Association study of promoter polymorphisms of interferon alpha and beta receptor subunit 1 (IFNAR1) gene and therapeutic response to interferon-beta in patients with multiple sclerosis

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Abstract

Background Multiple sclerosis (MS) is an autoimmune disease described by inflammatory neuronal losses and resultant failures. The disease could abate by interferon-beta (IFN-β) therapy in MS patients. However, the drug response productivity is changeable between patients, and the accurate mechanism of action of the IFN-β is not obvious. The present study aims to investigate the role of interferon alpha and beta receptor subunit 1 (IFNAR1) promoter polymorphisms towards IFN-β treatment response in MS patients.

Methods The subjects herein were separated into either responder (n = 57) or non-responder (n = 43) groups according to IFN-β treatment and Expanded Disability Status Scale score. The Sanger sequencing method was used for genotyping.

Results Among nearly 64 Single Nucleotide Polymorphisms (SNPs), we found a significant association between the rs2850015 polymorphism and the responders and non-responders to IFN-β treatment in the recessive model of inheritance (P = 0.02). The results also revealed a significant change in the two groups of responders and non-responders to the treatment for rs36158718 as an Insertion/Deletion (INDEL) (P = 0.02). Moreover, bioinformatic analyses predicted a remarkable role for both rs2850015 and rs36158718 related to the changes of binding affinity of transcription factors and alterations in their alleles.

Conclusion The present study results suggest that the genetic heterogeneity in the promoter region of IFNAR1 could affect the response to IFN-β. However, further studies with a larger sample size are needed to further demonstrate this relationship.

Keywords Multiple sclerosis · IFN-β · IFNAR1 · SNP · INDEL

Introduction

Multiple sclerosis (MS) is known as a disease damaging the central nervous system (CNS), in which the demyelinating of white matter occurs chronically, affecting approximately 2.5 million people worldwide [1]. This debilitating disease of the CNS generally follows a waxing and waning cycle over many years before when progressive disability appears [2]. It is believed that injury of axons is the primary mechanism of basic progressive disability [3]. MS is more prevalent in women than in men with a 3:1 ratio, yet the disease intensity is superior in men [4]. MS clinically manifests itself with multiple neurological dysfunctions (for example, bladder and bowel symptoms, bilateral Babinski signs, gait problems, visual and sensory disturbances, and limb weakness) followed by improvement or growing disability caused by irreversible functional disability in a duration of time [5]. It is assumed that genetic and environmental reasons could affect multiple sclerosis, and also, among genetic factors, immunological factors have been implicated in the pathophysiology of this disease [5]. Hence, given that disease-modifying drugs (for example, IFN-β) exist as the first line of treatment for recurrent MS (RRMS), which is the most common immunotherapy type of MS [6].
Numerous studies have shown that IFN-β protein expression is reduced in people with MS and disease advancements [7, 8]. In addition, evidence has shown that the optimal personalized therapy is essential in the therapeutic approach for MS because treatment response varies significantly among patients [9]. The clinical experiment has displayed that treatment with IFN-β is related to the inhibition of relapse compared with placebo across all relapsing subtypes of MS; meanwhile, up to 30–50% of patients display suboptimal answers to therapy [10]. Therefore, it is essential to define dependable predictors of response to IFN-β and decrease the risk of disease development in MS patients.

The biological effects of IFN-β as a pleiotropic cytokine happens through its binding to the IFN-β receptor (IFNAR) 1 and 2 subunits of heterodimeric cell surface receptor complex [11]. The interaction triggers the JAK-STAT signaling cascade, which finally causes transcriptional stimulation of several IFN-activated genes [12]. Particular transcription factors partly mediate the IFN-β mechanism with the so-called IFN-stimulated response elements (ISREs), which frequently originate in the promoter regions of IFN-inducible genes [13].

Pharmacogenomics identifies gene variants responsible for different responses to drugs in different patients. Given the ongoing innovations in genomic science, personalized medicine has provided the chance to optimize individual treatment products. Single Nucleotide Polymorphisms (SNPs) can affect pharmacodynamics, metabolism, or the mechanism of action of IFN-β in MS patients [14]. Remarkably, previous studies have reported precious results representing the associations between IFNAR1 SNPs and MS [15–18].

The current study was conducted to assess the role of the promoter sequence of the IFNAR1 gene for the first time, to the best of our knowledge, in the therapeutic response to IFN-β in an Iranian population with MS. Our study obtained an insight into the pharmacogenetics study on MS patients and rendered a hopeful tactic to predict therapeutic response to IFN-β.

