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Genetic Influences on Disease-Modifying Therapy Response in Multiple Sclerosis: Current Insights and Future Directions

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Multiple sclerosis (MS) is a clinically and biologically heterogeneous, immune-mediated disease of the central nervous system, with substantial interindividual variability in disease course and response to disease-modifying therapies (DMTs). Over the past three decades, the MS therapeutic landscape has expanded considerably; however, treatment selection and switching remain guided primarily by clinical phenotype and imaging findings rather than molecular predictors of response. Despite extensive clinical trial evidence, prospectively identifying responders and non-responders to specific DMTs remains challenging.

Genetic variability appears to influence differences in treatment efficacy, tolerability, and long-term outcomes in people with MS. Numerous candidate pharmacogenomic variants have been reported across interferon-β, glatiramer acetate, oral agents, and monoclonal antibodies; nevertheless, replication has been inconsistent, effect sizes are modest, and no genetic marker has yet been clinically validated for routine use. Consequently, pharmacogenomics is largely absent from current MS treatment algorithms.

This review critically evaluates the existing pharmacogenomic literature across approved DMTs, highlighting reproducible findings, methodological limitations, and gaps that hinder clinical translation. We further discuss requirements for integrating pharmacogenomic markers into routine practice, emphasizing the need for large, multiethnic cohorts, standardized response definitions, and functional validation. Overall, these insights underscore both the potential and current limitations of pharmacogenomics in advancing precision medicine for MS.

INTRODUCTION

Multiple sclerosis (MS) is a complex, immune-mediated disorder with a multifactorial etiology shaped by the interplay of genetic predisposition, epigenetic regulation, and environmental exposures.[1] The treatment of MS progresses according to disease manifestations and involves several stages: management of severe attacks, administration of disease-modifying therapies (DMTs) that reduce MS biological activity, and symptom-targeted interventions.[2] Integrating clinical phenotypes and magnetic resonance imaging (MRI) characteristics with demographic data enables a precision-based approach to MS management, guiding transitions between acute attack therapy, disease-modifying protocols, and symptomatic support.[3] Currently, no treatment completely eradicates MS. Predicting long-term prognosis and selecting the most appropriate therapeutic approach at diagnosis in people with MS (pwMS) are crucial for refining personalized treatment strategies.

The heterogeneity of MS necessitates a departure from a one-size-fits-all approach, as treatment benefits vary significantly across the patient population.[4] This multifactorial nature complicates the identification of universal, reliable biomarkers, making personalized prognostic tools essential for modern clinical practice. Variability in response to DMTs in pwMS presents a significant clinical challenge, as delays in identifying effective therapies may expose patients to adverse effects without substantial benefit. Multi-parametric machine learning frameworks that integrate polygenic risk scores with clinical, imaging, and laboratory variables have shown promise in predicting treatment responses in MS; however, despite improved classification accuracy, no single reproducible genetic variant has yet emerged for routine clinical implementation.[5]

Ongoing research aims to validate potential pharmacogenomic variants in large, well-characterized patient populations, yet the routine use of pharmacogenetics in MS remains a distant goal. While

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genomic variation is a key determinant of this variability, identifying reliable pharmacogenomic markers is often hindered by the lack of standardized clinical definitions and the oversight of confounding variables. As illustrated in Figure 1, evaluating the multifactorial determinants of MS pharmacogenomics is essential to distinguish true biological drug non-responders. This framework requires the integration of demographic, clinical baseline, and environmental factors alongside high-resolution genomic data to capture the full landscape of treatment outcomes. We addressed this complexity by utilizing whole-exome sequencing (WES) and drug-associated *HLA* allele typing within a Turkish Familial MS (TuFaMS) cohort to identify specific risk alleles, including *DQB106:02* and *DQA101:02*, which are significantly associated with responses to Fingolimod and Ocrelizumab. By coupling these findings with pathway enrichment analysis, we identified significant involvement of cytokine signaling pathways, further validated by differential gene expression in Fingolimod responders and non-responders from RNA-seq data (GSE250453).[6] This integrated approach demonstrates that combining clinical metrics with high-resolution genomic profiling can bridge the gap between statistical associations and a functional, mechanistic understanding of individual treatment trajectories in MS. By consolidating evidence across multiple pharmacogenomic studies, this review characterizes the collective impact of genetic variation on the heterogeneity of DMT therapeutic responses in MS.

Clinical phenotyping and covariates in MS pharmacogenomics

Effective pharmacogenomic analysis in MS requires a clear distinction between biological treatment failure and alternative reasons for medication switching. To ensure the accuracy of genetic associations, defining treatment non-response is critical; the core phenotype should be characterized by breakthrough disease activity despite adherence, including new clinical relapses, confirmed disability progression (Expanded Disability Status scale increase), or new/enlarging T2 or Gadolinium-enhancing lesions on MRI. Confounding Discontinuation: Medication switches due to allergic reactions, adverse events (e.g., lymphopenia, liver enzyme elevation), or patient non-adherence must be treated as confounders and distinguished from pharmacodynamic non-response.

