and Caucasian MS patients and controls in the distribution of $IL10_{-1082}$ and $IL10_{-819}$ SNP genotypes [16, 26]. However, the third SNP of *IL10* ($IL10_{-592}$) was significantly associated with MS in the current sample of patients; an

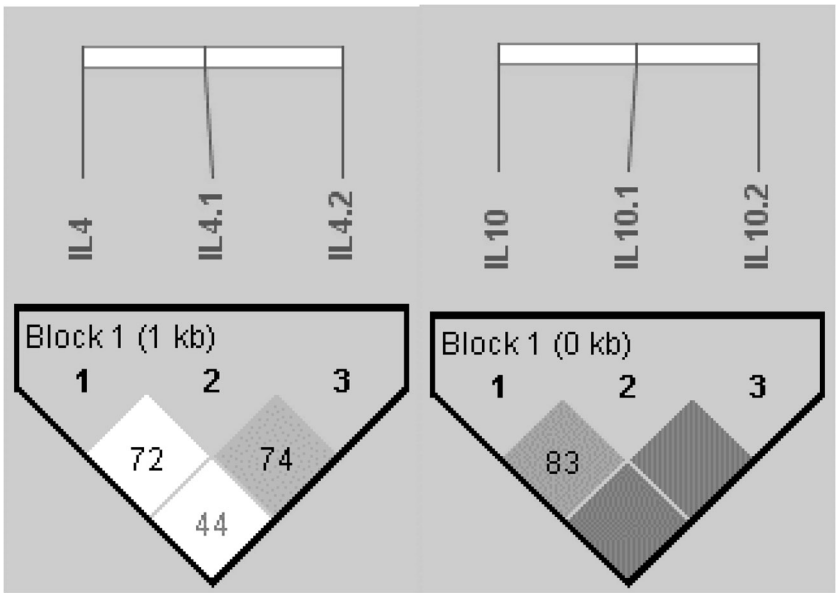

Fig. 1 Haploview pairwise analysis of $IL4_{-1098}$, $IL4_{-590}$, and $IL4_{-33}$ SNPs (IL4, IL4.1, and IL4.2, respectively) and $IL10_{-1082}$, $IL10_{-819}$, and $IL10_{-592}$ SNPs (IL10, IL10.1, and IL10.2, respectively). The numbers inside the boxes represent disequilibrium coefficient (D′).White boxes indicate weak linkage disequilibrium (LD), whereas grey boxes indicate strong LD. Dark grey boxes represent a complete LD (D′ = 1, LOD > 3).

observation that is contradicted by the latter two studies, but it was in agreement with the findings of Mihailova and colleagues in Bulgarian RRMS patients [17]. The authors reported a significantly increased frequency of $IL10_{-592}$ CC genotype in patients. The present study reported a similar increased frequency of CC genotype in MS patients, but the difference was significant before correction. However, a corrected significant level was reached when the comparison between patients and controls was based on the frequency of *C* allele, which showed a significant increase in MS patients. The three presented SNPs of *IL10* have also been the subject of a recent meta-analysis that involved nine case-control studies. The analysis revealed that $IL10_{-1082}$, $IL10_{-819}$, and $IL10_{-592}$ SNPs may not be risk factors for the development of MS in Asian and Caucasian populations [18]. Possibly, the ethnicity might have contributed to such variation, as cytokine SNP allele and genotype frequencies show significant variations between populations of different ethnicities [27].

The SNP's role of both cytokine genes (*IL4* and *IL10*) in MS susceptibility can be better understood when the comparison between patients and controls was based on the estimated haplotype frequencies. Two haplotypes, TCC ($IL4_{-1098}$-$IL4_{-590}$- $IL4_{-33}$) and GCC ($IL10_{-1082}$-$IL10_{-819}$-$IL10_{-592}$), showed a significantly increased frequency in MS patients compared to controls and the OR of such differences was 2.81 and 2.24, respectively. This means that both haplotypes were associated with an increased risk to develop MS. In addition, some of these loci were in a strong LD. These results suggest that haplotype association and LD of *IL4* and *IL10* genes may have an important role in the etiology and pathogenesis of MS. However, such findings have to be further investigated in order to determine the susceptibility role of *IL4* and *IL10* gene SNPs in MS.

It is possible to conclude that *IL4* and *IL10* genes harbor important SNPs that confer MS susceptibility. In addition, their role in reducing the risk of disease is also suggested. However, the susceptibility role is better evaluated in terms of haplotype frequencies.

Acknowledgment The authors thank all Multiple Sclerosis Clinic physicians at Baghdad Teaching Hospital, especially Dr. Sarmad Al-Mashta, for their help and cooperation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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