Materials and methods

Patients

The present study examined 100 Iranian RRMS patients in Hamadan Province (IRSN). The patients were followed prospectively for 2 years (from July 2018 to June 2020) after the initiation of treatment with IFNβ-1a (intramuscular injection of CinnoVex [CinnaGen Co, Tehran, Iran]) in the Imam Khomeini clinic (Hamadan, Hamadan, Iran).

All the patients recruited in this study had clinically definite MS and specifically RRMS according to Poser’s criteria [19]. After 2 years of follow-up, the patients were classified as IFN-β responders (n = 57) once there was no sustained progression in the Expanded Disability Status Scale (EDSS) and no relapse during the follow-up period. Moreover, the patients who were considered non-responders (n = 43) were divided with a 6-month interval when at least one relapse happened during the follow-up, in addition to a growth of at least one point in the EDSS that continued for two consecutive visits [10]. Hamadan University of Medical Sciences Institutional Ethics Committee approved this study (IR. UMSHA.REC.1397.258). All the patients signed informed consent before participating in the study.

DNA extraction and PCR analysis

According to the manufacturers’ protocol, genetic DNA was extracted from venous peripheral blood samples applying BioFACT Genomic DNA Prep Kit for Blood (Daejeon, Korea). Subsequently, IFN-β promoter sequence DNA augmented with PCR using forward primer (Plus): CAAGTC GCCCGGAAAAACGAG and reverse primer (Minus): GCT GCCGTGCCCTACCTC. Following PCR amplification, the PCR products were analyzed using 2.0% agarose gel. The PCR products were sequenced employing Plus and Minus primers via the Sanger sequencing method. High-quality sequence data were produced, which was reflected by a long contiguous read length (CRL) (up to 850 bp) and a high Phred quality value (QV20+ for over 95% of the bases) sequencing. The results were analyzed utilizing the sequencer 5.4.6 (Gene Codes Corporation).

Statistical analysis

Statistical analysis was carried out using SPSS version 20 (SPSS Inc., Chicago, IL) with a chi-square test with Yates’ correction or Fisher’s exact test. The risks contributed by genotype were measured by calculation of odds ratio (OR) with 95% CI. In addition, an independent t-test was calculated to compare the quantitative data between the two groups. More precise and genetic analyses were performed utilizing MedCalc statistical software (ver. 15.8). The main bioinformatic analyses were also performed with TFBIND [20].

Results

Table 1 represents the baseline and clinical characteristics of 100 RRMS patients according to the responsiveness to IFN-β therapy.

As shown in Table 1, 82% of the patients were female, and 18% were male, yet no significant differences were found between the two groups in response to the treatment
However, concerning age, a study of people under 30 and over 30 years of age in the two groups of response and non-response to treatment showed that people over 30 years of age were more likely not to respond to treatment; this difference was statistically significant (P = 0.04). The disease’s adverse drug reactions were significantly lower in the responders compared to the non-responder group of the patients (P < 0.001). The mean points for EDSS at the baseline (2.04 ± 1.1 vs. 2.33 ± 1.25; P = 0.23) and at the study endpoint (1.97 ± 1.05 vs. 3.44 ± 1.73; P < 0.001) were also significantly different between the responders and non-responders.

Bioinformatics analysis revealed 11 SNPs within the promoter region that altered putative transcription factor binding sites. Sequencing analysis revealed six SNPs within the promoter region of the IFNAR1 gene, which was different between the responders and non-responders. These SNPs are rs16997869, g.269T > A, rs1342763478, g.346C > T, rs1568923491, and rs2850015 from the start codon. The results of the statistical analysis are shown in Table 2.

According to the results, in rs16997869, g.269T > A, rs1342763478, g.346C > T, and rs1568923491, there were no statistically significant differences between the responder and non-responder groups. However, rs2850015 SNP indicated a statistically significant difference between the responders and non-responders. (P < 0.05).

Considering the results of Table 3, the frequency of SNP TT (rs2850015) genotype of IFNAR1 promoter was 33 (60%) in the responders and 22 (40%) in the non-responders. The frequency of SNP TC (rs2850015) IFNAR1 promoter genotype was 12 (80%) in the responders and 3 (20%) in the non-responders. The frequency of CC SNP (rs2850015) IFNAR1 promoter genotype was 12 (40%) in the responders and 18 (60%) in the non-responders. There was a significant difference between the responders and non-responders concerning the TC genotype (P < 0.05). In contrast, the frequency of TT and CC (rs2850015) genotype of the IFNAR1 promoter was not significantly different between the two groups.

