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HUMAN GENETICS

# Association between Allelic Variants of *IL2*, *IL2RA*, and *IL7R* Genes and Multiple Sclerosis[1]

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**Abstract**—Multiple sclerosis is a chronic progressive disease of nervous system caused by a combination of genetic and environmental factors leading to the development of a complex of autoimmune and neurodegenerative processes. We performed the analysis of association between multiple sclerosis and polymorphic markers of interleukin-2 (*IL2*), interleukin-2 receptor alpha chain (*IL2A*) and interleukin-7 receptor alpha chain (*IL7R*) in the group of Russians, Tatars, and Bashkirs from the Republic of Bashkortostan ($N = 1620$). In the total study group, we detected the association of *IL7R* rs10624573*I (OR = 0.79, $P_{Bonf} = 0.018$) and rs1494558*T (OR = 1.44, $P_{Bonf} = 2.33 \times 10^{-4}$) variants with multiple sclerosis. When analyzed separately according to the ethnic origin, the association with *IL7R* rs1494558*T (OR = 1.49, $P_{Bonf} = 0.005$) remained significant in the group of Russians, and the association of *IL7R* rs10624573*I remained significant in the group of Bashkirs (OR = 0.56, $P_{Bonf} = 0.02$). We performed the multilocus analysis of association using the APSampler algorithm, and found seven combinations of the alleles and/or genotypes of the studied polymorphic loci, significantly associated with multiple sclerosis, most frequently including *IL7R* rs1494558 and *IL7R* rs10624573 allelic variants.

*Keywords:* multiple sclerosis, genetic polymorphism, association study, interleukins, interleukin-7 receptor alpha chain

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## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease characterized by focal demyelination of central nervous system and resulting in early development of permanent disability. According to modern concepts, MS occurs in genetically predisposed individuals in response to environmental trigger factors. Most often, the disease manifests between the ages of 20 and 40; women suffer from MS twice as often as men [1]. The relative risk of developing a disease in monozygotic twins, according to various sources, varies from 17.25 to 30%; in dizygotic twins – from 3 to 4.4%; in ordinary siblings, if both parents are healthy—2.2%; if one parent and brother/sister suffers from MS—9.1%; if both parents have MS—7.4% [2, 3].

The disease is considered to have ethno-geographical specificity: the highest prevalence of MS is observed in white populations of Europe, Canada, USA and Australia. The highest prevalence rates of MS are found in Canada (291 per 100,000 population), Denmark ($227^0/_{0000}$) and Sweden ($189^0/_{0000}$) [4]. Nevertheless, there is evidence that the incidence of MS in African Americans is higher than that in white Americans [5, 6]. In addition, it was noted that the prevalence of MS among people from Africa and Asia living in Europe is significantly higher than among representatives of the respective ethnic groups living in the original habitats [7]. In Russian Federation, the prevalence of MS is $50^0/_{0000}$, in the Republic of Bashkortostan it is $38^0/_{0000}$ [4, 8]. Epidemiological features of MS dictate the need to take into account ethno-regional factors while analysing the molecular genetic basis of the disease susceptibility.

To date, over 200 genetic markers of MS have been identified by genome-wide association studies (GWAS) in various world populations, including Spanish ($N = 484$), Italian ($N = 431$), Finnish ($N = 203$), Dutch ($N = 240$), German ($N = 1415$), as well as trans-ethnic GWAS by IMSGC (International Multiple Sclerosis Genetics Consortium, $N = 931$), and

[1] The article was translated by the authors.

