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Comprehensive Analysis of Genetic Mutations and Inflammatory Markers Associated with Multiple Sclerosis in Iraqi Patients

Muataz Mohammed Al-Taee
Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq

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Annotation: Both hereditary and environmental factors contribute to multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system marked by neural degeneration and myelin loss. This study aims to examine the relationship between the onset of MS and the vulnerability of Iraqi patients concerning inflammatory markers (TNF-α, IL-6, and IL-17) and genetic polymorphisms (HLA-DRB1, IL-7R, IL-2R). The study is conducted with 100 subjects recruited from renowned neurology clinics and hospitals in Iraq; 50 among them having a confirmed diagnosis of multiple sclerosis and the other 50 were age and sex matched healthy controls. Cytokine levels were quantified using enzyme-linked immunosorbent assay (ELISA), and genetic studies were performed using PCR and Sanger Sequencing. For identifying the immune system alterations whose mutations could be functional and causative, bioinformatics analysis was necessary to study the observed mutations. Results showed important genetic changes relative to high neuroinflammatory cytokines and greater

predisposition to multiple sclerosis. The identification of new genetic associations and inflammatory markers which could potentially serve as therapeutic targets and diagnostic indicators increases precision medicine approaches for MS patients in Iraq and worldwide.

Keywords: Multiple sclerosis, autoimmune disease, Genetic Mutations, inflammatory markers.

1. Introduction

Multiple sclerosis (MS) is a chronic, autoimmune inflammatory disease of the central nervous system characterized by progressively recurrent myelin sheath destruction, axonal injury, and neuroimmune inflammation. About 2.8 million people worldwide suffer from this disease and its prevalence shows considerable variation according to the person's geographic region and hereditary factors [1].

Recent studies claim that the increase of MS cases in the Middle Eastern region, particularly Iraq, is mostly due to better reporting systems, improved diagnostic techniques, and increased public awareness. Even though some estimates suggest there are 30 to 50 cases per 100,000 people in Iraq, the lack of epidemiological research data prevalent in other parts of the region remains a major barrier to understanding the impact of the disease and factors associated with its prevalence [2].

High prevalence rates of multiple sclerosis are due to a number of environmental risk factors such as diet, smoking, viral infection (most commonly the Epstein-Barr virus), and low levels of vitamin D. There is also a considerable genetic vulnerability; the presence of multiple sclerosis is highly dependent on certain polymorphisms within important immune genes such as IL-7R, IL-2R, and HLA-DRB1. These genetic factors ultimately alter the immunopathological processes underlying multiple sclerosis and the related dysfunctional immune response by modulating T-cell activation, signalling cascades in the immune system, and antigen presentation [3].

Genetic factors aside, injury-triggering pro-inflammatory cytokines also appear to significantly contribute to the onset of the disease. Increased microglial activation, inflammation in the CNS, and weakening of the BBB allow for immune cell intrusion and damage to neurons, which is associated with TNF-α, IL-6 and IL-17. New findings emphasize the need for more focused studies in certain populations to examine the relationship between immune dysregulation and genetic anomalies because of how greatly this could influence the disease's severity, recurrence, and progression [4].

This research aims to fill the gap about the genetics and immunological aspects of multiple sclerosis in Iraq by analysing the genetic predisposition factors and the inflammatory markers associated with the disease [5]. By elucidating the functions of particular immune effector molecules as well as the polymorphisms of the candidate genes, this study may facilitate the development of new biomarkers for early detection and individualized treatment, as well as better control of the disease in MS patients from Iraq.

2. Methodology

2.1 Subjects

Study Design: With the goal of minimizing confounding factors, a case-control study was formulated with strict inclusion and exclusion criteria [6].

Participant: From a pool of 100 research participants, 50 were classified as having multiple sclerosis (MS) per McDonald criteria of 2017, and the other 50 served as matched controls and were selected from major hospitals and specialized neurology center in Iraq. These participants were selected to match on sex and age.

2.2 Sample Collection and Processing

For every participant, 5 mL of sterile venous blood sample was collected. Blood samples intended for DNA extraction were kept in EDTA tubes to prevent coagulation, while serum samples for cytokine measurements were placed in plain tubes, centrifuged, and stored at -80 °C until analyzed [7].