The results implied that compared to the CC genotype, the probability of response to treatment was higher in the TC genotype (OR [95% CI] = 6.95 [1.4–25.8]). There wasn’t a statistically significant relationship in terms of probability or less response to treatment was found in the individuals carrying the TT genotype than in those carrying the CC genotype. (OR [95% CI] = 2.25 [0.91–5.6]). Compared to the CC genotype, the probability of response to treatment was higher in the dominant model. (OR [95% CI] = 2.22 CI = 0.92–5.4) (Table 3). Moreover, in the outcomes of allele frequency, a significant difference wasn’t detected between the alleles in the responder and non-responder individuals (P < 0.07) (Table 3).

The second marker was the GTn repeat element ranging from 542 to 551 bp from the start codon. According to the results (Table 4), there was a significant difference between the responders and non-responders to the treatment regarding the presence or absence of insertion before GT repeats dinucleotide microsatellite (P = 0.02). These insertions contained one to three nucleotide sequences, including SK, KSK, TGG, and K (S = G or C, K = G or T). The results in Table 5 indicate that the number of GT sequences tended to be positively associated with the therapeutic response but were not significant (P = 0.3).
Discussion

The advantageous possessions of IFN-β therapy in MS have been exposed in several studies, which decrease the relapse rate by nearly 30% [21, 22]. However, a long-term variation in the standard history of the disease has not been recognized. Additionally, numerous patients are refractory or show undesirable answers following IFN-β therapy [23]. IFN-β binds to type I interferon receptors and persuades a complex transcriptional response, allowing multiple immunomodulatory proteins expression. Thus, up-or down-regulation of the IFNAR1 and IFNAR2 receptors could affect the IFN-β therapy. Genome-wide pharmacogenomics analyses have exposed a relationship between response to immunotherapy and genetic heterogeneity [24].

The present study investigated the IFNAR1 gene polymorphisms located on its promoter and its relationship with immunotherapy response. Our outcomes revealed a significant connotation between the rs2850015 genotypes and the responses to IFN-β therapy. In non-coding regions, such as a promoter, SNPs can change transcription factor binding sites, resulting in a modification in the protein expression. Numerous studies have reported that an SNP in the promoter can influence protein expression. Liu et al. displayed that polymorphism in the promoter region of interleukin-12B can upregulate the gene expression and grow the colon cancer possibility [25]. Russa et al. established that polymorphism in the promoter region was associated with MS in Italian patients [26]. In line with these results, Ibayyan et al. showed that the SNP in the promoter of interleukin-7 receptor alpha was linked to MS in Jordanian patients [27].

The results also displayed a significant variance between the two groups in terms of the presence or absence of insertion before GT repeats dinucleotide microsatellite. Insertion in the promoter area could influence the protein expression. Moshynska et al. showed that brief sequence insertion in the MCL-1 promoter allows advanced protein expression.

| Genotype | N  | %  | P-value | P-value   |
|----------|----|----|---------|-----------|
| rs16997869 | 49 | 86 | 0.26    | 0.3959    |
| CC       | 40 | 93 | 0.18    |           |
| Responder  | 5  | 8.8|         |           |
| Non-responder | 1 | 2.5|         |           |
| CT       | 3  | 5.3| 0.89    |           |
| Responder  | 2  | 4.7|         |           |
| Non-responder | 3 | 5 | 0.89    |           |
| g.269T>A  | 56 | 98.2| 0.84  |           |
| TT       | 42 | 97.7|        |           |
| TA       | 1  | 1.8|         |           |
| Responder  | 41 | 95.3|       |           |
| Non-responder | 2 | 4.7|         |           |
| AA       | 0  | 0  |         |           |
| Responder  | 0  | 0  |         |           |
| Non-responder | 0 | 0 |         |           |
| rs1342763478 | 51 | 89.5| 0.28  | 0.8036    |
| CC       | 41 | 95.3|        |           |
| Responder  | 2  | 4.7|         |           |
| Non-responder | 0 | 0 |         |           |
| AT       | 1  | 1.8| 0.4     |           |
| Responder  | 6  | 10.5| 0.28  |           |
| Non-responder | 2 | 4.7|         |           |
| TT       | 0  | 0  |         |           |
| Responder  | 0  | 0  |         |           |
| Non-responder | 0 | 0 |         |           |
| g.346C>T  | 53 | 93 | 0.62    | 0.4840    |
| CC       | 41 | 95.3|        |           |
| Responder  | 2  | 4.7|         |           |
| Non-responder | 0 | 0 |         |           |
| AT       | 0  | 0  |         |           |
| Responder  | 0  | 0  |         |           |
| Non-responder | 0 | 0 |         |           |
| rs1568923491 | 53 | 93| 0.62    |           |
| CC       | 41 | 95.3|        |           |
| Responder  | 2  | 4.7|         |           |
| Non-responder | 0 | 0 |         |           |
| AT       | 0  | 0  |         |           |
| Responder  | 0  | 0  |         |           |
| Non-responder | 0 | 0 |         |           |
| TT       | 4  | 7  | 0.62    |           |