**Table 1.** Nomenclature and chromosomal localization of the studied polymorphic loci, primer sequences, restriction endonucleases, nomenclature of alleles and amplified fragments lengths

| Gene | Polymorphism | Chromosome localization | Primers, restriction endonuclease | Alleles, fragment lengths |
|---|---|---|---|---|
| *IL2* | rs2069772 4463A>G | 4:122451978 intron 3 | F 5'-agcttctgtgttactatcatt-3' R 5'-tggttgctgtctcatcag-3' *Vsp*I | G 253 A 167 + 86 |
| *IL7R* | rs10624573 (598(5)I/D) | 5:35857481–35857482 intron 1 | F 5'-act gga ttc att ttg ttt g-3' R 5'-gag gat ata gca ctg gtc a-3' | I 110 D 115 |
| *IL7R* | rs1494558 (197T>C, Thr66Ile) | 5:35860966 exon 2 | F 5'-cag ctg cat gtt tgt tcc-3' R 5'-cat att ctt tct ttt gtg g-3' *Bst*XI | C 147 + 106 T 253 |
| *IL2RA* | rs1570538 (50547C>T) | 10:6011605 3'UTR | F 5'-atg ctg aac ttt ttg ata atg t-3' R 5'-tct tga ggc cag gag ttt-3' *Bsh*NI | C 143 + 138 T 281 |
| *IL2RA* | rs12722580 (39504(73)I/D) | 10:6022806–6022878 intron 3 | F 5'-ctt aca gct tcc att att tta ttt-3' R 5'-act tgt gtt ttg gtc tca gg-3' | I 354 D 281 |

According to the data of the Genome Reference Consortium Human build 38 (GRCh38.p12), 3'UTR—3'-untranscribed region.

WTCCC1 (Wellcome Trust Case Control Consortium, $N = 2441$) [9–17].

The functional role of the identified polymorphic markers is usually unclear. However, they are often localized in the immune response genes and are often associated with other autoimmune disorders [18]. In addition, when interpreting GWAS results, it is necessary to take into account epistatic interactions of allelic variants of genes associated with the disease, using methods that allow to evaluate the joint contribution of a number of alleles and/or genotypes by identifying effects that are not detectable for each of them by the individual analysis [19].

The aim of our study was to analyse the associations between MS and polymorphic variants in genes of interleukin-2 (*IL2*), alpha chain of the interleukin-2 receptor (*IL2RA*) and alpha chain of the interleukin-7 receptor (*IL7R*), that were selected based on their pathogenic role, and to perform multilocus association analysis in a sample of patients with MS and representatives of the control group residing in the Republic of Bashkortostan.

## MATERIALS AND METHODS

The study group consisted of 1620 individuals, Russians ($n = 660$), Tatars ($n = 632$) and Bashkirs ($n = 327$) by ethnic origin, permanently residing in the Republic of Bashkortostan. The patient group ($n = 641$) was comprised from persons registered at the Republican Multiple Sclerosis Center (RMSC). MS was diagnosed according to the McDonald criteria (2010). The ratio of women to men in the MS patients group was 1 : 89. The control group ($n = 979$) consisted of healthy individuals without neurodegenerative or other chronic diseases, and matched the group of patients by age and sex. Ethnic origin was established according to the data from a questionnaire containing questions about ethnicity and the place of birth of ancestors in three generations.

DNA was isolated from 8 mL of whole venous blood by standard phenol-chloroform extraction. Genotyping was performed using polymerase chain reaction (PCR) or PCR with subsequent restriction fragment length polymorphism (RFLP) analysis using T100™ thermal cycler (BioRad, USA). Oligonucleotide primers were selected using the DNAStar v. 5.05 and NCBI databases (http://www.ncbi.nlm.nih.gov/SNP). The list of polymorphic markers, primer sequences, restriction enzymes, amplification fragments are shown in Table 1. The resulting amplification and restriction fragments were separated using electrophoresis in 2% agarose gel and identified using Mega-Bioprint 1100 video gel documenting system (Vilber Lourmat, France).

