

RESEARCH ARTICLE

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A Study on the Association of Ccr12 Atypical Chemokine Receptor Polymorphism with the Disease Progression of Multiple Sclerosis in Turkish Patients: Insights From a Negative Study

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a multifactorial disease resulting from the interaction of genetic and environmental factors. Although several genetic polymorphisms have been associated with MS pathogenesis, the role of atypical chemokine receptors (ACKRs) remains insufficiently elucidated. Experimental studies suggest that CCRL2, an ACKR, may play a role in the chronic phase of the disease. This study aimed to investigate whether the CCRL2 F167Y polymorphism is associated with MS susceptibility, age at disease onset, and disease severity.

Methods: A total of 134 patients with MS, diagnosed according to the 2017 McDonald criteria, and 44 healthy controls were included. The CCRL2 F167Y (rs3204849) polymorphism was analyzed using the PCR-

RFLP method. Genotype and allele frequencies and their associations with clinical parameters were evaluated using appropriate statistical analyses.

Results: No significant differences in genotype or allele distributions were observed between patients and controls. The F167Y polymorphism was not associated with MS susceptibility, age at onset, or EDSS scores.

Conclusion: The CCRL2 F167Y polymorphism is not associated with MS pathogenesis or disease severity in the Turkish population. However, the present findings need to be confirmed and reinforced in future studies using large-scale populations with different ethnicities.

Keywords: CCRL2, multiple sclerosis, polymorphism, ACKR, F167Y

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INTRODUCTION

Evidence is mounting that multiple sclerosis (MS) is immunologically induced in genetically susceptible individuals through a combination of environmental factors (1–4). As a complex disease, MS susceptibility is conferred by multiple genes, which influence not only the susceptibility to MS but also its clinical course and severity. Over the past decade, multiple genetic factors have gradually emerged from genome-wide and targeted studies. Besides the strongest associations lying within the major histocompatibility complex (MHC), more than 200 risk loci in the autosomal non-MHC genome have been identified as contributing to MS disease susceptibility and progression, with most predicted to shape the immune system (2, 5–9). In this context, genes that influence specific components of the immune system are attractive candidates for identifying the susceptibility loci of MS.

The infiltration of leukocytes into the central nervous system (CNS) is an essential step in the neuropathogenesis of MS, controlled by chemokines and their receptors. In humans, chemokine receptors are classified into two main groups: the conventional G protein-coupled chemotactic chemokine receptors (cCKRs), which induce cell migration after binding

their cognate chemokine ligand, and the atypical G protein-uncoupled chemokine receptors (ACKRs), which scavenge, sequester, or transport chemokines to control cCKR-driven responses (10–12). Although a large number of studies have shown the association of the cCKR family with the development of MS, only a few studies have evaluated the involvement of ACKRs in MS pathogenesis. C-C motif chemokine receptor-like 2 (CCRL2) is one of the recently defined members of the ACKR family (13, 14). CCRL2 is encoded on chromosome 3p21 along with several other chemokine genes. The F167Y polymorphism is believed to affect the binding and internalization capacity of CCRL2 ligands such as chemerin and CCL19 (15). Based on the accumulation of new evidence supporting the importance of CCRL2 for autoimmune diseases, primarily from experiments performed in mouse models (16, 17), we hypothesized that elevated levels of CCL19 and chemerin in individuals carrying the single nucleotide polymorphism encoding CCRL2 F167Y could be associated with increased susceptibility to or progression of MS. In this study, we investigated the association of the CCRL2 F167Y polymorphism in a Turkish MS cohort through their correlations with different demographic and clinical parameters.

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Highlights

- CCRL2 F167Y polymorphism is not associated with MS susceptibility.
- The F167Y variant shows no association with age at onset or EDSS scores.
- This study provides population-based data on ACKRs in Turkish MS patients.
- Findings highlight discrepancies between experimental models and human data.

METHODS

The study was approved by Hacettepe University local ethics committee (approval no.: GO 15/178). The study was conducted according to the Declaration of Helsinki Principles, and all of the participants signed an informed consent form before enrolment in the study.