Demographic covariates such as age at onset, biological sex, and ancestry are essential because they independently influence both immune baseline and therapeutic trajectories. Environmental modulators, including vitamin D levels, smoking status, and BMI, should be incorporated into multifactorial models due to their established role in influencing drug efficacy.

DMTs in MS

Therapeutic management of MS encompasses a broad spectrum of DMTs, including immunomodulators, immunosuppressants, and targeted monoclonal antibodies. These consist of injectable formulations such as subcutaneous or intramuscular interferons (IFNs) and subcutaneous glatiramer acetate (GA); intravenous natalizumab, mitoxantrone, alemtuzumab, and ocrelizumab; and orally administered agents including fingolimod, teriflunomide, and dimethyl fumarate (DMF). Collectively, these therapies have demonstrated robust efficacy in reducing annualized relapse rates during the initial phases of the disease.[7]

According to the European Medicines Agency, the initial era of DMT development in the 1990s established the foundation with injectable agents such as IFN beta (IFN-β)-1b (Betaferon®, 1995), IFN-β-1a (Avonex®, 1997, and Rebif®, 1998), and Mitoxantrone (Novantrone®, 1998). Subsequent advancements in the 2000s introduced GA (Copaxone®, 2004) and the targeted monoclonal antibody Natalizumab (Tysabri®, 2006) (Figure 2). Between 2010 and

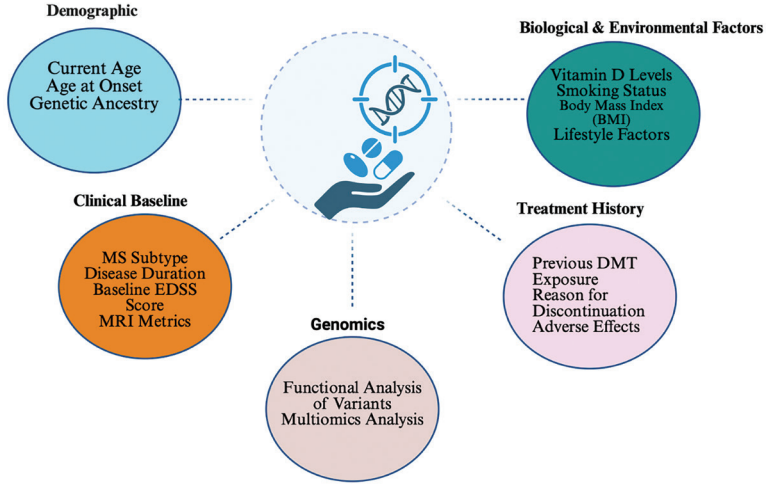

FIG. 1. Multifactorial determinants of multiple sclerosis (MS) pharmacogenomics. The figure outlines the multifactorial determinants that influence pharmacogenomic outcomes in MS, categorized into five core domains: Demographic, Biological & Environmental, Clinical Baseline, Treatment History, and Genomics. Central to this framework is the necessity of distinguishing true biological non-response, characterized by breakthrough disease activity such as Expanded Disability Status scale progression and new magnetic resonance imaging (MRI) metrics, from confounding factors including adverse effects or treatment discontinuation due to patient lifestyle.

2015, orally bioavailable agents such as Fingolimod (Gilenya®, 2011) and Teriflunomide (Aubagio®, 2013) emerged alongside potent intravenous treatments, including Alemtuzumab (Lemtrada®, 2013). The most recent approvals, including Ocrelizumab (Ocrevus®, 2018) and the S1P modulators Siponimod (Mayzent®, 2020), Ponesimod (Ponvory®, 2021), and Ofatumumab (Kesimpta®), further reflect the growing heterogeneity of therapeutic options (Figure 2).

Despite this diversity, IFN-β and GA remain the most commonly prescribed first-line interventions worldwide (Figure 3).[8] These agents offer substantial clinical benefits, including reduced relapse risk, slower disability progression, and improved MRI parameters, while maintaining a relatively mild adverse effect profile. Nevertheless, their therapeutic effect is incomplete, and the magnitude of benefit varies widely among individuals. Current evidence suggests that approximately 30–50% of patients fail to meet established response benchmarks, a variability thought to be driven in part by interindividual genetic differences.[9,10] In clinical practice, therapeutic decision-making in MS typically follows a line-of-therapy paradigm, stratifying DMTs into first-, second-, and third-line options according to relative efficacy, safety profile, and cumulative risk (Figure 3).[11] First-line therapies generally provide moderate efficacy with favorable long-term tolerability, whereas second- and third-line agents include high-efficacy therapies associated with more pronounced immunosuppressive effects and monitoring requirements. Although this hierarchical framework facilitates standardized treatment algorithms, it assumes a stepwise and homogeneous disease trajectory, inadequately accounting for interindividual variability in disease activity, treatment response, and long-term prognosis.[12]

Given the heterogeneity of MS pathogenesis and treatment response, identifying genomic variants that predict individual responsiveness to specific DMTs is crucial.[13] Pharmacogenomic profiling represents a promising strategy for patient stratification, enabling the identification of molecular signatures that correlate with differential therapeutic efficacy and tolerability.[14,15] Early identification of likely responders could facilitate timely initiation of the most appropriate DMT, maximizing disease control, reducing the risk of irreversible neuroaxonal loss, and minimizing exposure to ineffective or poorly tolerated therapies. Integrating pharmacogenomic marker-driven strategies into routine clinical pathways would support a transition from empirical, trial-and-error prescribing to a precision medicine model, in which treatment selection is guided by objective, patient-specific molecular and clinical data.