Statistical analysis of the study results was performed using PLINK software [20]. Compliance of the observed genotype and allelic frequencies distribution of the studied markers with theoretically expected according to Hardy–Weinberg equilibrium was assessed using Fisher's test. Associations of the studied polymorphic variants with MS were analyzed using logistic regression under additive genetic model with sex as covariate. The additive model assumes that the presence of two copies of the allele predisposing to the development of the disease has twice the effect on phenotype than the presence of a single copy. The relative risk of the disease for the carriers of the minor allele was calculated as odds ratio (OR). The association analysis of the alleles and/or genotypes with MS

**Table 2.** The results of the analysis of association of the studied polymorphic loci with multiple sclerosis

| Gene, polymorphism | Genotype | Control group | | MS patients | | $P_{HWE}$ | OR (95% $CI_{OR}$) | $P$ | $P_{Bonf}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | $n$ | $p$, % | $n$ | $p$, % | | | | |
| *IL2* rs2069772 | A/A | 403 | 51.53 | 274 | 48.07 | 0.859 | 1.15 (0.97–1.36) | 0.119 | 0.594 |
| | A/G | 319 | 40.79 | 244 | 42.81 | | | | |
| | G/G | 60 | 7.67 | 52 | 9.12 | | | | |
| *IL7R* rs10624573 | I/I | 133 | 16.06 | 71 | 12.2 | 0.066 | **0.79 (0.68–0.93)** | **$3.66 \times 10^{-3}$** | **0.018** |
| | I/D | 366 | 44.2 | 225 | 38.66 | | | | |
| | D/D | 329 | 39.73 | 286 | 49.14 | | | | |
| *IL7R* rs1494558 | C/C | 214 | 38.49 | 164 | 28.98 | 0.788 | **1.44 (1.21–1.71)** | **$4.66 \times 10^{-5}$** | **$2.33 \times 10^{-4}$** |
| | C/T | 259 | 46.58 | 267 | 47.17 | | | | |
| | T/T | 83 | 14.93 | 135 | 23.85 | | | | |
| *IL2RA* rs1570538 | T/T | 202 | 24.02 | 110 | 22 | 0.783 | 0.96 (0.81–1.12) | 0.588 | 1 |
| | T/C | 416 | 49.46 | 255 | 51 | | | | |
| | C/C | 223 | 26.52 | 135 | 27 | | | | |
| *IL2RA* rs12722580 | I/I | 312 | 47.27 | 300 | 49.83 | 0.271 | 1.1 (0.92–1.3) | 0.3 | 1 |
| | I/D | 293 | 44.39 | 217 | 36.05 | | | | |
| | D/D | 55 | 8.33 | 85 | 14.12 | | | | |

Here and below: $n$—number, $p$—frequency, $P_{HWE}$—significance level for the Hardy–Weinberg equilibrium, OR—odds ratio, 95% $CI_{OR}$—95% confidence interval for the odds ratio, $P$—significance level, $P_{Bonf}$—significance level with Bonferroni correction. The results of the analysis of associations reaching the level of statistical significance are shown in bold.

was performed using APSampler 3.6.0 program. The program and its description can be found elsewhere http://sourceforge.net/projects/apsampler, the main algorithm is described in the paper by A.V. Favorov et al. [21]. Bonferroni correction was applied to eliminate type I errors. Differences were considered significant at $P_{Bonf} < 0.05$.

## RESULTS

In the control group, the observed distribution of the genotype frequencies of all studied polymorphic markers was in agreement with Hardy–Weinberg equilibrium. There were no significant differences in genotype and allele frequency distribution among healthy individuals in the Russian, Tatar, and Bashkir ethnic groups; therefore, the analysis was performed in the total study group, and the association with MS was found for the *IL7R* rs10624573*I (OR = 0.79, $P_{Bonf}$ = 0.018) and *IL7R* rs1494558*T (OR = 1.44, $P_{Bonf} = 2.33 \times 10^{-4}$) alleles (Table 2). Further analysis accounting for the ethnicity has revealed the association between MS and the *IL7R* rs1494558*T allele in the Russian group (OR = 1.49, $P_{Bonf}$ = 0.005) (Table 3), and the *IL7R* rs10624573*I allele in the Bashkir group (OR = 0.56, $P_{Bonf}$ = 0.02) (Table 4). In Tatars, the association between MS and the *IL7R* rs1494558*T allele did not reach statistically significance after the correction for multiple testing was applied (OR = 1.39, $P$ = 0.045, $P_{Bonf}$ = 0.223) (Table 5).

