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ORIGINAL ARTICLE

# Significant Association of rs77493513 Polymorphism in 3'-UTR of the *NRG1* Gene with the Risk of Multiple Sclerosis Disease

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## Abstract

Multiple sclerosis (MS) is a chronic inflammatory and autoimmune disease characterized by demyelination of the central nervous system (CNS). Neuregulin 1 (NRG1) is a signaling protein that plays an important role in a variety of biological processes, including potentiate oligodendrocyte differentiation and myelination in the CNS, immune response regulation, and inflammation. Single nucleotide polymorphism (SNP) rs77493513 is located in the untranslated region of the 3' mRNA (3'-UTR) of the *NRG1* gene, which is predicted to be the binding site of several microRNAs and may play an important role in post-transcriptional regulation. Study aimed to investigate the association of SNP rs77493513 in the *NRG1* gene with the risk of MS disease. In this study, genomic DNA was extracted from whole blood samples of 182 patients with relapsing-remitting multiple sclerosis (RRMS) and 198 controls. Different genotypes of rs77493513 polymorphism were determined using RFLP-PCR technique. Statistical analysis was performed using SPSS 21.0 software and by t, $\chi 2$ and logistic regression tests. Our data showed that genotypes AC (OR=3.63, CI= 1.93-6.81, p<0.001) and CC (OR=7.90, CI= 4.13-15.11, p<0.001) significantly increased the risk of MS disease and C allele is risk allele. Also, AC (OR=0.16, CI= 0.04-0.63, p= 0.009) and CC (OR=0.14, CI= 0.03-0.53, p=0.04) genotypes significantly decrease the age of onset of the disease. The results show that allele C of rs77493513 polymorphism in the *NRG1* gene can be a risk factor for MS.

**Keywords** Multiple Sclerosis · *NRG1* Gene · Polymorphism · rs77493513

## Introduction

Multiple Sclerosis is an inflammatory, demyelination and axonal degenerative disease of the central nervous system (CNS) that is associated with physical disability (Browne et al. 2014; Oh et al. 2018; Zhang et al. 2011).

Many demyelinated axonal lesions in the mammalian CNS are repaired by oligodendrocytes and Schwann cells (Kremer et al. 2019). In MS disease, oligodendrocyte progenitor cells (OPCs) migrate to the demyelinated lesions, proliferate and differentiate to remyelinate axons. Also, although Schwann cells are responsible for axonal myelination in the peripheral nervous system (PNS) (Miller and Leary 2007; Bhatheja and Field 2006), in pathological conditions such as MS, a large number of Schwann cells have been found in the peripheral nervous system. (Ma et al. 2018). These cells, are able to cross the CNS-PNS border to remyelinate central axons in the early stages of lesion repair process (Assinck et al. 2017; Zawadzka et al. 2010). On the other, Schwann cells derived from the central OPC, are the dominant Schwann cells involved in the remyelination of demyelinated central axons lesions and it has been suggested that Schwann cells be used to treat demyelinating diseases (Garcia-Diaz and Baron-van Evercooren 2020).

Despite all these mechanisms, factors including OPC differentiation inhibitors (Kremer et al. 2019), aging and the disease duration (Kemppinen 2011; Zhang et al. 2011) limit and reduce OPC cell efficiency, leading to defects in remyelination and regeneration of many MS lesions (Bahadori et al. 2015; Loeb 2007).

Immune-modulatory drugs are now available that reduce the recurrent rate of MS, but there are no current neuroprotective treatments to improve the remyelination efficiency and progressive disability in patients (Zhang et al. 2011;

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Kremer et al. 2019). Therefore, understanding the causes of myelin repair failure is essential to finding appropriate treatment strategies for MS.

Neuregulin-1 (Nrg1) is a protective growth factor in the central nervous system and an essential regulators for the survival of OPCs (Kataria et al. 2017), the differentiation and maturation of oligodendrocytes (Nave 2010) and promotes myelination by oligodendrocyte in the CNS (Wang et al. 2007). Also, Nrg1 regulates the expression of myelin related genes through the PI3K-AKT-mTOR signaling transduction pathway (Birchmeier and Nave 2008), so that impaired NRG1 regulation, is one of the main causes for loss of remylination of spinal cord demyelinating lesions (Kataria et al. 2017). In this regard, it has been shown that the diversity of functional polymorphisms in the promoter of the *NRG1* gene may play a role in the remyelination potential and MS disease progression (Bahadori et al. 2015).

