# Association between NFKB1 (-94 ins/del ATTG) gene polymorphism and Multiple Sclerosis in the Turkish Population

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Name of the Author (s):

**Arman A[1], Erzaim N [2], Isik N [3], Saridal M [4], Hoscan AY [5] and List EO [6]**

[1]*The Department of Medical Genetics, School of Medicine, Marmara University, Istanbul/ Turkey*
[2]*The Department of Genetics and Bioengineering, Yeditepe University, Istanbul/Turkey*
[3]*The Department of Neurology, Göztepe Government Hospital, Istanbul/Turkey*
[4]*The Department of Biology, Marmara University, Istanbul/Turkey*
[5]*School of Medicine, Marmara University, Istanbul/Turkey.*
[6]*The Edison Biotechnology Institute, Ohio University, Athens, OH, USA.*

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**ABSTRACT**

Multiple sclerosis (MS) is a chronic inflammatory and an autoimmune disease affecting the central nervous system (CNS). It is suggested that the NFκB signaling pathway is involved in MS development and that NFκB is a key transcription factor involved in the regulation of immune response, apoptosis and pathology of autoimmune diseases. A recently discovered promoter polymorphism in NFKB1 (-94 insertion/deletion ATTG) gene may be associated with MS development.

The purpose of this study was to reveal the relationship between NFKB1 -94 insertion/deletion ATTG polymorphism and MS in a Turkish population.

A total of 379 patients with MS and 214 healthy individuals from the Turkish population were investigated. The promoter region of NFKB1 gene was amplified DNAs from patients and controls by specific primers and their PCR products were digested by suitable enzyme.

NFKB1 (-94 ins/del ATTG) genotype distribution showed a strong association with MS (p=0.0001), and the NFKB1 (-94 ins /del ATTG) allele frequency also showed a significant association to the disease (p = 0.011).

Our results suggested that the NFKB1 -94 ins/del ATTG gene promoter polymorphism is associated with MS in the Turkish population.

**KEYWORDS:**

Inflammation, Multiple Sclerosis, NFKB1, Polymorphism, Transcription Factors

## I. INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and autoimmune disease characterized by demyelination and axonal damage (1). There are more than 2.5 million individuals with MS worldwide and in Istanbul and Edirne, Turkey the prevalence of MS was determined to be approximately 30-100 in 100,000 individuals (2-3). The etiology of MS is unknown but multiple factors such as genetic, environment, and geography play an important role in the development of MS. Concordance rate of MS is 26% in monozygotic twins and 2.3% in dizygotic twins suggesting an important genetic contribution for MS development (4). It has been shown that the HLA-DRB1*1501 allele occurs frequently (~50%) in MS cases (5). Genome-wide association studies (GWAS) have identified IL-7R along with IL-2R as significantly linked with MS susceptibility (6). Furthermore, several genes such as IL-1B, IL-1Ra, TNFA, TNFB, CCR5, and HLA have been shown to have disease modifying effects on MS (7) and up regulation of p65 was observed in both macrophages and oligodentrocytes from active MS lesions compared to control white matter and silent MS plaques (8-9). Thus, multiple genes are thought to be associated with MS development and identification of these genes provides insight into disease development may provide targets for novel diagnostics and therapeutics.

NF□B is a key transcription factor involved in the regulation of immune response, apoptosis, and pathology of autoimmune diseases (10). Abnormalities in activation and expression of NF□B are involved in variety of human diseases such as inflammatory diseases, immune deficiencies, diabetes, cancer, and atherosclerosis (11). There are five members of the NF□B family including: NF-□B1 (p105/p50), NF-□B2 (p100/p52), RelA (p65), RelB and c-Rel. The NFKB1 gene encoding NF□B maps to chromosome 4q23-q24 and is composed of 24 exons (12). Recently, a polymorphism was identified in the promoter region of the NFKB1 gene encoding p105 and p50 subunits of NF□B. This polymorphism is located within the promoter between the AP-1 and kB binding site and appears to be involved in the transcriptional regulation of NFKB (13). More specifically, there is a -94ATTG 4 bp insert/deletion polymorphism site (correct nomenclature: c-24514-24517delATTG). The presence or absence of this polymorphism in humans can be divided into three genotypes: DD (del/del), WW (ins/ins) and heterozygous. Since NF□B is involved in immune response and since a polymorphism has recently been identified in NFKB, the currently study was designed to determine if there is an association between MS and NFKB-94ins/delATTG promoter polymorphism in the Turkish population.

## II. MATERIALS AND METHODS

Patients: In this study, 379 MS patients (122 male, 257 female) and 214 healthy controls (73 male, 141 female) were investigated. All MS patients were diagnosed according to McDonald Criteria (14). The diagnoses were done by MS Clinic of Goztepe Training Hospital Neurology Department. 214 age and gender matched healthy controls, which have no inflammatory and autoimmune diseases were included the study.

