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RESEARCH ARTICLE



# Determination of *SIRT7, SEMA3A, SEMA3F* Gene Expressions in Patients with Multiple Sclerosis

Feti Cetin[1], Yigit Can Guldiken[2], Kursat Kargun[3], Caner Feyzi Demir[4]

[1]Tunceli State Hospital, Clinic of Neurology, Tunceli, Turkey

[2]Bahcesehir University, Goztepe Medical Park Hospital, Clinic of Neurology, Istanbul, Turkey

[3]Firat University, Vocational School of Health Services, Department of Medical Laboratory, Elazig, Turkey

[4]Firat University Faculty of Medicine, Department of Neurology, Elazig, Turkey

## Abstract

**Objective:** In this study, we aimed to analyze the expression levels of specific genes that may contribute to the pathogenesis of multiple sclerosis (MS) in patients and explore the applicability of biomarkers. These biomarkers could serve as valuable diagnostic and prognostic tools, contributing to a better understanding of disease etiology, facilitating disease monitoring, and evaluating treatment efficacy.

**Materials and Methods:** We analyzed the expression levels of *SIRT7, SEMA3A,* and *SEMA3F* genes using samples obtained from both MS patients and healthy controls.

**Results:** Our research findings suggest that these genes have increased expression in the specific tissues of patients with MS, with blood samples showing the most pronounced increase in their expression levels.

**Conclusion:** Although these increases were not statistically significant, our study provides valuable insights for further research on gene expression in MS patients. This study demonstrates that potential biomarkers are essential in comprehending the molecular basis of MS. Additional research is needed to substantiate the findings presented in our study and enhance our understanding of the role of genes in the pathogenesis of MS.

**Keywords:** Multiple sclerosis, *SIRT7, SEMA3A, SEMA3F*

## Introduction

Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system, marked by inflammation, demyelination, and axon damage. Damage occurs to the myelin sheaths, oligodendrocytes, and, to a lesser degree, the axons and nerve cells. The disease commonly manifests in young adults, with a prevalence ranging from 2 to 200 per 100,000 based on geographic location (1). The incidence of MS is 2-3 times higher in female patients than in male patients.

The exact cause of MS remains unknown (source). However, it is widely believed that genetic and environmental risk factors interact in a complex inheritance pattern. This disease is the leading cause of disability among non-traumatic neurological conditions in young adults. MS, defined as a chronic, neuroinflammatory, neurodegenerative disease, encompasses diverse clinical subtypes with complex pathogenesis and distinct prognoses (1). It is crucial to comprehend the molecular and chemical structure of *SIRT* genes to analyze their biological role, given the positive outcomes of recent studies in treating various health issues (2).

Sirtuins, a protein family involved in protein deacetylase and adenosine diphosphate-ribosyl transferase activities, were initially detected in yeast. Thus far, mammalian cells have been found to possess seven isoforms of sirtuins, namely *SIRT 1-7*. While *SIRT1* is located in both the cytoplasm and nucleus, *SIRT6* and *SIRT7* are strictly nuclear, and *SIRT3*, *SIRT4*, and *SIRT5* are

**Address for Correspondence:** Feti Cetin, Tunceli State Hospital, Clinic of Neurology, Tunceli, Turkey
**E-mail:** doctor144@hotmail.com **ORCID-ID:** orcid.org/0009-0007-9817-9094
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confined to the mitochondria (3). These proteins are involved in numerous cellular functions, such as transcription, aging, inflammation, and apoptosis (4).

Recent studies suggest that *SIRT7* is involved in ribosome biogenesis, particularly in dividing cells, and may have implications for the development of thyroid and breast cancer (5). The *SIRT7* gene, which we intend to study, is located on chromosome 17q25.3 (6). It encodes a protein that belongs to class IV of the sirtuin family, homologous to yeast Sir2 protein (7). Similar to yeast sirtuin proteins, *SIRT7* is also involved in regulating epigenetic gene silencing and suppressing rDNA recombination.

*SIRT7* expression is higher in metabolically active tissues, such as the liver and spleen, and lower in non-proliferating tissues, such as the heart and brain (8). The mammalian homolog of Sir2, *SIRT7*, serves as an activator of RNA polymerase I transcription (9).

Semaphorins were initially discovered in invertebrates in 1992 (10). Semaphorin 3A (*SEMA3A*) is the first member of this family identified in vertebrates and was initially isolated from extracts of poultry brains in 1993.