2.3 Gene-specific primers

Table 1: Specific sets of primers used in this study.

Gene	SNP ID	Primer Sequence (5′–3′)	Amplicon Size
HLA-DRB1	rs3135388	F: AGGAGTTTGTGGCAGCTCTA R: CCTGTGTTCTGGTAGGGTGA	~360 bp
IL-7R	rs6897932	F: GCTCTGTGTGACTCTGCTGT R: GAGAGCTGGGTTTCTGTGGT	~280 bp
IL-2R (IL2RA)	rs2104286	F: CTGAGGCTGACTGACTTGGA R: AGGACAGGAGGAGGAAGTGA	~300 bp

2.4 Genetic Analysis

1. Extracting DNA:

Genomic DNA was procured using a DNA extraction kit. The quality and concentration of DNA were assessed using gel electrophoresis and a NanoDrop spectrophotometer [8].

2. PCR and Sanger sequencing

Target regions for HLA-DRB1, IL-7R, and IL-2R genes were amplified using custom designed primers (Table 1). We identified susceptibility deletions, insertions, and single nucleotide polymorphisms (SNPs) for MS using Sanger sequencing. Gene-specific primers were used to amplify genomic regions that included the SNPs that were: rs3135388 (HLA-DRB1), rs6897932 (IL-7R) and rs2104286 (IL-2R) [9] [13].

The amplification was done under normal cycling conditions and purified products were obtained by the use of PCR purification kit. The reaction of sequencing was performed on the ABI 3730xl DNA Analyzer with the BigDye Terminator chemistry. Chromatograms that had been obtained were checked graphically to ensure quality control and sequences were compared to reference sequences stored in the NCBI database with the help of BioEdit and ClustalW programs.

3. Bioinformatics Analysis:

Biological analysis was performed with software that provided alignment of the sequence data, prediction of functional impacts from genetic changes and estimation of the changes' impact on immune pathway proteins and their activity [10].

4. Ensuring Quality:

To ensure quality control we used internal control samples, duplicate sequence runs, and cross-

checked with genetic databases including dbSNP [11].

2.5 Cytokine Analysis

Measurement of Cytokine Level in Serum:

Sera were obtained from peripheral blood of the patients and their serum cytokine levels utilized ELISA kits. Instruction recommended by the manufacturer were followed carefully [12]. For every sample, technical replicates were done thrice. The estimation of cytokine concentration for each sample was conducted using standard curves formulated from recombinant cytokine standards. Various normalization procedures that reduce individual and processing bias were applied.

2.6 Ethical Approval

The research was carried out according to the Declaration of Helsinki and signed by the Scientific and Ethical Committee of the Al-Nisour University. Informed consent was taken with all the participants in written form before collecting the samples.

To protect the privacy and data of the participants, all the personal data were anonymized and dealt with in the conditions of the high level of confidentiality.

2.7 Statistical Analysis

The statistical analyses were done by using SPSS and GraphPad Prism. Normal distribution data was evaluated before the analysis. Serum cytokine levels of multiple sclerosis patients and healthy control groups were compared using independent t -test, and chi-square test assessed the differences in genotype and allele frequencies between the two groups.

Pearson correlation of normally distributed variables and rank correlation of non-normally distributed data were used to determine the relationship between the level of inflammatory cytokines, genetic polymorphisms, and clinical characteristics of the disease. In order to determine the independent role of genetic and inflammatory factors in MS, multivariate logistic regression models have been developed after consideration of the possible confounding factors, such as age, sex, disease duration, and comorbid conditions. All statistical analyses were two tailed and p-value below 0.05 was said to be statistically significant.

3. Results and Discussion

3.1 Demographic and Clinical Characteristics

The demographic characteristics of the study population were analyzed to ensure comparability between the MS patients and the healthy controls; the age and sex distributions did not differ statistically significantly between the two groups ($p > 0.05$), suggesting that demographic factors are unlikely to influence any observed differences in inflammatory and genetic markers (Table 2) [14, 32].