Table 2 (continued)

| Genotype | N  | %  | P-value | P-value   |
|----------|----|----|---------|-----------|
| rs2850015 | 33 | 60 | 0.14    |           |
| TT       | 22 | 40 |         |           |
| Responder  | 12 | 80 | 0.01    |           |
| Non-responder | 3 | 20|         |           |
| AA       | 0  | 0  |         |           |
| Responder  | 0  | 0  |         |           |
| Non-responder | 0 | 0 |         |           |
| rs1342763478 | 33 | 60| 0.14    |           |
| TT       | 22 | 40 |         |           |
| Responder  | 12 | 80 | 0.01    |           |
| Non-responder | 3 | 20|         |           |
| CC       | 0  | 0  |         |           |
| Responder  | 0  | 0  |         |           |
| Non-responder | 0 | 0 |         |           |
and insufficient chemotherapy response [28]. The current study indicated that the promoter GT repeat dinucleotide microsatellite polymorphism of the IFN-β gene might be related to the response to IFN-β. Promoter microsatellite polymorphism has been explored in numerous studies; for example, Fiotti et al. described that the microsatellite of the promoter area of matrix metalloproteinase 9 (MMP-9) was upper in the MS than that in the control group and can influence a function in susceptibility to multiple sclerosis (MS) [29]. Matsuyama et al. stated that the 5/5 or 5/14 genotype of the GT repeat dinucleotide microsatellite polymorphism was associated with the higher antiviral activity of IFN-α [30].

rs2850015, as a 5'UTR-SNP, is situated in the promoter region; thus, the alteration of its major allele (T) to minor allele (C) may change the binding affinity of some transcription factors. The procedure utilized here for finding the putative changes in the transcription factor affinity was to extract a 30 bps region with selected SNP in its center; in the next, there were two FASTA files for each SNP to investigate the plausible alterations; Finally, similar transcription factors which could bind in both alleles of the SNP were discarded, and transcription factors which could only bind to one of the alleles were selected to be discussed. Based on the bioinformatics predictions (TFBIND available at: http://tfbind.hgc.jp), MYOD (binds on the negative strand, binding sequence: SRACAGGTGKYG; signal sequence including SNP: CAG CGCGTGTC GC; score: 0.79) (Fig. 1) and LMO2COM (binds on the positive strand, binding sequence: SNACAGGTGNNN; signal sequence including SNP: GCGCGTGTC GAG; score: 0.80) transcription factors can only bind to the genomic region of rs2850015 of individuals with T allele and TT genotypes. Meanwhile, the C allele and CC genotype make a new binding site for transcription factor OLF1 (binds on the positive strand, binding sequence: NNCNANTCC YNGRGARNNKGN; signal sequence including SNP: AGCGCGCGTGTCAG; score: 0.76). Consequently, alteration of T allele to C allele disrupts binding affinity of MYOD and LMO2COM and makes a new affinity for OLF1 to bind the aforementioned site. There were bioinformatically found notable changes in the binding affinity of transcription factors corresponding to GT repeat INDEL (rs36158718); more specifically, in (GT)8 and (GT)9 compared with (GT)5, transcription factors CDPCR3, NGFIC, EGR1, EGR2, EGR3, and GC had affinities to bind with added GTs. Furthermore, there were certain differences between (GT)8 and (GT)9 alleles, which cause one more binding site in (GT)9 rather than (GT)8 for each of NGFIC (binds on the positive strand, binding sequence: WTG CGT GGG YGG; signal sequence including SNP: GTG TGT GTG GGG) and MYOD and LMO2COM and makes a new affinity for OLF1 to bind the aforementioned site.

