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Exon 7 Sequences of IL7RA Gene Identify Two New Variants with Susceptibility to Multiple Sclerosis in Iranian Patients

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder with neurodegenerative effects. It is usually seen among young adults and women. The aim of the present investigation was the study of IL7RA gene exon 7 and flanking intronic regions in MS patients compared with healthy control. In this case-control study, 100 MS patients in Relapsing-Remitting phase and 87 healthy individuals were studied. DNA was extracted from whole blood cells, using Salting-out method. Samples were screened for variations in exon 7 and flanking intronic regions by direct sequencing. No mutation was found in the exon7, however 39 single nucleotide polymorphisms (SNPs) were investigated. In addition, we found 2 variations that were significantly associated with MS in our population. Our study demonstrated no significant variation in Iranian MS population in exon 7 but we found 2 variations in flanking regions which were associated with MS. Further studies are required to define the effects of these SNPs on the IL7R protein in multiple sclerosis.

Key words: Multiple Sclerosis, IL7RA, Exon7, Polymorphism.

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1. INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disorder in central nervous system (CNS) that characterized by numbness, vision loss and difficulties in walking and is more common in young adults and occurs 2 to 3 times more in women. According to the expanded disability status scale (EDSS), clinical disease progression is determined and included to four clinical phenotypes, that Relapsing-Remitting (RR-MS) phase is the most common (1, 2). Interaction of genetic and environmental factors is cause of the disease (3). Living in temperate climate, vitamin D deficiency, geographic differences in the amount of sun light, month of birth, diet, smoking, infection with Epstein-Barr virus (EBV) are considered as environmental risk factors for MS (4-8). Inheritable risk factors are including HLA locus and IL7 receptor α chain (CD127) (9). The gene of IL7RA is located on chromosome 5p13. IL7 is a 25 kilodalton glycoprotein that is secreted by stromal cells in the bone marrow and thymus (10, 11). IL7 and its receptor are responsible for homeostasis and T cells longevity and cytotoxicity reactions (12, 13). The inflammatory damages display the autoimmune trait of MS, that we studied some genes, especially HLA and cytokine genes, in Iranian patients with MS Previously (14-16). Nowadays increasing evidences for an important role of CD8+ cytotoxic T cells has emanated in MS patients (17, 18). IL7 is recognized as a Pre B cell growth factor, too. IL7 receptor is made of two portions: IL7RA and IL2RG (CD132); the second one also heterodimerizes with receptors for other interleukins, such as IL2, IL4, IL9, IL15, and IL21. Both portions are

necessary for the biological effects of IL7 and the downstream signaling cascade. IL7RA is recognized as the first non-major histocompatibility complex (non-MHC) MS susceptibility locus (19). IL7RA subunit are consisted of 4 paired cycteines in extracellular domain and closer to the transmembrane a WSXW motif. The intracellular domain has a BOX1 motif and finally 2 tyrosines (Y401, Y449) that comprised in signal transduction (20). The cell-signaling cascade starts following to binding of IL7 to its surface receptor. The small juxta-membrane Box1 motif is a part of IL7RA. When JAK1 binds to Box1 motif, signaling cascade will be started (21). Signaling cascade involves the activation of Janus kinases (Jacks) and signal transducer activators of transcription (STATs). Cytoplasmic tail of IL7RA contains several structural and functional motifs such as motif BOX1 that mediates activation of Jak1 in cell signaling (22-24). According to the prior knowledge, it is plausible that IL7/IL7RA pathway is involved in the autoimmune aspects of the disease. The goal of this study was to identify variations in IL7RA gene particularly in region of BOX1 motif in Iranian patients with MS. This investigation was planned in order to study of IL7RA gene exon 7 and flanking intronic regions variations in MS patients compared with healthy control.

2. MATERIALS AND METHODS

2.1. Patients and Controls

In this case-control study, our patients group included 100 clinically MS cases, that their expanded disability status scale (EDSS) was 2.5 (Mild disability in 1 or Minimal disability in 2 Functional systems) up to 5.5 (Ambulatory for 100 meters, disability precludes full daily activities) (2). They were assessed according to the revised 2005 McDonald criteria, also we tried to include patients of more provinces of Iran in our study (25). Ethical Committee of Tehran Imam Hossein hospital allowed this study and patients were aware of study goals. 87 persons without any symptoms of MS or any neurological or inflammatory disease were selected as healthy control group. Controls were matched age and sex to MS patients (Table 1).

Table 1. Demographic and clinical data of MS patients and healthy control

Variables	MS patients	Healthy control
Female/Male (no, %)	85/15 (85/15%)	75/12 (86/14%)
Age (mean,Y)	31.1	31.4
Age at onset (mean, Y)	25	-
Relapsing-Remitting (no, %)	100 (100%)	-
Duration (mean, Y)	5.6	-
EDSS (mean)	3.5	-

2.2. Blood sampling

EDTA-containing tubes (FL medical Company, Italy) were used to collect 3 ml whole blood from all subjects.

2.3. DNA extraction

Salting- out method was applied to extract DNA from whole blood samples (26).