Genotyping: Genomic DNA was isolated from blood samples of 379 patients diagnosed with MS and 214 healty controls using the salting out method as previously described (15) and kept in -20˚C for future use. NFKB1 gene was amplified by polymerase chain reaction (PCR) from isolated genomic DNA using specific forward 5'-TGGGCACAAGTCGTTTATGA-3' and reverse 5'- CTGGAGCCGGTAGGGAAG-3' primers. PCR was carried out under 94°C, 3 min x 1 94°C, 30 sec, 60°C, 30 sec, 72°C, 45 sec 40 cycles; 72°C, 10 min conditions. . In order to genotype of NFKB1 gene -94 region, PCR products were digested overnight with 5u *PflMI* enzyme at 37˚C. Digested PCR products were run on a 2.5% agarose gel and genotypes were detected based on digested fragments. . The whole 285 bp PCR product that contains ins/ins allele produced 40 and 245 bp fragments after digestion. If no cleavage site was present on the PCR product, this genotype was identified as del/del and produced a unique 285 bp fragment. When both 285 and 245 bp fragments were observed, a heterozygote ins/del genotype was determined.

Ethics Approval: Marmara University Ethics Committee in Turkey permitted this research. All rights of human subject were protected and any required approval was secured from the ethics committee. All procedures were carried out with the adequate understanding and written consent of the subjects.

## III. STATISTICAL ANALYSIS and GRAPHICAL PRESENTATION

Genotype distributions and allele frequencies among cases and controls were compared and p value was calculated with $x^2$–analysis. The association between disease and genotypes has been shown by Odds Ratio (OR) and 95% Confidence Interval (CI). For comparison of the age of disease onset Mann-Whitney U test was used. Probability of values of $p<0.05$ (2-sided) was considered statistically significant. SPSS 17.0 software program was used for all statistical analysis.

**Table 1:**

| **A) Age and gender distribution of MS patients and controls** | | |
|---|---|---|
| Age and gender | Controls (*n* = 214) | MS (*n* =379) |
| age (years ± sd) | 55,2± 10,8 | 54,1± 11,6 |
| gender | | |
| male | 73 (% 34,1) | 122 (32,1%) |
| female | 141 (% 65,8) | 257 (67,8%) |
| **B) Primers Sets Used For Genotyping** | | |
| PCR primers / Additional treatment | | polymorphism |
| F: 5'-TGGGCACAAGTCGTTTATGA-3' | | NFKB -94ins/delATTG |
| R: 5'- CTGGAGCCGGTAGGGAAG-3' | | |
| *PflMI* digestion | | |

**Table 2 Genotype distribution and allele frequency of the NFkB (-94 ins/delATTG) polymorphisms in MS and control groups in Turkish Population**

| | NFKB Genotypes | | | TOTAL | MS vs Control |
|---|---|---|---|---|---|
| | ins/ins | ins/del | del/del | | |
| **Control** | 39 (18,2 %) | 163 76,2%) | 12 (5,6 %) | 214 (100 %) | *p=0.001* |
| **MS** | 149 (39,3) | 187 (49,3%) | 43 (11,3%) | 379 (100%) | |
| | **NFKB Alleles** | | | | |
| | **ins** | **del** | **TOTAL** | **MS vs Controls** | |
| **Control** | 241 (56,3%) | 187 (43,7 %) | 428 (100 %) | *p=0.01* | |
| **MS** | 485(63,9) | 273 (36%) | 758 (100 %) | | |

Genotypes are expressed as number of patients (proportion in % within brackets), p values are from Chi-Square exact test. P < 0.05 was taken as the level of significance.

**Table 3: Comparisions of NFkB (-94 ins/delATTG) genotypes and MS age at onset**

| | NFKB Genotypes | | | | Early vs Late |
|---|---|---|---|---|---|
| | ins/ins | ins/del | del/del | TOTAL | |
| **Early age onset** | 92 (39,1 %) | 118 (50,2 %) | 25 (10,6 %) | 235 (100 %) | *p=0.825* |
| **Late age onset** | 57 (39,6 %) | 69 (47,9 %) | 18 (12,5 %) | 144 (100 %) | |
| | **NFKB Alleles** | | | **Early vs Late** | |
| | **ins** | **del** | **TOTAL** | | |
| **Early age onset** | 302 (64,3 %) | 168 (35,7) | 470 (100 %) | *p=0.9* | |
| **Late age onset** | 183 (63,5 %) | 105 (36,5 %) | 288 (100 %) | | |

Genotypes are expressed as number of patients (proportion in % within brackets), p values are from Chi-Square exact test. P < 0.05 was taken as the level of significance.

