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ORIGINAL ARTICLE

TRAILR1 (rs20576) and *GRIA3 (rs12557782)* are not associated with interferon-β response in multiple sclerosis patients

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Abstract

Multiple sclerosis (MS) is an autoimmune-type inflammatory disorder in human central nervous system. Recombinant interferon beta (IFN-β) decreases the number of relapses and postpones disability progression in MS. However, up to 50% of patients treated with interferon beta continue experiencing relapses and/or worsening disability. Single nucleotide polymorphisms in different genes have been known to show significant associations with response to IFN-β in MS patients. In the present work, we examined the potential role of *TRAILR1* and *GRIA3* genes polymorphisms on response to IFN-β therapy in Iranian MS patients. The DNA was extracted from blood samples by standard procedures from 73 patients diagnosed with Multiple Sclerosis that were either responded to IFN-β or did not. We carried out RFLP -PCR and tetra-primer ARMS-PCR methods to study of *rs20576* and *rs12557782*, respectively. All results were analyzed using the SPSS software. *TRAILR1 rs20576* genotype frequencies in responders and non-responders were similar ($\chi^2 = 0.26$, $P = 0.87$, Fisher' s Exact test). Our results showed that response to IFN-β has not association with sex ($p = 0.73$). Also, genotypic frequencies of *GRIA3 rs12557782* had no significant differences between two groups of female population ($\chi^2 = 3.75$, $p = 0.15$). Furthermore, it had not been any statistical differences between responder and non-responder males ($\chi^2 = 0.7$, $p = 0.4$) related to the SNP. Our results analysis revealed no significant association between the studied SNPs (*TRAILR1 rs20576* and *GRIA3rs 12,557,782*) and response to IFN-β in Iranian MS patients.

Keywords Pharmacogenetics · Multiple sclerosis · Gene polymorphisms · Interferon-β

Introduction

Multiple sclerosis (MS) is an autoimmune, demyelinating neurodegenerative disorder which affects central nervous system (CNS) and it is widely assumed to be responsible for non-traumatic disability in youngsters. Like most autoimmune diseases, MS occurs three times more common in women than men [1, 2]. MS can cause demyelination, oligodendrocyte destruction and eventually axonal injury. The exact etiology of MS is still unknown; however, based on the recent researches and evidences it is clear both genetic and environmental factors are involved in the disease. Human leukocyte antigen- (HLA-) *DRB1*1501* has the strongest association with MS susceptibility [3, 4]. Various environmental factors have been identified to be associated with MS; these factors include vitamin D level, usage of tobacco, geographical latitude and exposure to infectious organisms such as Epstein-Bar virus [5–8].

Multiple sclerosis is classified into four types due to the disease progression process. Relapsing-remitting MS(RRMS) that is characterized by clearly defined attacks (relapses) which is followed by partial or complete recovery (remission). Secondary progressive MS (SPMS), relapsing-remitting MS often proceeds to secondary progressive MS and SPMS patients continuously experience the symptoms. In third kind, primary progressive MS patients show the disease' s symptoms which slowly worsen without any remission periods. Fourth type of MS contains relapsing progressive MS which the symptoms gradually worsen

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with possibility of one or more relapses [9]. No therapies have been found to reverse neurodegenerative process of MS however within the last two decades, disease-modifying therapies such as interferon beta, glatiramer acetate, mitoxantrone, natalizumab have been able to reduce the amount of relapses and reduce the progression of the disease [10]. Clinical trials have revealed that interferon beta can prevent the progression of the disease and reduce the number of relapses in all relapsing forms of MS when compared with placebo [11–13]. The precise molecular mechanism for preventing of the disease progression is still unknown but it is assumed that it inhibits the activation and proliferation of T cells and also decreases the production of proinflammatory cytokines through activating Jak-Stat signaling pathway [14]. However, up to 50% of MS patients do not respond to this drug properly [15, 16].