No association of the polymorphic markers in *IL2* and *IL2RA* genes with MS was detected either in the total study group or when dividing the sample into subgroups according to the ethnicity. No association was found when the analysis was performed accounting for gender.

As a result of the multilocus association analysis, we identified seven genotypes and/or alleles combinations of the studied polymorphic loci, significantly associated with MS. *IL7R* rs1494558 alleles were present in five patterns, and the combinations containing *IL7R* rs1494558*T allele were associated with an increased risk of MS, while the combination that included *IL7R* rs1494558*C allele was associated with a reduced risk of the disease (Table 6). The second most frequent component of the identified combinations was *IL7R* rs10624573 polymorphism (four combinations). It is worth noting that we discovered the inversion of association: in the individual analysis, *IL7R* rs10624573*I allele was shown to be associated with the decreased risk of the disease, while the multilocus approach has revealed that *IL7R* rs10624573*I/I genotype in combination with *IL2* rs2069772*G allele was associated with the increased risk of MS (OR = 2.57, $P_{Bonf}$ = 0.002). The most pronounced risk of the disease was found for the homozygous carriers of the

**Table 3.** The results of the analysis of association of the studied polymorphic loci with multiple sclerosis in the ethnic group of Russians

| Gene, polymorphism | Genotype | Control group | | MS patients | | $P_{HWE}$ | OR (95% $CI_{OR}$) | $P$ | $P_{Bonf}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | $n$ | $p$, % | $n$ | $p$, % | | | | |
| *IL2* rs2069772 | A/A | 178 | 50.42 | 118 | 45.91 | 0.696 | 1.19 (0.93–1.53) | 0.176 | 0.878 |
| | A/G | 148 | 41.93 | 110 | 42.8 | | | | |
| | G/G | 27 | 7.65 | 29 | 11.28 | | | | |
| *IL7R* rs10624573 | I/I | 54 | 15.7 | 36 | 13.48 | 0.083 | 0.88 (0.7–1.11) | 0.282 | 1 |
| | I/D | 145 | 42.15 | 99 | 37.08 | | | | |
| | D/D | 145 | 42.15 | 132 | 49.44 | | | | |
| *IL7R* rs1494558 | C/C | 129 | 38.97 | 66 | 26.09 | 0.485 | **1.49 (1.17–1.9)** | **0.001** | **0.005** |
| | C/T | 150 | 45.32 | 129 | 50.99 | | | | |
| | T/T | 52 | 15.71 | 58 | 22.92 | | | | |
| *IL2RA* rs1570538 | T/T | 96 | 27.67 | 56 | 25.34 | 0.133 | 1 (0.79–1.27) | 0.999 | 1 |
| | T/C | 159 | 45.82 | 109 | 49.32 | | | | |
| | C/C | 92 | 26.51 | 56 | 25.34 | | | | |
| *IL2RA* rs12722580 | I/I | 153 | 44.74 | 129 | 48.13 | 0.537 | 1.04 (0.82–1.32) | 0.747 | 1 |
| | I/D | 156 | 45.61 | 98 | 36.57 | | | | |
| | D/D | 33 | 9.65 | 41 | 15.3 | | | | |

two deletions—*IL7R* rs10624573 and *IL2RA* rs12722580 (OR = 3.20, $P_{Bonf} = 0.005$), and the most significantly associated with MS was the *IL7R* rs10624573*D + *IL7R* rs1494558*T + *IL2RA* rs1570538*C combination (OR = 1.81, $P_{Bonf} = 7.1 \times 10^{-4}$).