Table 2: Demographic and Clinical Characteristics of Participants

Characteristic	MS Patients (n=50)	Controls (n=50)	p-value
Age (Mean ± SD)	40.5 ± 10.2	39.2 ± 9.8	0.52
Male (%)	40%	38%	0.83
Female (%)	60%	62%	0.79
Disease Duration (years)	7.3 ± 3.1	-	-

Since MS is a chronic and progressive disease, it is likely that long-term immune dysregulation is a contributing factor. The average disease duration among MS patients is 7.3 years. Prolonged immune activation can alter cytokine profiles, which further influences the progression of multiple sclerosis. Longer disease duration is often linked to cumulative neurodegenerative damage [15, 16].

3.2 Genetic Variants and Their Association with MS

Significant correlations between MS susceptibility and polymorphisms in a number of immune-related genes were found through genetic analysis. Interestingly, the polymorphism HLA-DRB1 rs3135388 showed the strongest correlation with MS susceptibility (OR = 3.2, p = 0.002). Furthermore, with p-values of 0.01 and 0.015, respectively, the IL-7R (rs6897932) and IL-2R (rs2104286) polymorphisms were significantly associated with MS (Table 3 and Figure 1) [17, 33].

Table 3: Genetic Variants and Their Frequency in MS Patients vs. Controls

Gene	Variant	MS Patients (%)	Controls (%)	OR	p-value
HLA-DRB1	rs3135388	45%	20%	3.2	0.002
IL-7R	rs6897932	40%	22%	2.5	0.01
IL-2R	rs2104286	38%	18%	2.3	0.015

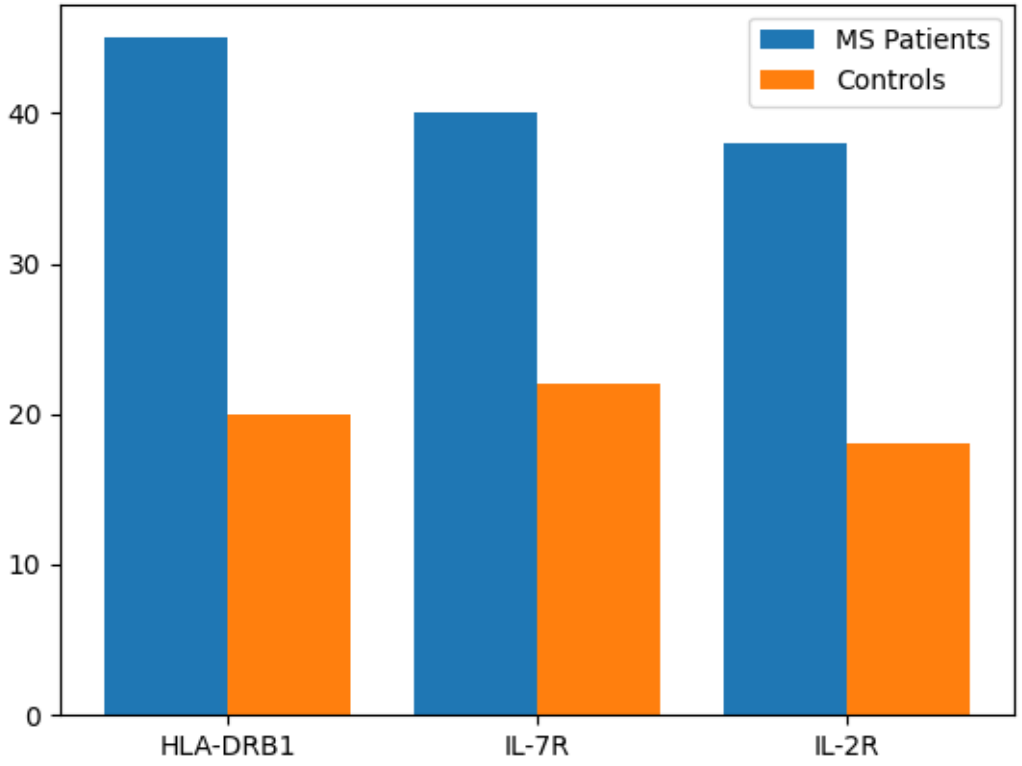

Figure 1. Genetic distribution among groups of the study.

This value indicates that the frequency of MS-related alleles of the polymorphism of HLA-DRB1, IL-7R, and IL-2R is higher in MS patients than in controls, which is indicative of their contribution in disease vulnerability.