Some genetic variations may be associated with response to interferon beta and these variations identifying may help physicians to proper choice of treatment and also prevention of drug's adverse effects on patients who do not respond to the drug. The recent genome wide association study (GWAS) on interferon beta pharmacogenetics has demonstrated polymorphisms in multiple genes which might be associated with response to treatment with interferon beta in RRMS patients [17]. TRAIL is a tumor necrosis factor which induces apoptosis in various cells. All TRAIL receptors are expressed in oligodendrocytes, neurons and astrocytes [18]. *TRAIL* and *TRAIL-R1* genes are related to Multiple Sclerosis. While treating with IFN-β, the enhancement of *TRAIL* expression might both induce apoptosis in granulocytes or monocytes and also it could perish or inhibit the activation of auto-reactive T cells, or even promote the production of regulatory T cells. Several studies have shown that single nucleotide polymorphisms in the genes are effective in the response to IFN-β therapy. *TRAILR-1* single nucleotide polymorphism rs20576 is in the exon 5 of the gene. The *rs20576-C* allele causes substitution of pGlu228Ala adjacent to the membrane anchoring and it might affect TRAIL binding and the apoptotic signaling. The SNP, *rs20576-C*, has been associated with susceptibility to various cancer types [19–22] as well as with an enhanced risk of metastasis [23]. *Rs20576-C* allele has also been studied in different diseases, it has been demonstrated that this polymorphism is associated with mantle cell lymphoma and chronic lymphocytic leukemia [21]. *GRIA3* encodes an AMPA-type glutamate receptor, an excitatory neurotransmitter that takes part in learning, memory, neural formation, habit formation and sensory gating [24]. Excessive activation of this receptor may cause central neurons degeneration to die. Glutamate receptors play a pivotal role in the central nervous system and are associated with various brain disorders. They play a crucial role in the pathogenesis of different neurodegenerative diseases (NDDs) such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis [25]. A positive association was also found between *GRIA3* with schizophrenia, bipolar disorder and it has been suggested that *GRIA3* might play a crucial role in the development of the aforementioned diseases [26]. It has also been reported to be associated with mental retardation and sexual dysfunction in major depression [27, 28]. Moreover, a variant of *GRIA3* gene, *rs3761555*, has been found to be associated with migraine phenotype in Italian population [29]. The SNP *rs12557782* resides on the x chromosome, in the second intron of *GRIA3* gene and has been selected as a potential candidate for determining response to treatment with IFN-β in RRMS patients by the GWAS study [17]. In the current research we have studied the association of two candidate genes polymorphisms, *TRAILR1*rs20576 A > C and *GRIA3*rs12557782 G > A, with response to interferon beta therapy in Iranian patients.

Materials and methods

Subjects

In this study, 73 relapsing – remitting MS patients including 19 men and 54 women met McDonald's criteria and were treated with interferon beta [9]. Written informed consent was gathered from the patients and the project had been approved by local ethics committee.

The 37 patients who were classified as responders to the treatment did not have increase in relapses during the first 2 years of treatment's initiation. The 36 patients who were categorized as non-responders to the treatment had experienced at least one or more relapses during the first 2 years of treatment usage [30]. The patients were not related by blood.

Genotyping

Peripheral blood samples were collected in tubes contained EDTA and DNA was extracted from blood nucleated cells using Rapid Genomic DNA Isolation kit (Gen Fanavaran, Iran) according to manufacturer`s guideline. The purity and amount of isolated DNA was checked by agarose gel electrophoresis (1%) and a Nanodrop spectrophotometer (Thermo Scientific, USA), respectively.

Primers and PCR Conditions

The specific primers were designed for the studied genes using Primer3 online software v4.1.0 and were analyzed by NCBI Primer- BLAST tool (http://www.ncbi.nlm.nih.gov/). The *TRAILR1*rs20576 primers were as follow: 5′-GTGTGCATGCTCAGACCCTT −3'and 5′- CGGAAC AACCAAAGTCACAAC -3′. Restriction fragment length

polymorphism- polymerase chain reaction (RFLP-PCR) method was done. PCR reaction was carried out in 25 µL mixture, containing 30 ng of template DNA, 1 µl of each 10 pmol/µl primer (Sinaclone, Iran), 5 µl of 2x Master mix red (Ampliqon, Denmark) and 17 µl dH_2O. PCR amplification was conducted by an automated thermocycler (TC512 TECHNE, United Kingdom). The following conditions were used: 94 °C for the first denaturation at 5 min, 35 cycles of 30s for second denaturation at 94 °C, 30s for primers annealing at 60 °C and 30s DNA extension at 72 °C, respectively, ending with 7 min at 72 °C to complete extension. The PCR product was electrophoresed on 2% agarose gel and a 390 bp replicon was detected. The PCR products digestion was carried out by *Taq1*(Sinaclone, Iran) restriction enzyme and two DNA fragments, 239 bp and 151 bp, were obtained related to 683AA genotype for *TRAILR1*. However, the enzyme did not digest the amplified fragment obtained from 683CC genotype and after digestion reaction a 390 bp DNA segment was detected for this variant (Fig. 1).