2.4. PCR amplification

A pair of primers spanning the intron 6, exon 7 and intron 7 of IL7RA gene was used to amplify the related DNA fragment with 1269 bp length. The nucleotide sequences of the forward and reverse primers have been demonstrated in Table 2. The amplification was carried out in Analytik Jena thermocycler (Analytik Jena Company, Germany) by using the Ampliqon master mix (Ampliqon Company, Denmark and cat. No 18031, 0.2 Units / ml Taq DNA polymerase in PCR buffer with 3 mM $MgCl_2$, 0.4 mM dNTP). We designed PCR amplification, was performed in standard reaction wells in a final volume of 25µl. This was consisted of initial denaturation for 5 minutes at 94°C, followed by secondary denaturation for 1 minute at 94°C, annealing for 1 minute at 65.8°C, primary extension in 1 minute at 72°C, secondary extension in 1 minute at 72°C and cooling for 5 minutes at 4°C. PCR products were electrophoresed on 1% agarose gel contained Ethidum Bromide with TBE 0.5 x solution.

2.5. Sequence analysis

PCR products were sequenced. DNA sequencing was performed by Sequencer: ABI PRISM, Sequencing Kit: ABI PRISM (Macrogen Company, Korea).

2.6. Statistical analysis

Statistical analysis was performed using chi 2 test in SPSSv18. The p value <0.05 was considered as significant.

3. RESULTS AND DISCUSSION

Table 2 shows demographic and clinical data obtained patients and healthy control group. All of patients were Iranian and in Relapsing-Remitting phase. 22 SNPs were detected in intron 6. Genotype frequency was significantly different for rs987106 in patients compared with control group (p: 0.02, OR: 2.259, 95%CI: 1.125-4.536) (Table 3). The other SNPs of intron 6 were similar to reference sequence. In exon7, no significant alteration was observed.

Table 2. The nucleotide sequences of the forward and reverse primers

primer	sequence	Tm(°C)
Forward	5´-TTGATATCTGTGGTCTCTGGT-3´(21-mer)	57.4
Reverse	5´- GGGAGACTAGGAACTCTAGAC-3´(21-mer)	61.3

Table 3. Allele and genotype frequencies for rs987106 in IL7Ra gene

	Patients	Healthy control	P value	OR	95%CI
A	116 (58%)	84 (48.27%)	0.06	1.48	0.983-2.227
T	84 (42%)	90 (51.72%)			
	n:200	n:174			
A/A	32 (32%)	15 (17.24%)	0.02	2.259	1.125-4.536
A/T	52 (52%)	54 (62.06%)	0.17	0.662	0.369-1.188
T/T	16 (16%)	18 (20.68%)	0.41	0.73	0.347-1.538
	N:100	N:87			

We found an alteration in start of intron 7 (Figure 1), that T allele was significant (p: 0.0043, OR: 0.3799, 95%CI: 0.1953-0.7387), also T/T genotype frequency was significant in patients compared with control group (p: 0.0097, OR: 0.4470, 95%CI: 0.2427-0.8232) (Table 4).