In the human genome, up to 60 % of protein coding genes are regulated by MiRNAs at the translational level. Thus, miRNAs are involved in many cellular processes such as proliferation, apoptosis and differentiation (Cai et al. 2009; Catalanotto et al. 2016). The seed region of miRNAs (the sequence from position 2 to 8 at the 5' end), is crucial for target recognition and it is mainly paired with the sequences in the 3'-UTR of target mRNA (Catalanotto et al. 2016), inhibiting the translation process or facilitating mRNA degradation (Guo and Chen 2014; Meijer et al. 2013). SNPs in the seed sequences (in the miRNA) or miRNA binding site (in the mRNA) can affect miRNA: mRNA interaction, leading to create (or increasing strength binding) or loss (or decrease strength binding) miRNA target sequences and play an important role in the susceptibility to diseases (Moszyńska et al. 2017).

SNP rs77493513; A>C, in the 3'-UTR of the *NRG1* gene is predicted as binding site for several microRNAs. Given the role of NRG1 in the axons remyelination and the assumption that this polymorphism is involved in regulation of the *NRG1* gene expression, in this study was investigated the association of the rs77493513 with the risk of MS.

## Materials and Methods

Based on minor allele frequency (MAF) ≥0.05 and positioning in the 3′-UTR, we selected SNP rs77493513 in the *NRG1* gene that miRNASNP-v3 database (http://bioinfo.life.hust.edu.cn/miRNASNP/) was predicted the possible effect of candidate SNP on miRNAs: mRNA interaction (Liu et al. 2021). Then, the RNAhybrid (http://bibiserv.techfak.uni-bielefeld.de/rnahybrid/) was also used to evaluate the effect of different alleles in rs77493513 for the predicted targets (Kruger and Rehmsmeier 2006).

This study included 182 patients RRMS with age mean: 33.92±9.28 (60 men and 122 women) and 198 controls with age mean: 35.81±10.15 (72 men and 126 women). Patients were diagnosed based on clinical finding including at least two separate attacks with signs of two or more CNS lesions in MRI scan at the Neurology Division of AL-Zahra Hospital (Isfahan, Iran) from August 2015 to January 2016. In addition, matched healthy blood donor volunteers who did not have a history of clinical evidence MS themselves and their families (from the same geographic location of patient subjects) were included as control group. The Institutional Review Board of the Islamic Azad University, Shahrekord Branch approved the study protocol and the informed consent forms were obtained from the participants.

DNA was extracted from whole blood samples using kit (GeNet Bio, South Korea) according to the manufacturer's instructions. SNP rs77493513 of the *NRG1* gene was genotyped using the PCR-RFLP technique by MslI restriction enzyme. Primers (F: 5'-CCAAGACCCTATTGCTGT ATAA-3' and R: 5'- TGTTGGATCTACTATTATCTCAG-3') were designed by OLIGO 7 software and were verified for non-specificity using 'BLAST' program at http://www.ncbi.nlm.nih.gov/blast.

PCR was carried out using 10 µL master mix PCR (Ampliqon), 1 µl DNA (50–100 ng) of genomic DNA, 7 µL of distilled water and 1 µl of each primer (10 picomoles). PCR was performed at 94 °C for 5 min for initial denaturation, followed by 30 cycles of denaturation at 94 °C for 35s, annealing at temperature 50°C for 40s, extension at 72 °C for 40s and final extension at 72 °C for 5 min. Then, the PCR products were treated with the *MslI* enzyme (Thermo Scientific, Lithuania) for 2 hours at 37 °C. Finally, digested products were electrophoresed on 1.5% agarose gel, followed by safe staining rather than ethidium bromide and photographed under gel documentation system.

Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to assess the associations between the rs77493513 *NRG1* gene polymorphism and the risk of MS disease. The probability level of 0.05 was used as the criterion of significance and all the tests were two-sided tests. Statistical analysis was performed using IBM SPSS 16.0 software.

## Results

The clinical and demographic data of patients and controls are summarized in Table 1. The mean age of onset in patients was 27.30±9.32 years. More than 28% of MS patients have a family history of MS in first-degree family members that is significantly higher in the patient group than in the control group (14.1%). Also, the level of vitamin D in patients was significantly lower than the control group.

**Table 1** Characteristics of study subjects

| Characteristics | Classification | Controls | Patients | p |
|---|---|---|---|---|
| Age (year) | *Age range*<br>*Mean ±SD* | 10-61<br>35.81±10.15 | 10-61<br>33.92±9.28 | 0.06 |
| Family History in of MS in first-degree relatives | No | 170 | 130 | 0.002 |
| | Yes | 28 | 52 | |
| Age on onset | Age range | - | 9-47 | - |
| | *Mean±SD* | - | 27.30±9.32 | |
| EDSS | Mean±*SD* | | 1.99±*0.91* | |
| | | 41.53±*9.96* | 16.97±*5.51* | <0.001 |