## DISCUSSION

We detected an association of two allelic variants in *IL7R* gene (rs10624573*I and rs1494558*T) with MS in the group of 1620 residents of the Republic of Bashkortostan (Russians, Tatars and Bashkirs). *IL7R* gene is located on the short arm of chromosome 5 and encodes the alpha chain of IL7R, which is involved in the formation of the functional receptor for interleukin 7 (IL7), creating a heterodimer with the IL2R gamma chain. *IL7R* gene product can also participate in thymus lymphopoietin stroma signaling (TSLP), binding to a unique TSLP receptor.

We investigated two polymorphic variants of *IL7R* gene: rs1494558, located in the second exon and associated with cytosine to thymine substitution, leading to the replacement of threonine (ACC) with isoleucine (ATC) at position 66 of the amino acid sequence (Thr66Ile); and rs10624573, which is a 5 nucleotides (AGAAG) insertion in the intron 1 of *IL7R* gene.

It has been previously shown that the haplotype containing *IL7R* rs1494558*T allele is associated with higher solubility of the IL7R alpha chain than the haplotype containing rs1494558*C. Thus, the rs1494558*T allele may be associated with decreased IL7 and TSLP signaling, thereby inhibiting the proliferation and survival of T-lymphocytes [22]. The carriers of the haplotype containing rs1494558*T allele have been demonstrated to have significantly increased susceptibility to MS [23]. The association of the allelic variants of this polymorphism with a number of autoimmune and allergic disorders has been reported: homozygotes for the *IL7R* rs1494558*T allele were at increased risk of Berger's disease (IgA nephropathy) and associated proteinuria, as well as an unfavorable outcome of allogeneic hematopoietic stem cells transplantation [24, 25]. Association of *IL7R* rs1494558*C/C genotype with elevated IgE level was observed in healthy children in Taiwanese population [26]. The analysis of association with bronchial asthma in a group of children from Germany and Hutterites living in North Dakota has shown that *IL7R* rs1494558 polymorphism was the only one associated with asthma in both populations [27]. The rs1494558*T allele was associated with newly diagnosed diabetes after kidney transplantation in Koreans [28]. A significant decrease of *IL7R* gene expression was previously reported in the rs1494558*T allele carriers [29]. There is evidence of interaction between rs1494558 and rs6512227, localized in the tyrosine kinase gene *JAK3*, which is involved in signal transduction after cytokine binding to the receptor, possibly indicating a functional role for this polymorphism [30].

**Table 4.** The results of the analysis of association of the studied polymorphic loci with multiple sclerosis in the ethnic group of Bashkirs

| Gene, polymorphism | Genotype | Control group | | MS patients | | $P_{HWE}$ | OR (95% $CI_{OR}$) | $P$ | $P_{Bonf}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | *p*, % | *n* | *p*, % | | | | |
| *IL2* rs2069772 | A/A | 102 | 56.04 | 45 | 52.33 | 0.444 | 1.09 (0.73–1.64) | 0.665 | 1 |
| | A/G | 66 | 36.26 | 35 | 40.7 | | | | |
| | G/G | 14 | 7.69 | 6 | 6.98 | | | | |
| *IL7R* rs10624573 | I/I | 31 | 14.98 | 10 | 11.63 | 0.564 | **0.56 (0.37–0.83)** | **$3.97 \times 10^{-3}$** | **0.02** |
| | I/D | 104 | 50.24 | 27 | 31.4 | | | | |
| | D/D | 72 | 34.78 | 49 | 56.98 | | | | |
| *IL7R* rs1494558 | C/C | 17 | 33.33 | 23 | 27.06 | 0.569 | 1.57 (0.95–2.6) | 0.08 | 0.384 |
| | C/T | 27 | 52.94 | 35 | 41.18 | | | | |
| | T/T | 7 | 13.73 | 27 | 31.76 | | | | |
| *IL2RA* rs1570538 | T/T | 36 | 21.43 | 11 | 14.1 | 1 | 0.77 (0.52–1.14) | 0.196 | 0.98 |
| | T/C | 84 | 50 | 40 | 51.28 | | | | |
| | C/C | 48 | 28.57 | 27 | 34.62 | | | | |
| *IL2RA* rs12722580 | I/I | 61 | 53.98 | 46 | 50.55 | 1 | 1.5 (0.94–2.41) | 0.088 | 0.441 |
| | I/D | 45 | 39.82 | 30 | 32.97 | | | | |
| | D/D | 7 | 6.19 | 15 | 16.48 | | | | |