The *SEMA3A* gene is located on chromosome 7q21.11 (11), while *SEMA3F* is located on chromosome 3p21.3 (12). *SEMA3F* is regarded as a potential tumor suppressor gene (13). Both *SEMA3A* and *SEMA3F* are recognized for their significant involvement in directing certain CNS pathways and peripheral nerves during the development of the nervous system. In this study, our objective was to examine the expression levels *of SIRT7*, *SEMA3A*, and *SEMA3F* in the gene regions associated with RNAs (*SIRT7*, *SEMA3A*, *SEMA3F*) extracted from the CSF and blood of newly diagnosed, drug-free patients with MS and individuals in the control group. This investigation aims to reveal the correlation between these molecular changes and MS while offering guidance for future studies.

## Materials and Methods

The study was conducted at T.C. Firat University Faculty of Medicine (approved by Firat University Medical Research Ethics Committee with decision number 14 dated 26.10.2017 and session number 2020/03-18 dated 02.06.2020) by the Helsinki Declaration rules.

A total of 59 individuals participated in the study conducted at the Department of Neurology at Firat University Faculty of Medicine. The patient group comprised 31 newly diagnosed individuals with relapsing-remitting MS (RRMS) who met the revised McDonald 2017 criteria, while the control group consisted of 28 individuals diagnosed with benign intracranial hypertension.

All participants in both the patient and control groups were given comprehensive details about the informed consent form, and written consent was obtained from each participant. The study was performed by the principles of the ethics committee.

A total of 5 mL of CSF and 2 mL of blood samples were collected from individuals in an ethylenediamine tetraacetic acid tube and subjected to further analysis at the Molecular Genetics Laboratory of the Faculty of Health Sciences at Firat University. The CSF was obtained from 16 patients with MS and 14 controls diagnosed with benign intracranial hypertension. Blood samples were collected from 15 patients diagnosed with MS and 14 patients in the control group diagnosed with benign intracranial hypertension. However, no serological or CSF indices of inflammation were detected in the control group diagnosed with intracranial hypertension.

We isolated RNA from both CSF and total blood using the EXTRACTME Total RNA Kit (BLIRT, EM09.1). We assessed the quality and quantity of the isolated RNA samples in our study using a Nanodrop device, evaluating their suitability for expression analysis. The RNA samples were stored at -20 ºC until the analysis of RNA expression. The high-capacity cDNA Synthesis Kit (WIZ Biosolutions, W2211) was utilized to synthesize cDNA from RNA.

Gene Expression Assay (GENEX-250, Suarge Biyoteknoloji, Turkey) was used to prepare quantitative polymerase chain reaction (PCR) experiments with Forward and Reverse Primers specific for *SIRT7*, *SEMA3A*, and *SEMA3F* genes while adhering to the AMPLIFYME SYBR Universal Mix (AM02, BLIRT, Poland) protocol. Finally, RNA expression levels were quantified using the StepOnePlus Real-Time PCR System (ThermoFisher Scientific, USA). RNA expression levels were determined using the ΔΔCt method normalized with ACTB as an endogenous control.

### Statistical Analysis

The gene expression scores were analyzed using SPSS for Windows (version 21). The results were presented as mean ± standard deviation (SD). Analysis of variance was conducted to determine differences between the groups. The $RT^2$ Profiler Data Analysis Software, provided by Qiagen, was used for the analyses, with 2'Average delta CT values utilized. The 2-ΔΔCt method was employed for relative gene expression. The result was considered statistically significant if the p-value was <0.05.

## Results

In this study, the patient group consisted of individuals diagnosed with MS and controls without MS. Total RNA was extracted from CSF and blood samples of these individuals, and gene expression levels for *ACTB*, *SEMA3A*, *SEMA3F*, and *SIRT7* were examined. A total of 59 participants were included in the study group, consisting of 31 patients and 28 controls. CSF

samples were obtained from 16 out of the 31 patients, while blood samples were obtained from the remaining 15 patients. Meanwhile, CSF samples were collected from 14 individuals in the control group, and blood samples were collected from the remaining 14 individuals. No additional subjective assessments were conducted in this section.

The age of the 31 patients ranged from 16 to 50 years with a mean age of 31.19 years (SD: 2.16). The gender distribution was four male and 27 female patients. The age of the 28 patients in the control group ranged from 19 to 82 years with a mean age of 50.17 years (SD: 2.16). The distribution included nine male and 19 female patients.

Table 1 summarizes the general characteristics of the patient and control groups based on CSF samples, while Table 2 summarizes the general characteristics based on blood samples. The comparison of CSF samples from patients and controls is presented in Table 3, and the results are shown in Figure 1. Abbreviations are explained upon first use.