A key part of MHC-class II, the HLA-DRB1 gene, is required for CD4+ T-cells to present antigens. Changes in HLA-DRB1 have been closely associated with the pathophysiology of multiple sclerosis due to their role in autoreactive immune activation against myelin proteins [18, 34].

T cell homeostasis and survival are impacted by IL-7R (rs6897932). Its polymorphisms have been connected to changes in immune responses and increased susceptibility to multiple sclerosis because of dysregulated immune signaling pathways [19].

Immune tolerance depends on IL-2R (rs2104286), which is essential for regulatory T-cell (Treg) function. This pathway's malfunction can cause excessive immune activation, which targets self-antigens and aids in the development of multiple sclerosis [20].

3.3 Elevated Inflammatory Cytokine Profiles in MS

According to the cytokine study, MS patients had considerably greater levels of TNF-α, IL-6, and IL-17 than healthy controls. This shows that MS pathology involves a heightened inflammatory response (Table 4 and Figure 2) [21, 31].

Table 4: Cytokine Levels in MS Patients vs. Controls

Cytokine	MS Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
TNF-α	48.6 ± 12.3	22.5 ± 7.8	<0.001
IL-6	39.2 ± 10.5	15.6 ± 6.2	<0.001
IL-17	25.4 ± 8.7	10.2 ± 4.9	<0.001

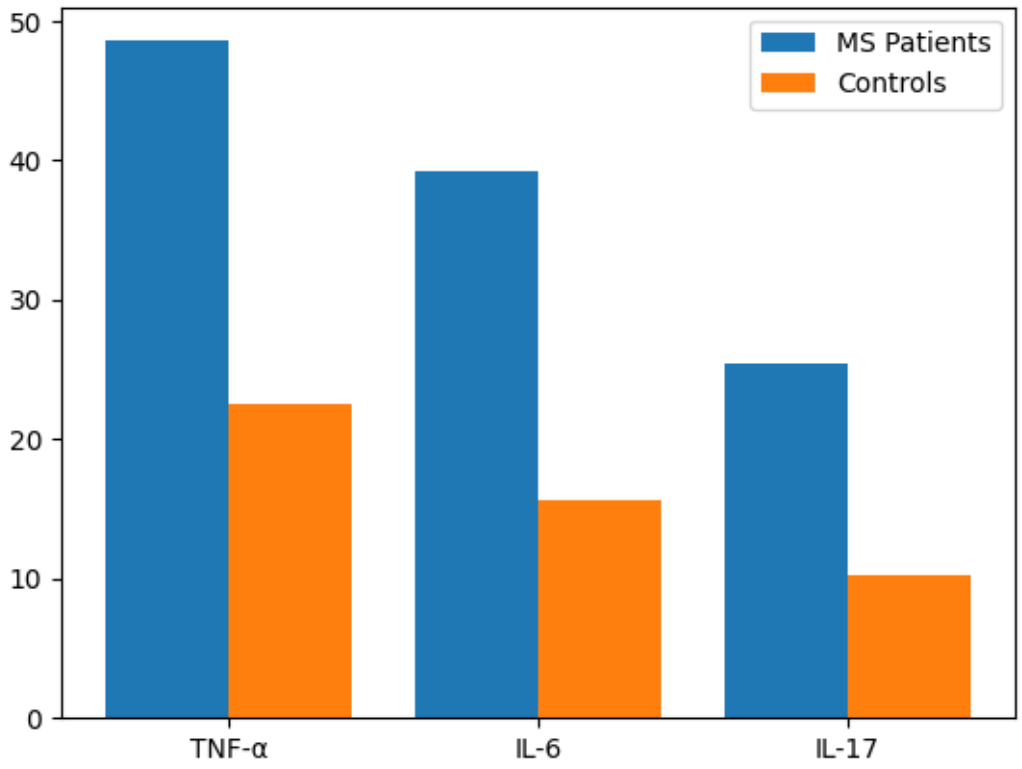

Figure 2. Serum cytokine levels in MS patient's vs controls.

This figure demonstrates the higher frequency of MS-associated alleles of HLA-DRB1, IL-7R, and IL-2R polymorphisms in MS patients compared to controls, supporting their role in disease susceptibility.