To clarify the relationship of the *GRIA3 rs12557782* and IFN-β resistance, DNA samples from both responder and non-responder groups were amplified by tetra ARMS- PCR method using two pairs of specific primers to amplification of different alleles. The outer primers for *GRIA3 rs12557782* were: 5´-AGAACGTGATAATCACACATTGGTATGATT -3′ and 5′- TACTTGAATGTAACTGCTAGCAAATGCA −3′ as forward and reverse, respectively. Additionally, 5′-TGCTTAACCATATTATCTCGATATAAACGG −3′ and 5′- TGGGCTAAGAGGGTGCTTTTTAGTCT −3′ were used as inner forward and reverse primers, respectively. Polymerase chain reaction was performed in 25 µL volume mixture containing 30 ng of template DNA, 1 µl of each 10 pmol/ul primer (Sinaclone, Iran), 5 µl of 2x Master mix blue (Ampliqon, Denmark) and 17 µl dH_2O. The amplification reaction was done as follows: 5 min at 94 °C for first denaturation, 35 cycles of 40 s at 94 °C, 58 °C and 72 °C, respectively, ending with 10 min at 72 °C to complete extension. 5 µL of the PCR product was electrophoresed on an agarose gel (2%). The SNP, *GRIA3 rs12557782*, was identified based on the PCR products lengths. Outer primers amplified a 410 nucleotide amplicon containing *GRIA3 rs12557782*, while inner primers led to amplification of different replicons based on the allele types. For *rs12557782-G* allele a 194 bp length fragment was amplified while a 273 bp for *rs12557782-A* allele were obtained (Fig. 2).

Statistical analysis

We performed a Mann–Whitney U test, one non-parametric test, to compare number of relapses between responder and non-responder patients. Genotypic and allelic frequencies were compared between the two groups using Fisher's Exact test with GraphPad Prism program (version 7.05 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com). Chi-square and *P* values were calculated. We used SPSS v.19.0 software (SPSS, Chicago, IL, USA) for data statistical analysis. For all statistics, *p* values less than 0.05 was considered as statistically significant.

Results

In this association study, we investigated the relationship of two genetic polymorphisms, *TRAILR1* rs20576 A > C and *GRIA3 rs12557782* G > A, with response to interferon beta therapy in patients diagnosed with relapsing-remitting multiple sclerosis (RRMS). The subjects included responder group and non-responders with 37(27 women and 10 men) and 36(27 women and 9 men) patients, respectively. All studied patients had been using interferon beta and follow-up

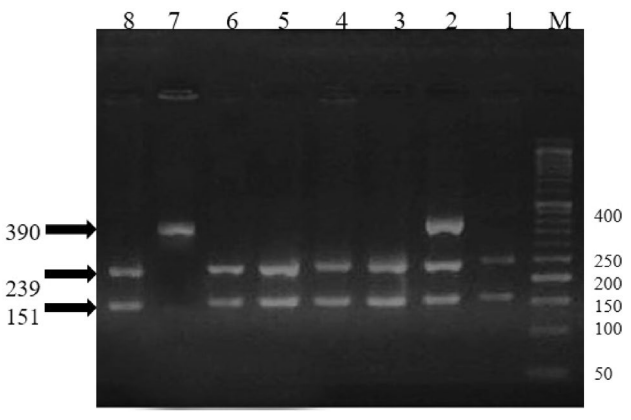

Fig. 1 RFLP-PCR genotyping of *TRAILR1rs20576* A > C by *Taq1* digestion Lanes: M, DNA ladder; 1, 3, 4, 5, 6 and 8 show AA; 2 indicates AC; 7 represents CC genotypes

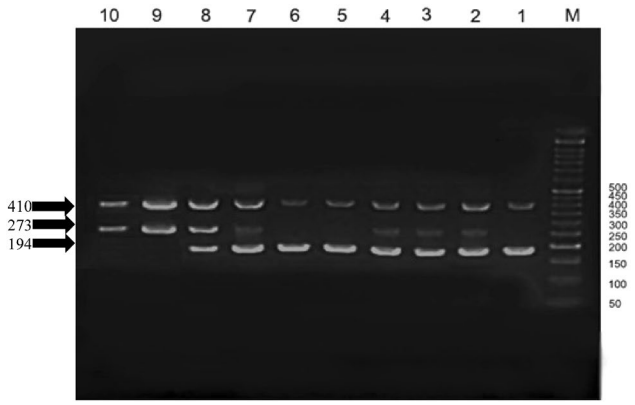

Fig. 2 Agarose gel electrophoresis pattern of *GRIA3* rs4938723 G > A genotyping by tetra ARMS-PCR. Lanes: M, DNA ladder; 1, 5 and 6, GG; 2, 3, 4, 7 and 8 represent AG; 9 and 10 indicates AA genotype