**Table 1. General characteristics of CSF sample**

| | Patient (16) | Control (14) |
|---|---|---|
| Age | 31.62 (19-43) | 44 (19-82) |
| Male | 1 (6%) | 4 (29%) |
| Female | 15 (94%) | 10 (71%) |

CSF: Cerebrospinal fluid

**Table 2. General characteristics of blood sample**

| | Patient (16) | Control (14) |
|---|---|---|
| Age | 30.73 (16-50) | 56.35 (25-82) |
| Male | 3 (20%) | 5 (36%) |
| Female | 12 (80%) | 9 (64%) |

**Table 3. Comparison of patient and control CSF samples**

| Gene | Control | Patient | |
|---|---|---|---|
| | 2^[-Avg. Delta (Ct)] | 2^[-Avg. Delta (Ct)] | Fold change |
| SEMA3A | 0 | -5,1818 | 36,299^ |
| SEMA3F | 0 | -4,1698 | 17,998^ |
| SIRT7 | 0 | -2,3189 | 4,989^ |

CSF: Cerebrospinal fluid, Avg.: Average

**Table 4. Comparison of *SEMA3A, SEMA3F,* and *SIRT7* in patient and control blood samples**

| Gene | Control | Patient | |
|---|---|---|---|
| | 2^[-Avg. Delta (Ct)] | 2^[-Avg. Delta (Ct)] | Fold change |
| SEMA3A | -7,2456 | –7,3374 | 161,735^ |
| SEMA3F | -7,7314 | –6,1099 | 69,068^ |
| SIRT7 | 0,7535 | –0,8987 | 1,864^ |

Avg.: Average

The results show a significant increase in *SEMA3A* (36-fold), *SEMA3F* (17-fold), and *SIRT7* (5-fold) (upregulation) in the patient group when comparing the levels of *SEMA3A*, *SEMA3F*, and *SIRT7* in the CSF samples with those of the control group. The results of the *SEMA3A*, *SEMA3F*, and *SIRT7* comparison between patient and control blood samples are shown in Table 4. Meanwhile, Figure 2 shows the gene expression comparison of *SEMA3A*, *SEMA3F*, and *SIRT7* in patient and control blood samples.

*SEMA3A* was upregulated 151-fold in the control group and 161-fold in the patient group. *SEMA3F* increased 212-fold in the control group and 69-fold in the patient group (downregulation). *SIRT7* increased 0.59-fold in the control group and 1.86-fold in the patient group (upregulation).

## Discussion

MS is a chronic, usually progressive disease characterized clinically by focal deterioration of the optic nerve, spinal cord, and brain, with varying degrees of improvement and relapse over the years. Typical features of MS include muscle weakness, paraparesis, paresthesias, visual loss, diplopia, nystagmus, dysarthria, tremor, ataxia, paresthesias, and bladder dysfunction.

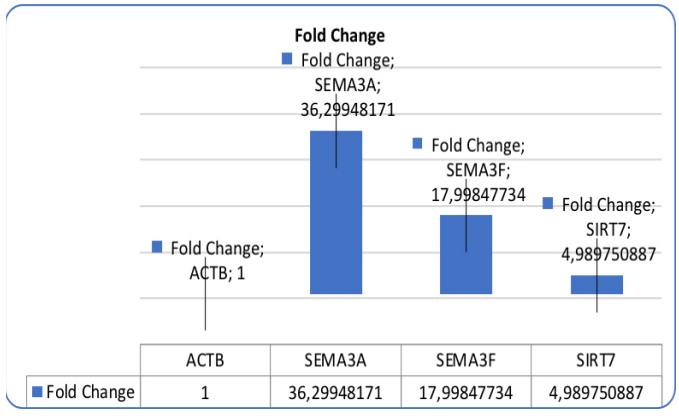


**Figure 1.** Comparison of patient and control CSF samples
CSF: Cerebrospinal fluid

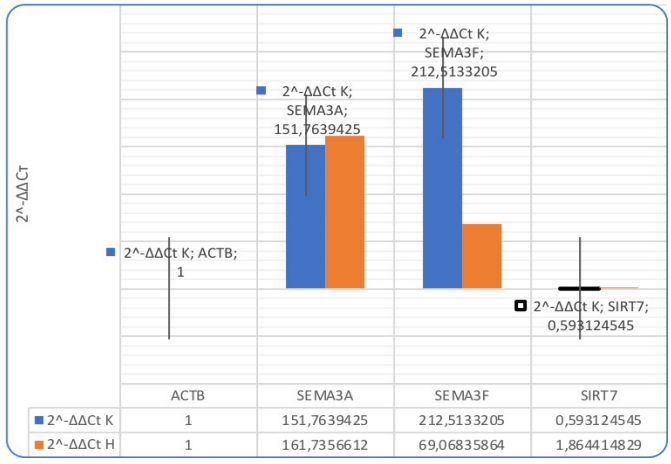


**Figure 2.** Comparison of patient and control blood sample

The disease is characterized by inflammation, demyelination, and axonal damage in the CNS. MS can be diagnosed both clinically and histopathologically (14). Clinical symptoms vary according to the location of the lesions and are often associated with the invasion of inflammatory cells across the blood-brain barrier, resulting in demyelination and edema (15).