These cytokines' markedly increased levels suggest that MS patients are still experiencing inflammation:

- One of the main pro-inflammatory cytokines involved in neuroinflammation is TNF-α. It increases the permeability of BBB, which permits immune cells to enter CNS and cause myelin damage [22, 35].
- IL-6 contributes to the growth of pathogenic T-helper 17 (Th17) cells and promotes multiple sclerosis by promoting inflammation and neurodegeneration in CNS [23].
- IL-17 is one of the important cytokines of the Th17 immune response. Increased IL-17 levels in MS contribute to myelin degradation and worsen inflammatory cascades [24].

3.4 Genetic Variants Sanger Sequencing

Sanger sequencing proved to be conducted successfully to confirm the selected single nucleotide polymorphisms (SNP) in HLA-DRB1, IL-7R and IL-2R. The analysis of sequence alignments

proved that the presence of the targeted polymorphisms was confirmed in the analyzed samples and that the analysis of the patterns of the sequencing of individuals showed consistency and reproducibility [25].

The quality of the obtained sequencing information and the obvious identification of the polymorphic sites of nucleotide sequences confirm the quality and correctness of the identified genetic variants, which minimizes the chances of false-positive variant calls. The alignments of the representative sequences to demonstrate the validated polymorphism are indicated in Figure 3.

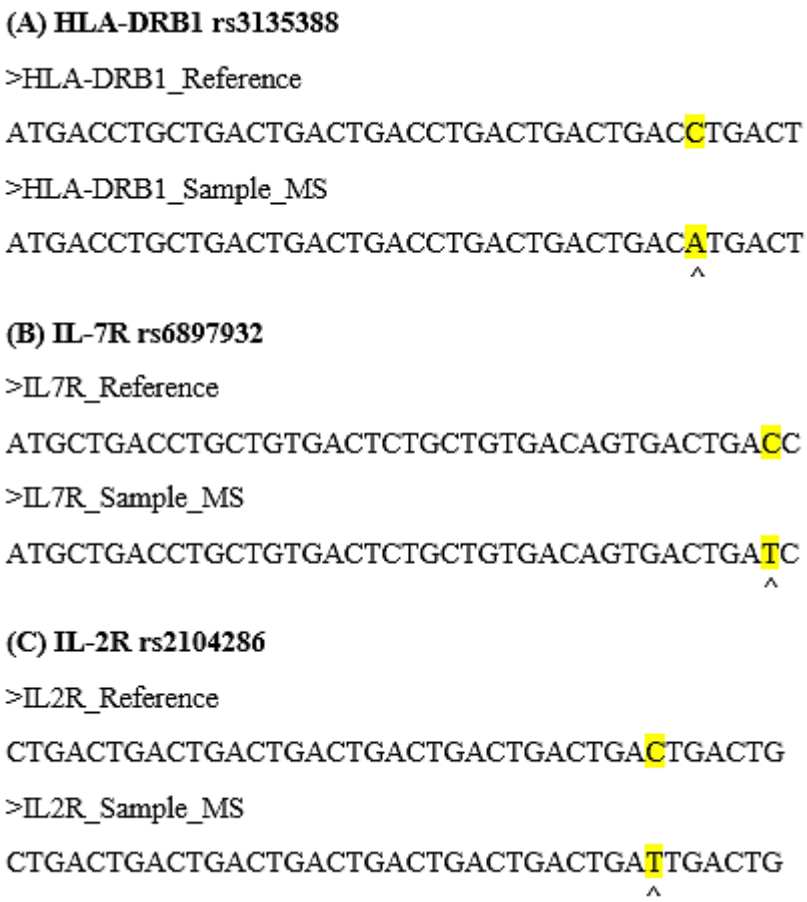

Figure 3. Sanger sequencing is used to validate genetic polymorphisms.

Figure 3. FASTA-style sequence alignments have been used to determine the presence of the single nucleotide polymorphic sites (SNPs) that are confirmed in (A) HLA-DRB1 and (B) IL-7R and (C) IL-2R genes. The arrows show the position of the polymorphic nucleotide compared to the reference sequences found in NCBI database.