Selection criteria and literature search strategy

To ensure a comprehensive and systematic overview of the pharmacogenomic landscape in MS, a two-tiered search strategy was implemented. First, the PharmGKB (Pharmacogenomics Knowledgebase) database was queried as of January 2026 to identify genetic variants with established clinical annotations and evidence levels using standardized MeSH terms and keywords, including "Multiple Sclerosis." It is important to note that all identified genetic variants associated with MS DMTs currently hold Level 3 evidence within the database. This evidence level signifies suggestive clinical associations that have not yet met the high evidentiary thresholds required for inclusion in formal clinical guidelines or Food and Drug Administration drug labels.

This was followed by a systematic literature search in PubMed/MEDLINE using a combination of MeSH terms and keywords:

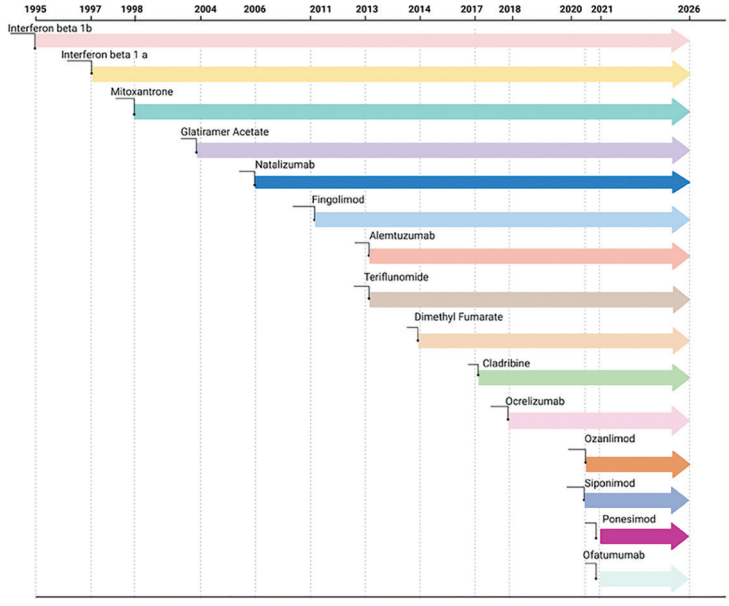

FIG. 2. Timeline of European Medicines Agency (EMA)-approved disease-modifying therapies in multiple sclerosis: the figure traces the chronological introduction of disease-modifying therapies approved by the EMA, showcasing the historical evolution from early platform injectables to the current era of high-efficacy therapeutic interventions.

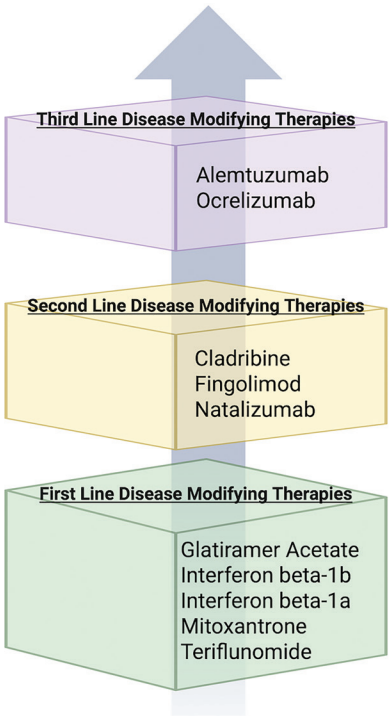

FIG. 3. Line-based classification of disease modifying therapies in multiple sclerosis: the figure showcases a hierarchical classification of disease-modifying therapies used in multiple sclerosis, organized by their clinical deployment into first, second, and third-line treatment categories.

("Multiple Sclerosis" OR "MS") AND ("Pharmacogenomics" OR "Pharmacogenetics") AND ("Genetic Variant" OR "SNP") AND ("Treatment Response" OR "Drug Toxicity") AND ("Disease-Modifying Therapies" OR "DMTs" OR "Dimethyl Fumarate" OR "Fingolimod" OR "Glatiramer Acetate" OR "Interferon-beta" OR "Natalizumab" OR "Ocrelizumab" OR "Teriflunomide").