The incidence of MS is 2-3 times higher in women than in men, although the exact cause is unknown, and the disease is typically observed in young individuals (16,17). However, it has been hypothesized that women are generally more susceptible to autoimmune and inflammatory diseases (18). In our study, the female-to-male ratio was also high (male/female: 4/27). The mean age of the patients was 31.19 years (16-50). MS results from a combination of both genetic predisposition and environmental factors. In other words, it is a multifactorial disease.

The objective of our study was to investigate the contribution of *SIRT7*, *SEMA3A*, and *SEMA3F* gene expression levels in CSF and blood samples of patients with MS to the pathogenesis of the disease. Magnetic resonance imaging is presently employed in the diagnostic criteria (19). Meeting these criteria can be challenging sometimes. Molecular biomarkers may help confirm the diagnosis, assess disease progression, and evaluate the efficacy of treatment (20).

The function of the sirtuin gene family is mostly related to protein acylation. Protein acylation is a post-translational modification that alters the surface charge of proteins, regulating protein conformation or protein-protein interactions, similar to phosphorylation. The implication of sirtuin genes in diabetes, metabolic syndrome, cancer, inflammation, neurodegenerative diseases, and similar chronic conditions has prompted extensive study of this gene family in these areas (21).

*SIRT7* is the most enigmatic of the sirtuin isoforms. It is localized in the nucleolus and appears to be involved in the regulation of ribosomal gene expression via RNA polymerase-1, cell proliferation, and ribosome synthesis. *SIRT7* also protects cells under stress, such as endoplasmic reticulum stress, genotoxic stress, and oxidative stress induced by unfolded proteins (22). *SIRT7* is less abundant in the heart, brain, and skeletal muscle, whereas it is more abundant in proliferative tissues, such as the testis, spleen, and liver (23). However, information regarding its role in the CNS is limited. *SIRT7* gene expression is reduced in aged human stem cells, which are characterized by increased apoptosis. Decreased *SIRT7* gene expression is associated with various diseases, apoptosis, and increased DNA damage (24).

In our study, when comparing *SIRT7* gene expression levels in blood samples from the patient and control groups, a 1.86-fold increase was observed in the patient group (upregulated) (Table 4). Similarly, when comparing CSF samples from the patient and control groups, a 5-fold increase in *SIRT7* gene expression was observed in the patient group (upregulated) (Table 3). Although these increases were not statistically significant as $p>0.05$, further studies will provide a better understanding of this upregulation.

Semaphorins are the major oligodendrocyte progenitor cell (OPC) guidance molecules. Two members of the semaphorin family, *SEMA3A* and *SEMA3F*, have been shown to play important roles in OPC migration (25). Their expression varies depending on the lesion type and the degree of inflammation. In active lesions (ongoing remyelination and more inflammation) the chemoattractant *SEMA3F* is more abundant than *SEMA3A*. Conversely, in chronic lesions (less inflammation and less remyelination) the chemorepellent *SEMA3A* is more abundant than *SEMA3F* (26).

*SEMA3A* induces a reversible dose-dependent inhibition of OPC differentiation. Therefore, overproduction of *SEMA*3A may prevent OPCs from migrating to the demyelinated area and differentiating into myelin-synthesizing oligodendrocytes. The presence of *SEMA3A* in demyelinated lesions is associated with impaired remyelination (27). In the central nervous system, inhibiting *SEMA3A* may allow OPC migration to demyelinated areas and facilitate the remyelination process. Therefore, novel approaches are needed.

Semaphorins are aberrantly expressed in central nervous system neurons during pathogenesis. For example, *SEMA3A* is expressed at the neuromuscular junction in amyotrophic lateral sclerosis and in neurons in Alzheimer's disease (28). It has been observed that *SEMA3A* and *SEMA3F* are involved in OPC migration and their expression is increased around MS lesions. The abnormal expression of *SEMA3A* in central nervous system neurons of patients with MS (29) suggests that *SEMA3A* plays a role in oligodendrocyte or axon regeneration. In this study, we aimed to elucidate the contribution of these genes to the pathogenesis of the disease by examining their expression levels in patients with MS.