*IL7R* rs10624573 polymorphism has been little studied, and there is currently no information about its association with MS or other diseases. According to the 1000 Genomes Project, the frequency of the insertion allele varies from 19% in East Asian populations to 47% in African populations; in Europeans, its frequency is 43%. In populations of the Republic of Bashkortostan, the frequency of rs10624573*I allele was 38.16%, in Russians, its frequency was 36.77%, in Tatars—38.45%, and in Bashkirs—40.1%. Using data from the 1000 Genomes Project, we also detected linkage disequilibrium between the rs10624573 polymorphic variant in *IL7R* gene and rs11957503, located between *IL7R* and *CAPSL* genes (D' = 0.98, $r^2$ –0.95). The rs10624573*I allele was correlated with rs11957503*G allele ($P < 0.0001$) that was associated with blood levels of *IL7R* alpha chain, according to the results of a genome-wide association study reported by K. Suhre and M. Arnold [31].

It should be noted that the association testing with consideration of ethnicity has shown that the association between *IL7R* rs1494558 allelic variant and MS previously observed in the total study group was present only in Russians, and *IL7R* rs10624573—only in Bashkirs. This may indicate a variability of polymorphic markers of MS in *IL7R* gene locus in different ethnic groups, which may be due to the existence of various linkage patterns in different ethnicities. The interaction of IL2 with a receptor complex consisting of alpha and gamma chains plays a key role in the proliferation and survival of T-lymphocytes. Currently, clinical trials are underway, testing drugs that inhibit pathogenic T-lymphocytes by blocking alpha chain of IL2 receptor (CD25) after transplantation and in autoimmune diseases, in particular, in relapsing-remitting MS [32].

An association was found between MS and polymorphic markers in *IL2RA* gene [9, 11, 33, 34]. We studied two polymorphic variants in *IL2RA* gene: rs1570538 (C to T substitution in the 3'-untranslated region of the gene) and rs12722580 (73 nucleotides deletion in the intron), as well as rs2069772 polymorphism in the intron 3 of *IL2* gene. Polymorphic variants of *IL2* and *IL2RA* genes were not associated with MS in the individual analysis, but the alleles and genotypes of these genetic markers were found in combinations associated with MS according to the results of the multilocus analysis. Analyzing data from the GWAS Catalog (https://www.ebi.ac.uk/gwas/home), we found that *IL2* rs2069772 polymorphism is in disequilibrium linkage with a variety of genetic markers associated with autoimmune, inflammatory and allergic diseases, including type 1 diabetes, ulcerative colitis, IgA deficiency, IgE-sensitization, etc. It has also been shown that *IL2* rs2069772*G allele, found in combinations associated with an increased risk of MS, is linked with *IL2* rs2069762*A allele, associated with the reduced production of IL2 [35, 36]. Earlier an association between *IL2RA* rs1570538 allele and MS was reported in a Spanish population [37]. *IL2RA*