The selection process adhered to strict inclusion and exclusion criteria to maintain translational relevance. Inclusion criteria encompassed: (i) clinical studies involving human subjects reporting statistically significant associations between specific genotypes and outcomes, such as relapse rate, EDSS progression, or MRI activity; and (ii) functional studies using validated human-derived cell lines (e.g., Jurkat, T cells, or B cells) to investigate molecular mechanisms, including gene expression or signaling pathways under drug exposure. Exclusion criteria applied to: (i) studies relying exclusively on non-human animal models (e.g., EAE); (ii) research focusing solely on disease susceptibility without assessing treatment response; and (iii) low-quality data lacking sufficient statistical power, missing p-values, or non-peer-reviewed sources, such as conference abstracts.

By synthesizing curated database evidence with mechanistic insights from cell-based assays, this review prioritizes variants supported by both clinical relevance and functional validation.

Genetic variants associated with treatment response in MS

IFN-β is a first-line therapy available as intramuscular or subcutaneous formulations of recombinant IFN-β-1a and subcutaneous IFN-β-1b. Its mechanism of action involves binding to type I IFN receptors *(IFNAR1/2)* and activating the JAK–TYK2–STAT signaling pathway, which shifts the cytokine profile toward an anti-inflammatory state, decreases antigen presentation, and limits T-cell migration into the central nervous system (CNS).[16] Pharmacogenomic studies have identified variants in *IFNAR1*, *IFNAR2, TYK2*, and downstream *IFN*-stimulated genes such as *OAS1* and *MX1* as potential modulators of therapeutic response.[16,17] Transcriptomic "type I interferon signature" gene expression in monocytes has been associated with poorer response to *IFN-β* in MS.[18] A recent genome-wide association analysis reported that rs7665090, located near *NF-κB*–related genes, is associated with favorable clinical outcomes under IFN-β therapy (Supplementary Table),[19] whereas earlier studies suggested that common *IFNAR1/IFNAR2* variants may influence MS susceptibility but do not robustly predict IFN-β response.[17] Certain *HLA* class II alleles *(HLA-DRB10*401 and HLA-DRB1*0408)* and innate immune pathway variants have been linked to an increased risk of neutralizing antibody formation, which can reduce drug efficacy.[20,21] In IFN-β–treated relapsing-remitting MS (RRMS), pharmacogenomic signals have been reported at both single-locus and polygenic levels. Replication data support an association between *GPC5* and clinical response, most notably rs10492503 ($p = 0.0005$), while *HAPLN1* variants showed no association in the same analysis.[22] Complementing this, a genome-wide pharmacogenomic study of 206 patients identified significant genotype-frequency differences between responders and non-responders at multiple loci, including *GPC5, COL25A1, HAPLN1, CAST*, and *NPAS3*.[23] Candidate-gene analyses demonstrated that allelic combinations were informative, with *JAK2–IL10RB–GBP1–PIAS1* (permutation $p = 0.0008$) and *JAK2–IL10–CASP3* ($p = 0.001$) differing in frequency between response groups.[24] Positive response to IFN-β treatment was significantly associated with *MXA* rs464138 AA, *MXA* rs2071430 G, and *MXA* rs17000900 GG genotypes ($p < 0.0001$, 0.015, and 0.018, respectively) (Supplementary Table 1).[25-27]

Within the *IFNAR1* gene, the rs1012335 G allele has been linked to a negative response to IFN-β therapy ($p = 0.036$),[27,28] and *IRF5* rs2004640 ($p = 0.0006$) has been associated with poor pharmacological response, characterized by increased T2 lesion burden (Supplementary Table 1).[29] The rs4774388 variant within the *RORA* gene has also been identified as significantly associated with reduced responsiveness to IFN-β therapy in patients with MS.[30]

Additional genetic variations associated with suboptimal or negative responses to IFN-β in RRMS include *CD46* (rs2724385),[31] *CD58* (rs12044852),[32] *GAPVD1* (rs10819043, rs10760397),[25] *GPC5* (rs10492503, rs1411751), *GABRB3* (rs832032),[33] *IRF5* (rs2004640), *MXA* (rs464138), *PELI3* (rs2277302),[33] and *ZNF697* (rs10494227). Conversely, *GAPVD1* (rs2291858)[25] and *FHIT* (rs760316)[25] have been linked to positive responses to IFN-β therapy (Supplementary Table 1).[34]