## IV. RESULTS

The NFKB -94ins/delATTG polymorphism was genotyped in 379 MS patients and 214 control groups. Age and gender distributions of MS and control groups as well as primer sets for genotyping are shown in Table 1. Observed genotype frequencies did not deviate from the Hardy-Weinberg equilibrium. The genotype distribution and allele frequency of NFKB -94ins/delATTG polymorphism are shown in Table 2. Significant association for genotype distribution of NFKB -94ins/delATTG polymorphism was seen between MS and control group ((p=0.0001, OR:1.771, CI: 0.514-0. 2.214 ); (Table 2). The NFKB -94ins/ins genotype was found in 39.3% of MS patients and in 18.2 % of the control group (Table 2). Furthermore, a significant difference was observed in allelic frequency between MS and the controls (p=0,011), OR:0.730, CI: 0.573-0.930; (table 2). Allele insertion was found in 63.8% of MS patients and in 56.3% of controls.

The MS group was further analyzed for genotype distribution of NFKB 94ins/delATTG based on early and late age onset. An association for genotype and allele frequency of -94ins/delATTG was not found between early and late age onset of MS disease, respectively (p=0.827, p=0.9 see Table 3).

## V. DISCUSSION

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by area of inflammation, axonal damage, and demyelination (16). Although, the etiology of this disease is still unknown, genetic, environmental, and geographical factors are thought to play important a role for development of MS. Inflammatory markers are an important for assessing MS severity and it has been shown that genetic variation influences both susceptibility to MS and severity of MS (17-18). It was reported that NFkB signaling may be involved in development of MS (19) since NF□B is an important transcription factor for regulation of many genes for immune system response, cell adhesion, differentiation, proliferation, angiogenesis, and apoptosis (20). In the spinal cord of rats with experimental allergic encephalomyelitis (EAE), it has been shown that p50 and p65 levels are increased during the exacerbation period and decreased with recovery (21). Interestingly, mice carrying a defective p50 gene showed resistance to EAE (22). Taken together, these studies suggest that NF□B is important for development of this disease.

The promoter region of the NFKB gene has a polymorphism (-94ins/delATTG) which affects NFKB gene transcription. Furthermore, it was shown that a 4 base deletion in the promoter results in loss of nuclear proteins and reduced promoter activity (13). In the current study our hypothesis was that the NFKB (-94 insertion/deletion ATTG) gene polymorphism may be involved in MS development. Since several autoimmune diseases including MS show dysfunction in regulatory genes for apoptosis (23), it is possible that ins/ins polymorphism in the promoter regions of NFKB results in increased NF-□B1 protein expression and this causes the change of the transcription of inflammatory cytokines. This hypothesis may explain the overexpression of these cytokines and increased serum concentrations in MS.

Prior to the current study, only a single study has attempted to determine a relationship between the -94ins/delATTG polymorphism and Iranian MS cohorts. Analysis of this polymorphism in Iranian cohorts did not show an association with MS (24). While we are not sure why these associations were not observed in the Iranian cohort study, it is possible that the differences arise from population differences (also discussed later in this discussion). Our study for the NFκB (-94 insertion/deletion ATTG) polymorphism contains 379 MS patient and 214 healthy controls and our results showed that both genotype distribution and allele frequency of NFκB (-94 insertion/deletion ATTG) polymorphism has strong association with MS respectively (Table 2); (p=0001 and p=0.01). The ins/ins genotype of NFKB1 -94 polymorphism was found to be higher in MS patients than healthy people (39.3 % and 18.2 %, respectively). We assume that the mechanism of genotype distribution of NFκB (-94 insertion/insertion ATTG) increasing risk of MS disease may be as result of higher promoter activity of NFKB1 gene. It has been reported from two different studies that insertion of ATTG sequence at -94 region of promoter for NFKB increases transcriptional activity when compared to deletion allele of NFKB (13, 25). In agreement, it was also found that high levels of p105 and p50 proteins are present in human carrying -94 ins/ins ATTG genotype (25).

A growing number of studies are evaluating associations between NFKB -94ins/delATTG polymorphism and inflammatory/auto immune diseases. A number of studies have shown that NFKB -94ins/delATTG polymorphism is associated with inflammatory/auto immune diseases such as ulcerative colitis (26-30). However, other inflammatory/auto immune diseases do not show a relationship with NFKB polymorphism such as RA (31- 32) indication that inflammatory/auto immune diseases are complex and likely involve distinct modes of development. Furthermore, meta-analysis of NFKB -94ins/delATTG polymorphism showed an association with autoimmune and inflammatory diseases in Asian populations but not Caucasian populations (33). Thus, differences in populations add further complexity to studies attempting to identify associations between NFKB -94ins/delATTG polymorphism and inflammatory/auto immune diseases. As stated earlier, this may explain the differences between results from this study compared to that reported for Iranian MS cohorts (24). Additionally, meta-analysis of NFKB -94ins/delATTG polymorphism found that D allele provides protection against autoimmune and inflammatory diseases (33). Similarly, our study showed that a higher percentage of the D allele was found in healthy people, suggesting that it may provide protection for the development of MS.

## VI. CONCLUSION

In conclusion, we show for the first time a significant relationship between MS and NFKB -94ins/delATTG polymorphism in the Turkish population.

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