for at least 2 years during from June 22, 2017 to September 30, 2019. Some of the important clinical characteristics of the studied patients, concerned to our study, are shown in Table 1. No significant differences were seen between two groups about the age at disease onset and the age at treatment onset, $p=0.09$ and $p=0.1$, respectively. After taking the IFN-β, the number of relapses was significantly lowered in responder group than to non-responders ($p=0.03$). Therefore, responder subjects had fewer or no relapses in the 2 years while non-responders had more relapses within the 2 years (Table 1).

The genotypic frequencies for *TRAILR1 rs20576* were as follows: AA (67%), AC (30%) and CC (3%) in responder population while the same were 69%, 28% and 3% in non-responders, respectively. However, the frequencies of *TRAILR1 rs20576* genotypes had no statistical differences between responder and non-responder groups ($\chi^2=0.26$, $P=0.87$). Also, the frequencies of A and C alleles had no significant differences between two groups ($P>0.05$). In the other hand, because *GRIA3* is a sex-linked gene, genotypic and allelic frequencies of *GRIA3 rs12557782* were separately assessed in both responder and non-responder patients based on patients' gender. Our results showed that response to IFN-β had not association with sex ($p=0.73$). Also, genotypic frequencies had no significant differences between two groups of female population ($\chi^2=3.75$, $p=0.15$). The frequencies were GG (15%), AG (81%) and AA (4%) in responder females while the proportions were 26%, 70% and 4%, respectively, in non-responders. Furthermore, it had not been any statistical differences between responders and non-responder males ($\chi^2=0.7$, $p=0.4$). The detailed distribution of genotypic frequencies of the two studied SNPs are presented in Table 2. Combination analysis was carried out to investigation of dominant and recessive genetic models for both SNPs, rs20576 A > C and *rs12557782* G > A. The combined genotypes were not associated with response to IFN-β treatment (Table 3).

Table 1 Clinical features of the examined population

Characteristic	Responders	Non-responders
Female	72.9%	75%
Male	27.1%	25%
Age at disease onset, y, mean, SD	24.70 ± 7.6	24.44 ± 3.9
Age at treatment Onset, y, mean, SD	28 ± 8.7	26.69 ± 3.6
Relapses in 2 y prior to treatment, mean, SD	2.3 ± 1.3	3.4 ± 2.2
Relapses during 2 y of treatment, mean, SD	0.35 ± 0.58	3.3 ± 2.1

Discussion

Multiple sclerosis (MS) is an autoimmune disease that leads to neurons demyelination in central nervous system (CNS) and it is suggested to be one of the causes of disability at a young age [1, 2]. The precise pathogenesis of the disease is still unknown; however, genetic factors are involved in MS disease. Relapsing-remitting MS (RRMS) is determined by defined attacks (relapses) which is followed by partial or complete recovery (remission). Clinical experiments have revealed that interferon beta can prevent the progression of the disease and reduce the number of relapses [11–13]. But half of the patients do not respond suitably [15, 16]. Some genes and genetic variations may be related to the response to interferon beta therapy. We have studied the association of two candidate gene polymorphisms, *TRAILR1 rs20576* A > C and *GRIA3 rs12557782* G > A, with responsiveness to interferon beta treatment in Iranian patients. According to our results, *TRALR1 rs20576* and *GRIA3 rs12557782* did not show any significant association with response to IFN-β treatment in RRMS patients.