Glatiramer acetate

GA, a first-line therapy administered subcutaneously, is a synthetic myelin-mimetic copolymer that promotes a shift in T-cell polarization from proinflammatory Th1 toward anti-inflammatory Th2 and regulatory T-cell phenotypes while also modulating antigen-presenting cell function.[35,36] The most consistent pharmacogenomic signals for GA reside within the HLA region rather than individual non-HLA SNPs. Multiple cohort studies have linked *HLA-DRB1*15:01* and related class II haplotypes with differential therapeutic responses, showing in some populations better relapse control and in others poorer outcomes, reflecting substantial population-specific heterogeneity and limited replication.[37] *HLA* association analyses indicate that the presence of *DR15* or *DQ6*, or the absence of *DR17* and *DQ2* alleles, is associated with favorable clinical response. Specifically, the *DR15-DQ6* positive/*DR17-DQ2* negative haplotype combination strongly predicts a good response (71%), whereas the *DR15-DQ6* negative/*DR17-DQ2* positive combination strongly predicts a poor response (17%) (Supplementary Table 1).[37] In a cohort of 139 MS patients stratified as GA responders (n = 81) and non-responders (n = 58), genotyping of *HLA-DRA* (rs3135388, rs3135391), *HLA-DQA1* (rs9272346), and *IL6* (rs1800795, rs1900796) showed no significant association with treatment response, with female predominance observed in both groups. Non-responders exhibited higher EDSS scores and greater MRI lesion burden, highlighting the need for larger, adequately powered pharmacogenetic studies to define robust GA response markers and enable personalized therapy.[38]

Among GA-treated MS patients, *HLA-DRB115:01* was associated with decreased treatment response in a European cohort ($p = 0.0056$). The risk of non-response increased when *DRB115:01* co-occurred with the rs1800469 A allele and further rose with combined haplotypes including the rs333 *(CCR5)* deletion and rs1012335 G allele.[39] In the same study, *IFNB1* rs1051922 (G vs. A) and *CTLA4* rs231775 (G vs. A) showed no association with GA response. Beyond HLA, the *EOMES* rs2371108 T allele was linked to greater GA responsiveness in Europeans ($p = 0.018$), remaining significant after multiple-testing correction when responders were contrasted against non-responders plus intermediate responders.[28] Overall, these findings suggest predominantly HLA-anchored effects with a few non-HLA candidate variants, alongside several null or inconsistent results, underscoring the need for larger, well-controlled pharmacogenomic studies prior to clinical implementation. Additionally, the rs1799752 polymorphism within the *ACE* gene has been associated with a negative response to IFN-beta therapy, showing a particularly notable correlation with treatment outcomes in male patients.[40]

Teriflunomide

Teriflunomide, an oral first-line therapy, is a selective, non-competitive inhibitor of dihydro-orotate dehydrogenase (DHODH), an essential mitochondrial enzyme for *de novo* pyrimidine synthesis. By limiting the clonal expansion of activated T and B lymphocytes while sparing resting cells, teriflunomide modulates immune responses in MS.[41] Unlike GA or IFN-β, pharmacogenomic research on teriflunomide in MS is sparse, and no single-nucleotide polymorphism (SNP), either within HLA or non-HLA regions, has been reproducibly associated with therapeutic response in prospective cohorts. Candidate studies have examined *DHODH* gene variants, including rs3213422 and rs3213421, which in other autoimmune diseases (e.g., rheumatoid arthritis) have been linked to altered leflunomide or teriflunomide metabolism; however, these variants have not shown a clear responder/non-responder effect in MS.[42] To date, no validated *HLA* or non-HLA SNP can be used to stratify teriflunomide responders from non-responders in clinical practice, and treatment selection continues to rely on clinical, MRI, and safety profiles rather than genetic testing.

Dimethyl fumarate

DMF, an oral first-line therapy, is rapidly hydrolyzed to its active metabolite, monomethyl fumarate, which penetrates immune cells and activates the NRF2 antioxidant pathway through covalent modification of KEAP1 cysteine residues.[43,44] In MS, *NRF2* activation reduces oxidative stress–mediated axonal injury and shifts immune cell phenotypes toward an anti-inflammatory profile.[45] DMF decreases the proportion of proinflammatory Th1 and Th17 lymphocytes, enhances regulatory T-cell function, and promotes neuroprotective phenotypes in microglia and astrocytes. It also inhibits NF-κB signaling in antigen-presenting cells, reducing the production of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, thereby limiting CNS infiltration by activated lymphocytes. A recent patient-level, population-specific pharmacogenomic study identified two promoter polymorphisms in the long intergenic non-coding RNA *linc00513* with drug-specific effects across DMTs: rs205764 (G allele) was associated with a significantly lower response to DMF, whereas rs547311 showed no significant association with DMF response but correlated with higher EDSS.[46]

Fingolimod

Fingolimod (FTY720), an oral second-line therapy, is a sphingosine analog phosphorylated *in vivo* to its active phosphate form, which binds with high affinity to sphingosine-1-phosphate receptor subtype 1 (S1PR1) on lymphocytes.[47] This interaction induces receptor internalization and functional antagonism, preventing lymphocyte egress from secondary lymphoid tissues into the circulation.[48] In MS, this mechanism reduces CNS infiltration by autoreactive T and B cells, thereby lowering inflammatory lesion activity and relapse rates.[49,50] Pharmacogenomic studies in MS have identified the long intergenic non-coding RNA promoter variant linc00513 rs205764 as a potential responder marker, associated with greater relapse rate reduction in fingolimod-treated patients, whereas rs547311 in the same locus showed no association with treatment response.[46] Direct analyses of *S1PR1* coding and regulatory SNPs in MS cohorts have not demonstrated significant associations with clinical efficacy or immunologic parameters such as *IL-17* modulation, suggesting limited predictive value for single-locus *S1PR1* variation.[51] To date, despite consistent cohort-level associations for rs205764, no validated *HLA* or non-HLA SNP can be implemented in routine clinical practice to stratify fingolimod responders from non-responders in MS. A strong association between the MHC region and