Study participants

All MS patients were enrolled in the Department of Neurology, Hacettepe University Faculty of Medicine, from April 2015 to April 2019. All of the patients received physical and neurological examinations to determine disease types and Expanded Disability Status Scale (EDSS) scores. A total of 134 patients who met the definitive multiple sclerosis diagnosis criteria, as specified in the International 2017 McDonald Criteria were diagnosed with RRMS, PPMS, and SPMS. Furthermore, 44 age-matched healthy volunteers with no history of neurological or immunological diseases were included in the study.

PCR-RFLP

Whole blood samples were collected from participants in accordance with the relevant guidelines and regulations. Genomic DNA (gDNA) was isolated from the samples using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) following the manufacturer's instructions. CCRL2 gene polymorphism was analyzed by the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. Firstly, the extracted gDNA was amplified using primers targeting CCRL2 with the following primers: forward, 5' tcccggttgcttcagacgct reverse, 5' acaagtggtaggaggcgaaggag. The resulting PCR product (2076 base pairs, bp) was treated with EcoRI restriction enzyme. PCR-RFLP products were separated on 1% agarose gel electrophoresis and visualized under UV light using the Gel Logic 1500 imaging system (Rochester, NY, USA). If the T allele (F167-CCRL2) was present, the EcoRI enzyme cut the PCR product into 745 bp and 1331 bp fragments. If the A allele was present, no cutting occurred, indicating the presence of the A allele (Y167-CCRL2). In cases of heterozygosity, fragments corresponding to both alleles were observed. Representative gel images are presented in supplementary Figure 1.

Supplementary Figure 1: Representative gel electrophoresis images showing the digestion patterns of the CCRL2 gene PCR products with the EcoRI enzyme. Lane 1 shows the PCR product without EcoRI digestion, indicating the presence of the A allele (Y167-CCRL2), resulting in a single band of 2076 bp. Lane 2 displays the digestion pattern for a sample homozygous for the T allele (F167-CCRL2), with two bands at 745 bp and 1331 bp. Lane 3 represents a heterozygous sample, exhibiting three bands corresponding to 745 bp, 1331 bp, and 2076 bp.

Statistical analysis

Descriptive statistics summarized the baseline characteristics of the study population, with continuous variables as means \pm standard deviations

(SD) and categorical variables as frequencies (%). The median Expanded Disability Status Scale (EDSS) scores were also reported. Genotype and allele frequencies for the CCRL2 polymorphism were calculated and compared between MS patients and controls using the chi-square (χ^2) test. Hardy-Weinberg equilibrium (HWE) was assessed for both groups. Comparisons of allele frequencies between groups used the chi-square test. One-way ANOVA tested the relationship between genotype and age at disease onset. Linear regression analyzed the association between allele status and age at onset. Logistic regression evaluated the impact of the F167Y polymorphism on MS susceptibility, with results as odds ratios (OR) and 95% confidence intervals (CI). Linear regression assessed the effect on disease severity (EDSS scores). All analyses were performed using SPSS software version 25, with a significance threshold of $p < 0.05$.

RESULTS

Baseline features of the study population

We enrolled a total of 134 patients, comprising 94 females and 40 males (Table 1). Among these patients, 17 of them were newly diagnosed with multiple sclerosis (MS). The mean age of the cohort was 41.57 ± 8.81 years. The average age at disease onset was 27.44 ± 8.50 years, and the mean disease duration was 14.43 ± 5.43 years. The mean age of the newly diagnosed group was 30 ± 9.67 years. The overall median Expanded Disability Status Scale (EDSS) score was 5.0 (range: 0.0–8.0), whereas in the newly diagnosed group, it was 1.0 (range: 1.0–4.0).

Table 1. Demographic variables

All patients (n=134)	
Female: Male (%)	94 : 40 (70.1: 29.9)
Age \pm SD	41.57 \pm 8.81
Age at onset \pm SD	27.44 \pm 8.5
Disease duration (year) \pm SD	14.43 \pm 5.43
EDSS (min - max)	5.0 (0-8.0)
Newly diagnosed patients (n=17)	
Female: Male (%)	12: 5 (70.6: 29.4)
Age \pm SD	30 \pm 9.67
EDSS (min - max)	1.0 (1.0- 4.0)

EDSS: Expanded disability status scale; SD: Standard deviation; min: minimum; max: maximum

Genotype and allele frequencies of the CCRL2

The frequencies of the investigated genotypes in the studied population are presented in Table 2. Our PCR-RFLP analyses showed that 48 patients (35.8%) and 11 controls (25%) had homozygous AA alleles. The AT allele frequency was 41.8% (n=56) among patients and 52.3% (n=23) among controls. The TT allele frequency was 22.4% (n=30) in patients and 22.7% (n=10) in controls. There was no significant difference in allele distribution between patients and controls ($p=0.369$). The age at disease onset was similar across different alleles: AA allele (26.28 ± 9.02 years), TT allele (28.00 ± 9.23 years), and AT allele (27.80 ± 7.65 years), with a p -value of 0.731. The allele status did not have an effect on disease onset ($p=0.491$; 95% CI: -0.961 – 1.984).