| Variable                  | All patients | Responder | Non-responder | P-value |
|---------------------------|--------------|-----------|---------------|---------|
| Insertions before GT      | N %          | N %       | N %           |         |
| No                        | 89 89        | 47 82.5   | 42 97.5       | 0.02    |
| Yes                       | 11 11        | 10 17.5   | 1 1.8         | 2.3     |

| Number of GT repeat       | N %          | N %       | N %           | P-value |
|---------------------------|--------------|-----------|---------------|---------|
| 5                         | 91 91        | 51 89.5   | 40 93         | 0.3     |
| 8                         | 6 6          | 5 8.8     | 1 2.3         | 0.3     |
| 9                         | 3 3          | 1 1.8     | 2 4.7         |         |

Table 3 Genotype and allele distribution of IFNAR1 gene variant rs2850015 among responders and non-responders to treatment

| SNP       | Subjects | Genotype (%) | Allele (%) | P-value | Dominant model | Co-dominant model | Recessive model |
|-----------|----------|--------------|------------|---------|----------------|-------------------|-----------------|
| rs2850015T>C | Case     | 33 (58)      | 12 (21)    | 78 (48.4) | 0.031          | 0.76 (0.34–1.69) | 3.55 (0.94–13.51) |
|           | Control  | 22 (51)      | 3 (7)      | 18 (42)  | 47 (54.6)      | 39 (45.4)        |                 |

Table 4 Investigation of insertion before GT repeat dinucleotide microsatellite (rs36158718) in the promoter region of IFNAR1 gene

Table 5 Investigation of (GT)n repeat dinucleotide microsatellite (rs36158718) in the promoter region of IFNAR1 gene
TGT; score: 0.76), EGR1 (binds on the positive strand, binding sequence: WTGCGTGCGCG; signal sequence including SNP: GTG GTG GTG; score: 0.76), EGR2 (binds on the positive strand, binding sequence: NTGCGTGGCG; signal sequence including SNP: GTG GTG GTG; score: 0.79), EGR3 (binds on the positive strand, binding sequence: NTGCGTGGCG; signal sequence including SNP: GTG GTG GTG; score: 0.75) transcription factors. There is some evidence as to the relationship of the aforementioned transcription factors with the neuronal system; for instance, Hosseini et al. suggested that might have an impact on MS progression through the suppression of miR-223, which controls the progression of the relapsing phase of MS and LMO2 inonemiR-223 target [31]. Chevral et al. stated that Egr1-3 transcription factors are predominantly known in the nervous system, where Egr1 and 3 play crucial roles in learning and memory by regulating the genes related to synaptic plasticity and long-lasting potentiation [32]. Based on these studies and the current study results, there might be certain unknown associations between IFNAR1 promoter SNPs and MS on the binding affinity level of the aforementioned transcription factors.

**Conclusion**

The present study investigated the genetic heterogeneity in the IFNAR1 promoter and its relation to IFN-β therapy in MS patients. Herein, we established a significant relationship between rs2850015 in the responders and non-responders to IFN-β therapy. The obtained findings also revealed a significant difference between the two groups concerning the presence or absence of insertion before GT repeats dinucleotide microsatellite (rs36158718). Furthermore, positive findings using bioinformatics predictions proposed the putative effects of these two variants on binding affinities of some transcription factors. Therefore, further studies with a larger sample size are required to establish this relationship more accurately. Moreover, the possible effects of the mentioned SNP, insertion and microsatellite polymorphism on protein expression must be assessed in vitro and in vivo. These studies could be conducive to selecting the best therapy for MS patients.

**Author contributions** All authors contributed to the study’s conception and design. Material preparation, data collection, and analysis were performed by MM, FN, GR, and MS. SH wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Declarations**

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

![Fig. 1](image) The binding sequence of human transcription factor MYOD from JASPER overlapped with the signal sequence including rs2850015 flanking region
Consent to participate  This study was approved by the Ethics Committee of Hamadan University of Medical Sciences IR.UMSHA. REC.1397.258. Informed consent was obtained from all study participants before the project began.

Consent to publish  Neither the article nor portions of it have been previously published elsewhere. The manuscript is not under consideration for publication in another journal and will not be submitted elsewhere until the Molecular Biology Report editorial process is completed. All authors consent to the publication of the manuscript in the Molecular Biology Report.

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