MS susceptibility has been identified, with *HLA-DRB11501* having the most significant impact.[52] Variants linked to DMTs in MS include HLA risk alleles *DQA101:02, DQB106:02*, *DRB115:01, DQA103:01,* and *DQB103:02*. An analysis of 138 WES datasets from the TuFaMS cohort assessed medication switches and genetic correlations.[53] Fisher's exact test indicated significant associations between drug-*HLA* allele pairs, with the strongest link observed between fingolimod and *DQB1*06:02* ($p = 0.0166$), present in five individuals.[53]

Natalizumab

Natalizumab, a second-line intravenous therapy, is a humanized monoclonal antibody targeting the α4 subunit of VLA-4 (α4β1 integrin/CD49d) on lymphocytes. By blocking α4-integrin–VCAM-1 interactions, it prevents firm adhesion and transmigration of leukocytes across the blood–brain barrier (BBB), thereby suppressing CNS inflammatory activity in MS.[54] The largest genome-wide association study investigating pharmacogenomic response to natalizumab in MS revealed no single variant reaching genome-wide significance. However, polymorphisms within the Wnt/β-catenin signaling pathway, which is critical for BBB formation and maintenance, have been identified as potential modulators of treatment response.[55] These variants lead to downregulated β-catenin–mediated transcriptional activity, resulting in a leaky barrier phenotype that facilitates continuous leukocyte diapedesis and neuroinflammation, bypassing the mechanism of action of systemic DMTs. Consequently, these findings suggest that clinical non-responsiveness to natalizumab is significantly influenced by CNS-specific structural genetics, in which genetically determined failure of endothelial homeostatic repair limits the efficacy of current immunomodulatory protocols.[55]

Mitoxantrone

Mitoxantrone, a synthetic anthracenedione derivative, exerts cytotoxic effects by inhibiting topoisomerase II, impairing DNA repair and replication, and reducing lymphocyte and macrophage proliferation. This action decreases proinflammatory cytokine release and suppresses myelin degradation.[56] Two studies have investigated the pharmacogenetic associations between mitoxantrone response and genetic polymorphisms, yielding conflicting results. The first study identified SNPs in ABC-transporter genes (*ABCB1* and *ABCG2*) as potential pharmacogenetic markers associated with clinical response in patients with RRMS or secondary progressive MS (SPMS). In contrast, the second study, which included patients with primary progressive MS (PPMS), did not confirm any significant association, despite observing clinical response rates of 53.7% in PPMS and 78.1% in RR/SPMS ($p = 0.039$), with no correlation between treatment efficacy and *ABCB1* or *ABCG2* genotype.[57,58]

DISCUSSION

Several limitations hinder the translation of pharmacogenomic discoveries into clinical practice. Many studies are constrained by small sample sizes, limited replication, and a lack of diversity in patient populations. Differences in study design, treatment regimens, and outcome measures further complicate comparisons of results. Moreover, most findings originate from association studies without extensive functional validation, leaving the mechanistic underpinnings of many candidate variants unresolved.

A precise definition of treatment nonresponse is the cornerstone of pharmacogenomic research, as it must be strictly distinguished from voluntary discontinuation or allergic reactions. True therapeutic failure should be characterized by breakthrough disease activity despite treatment, specifically manifested as clinical relapses, disability progression, or increased MRI activity. Establishing a consensus on this definition is the first step toward a functional understanding of drug efficacy. Once defined, it is essential to integrate demographic, clinical, biological/environmental, and genomic factors, along with treatment history, into a unified analytical framework. This holistic approach ensures that genetic variants are evaluated not in isolation but as components of a complex biological system that dictates individual clinical trajectories. Ultimately, correlating these multilayered data points with functional assays in cell lines enables a transition from simple statistical associations to a comprehensive functional understanding of treatment response in MS.

From a clinical perspective, integrating pharmacogenomic insights into MS management could facilitate the development of more personalized treatment algorithms. Identifying genetic predictors of drug efficacy or toxicity may allow clinicians to optimize therapy selection, minimize unnecessary exposure to ineffective agents, and enhance patient outcomes. However, despite encouraging signals from candidate gene studies, no robust pharmacogenomic marker has yet reached clinical implementation for MS. Current therapeutic decisions remain largely guided by clinical features, imaging findings, and patient preferences rather than genetic data.