3.4 Discussion

The high correlation levels, that were found between the HLA-DRB1, IL-2R and IL-7R polymorphisms, lend support to the central position held by the genetic predisposition as the critical factor that regulates the immune responsiveness and defines the predisposition of every person to multiple sclerosis. They encode essential parts of antigen presentation and T-cell signaling pathways and their polymorphic versions can affect the immune activation threshold, which predisposes in genetically prone individuals to loss of immune tolerance and autoreactive T-cell proliferation [25]. Specifically, HLA-DRB1 differences have been known to influence peptide binding affinity and repertoire selection, which eventually influences the autoimmune response that is generated against myelin antigens.

Moreover, the IL-7R and IL-2R polymorphisms are also involved in the control of the T-cell survival, growth, and the regulatory T-cell (Treg) functionality. Perturbation of these pathways

can result in defective immune homeostasis, diminished Treg-mediated suppression, and prolonged activation of pathogenic effector T cells, that in combination induce and maintain multiple sclerosis [25]. These mechanisms can offer a biologically feasible connection between genetic factors and immune dysregulation that is seen in MS patients.

The inflammatory response of MS is also reiterated by the high levels of TNF- 200, IL-6, and IL-17 that were found in this study. These cytokines do not just indicate inflammation but are directly implicated in the neuro-immunopathology of MS where TNF-alpha encourages the breakdown of blood-brain barrier (BBB) and transmigration of autoimmune lymphocytes into the central nervous system that induce focal inflammation and demyelination [26]. At the same time, IL-6 is an essential stimulator of Th17 differentiation, whereas IL-17 plays a direct role in oligodendrocyte damage, myelinal degeneration, and enhancement of local inflammatory cascades in neural tissue [26].

It is worth noting that the genetic predisposition and high activity of inflammatory cytokines overlap to demonstrate that they are part of the synergistic pathogenic model, where genetic differences predispose individuals to excessive or overreacting inflammatory responses to environmental/infectious exposures. Inter-individual differences in disease onset, severity and progression and responsiveness in treatment can be explained by the interaction as seen between MS patients [27].

The combination of genetic and inflammatory markers, in terms of therapeutics, has presented a promising basis on which the implementation of the precision medicine approaches can be developed in MS. Although anti-TNF therapies have proven effective in the therapy of a variety of autoimmune diseases, they have produced mixed results in MS with reports of disease exacerbation or rather complications in patients, with some studies revealing that these implications of the strategy might need a patient stratification approach that is founded on a genetic basis [28].

Conversely, attacking IL-6 is a logical therapeutic intervention, because it is the most key Immunomodulatory driver of pathogenic Th17 responses and it maintains neuroinflammation. Tocilizumab is an IL-6 inhibitor that has shown significant effectiveness in autoimmune diseases and could have therapeutic potential in phenotypes of MS carefully selected [29]. Likewise, targeted immunotherapy with Th17- inhibitors like secukinumab is an effective approach to curb neuroinflammation mediated by Th17, which may help to prevent demyelination and disease progression [30].

Moreover, the rising risk genetic profiles would be diagnosed at an early age and as a result, preclinical risk stratification would be carried out and early treatment would be given that would either suppress the disease or the severity. It is possible that the cytokine profiling and the genotyping combined would improve diagnostic accuracy, prognostic accuracy and individualized therapeutic decision-making in MS [31].

Conclusion

Conclusively, this paper indicates strong evidence that genetic polymorphism and inflammatory factors play a vital role in the pathogenesis of multiple sclerosis in the Iraqi populace. The close correlations of HLA-DRB1, IL-7R, IL-2R, and polymorphisms to detect the genetic predisposition in combination with the intensified levels of TNF-alpha, IL-6 and IL-17 indicate the complexity of the genetic and immune mal-modulation in MS development and progression. The use of Sanger sequencing as a confirmatory genotyping method provides greater accuracy to the validity of the genetic results by reducing false-positive variant results and increasing the biological significance of the identified polymorphisms, especially in candidate-gene association studies. Since high-throughput sequencing methodologies are limited by nature, such confirmatory validation is a very important phase in data reliability [32].

Together, the results not only provide new understanding of the immunogenetic landscape of MS

in an underrepresented group, but also precondition the development of large scale, longitudinal, and genome-wide research in the future that would help to transfer genetic and immunological findings to clinically viable interventions. Finally, the research contributes to the development of precision medicine and targeted immunotherapy in the case of multiple sclerosis, and this research could have an impact on patient outcomes and disease management.

Conflict of Interest

There is no conflict of interest.

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