Table 2. Y167F Allele frequencies in MS patients and controls

Y167F	MS (n=134)	Control (n=44)	Total (n=178)	p
AA	48 (35.8%)	11(25.0%)	59(33.1%)	
AT	56 (41.8%)	23 (52.3%)	79 (44.4%)	
TT	30 (22.4%)	10 (22.7%)	40 (22.5%)	0.369
A	152 (56.7%)	45 (51.1%)	197 (55.3%)	
T	116 (43.3%)	43 (48.9%)	159 (44.7%)	0.388

In both MS patients and controls, the calculated X^2 values were less than the critical value, indicating that the observed genotype frequencies are consistent with Hardy-Weinberg equilibrium (HWE) ($p > 0.05$) in both groups. These results suggest that the F167Y polymorphism is in HWE in both our MS patient cohort and the control group, supporting the validity of our genetic analyses (Supplementary Table 1).

In our regression analysis evaluating the impact of the F167Y polymorphism on MS status, we found no evidence of the alleles influencing disease susceptibility ($p=0.162$; 95% CI: 0.503 - 1.122). Additionally, when assessing the effect of these alleles on disease severity, as measured by EDSS scores, we observed no association with disease progression ($p=0.702$; 95% CI: -0.779 - 0.528) (Table 3,4).

Table 3. Analysis of Y167F Alleles on MS Status

	Coefficient	95% CI		p	SE
Y167F allele	0.751	0.503	1.122	0.162	0.205
Constant	5.660			0.000	0.487

Cox & Snell R2 = 0.011 Nagelkerke R2= 0.017 CI: Confidence interval SE: Standard error

Table 4. Analysis of Y167F Alleles and Disease Duration on EDSS Scores

EDSS	Coefficient	95% CI		t	p	Zero-order	Partial
(Constant)	3.052	0.923	5.181	2.863	0.006		
Y167F allele	-0.126	-0.779	0.528	-0.384	0.702	-0.055	-0.048
Disease duration	0.127	0.024	0.230	2.465	0.016	0.296	0.295

F= 3.147 Adj. R²= 0.061 p=0.050 SE=2.271; CI: Confidence interval SE: Standard error

DISCUSSION

The pathophysiology of multiple sclerosis (MS) has been linked to various genetic predispositions, with certain genetic polymorphisms associated with chemokines or chemokine receptors playing a significant role. While CCRL2 polymorphisms have garnered attention in the area of infectious diseases, inflammatory conditions, and tumors, their potential implications in MS have yet to be extensively investigated (15, 18-21).

The role of atypical chemokine receptors, including CCRL2, has been studied in several experimental models of multiple sclerosis (MS), highlighting their diverse yet complementary roles in the immune dynamics of autoimmune neuroinflammation. For example, ACKR1 has been shown to regulate transcellular T-cell migration across the blood-brain barrier (BBB), with its upregulation in brain microvascular and CNS venular endothelial cells during experimental autoimmune encephalomyelitis (EAE) enhancing chemokine shuttling and contributing to neuroinflammation (22). Similarly, CCRL2 has been implicated in modulating neuroinflammation through its effects on microglial and macrophage activation. In CCRL2-deficient mice, an altered M1 (proinflammatory) to M2 (anti-inflammatory) balance was observed during the recovery phase of EAE, suggesting that CCRL2 plays a critical role in regulating the resolution of inflammation and influencing disease outcomes (17).

The role of atypical chemokine receptors, including CCRL2, has been studied in several experimental models of multiple sclerosis (MS). In a study exploring the roles of atypical chemokine receptors in T-cell diapedesis across the blood-brain barrier, atypical chemokine receptor 1 (ACKR1) emerged as a key regulator of transcellular T-cell migration.