Although B-cell–depleting therapies currently represent the most potent pharmacological interventions in the MS landscape, the specific genomic variants modulating individual responses to these high-efficacy agents remain largely uncharacterized. Future pharmacogenomic research must focus on identifying the molecular determinants of treatment failure to elucidate why a subset of patients exhibits breakthrough disease activity despite profound peripheral B-cell lymphopenia. Establishing these genetic profiles will be foundational for shifting the therapeutic paradigm toward a precision-based model, ensuring optimized selection of anti-CD20 protocols based on an individual's unique molecular signature. Moreover, comprehensive analyses of treatment outcomes, particularly in patients who require third-line therapies yet continue to show suboptimal responses, may facilitate the identification of novel variants associated with drug resistance or reduced efficacy, thereby expanding the scope of pharmacogenomic markers relevant to personalized treatment strategies in MS.

The PharmGKB database provides a curated collection of pharmacogenomic associations categorized by levels of evidence, ranging from preliminary findings (Level 4) to clinically actionable variants supported by replicated studies and clinical guidelines (Level 1A).[59] These evidence levels standardize the strength of genotype–drug response relationships and guide translation into clinical practice. For MS, only a limited number of variants related

to DMT response are listed in PharmGKB, most of which remain at lower evidence levels due to insufficient replication. According to PharmGKB classifications of variant–drug associations, as of January 2026, no clinically actionable variants with Level 1A or 1B evidence have been identified for DMTs in MS. This highlights the existing gap between research findings and clinically validated pharmacogenomic implementation in MS therapy.

Advancement in pharmacogenomics for MS relies on identifying genetic variations and specific antibody profiles to predict disease trajectory and personalize therapeutic interventions. Recent evidence indicates that functional polymorphisms within the SNARE complex, particularly the *VAMP2* Del/Del genotype and the synaptotagmin XI C allele, are significantly associated with increased MS susceptibility.[60] These genetic markers represent potential targets for novel medications designed to restore synaptic homeostasis and mitigate synaptopathy in early disease phases. Furthermore, the presence of anti-MOG-IgG serves as a critical biomarker influencing the selection of immunomodulatory treatments, as patients with this profile may require strategies such as rituximab or azathioprine to prevent relapses.[61] Integrating pharmacogenomic data with prognostic indicators, including advanced age at onset and spinal cord involvement, is essential for optimizing clinical outcomes and achieving precision management in neuroimmunology.

Future research should prioritize large-scale, multiethnic cohorts and integrate genomic data with other molecular layers, such as transcriptomics, epigenomics, and proteomics. Functional studies using advanced tools, including CRISPR-based genome editing and in vitro immune cell models, are critical to validating the biological relevance of identified variants. Ultimately, translating pharmacogenomic findings into clinical guidelines will require concerted efforts across genetics, neurology, and pharmacology. Establishing robust, clinically validated biomarkers could enable the integration of pharmacogenomics into personalized medicine for MS, reducing trial-and-error prescribing and improving long-term therapeutic outcomes.

CONCLUSION

This review highlights the substantial effort invested in identifying pharmacogenomic determinants of treatment response in MS and underscores the complexity of translating these findings into clinical practice. While numerous genetic variants have been associated with differential responses to DMTs, most reported associations originate from small or population-specific cohorts, lack robust replication, and are rarely supported by functional validation. Consequently, no pharmacogenomic marker has yet met the evidentiary threshold required for incorporation into clinical guidelines for MS.

Nevertheless, the collective evidence supports the role of genetic variability in shaping interindividual differences in treatment efficacy and disease trajectory. The challenge moving forward is not the absence of candidate signals but the need to distinguish clinically meaningful predictors from spurious associations. Addressing this challenge will require large, prospective, multiethnic studies with harmonized outcome measures, integration of genomic data with transcriptomic and immunophenotypic layers, and mechanistic validation using experimental models.

Ultimately, the successful integration of pharmacogenomics into MS care has the potential to shift therapeutic decision-making away from trial-and-error approaches toward a precision-based framework, enabling earlier optimization of therapy and improved long-term outcomes. Until such markers are rigorously validated, pharmacogenomic findings should be interpreted cautiously and regarded as hypothesis-generating rather than actionable tools.

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Supplementary Table 1: http://balkanmedicaljournal.org/img/files/Table-1.xlsx