In our study, we compared the expression levels of *SEMA3A* and *SEMA3F* genes in CSF samples obtained from the patient and control groups with the control group. We found a 36-fold increase for *SEMA3A* and a 17-fold increase for *SEMA3F* in the patient group (Table 3). In the blood samples obtained from the patient and control groups, *SEMA3A* and *SEMA3F* gene expression levels were found to be increased by 161-fold (upregulated) and 69-fold (down-regulated), respectively, in the patient group compared to the control group (Table 4). Comparison of *SEMA3A*, *SEMA3F*, and *SIRT7* in patient and control blood samples showed increases in up- or down-regulated levels. However, these changes were not statistically significant. This may be due to the small number of patients and controls.

One notable aspect of this study is that the increase in gene expression was more pronounced in the blood. Furthermore, it is important to substantiate this increase with larger studies. Biomarkers can be used for diagnosis, staging, prognosis, and monitoring of treatment response (30). Another requirement is easy access to the biomarker. For example, body fluids serve as the access point for MS. These fluids can be CSF, blood, urine, and tears. It may be possible to monitor disease progression by examining the expression levels of these genes in blood samples, eliminating the need for an interventional CSF sample. As MS is a multifactorial disease, it is crucial to genetically understand the pathogenesis of the disease to contribute to disease progression and treatment approaches. *SIRT7*, *SEMA3A*, and *SEMA3F* were significantly upregulated in MS patients. However, larger studies are needed to clarify the relationship between *SIRT7*, *SEMA3A*, and *SEMA3F* gene functions and MS.

### Study Limitations

This study has certain limitations. The primary constraint is within the inclusion and exclusion criteria. The inclusion criteria include a diagnosis of RRMS according to the revised McDonald 2017 criteria, the absence of any other neurological/autoimmune disease in the patient's history, and a diagnosis of benign intracranial hypertension. The exclusion criteria encompass a history of RRMS attack within the last 40 days, treatment for infection for any reason within the last 40 days, and receipt of high-dose anti-inflammatory treatment for any reason within the last 40 days.

In addition to the diagnosis of benign intracranial hypertension, the patient could have an additional disease that may be linked to the central nervous system. To overcome these limitations, examining the gene expression levels in blood samples, instead of the need to obtain CSF through interventional means, is a potential means to monitor the progression of the disease.

## Conclusion

In this study, we aimed to investigate the expressions identified in the relevant gene regions of RNAs (*SIRT7*, *SEMA3A*, and *SEMA3F*) obtained from the CSF and blood of newly diagnosed, untreated patients with MS and control group individuals. The objective was to unveil any relationship between these expression changes and MS and to guide future studies. The study yielded significant findings.

In the present study, when comparing the gene expression levels of *SEMA3A* and *SEMA3F* in CSF samples from both the patient and control groups with the control group, a 36-fold increase for *SEMA3A* and a 17-fold increase for *SEMA3F* was observed in the patient group. These findings indicate a potential involvement of *SEMA3A* and *SEMA3F* in the pathology of the disease. Gene expression levels of *SEMA3A* and *SEMA3F* were found to be upregulated 161-fold and 69-fold, respectively, in the patient group compared to the control group, as demonstrated by blood samples.

Notably, gene expression increases were more pronounced in blood, emphasizing the necessity for larger studies to substantiate these findings. It may be feasible to trace the advancement of the disease by examining the expression levels of the genes in blood samples, eliminating the necessity for intervention-based CSF sample collection from patients.

Given the complexity of MS, it is vital to elucidate its genetic pathogenesis, as this contributes to an understanding of the disease's progression and treatment methodologies. Significant upregulation of *SIRT7*, *SEMA3A*, and *SEMA3F* genes was observed in patients with MS. However, further studies are needed to elucidate the relationship between *SIRT7*, *SEMA3A*, and *SEMA3F* gene functions and MS.

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### Ethics

**Ethics Committee Approval:** The study was conducted at T.C. Firat University Faculty of Medicine (approved by Firat University Medical Research Ethics Committee with decision number 14 dated 26.10.2017 and session number 2020/03-18 dated 02.06.2020) by the Helsinki Declaration rules.

**Informed Consent:** All participants in both the patient and control groups were given comprehensive details about the informed consent form, and written consent was obtained from each participant.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: F.C., K.K., C.F.D., Concept: F.C., C.F.D., Design: F.C., C.F.D., Data Collection or Processing: F.C., K.K., Analysis or Interpretation: Y.C.G., K.K., Literature Search: F.C., Y.C.G., Writing: F.C.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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