It has been identified that TRAIL/TRAIL receptor system takes part in various steps in immune cell activation, migration, proliferation, differentiation and might be associated with different autoimmune disorders [31–34]. TRAIL can attach to its receptor and initiate apoptosis. In contrast to

Table 2 Genotypic frequencies of *TRAILR1 rs20576* and *GRIA3 rs12557782*

Gene	Genotype	Responders n(%)	Non-responders n(%)	χ2	*P- value*
	AA	25(67)	25(69)		
TRAILR1 (rs20576)	AC	11(30)	10(28)	0.26	0.87
Female	CC	1(3)	1(3)		
	GG	4(15)	7(26)		
	AG	22(81)	19(70)	3.75	0.15
	AA	1(4)	1(4)		
GRIA3 rs12557782					
Male	G	6(60)	7(78)		
	A	4(40)	2(22)	0.69	0.40

Table 3 Different models of the genotypic distribution of *rs20576* and *rs12557782* polymorphisms

Genetic models	Genotype	Responders N(%)	Non-Responders N(%)	OR (95% CI)	P Value
TRAILR1 rs20576					
Dominant	AA	25 (%67)	25 (%69)	1.00	–
	AC + CC	12 (%33)	11 (%31)	0.91(0.34–2.46)	0.86
Recessive	AA+AC	36 (%97)	35(%97)	1.00	–
	CC	1 (%3)	1 (%3)	1.02 (0.06–17.09)	0.98
GRIA3 rs12557782					
Dominant	GG	4(15)	7 (26)	1.00	–
	AG + AA	23 (85)	20 (74)	0.49 (0.12–1.94)	0.31
Recessive	AG + GG	26 (%96)	26(%96)	1.00	–
	AA	1 (4)	1 (4)	1.00 (0.05–16.85)	0.31

our results, López-Gómez et al. indicated *TRALR1 rs20576* to be statistically associated with response to IFN-β in an original cohort of Spanish MS patients. They found the SNP frequency significantly differed between responders and non-responder patients in the cohort, although the results were not obtained in the validation cohort [35]. The research showed relationship between rs20576-CC genotype with response to IFN-β while we did not obtain any association. These different results may be related to restricted number of the patients in current study because we detected only one responder patient with CC-genotype. However, we could not study a validation cohort due to limited number of the subjects. The genetic variant has also been studied in other neurological diseases such as Alzheimer's disease (AD) but no association was found between the mentioned polymorphism and AD [36]. Morales-Lara and et al. indicated that *TRAILR1 rs20575* affects rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patient's response to infliximab treatment [37]. Additionally, Taghavi et al. conducted a case-control study in Azeri patients in Iran. In the study, frequencies of genotypes and alleles of *TRAILR1 rs4872077* (T > C), and *TRAILR2 rs1001793* (G > A), were assessed. The frequencies were not different between MS patients and healthy controls ($\chi^2 = 0.42$, $p = 0.514$ for *rs4872077* and $\chi^2 = 2.3$, $p = 0.127$ for *rs1001793*). They did not obtain any association between the two polymorphisms and multiple sclerosis disease [38]. Taheri et al. (2016) evaluated TRAIL gene expression changes in relapsing- remitting MS patients who respond to IFN-β therapy. They found no significant difference between the patients and healthy controls [39].

GRIA3 encodes an AMPA-type glutamate receptor, so excessive activation of this receptor may cause central neurons degeneration and death. Our results showed that RRMS patients reflex to IFN-β treatment has no significant relationship with *GRIA3 rs12557782* in both males and females. Little research has been done on the association of the SNP with MS. Comabella et al. demonstrated different association between *GRIA3 rs12557782* and response to IFN-β therapy in MS patients due to gender. The study showed significant relationship between the polymorphism and IFN-β therapy response in women ($p < 0.001$, OR 8.5) but not in men ($p = 0.56$, OR = 1.7) [40]. We report the minor allele frequencies (MAFs) of *TRAILR1 (rs20576)* and *GRIA3 (rs12557782)* in Iranian population for the first time. The MAFs were obtained 0.18 for rs20576 A > C and 0.22 for rs12557782 G > A single nucleotide polymorphisms.

Conclusion

This is the first study about association between *TRALR1rs20576* and *GRIA3*rs12557782 genetic variations with response to IFN-β treatment in Iranian RRMS patients. We have not found any association between the two SNPs and response to IFN-β therapy. The possible explanations for our outcomes might be due to the limited number of studied patients. Due to this limitation we could not validate our results through a validation cohort. Also, ethnic characteristics can lead to different results in association studies. Therefore, further investigations with larger number of subjects is recommended. Also, future studies on different racial populations will be necessary to get further insight into the relationship between *TRAILR1 rs20576* and *GRIA3 rs12557782* with responsiveness to interferon beta treatment.

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Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

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

Ethics approval This study was approved by Iran National Committee for Ethics in Biomedical Research (IR. GUMS. REC. 1397.08) and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all participants of the study.

Consent to publish The participant was informed that the results of this research would be published in the journal.

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