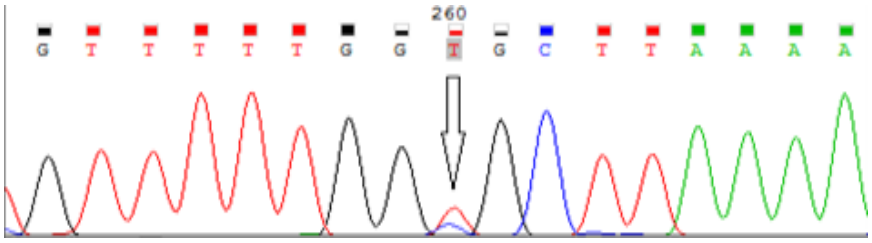

Figure 1. T/C genotype in +15bp far from start intron 7

Multiple sclerosis (MS) is the most common reason of chronic neurological disease in young adults particularly women. Usually, its prevalence in the most populations is about 0.1% (3, 27, 28). In Iran, the incidence of the disease is expanding and its prevalence is about 0.054% (29, 30). Lesions usually are located in optic nerve sheaths, brainstem and spinal cord which are characterized by clonally expanded CD8+ T cells (31). Full genetic basis for MS remains unexplained, but linkage and association studies have demonstrated that the MHC Class II DRB1501 allele and IL7RA are associated with MS (32-34). IL7 is a cytokine which has a significant role in peripheral T cells homeostasis and proliferation (35, 36). T cells have a functional role in MS pathogenesis. The cell signaling process in T cells starts following to binding of IL7 to its surface receptor. The small juxta-membrane Box1 motif is a part of IL7RA which, JAK1 binds to Box1 motif (21, 37, 38). Loss of Box1 motif leads to fast cell death also, any alteration or deletion of this protein elides JAK1 phosphorylation (39). Many studies have reported the association of IL7RA with MS. The majority of these studies have been carried out on promoter, exon 2, 4 and particularly exon 6. Exon 6 and its related soluble form of receptor have maximum association with MS (40, 41). In a study in Iranian MS population, rs11567685 in promoter and rs6897932 in exon 6, had significant association with MS also in other study in Khuzestan province, C allele and CT genotype in rs6897932 were significant in MS patients compared with controls (42, 43). Suzy M Teutsch identified 11 novel and common SNPs in IL7RA gene which were associated with MS in Caucasian MS patients (with 90% of Northern European origin). These SNPs were located in promoter, exonic and intronic regions that one of them was rs987106 in intron 6 which associated with MS also Z Zhang in a study about MS patients in Stockholm, Sweden, determined genotypes for 123 SNPs in 66 genes (according to their chromosomal positions or biological effects) (44). They notified IL7RA as MS susceptibility genes. Their results showed that rs987106 (allele T, p: 0.043, OR: 1.3, 95%CI: 1.0–1.6) and rs987107 (allele C, p: 0.015, OR: 0.58, 95%CI: 0.37–0.90) in intron 6 were associated with MS (34). Simon G Gregory in a case control study in MS population of non-Hispanic individuals of European descent in USA and European family (UK and Belgium) showed that allele T in rs987106 was associated with MS (p value: 0.0134) (45). rs987106 was studied in others autoimmune disorders, too. For example, in a study (Madrid, Spain), it was demonstrated that in patients with rs987106 TT genotype frequency of sever fibrosis was high (p: 0.009, OR: 3.09, 95%CI: 1.32–

7.22) (46), also it was reported that, patients with rs987106 TT genotype were associated with higher sIL7R levels and rapid progression of AIDS (47, 48). These studies suggest an important role of polymorphisms in promoter and other region of IL7RA gene in MS susceptibility and other autoimmune disorders. According to the role of IL7/IL7RA pathway in progress of MS, particularly CD8+ T cells activation and other findings about effect of IL7RA gene polymorphisms in MS, we decided to study IL7RA gene in order to reveal that if our population has any polymorphism resulting in alteration in splicing or increase or decrease the receptor activity in Iranian MS population as previously reported for rs6897932 in exon 6 for other populations. Therefore, we investigated 22 SNPs in intron 6, 8 SNPs in exon 7 and 8 SNPs in intron 6 by using direct sequencing. Although we didn't find any mutation in our population, we found 2 alterations in our samples which were associated with MS (Table 3, Table 4 and Figure 1).

Table 4. Allele and genotype frequencies for +15bp far from end of exon 7

	Patients	Healthy control	P value	OR	95%CI
T	161 (80.5%)	157 (90.22%)	0.0043	0.3799	0.1953-0.7387
C	39 (19.5%)	17 (9.77%)			
	n:200	n:174			
T/T	61 (61%)	70 (80.45%)	0.0097	0.4470	0.2427-0.8232
T/C	39 (39%)	17 (19.54%)			
C/C	0 (0%)	0 (0%)			
	N:100	n:87			

In addition, we found a variation in + 15bp far from of initiation of intron 7 that had not reported in previous studies. This variation is change of T to C in intron 7 which in our population was associated with MS. T allele and T/T genotype were significant (p: 0.0043, OR: 0.3799, 95%CI: 0.1953-0.7387),(p: 0.0097, OR: 0.4470, 95%CI: 0.2427-0.8232) respectively. In addition, our result about alleles frequency in rs987106 inintron 6 was similar to the previous studies(Sub-Saharan African population and European population) and was different with others (European (Caucasian) and Mexican) (49) (Table 5).

Table 5. Population Diversity

Population	Origin	Chrom.SampleCnt.	Genotype			Allele	
			AA	AT	TT	A	T
Our Iranian Population	Iranian	200	0.320	0.520	0.160	0.580	0.420
SC-95-C	European (Caucasian)	90	0.111	0.556	0.333	0.389	0.611
HAPMAP-MEX	Mexican	100	0.100	0.580	0.320	0.390	0.610
YRI-GENO-PANEL	Sub-Saharan African	120	0.350	0.483	0.167	0.592	0.408
CEU-GENO-PANEL	European	120	0.317	0.550	0.133	0.592	0.408

Any small variation in IL7RA gene and related isoform may affect IL7 signaling pathway and increase antigenic T cell response to myelin basic protein (50). We designed this study to reveal SNPs which increase MS risk. According to our results, homozygous genotypes were detected in our population suggesting that exon7 is not suitable for studying the population diversity. Observed differences in our results and others finding might depend on differences between populations such as ethnic, dietary, life style, migration, different latitudes in Iran, genetic and other risk factors which involved in MS. This investigation was performed on Iranian MS patients, it would be so interesting to do this analaysis on large sample size of populations with different ethnic in Iran and other countries are located in Middle East to demonestrae the role of IL7RA polymorphisms in MS patinents in this erea.

4. CONCLUSION

Although present study demonstrated no significant variation in Iranian MS population in exon 7, but we found 2 variations in flanking regions which were associated with MS. Further studies are required to define the effects of these variations on the IL7R protein in multiple sclerosis.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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