**Table 5.** The results of the analysis of association of the studied polymorphic loci with multiple sclerosis in the ethnic group of Tatars

| Gene, polymorphism | Genotype | Control group | | MS patients | | $P_{HWE}$ | OR (95% $CI_{OR}$) | $P$ | $P_{Bonf}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | *p*, % | *n* | *p*, % | | | | |
| *IL2* rs2069772 | A/A | 123 | 49.8 | 111 | 49.12 | 0.646 | 1.08 (0.8–1.46) | 0.617 | 1 |
| | A/G | 105 | 42.51 | 98 | 43.36 | | | | |
| | G/G | 19 | 7.69 | 17 | 7.52 | | | | |
| *IL7R* rs10624573 | I/I | 48 | 17.33 | 25 | 10.96 | 0.076 | 0.83 (0.63–1.08) | 0.169 | 0.844 |
| | I/D | 117 | 42.24 | 99 | 43.42 | | | | |
| | D/D | 112 | 40.43 | 104 | 45.61 | | | | |
| *IL7R* rs1494558 | C/C | 68 | 39.08 | 74 | 32.6 | 1 | 1.39 (1.01–1.92) | 0.045 | 0.223 |
| | C/T | 82 | 47.13 | 103 | 45.37 | | | | |
| | T/T | 24 | 13.79 | 50 | 22.03 | | | | |
| *IL2RA* rs1570538 | T/T | 70 | 21.47 | 43 | 21.39 | 0.27 | 0.96 (0.73–1.25) | 0.459 | 1 |
| | T/C | 173 | 53.07 | 106 | 52.74 | | | | |
| | C/C | 83 | 25.46 | 52 | 25.87 | | | | |
| *IL2RA* rs12722580 | I/I | 98 | 47.8 | 125 | 51.65 | 0.403 | 1.11 (0.81–1.52) | 0.51 | 1 |
| | I/D | 92 | 44.88 | 89 | 36.78 | | | | |
| | D/D | 15 | 7.32 | 28 | 11.57 | | | | |

**Table 6.** Genotype and allele combinations associated with multiple sclerosis

| Combinations | | | | | Control group | MS patients | OR | $CI_{OR}$ | $P_{Bonf}$ |
|---|---|---|---|---|---|---|---|---|---|
| *IL7R* rs10624573 | *IL7R* rs1494558 | *IL2* rs2069772 | *IL2RA* rs1570538 | *IL2RA* rs12722580 | | | | | |
| D/D | | | | D/D | 2.56 | 7.75 | 3.20 | 1.76–5.81 | 0.005 |
| I/I | | G | | | 5.75 | 13.54 | 2.57 | 1.63–4.04 | 0.002 |
| D | T | | C | | 39.51 | 54.11 | 1.81 | 1.39–2.35 | $7.1 \times 10^{-4}$ |
| D/D | T | | | | 54.62 | 66.97 | 1.68 | 1.31–2.17 | 0.003 |
| | T | G | | | 26.69 | 37.66 | 1.66 | 1.27–2.16 | 0.012 |
| | T | | C | | 45.82 | 57.51 | 1.60 | 1.24–2.06 | 0.019 |
| | C | | | I | 77.88 | 66.25 | 0.56 | 0.42–0.74 | 0.003 |

rs1570538 polymorphism was in linkage disequilibrium with rs6602364; notably, *IL2RA* rs1570538*C allele, which was part of the combinations associated with an increased risk of MS in our study, was correlated with *IL2RA* rs6602364*G allele, which was previously reported to have an association with atopic dermatitis [38].

As a result of our study, we discovered the association between MS and the *IL7R* rs10624573 allelic variant, and confirmed the association between MS and the *IL7R* rs1494558 allelic variant. In addition, multilocus association analysis using the APSampler algorithm allowed us to detect the association with MS of the alleles and/or genotypes of the polymorphic variants in *IL2* and *IL2RA* genes that was not identified during individual analysis.

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## COMPLIANCE WITH ETHICAL STANDARDS

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

*Statement of compliance with standards of research involving humans as subjects*. The study was performed in accordance with the ethical principles of medical research involving human subjects enshrined in the Declaration of Helsinki (2013). Written informed voluntary consent was obtained from each study participant.

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