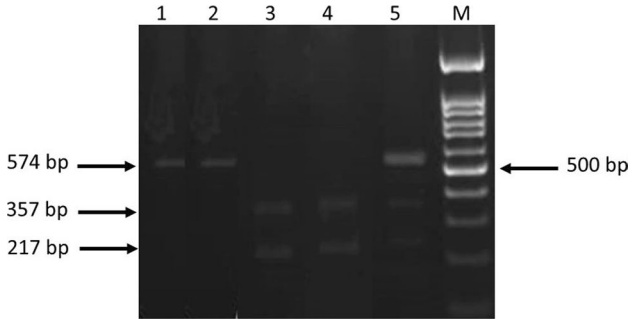


**Fig. 1** Genotyping of rs77493513 polymorphism by PCR-RFLP and gel electrophoresis on 1.5% agarose gel. Genotype AA – wells 3 and 4 – results in two bands (217 bp and 357 bp), genotype AC – well 5 – results three bands (574, 357 and 217 bp), genotype CC – wells 1 and 2 – (574 bp). Well M is the 100 bp DNA standard marker

**Table 2** Association between rs77493513 polymorphisms in 3'-UTR of *NRG1* gene with the risk of MS.

| rs77493513 | Controls (%) | Patients (%) | OR | 95% CI | P |
|---|---|---|---|---|---|
| Genotype | | | | | |
| AA | 66 (33.3) | 16 (8.8) | 1 | - | - |
| AC | 84 (42.4) | 74 (40.7) | 3.63 | 1.93-6.81 | <0.001 |
| CC | 48 (24.2) | 92 (50.5) | 7.90 | 4.13-15.11 | <0.001 |
| Allele | | | | | |
| A | 216 (54.5) | 106 (29.1) | 1 | - | - |
| C | 180 (45.5) | 258 (70.9) | 2.92 | 2.16-3.94 | <0.001 |

The PCR-RFLP technique precisely detected three genotypes for rs77493513 polymorphism (Fig. 1). The genotype distribution and allele frequencies of SNP rs77493513 in the *NRG1* gene for MS patients and controls are listed in Table 2. The observed genotypes frequencies of SNP rs77493513 were consistent statistically with Hardy-Weinberg equilibrium expectation in patient ($\chi 2 = 0.12$; df= 1, p= 0.77) groups but as borderline in controls ($\chi 2 = 3.95$; df= 1, p= 0.045).

The frequencies of genotype AA in the control and patient groups were 33.3 % and 8.8 %, respectively. Considering the genotype AA as the reference genotype (because the allele A is the ancestral allele) genotypes AC (OR=3.63, CI= 1.93-6.81, p<0.001) and CC (OR=7.90, CI= 4.13-15.11, p<0.001) significantly increased the risk of MS disease. Also, allele C (OR=2.87, CI= 1.60-5.15, p<0.001) as the risk allele significantly increases the susceptibility to MS. The results showed that age of onset of MS with AC (OR=0.16, CI= 0.04-0.63, p= 0.009) and CC (OR=0.14, CI= 0.03-0.53, p=0.04) genotypes was significantly decreased.

In addition, we evaluated the potential role of miRNA-mRNA binding strength of this SNP in silico analysis. Based on the miRNASNP-v3 database, the SNP rs77493513 located at the 3'-UTR of *NRG1* mRNA could affect the binding of six different miRNAs. Our analysis showed that in the presence of allele A, two miRNAs, miR-155-5p and miR-106a-3p, the target site is lost in the 3'-UTR mRNA *NRG1*. While, the allele C, creates a preferred site for four miRNAs including miR-124-3p, miR-3910, miR-506 and miR-3714 (Table 3).

To verify the effect of different alleles of SNP rs77493513 on the miRNAs binding, we calculated difference of minimum free energy (ΔMFE) formation of miRNA:mRNA duplex (ancestral allele MFE - variant allele MFE), by RNAhybrid online software (Manikandan and Munirajan 2014). We observed that the A (for miR-155-5p and miR-106a-3p) or C allele (for miR-124-3p, miR-3910, miR-506 and miR-3714) can decrease MFE miRNA:mRNA duplex, leading to increase the binding strength of miRNA.

## Discussion

According to the key role of neuregulin in myelin development and neurons remyelination after injury (Birchmeier and Bennett 2016), in this study, we analyzed the SNP rs77493513 in the 3'-UTR of *NRG1* gene with risk of MS disease.