During EAE, its upregulation in primary mouse brain microvascular endothelial cells and CNS venular endothelial cells was found to enhance chemokine shuttling across the BBB, thereby promoting autoimmune neuroinflammation (22). In a study specifically focused on CCRL2 on EAE models on CCRL2 deficient mice also showed a modulatory effect on neuroinflammation mainly affecting the microglial and macrophage activation processes. CCRL2 knock-out mice show altered macrophage/microglia M1(proinflammatory)/M2 (antiinflammatory) balance during the EAE recovery phase

Notably, a study by Mazzon et al. demonstrated that CCRL2-deficient mice developed a more severe form of the disease. This was associated with an imbalance in microglial and macrophage activation processes, highlighting the importance of CCRL2 in modulating neuroinflammatory responses (17).

The 167F allele has been identified as being associated with AIDS-defining conditions. Additionally, individuals carrying the 167F allele tend to progress through *Pneumocystis carinii* pneumonia faster. However, it's worth noting that in this study, the F167Y allele types did not demonstrate a significant effect on the progression of Kaposi's sarcoma, *Mycobacterium avium* complex infection, cytomegalovirus infection, or lymphoma. It is hypothesized that the substitution of the nonpolar amino acid phenylalanine (F) with the polar tyrosine (Y) alters the structure of the transmembrane domain and adjacent domains. This alteration is believed to influence the receptor responses (15). In this study, our aim was to investigate the effects of the F167Y polymorphism on MS patients. Within our cohort, we observed that MS patients exhibited similar F167Y polymorphisms compared to the healthy control group. Furthermore, the allele type did not impact the severity of MS or the age of disease onset. Additionally, CCRL2 expression levels were similar between MS patients and healthy controls.

In clinical settings, CCRL2 has been observed to be selectively expressed in tumor-associated macrophages (TAM) of cancer patients, including those with melanoma, liver, bladder, and lung cancer. Additionally, this study underscores that in the gene expression profiles of melanoma patients, CD8+ T cells exhibit elevated CCRL2 expression compared to other T cell types, where expression levels are not significant. Notably, higher levels of CCRL2 expression in melanoma patients have been associated with improved survival rates (20). Similarly, CCRL2 is constitutively expressed in breast cancer cells, with increased levels in immune-infiltrated tumors, and is upregulated by pro-inflammatory cytokines, especially IFN- γ (23). Although our study did not specifically target activation markers or assess the genetic expression of CCRL2 on specific cells, our findings indicated no significant differences in CCRL2 expression levels between MS patients and controls.

This study faced several limitations. Firstly, the mean EDSS score of the group was high. With a broader range of MS patients, the impact of this polymorphism might be more accurately assessed. Additionally, evaluating chemerin and CCL19 levels using a sensitive method could provide further insights. Considering the polymorphisms of interacting molecules such as CMKLR1 and CXCR2 could also offer a more comprehensive understanding of the disease mechanism. Finally, while our study was limited to the Turkish population, and the results may not be generalizable to other populations.

To conclude, in this study, we found no significant differences in CCRL2 polymorphism between patients and controls. Additionally, the CCRL2 F167Y polymorphism showed no notable effect on disease severity. Given the intricate mechanism of action of the CCRL2 receptor and the dynamic nature of the innate immune system, further research focusing on both CCRL2 and other atypical chemokine receptors in the context of

MS could provide valuable insights into their potential contributions to disease susceptibility, severity, and treatment response.

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Ethics Committee Approval: The study was approved by Hacettepe University local ethics committee (approval no.: GO 15/178).

Informed Consent: All of the participants signed an informed consent form before enrolment in the study.

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Author Contributions: Concept- NPAÖ, UH, AT; Design- NPAÖ, UH, AT; Supervision- NPAÖ, RK, AT; Resource- AT; Materials- NPAÖ, UH; Data Collection and/or Processing- NPAÖ, UH; Analysis and/or Interpretation- NPAÖ, UH, AT, RK; Literature Search- NPAÖ, UH; Writing- NPAÖ, UH; Critical Reviews- UH, AT, RK.

Conflict of Interest: The authors declared that there is no conflict of interest.

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SUPPLEMENTARY MATERIALS

https://www.noropsikiyatriarsivi.com/uploads/NPA_28943_EN_SUPPL.pdf

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