**Table 3** Analysis of the effect of different rs77493513 polymorphism alleles on miRNAs using miRNA target prediction databases

| SNP ID | Categories | miRNA | | MFE (kcal/mol) | | ΔMFE (kcal/mol) |
|---|---|---|---|---|---|---|
| | | | | Variant allele (C) | Wild allele (A) | |
| Rs77493513 | **Target gain with SNP in 3'UTR** | hsa-miR-3910 | 3'UTR: 5' UUUUGCUGGCUUCUUGUGCAUUGCCUUAUGAUGUUGAC 3'<br>miRNA: 3' ACAGAACCAAAAUACGGAAA 5' | -18.1 | -13.5 | 4.6 |
| | | hsa-miR-506-3p | 3'UTR: 5' UUUUGCUGGCUUCUUGUGCAUUGCCUUAUGAUGUUGAC 3'<br>miRNA: 3' AGAUGAGUCUUCCCACGGAAU 5' | -16.9 | -12.4 | 4.5 |
| | | hsa-miR-124-3p | 3'UTR: 5' UUUUGCUGGCUUCUUGUGCAUUGCCUUAUGAUGUUGAC 3'<br>miRNA: 3' AACCGUAAGUGGCGCACGGAAU 5' | -25.9 | -19.4 | 6.5 |
| | | hsa-miR-3714 | 3'UTR: 5' UUUUGCUGGCUUCUUGUGCAUUGCCUUAUGAUGUUGAC 3'<br>miRNA: 3' UGUCCCCUCGUGACGACGGAAG 5' | -21.6 | -18.0 | 3.6 |
| | **Target loss with SNP in 3'UTR** | hsa-miR-155-5p | 3'UTR: 5' UUUUGCUGGCUUCUUGUGCAUUGCAUUAUGAUGUUGACU 3'<br>miRNA: 3' UUGGGGAUAGUGCUAAUCGUAAUU 5' | -15.1 | -17.8 | -2.7 |
| | | hsa-miR-106a-3p | 3'UTR: 5' UUUUGCUGGCUUCUUGUGCAUUGCAUUAUGAUGUUG 3'<br>miRNA: 3' CAUUCUUCACGAAUGUAACGUC 5' | -17.1 | -19.1 | -2 |

In recent years have shown that the expression of many MS-related genes is controlled by miRNAs (Dehghanzad et al. 2021), so miRNAs play an important role in the MS pathogenesis (Regev et al. 2016). In line with, it has been suggested that miRNAs are involved in remyelination defects and have therapeutic potential to restore remyelination in MS (Teuber-Hanselmann et al. 2020).

In addition, it is reported that genetic variations including the SNPs play key roles on susceptibility to MS (Dehghanzad et al. 2020). Among them, especially SNPs located in the 3'-UTR of mRNAs, which are targets to miRNAs may change the ability of miRNAs binding, leading to altered expression of target genes and in turn, susceptibility to MS. Therefore, identifying the association of SNPs in miRNA binding sites with the risk of MS, is important for understanding the pathophysiology of this disease.

We found experimentally that the allele C, the AC and CC genotypes of rs77493513 polymorphism in the *NRG1* significantly increase the risk of MS, which to our knowledge has not yet been reported.

Several studies show that SNPs in binding site of miRNAs can change the energy needed to form miRNA:mRNA duplex (Minimum Free Energy or MFE) (Kozomara and Griffiths-Jones 2011).

Based on MFE of miRNA: mRNA duplex formation, both alleles of this SNP can be the preferred binding site for different miRNAs. However, the strength miRNA binding depends on the ΔMFE value so that higher ΔMFE value, has a greater effect on miRNA: mRNA binding (Manikandan and Munirajan 2014). ΔMFE is positive for miR-124-3p, miR-3910, miR-506 and miR-3714 miRNAs, thus bind more strongly in the presence of the allele C but is negative for miR-155-5p and miR-106a-3p which bind more tightly in the presence of allele A, therefore it seems that allele C has a stronger effect on miRNAs binding and may decrease the expression of *NRG1* gene and acts as a risk allele in susceptibility to MS.

Small sample size is the potential limitation of this study that may affect the strength of the results and it is suggested that our results be confirm in larger population samples.

## Conclusion

This study shows a statistically significant associations of SNP rs77493513 located in the 3-UTR of *NRG1* gene with the risk MS disease in the Iranian population. Our experimental and bioinformatics data suggest that the C allele of rs77493513 SNP in the microRNA recognition element (MRE-SNP) of *NRG1* gene, as a risk factor, can used as a biomarker in the screening of people susceptible to MS.

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**Availability of data and material** Not applicable

**Code availability** Not applicable

**Author Contributions** Maedeh Ghorbani participated to sample preparation and carried out the experiments. Parisa Mohamadynejad designed, planned, supervised the project and wrote the manuscript. Mehdi Moghanibashi advised and helped to the interpretation of the results and write the manuscript.

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## Declarations

**Conflict of interest** The authors have no conflict of interest.

**Ethics approval** The Institutional Review Board of the Islamic Azad University, Shahrekord Branch approved the study protocol.

**Consent to participate** The informed consent forms were obtained from the participants.

**Consent for publication** All authors discussed the results and commented on the manuscript. 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 "Metabolic Brain Disease" editorial process is completed, and all authors consent to the publication of the manuscript in "Metabolic Brain Disease".

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