REFERENCES

1. Benedict RH, Bobholz JH. Multiple sclerosis. *Semin Neurol*. 2007;27:78-85. [CrossRef]
2. Haki M, Al-Biati HA, Al-Tameemi ZS, Ali IS, Al-Hussaniy HA. Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. *Medicine (Baltimore)*. 2024;103:e37297. [CrossRef]
3. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286. [CrossRef]
4. Ziemssen T, Derfuss T, de Stefano N, et al. Optimizing treatment success in multiple sclerosis. *J Neurol*. 2016;263:1053-1065. [CrossRef]
5. Lorefice L, Pitzalis M, Murgia F, Fenu G, Atzori L, Cocco E. Omics approaches to understanding the efficacy and safety of disease-modifying treatments in multiple sclerosis. *Front Genet*. 2023;14:1076421. Erratum in: *Front Genet*. 2023;14:1169919. [CrossRef]
6. Sánchez-Sanz A, Muñoz-Viana R, Sabín-Muñoz J, et al. Response to fingolimod in multiple sclerosis patients is associated with a differential transcriptomic regulation. *Int J Mol Sci*. 2024;25:1372. [CrossRef]
7. Singer BA, Feng J, Chiong-Rivero H. Early use of high-efficacy therapies in multiple sclerosis in the United States: benefits, barriers, and strategies for encouraging adoption. *J Neurol*. 2024;271:3116-3130. [CrossRef]
8. Tsareva E, Kulakova O, Boyko A, Favorova O. Pharmacogenetics of multiple sclerosis: personalized therapy with immunomodulatory drugs. *Pharmacogenet Genomics*. 2016;26:103-115. [CrossRef]
9. Río J, Nos C, Tintoré M, et al. Defining the response to interferon-beta in relapsing-remitting multiple sclerosis patients. *Ann Neurol*. 2006;59:344-352. [CrossRef]
10. Sormani MP, De Stefano N. Defining and scoring response to IFN-β in multiple sclerosis. *Nat Rev Neurol*. 2013;9:504-512. [CrossRef]
11. Freedman MS, Selchen D, Prat A, Giacomini PS. Managing multiple sclerosis: treatment initiation, modification, and sequencing. *Can J Neurol Sci*. 2018;45:489-503. [CrossRef]
12. Oreja-Guevara C, Martínez-Yélamos S, Eichau S, et al. Beyond lines of treatment: embracing early high-efficacy disease-modifying treatments for multiple sclerosis management. *Ther Adv Neurol Disord*. 2024;17:17562864241284372. [CrossRef]
13. Grossman I, Knappertz V, Laifenfeld D, et al. Pharmacogenomics strategies to optimize treatments for multiple sclerosis: Insights from clinical research. Prog Neurobiol. 2017;152:114-130. [CrossRef]
14. Harris VK, Sadiq SA. Biomarkers of therapeutic response in multiple sclerosis: current status. *Mol Diagn Ther*. 2014;18:605-617. [CrossRef]
15. Cerqueira JJ, Compston DAS, Geraldes R, et al. Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest

advances in multiple sclerosis? *J Neurol Neurosurg Psychiatry*. 2018;89:844-850. [CrossRef]
16. Lee S, Son WS, Yang HB, et al. A glycoengineered interferon-β mutein (R27T) generates prolonged signaling by an altered receptor-binding kinetics. *Front Pharmacol*. 2019;9:1568. [CrossRef]
17. Leyva L, Fernández O, Fedetz M, et al. IFNAR1 and IFNAR2 polymorphisms confer susceptibility to multiple sclerosis but not to interferon-beta treatment response. *J Neuroimmunol*. 2005;163:165-171. [CrossRef]
18. Bustamante MF, Nurtdinov RN, Río J, Montalban X, Comabella M. Baseline gene expression signatures in monocytes from multiple sclerosis patients treated with interferon-beta. *PLoS One*. 2013;8:e60994. [CrossRef]
19. Vilaseca A, Urcelay E, Malhotra S, et al. The variant rs7665090 is associated with interferon-beta response in multiple sclerosis patients. *Eur J Neurol.* 2025;32:e70227. [CrossRef]
20. Hoffmann S, Cepok S, Grummel V, et al. HLA-DRB1*0401 and HLA-DRB1*0408 are strongly associated with the development of antibodies against interferon-beta therapy in multiple sclerosis. *Am J Hum Gene*t. 2008;83:219-227. Erratum in: *Am J Hum Genet*. 2008;83:541. [CrossRef]
21. Sorensen PS. Neutralizing antibodies against interferon-Beta. *Ther Adv Neurol Disord*. 2008;1:125-141. [CrossRef]
22. Cénit MD, Blanco-Kelly F, de las Heras V, et al. Glypican 5 is an interferon-beta response gene: a replication study. *Mult Scler*. 2009;15:913-917. [CrossRef]
23. Byun E, Caillier SJ, Montalban X, et al. Genome-wide pharmacogenomic analysis of the response to interferon beta therapy in multiple sclerosis. *Arch Neurol.* 2008;65:337-344. [CrossRef]
24. O'Doherty C, Favorov A, Heggarty S, et al. Genetic polymorphisms, their allele combinations and IFN-beta treatment response in Irish multiple sclerosis patients. *Pharmacogenomics*. 2009;10:1177-1186. [CrossRef]
25. Mahurkar S, Moldovan M, Suppiah V, et al; Australian and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene); King C. Response to interferon-beta treatment in multiple sclerosis patients: a genome-wide association study. *Pharmacogenomics J*. 2017;17:312-318. [CrossRef]
26. Sayad A, Ghafouri-Fard S, Omrani MD, Noroozi R, Taheri M. Myxovirus resistance protein A (MxA) polymorphism is associated with IFNβ response in Iranian multiple sclerosis patients. *Neurol Sci*. 2017;38:1093-1099. [CrossRef]
27. Cunningham S, Graham C, Hutchinson M, et al. Pharmacogenomics of responsiveness to interferon IFN-beta treatment in multiple sclerosis: a genetic screen of 100 type I interferon-inducible genes. *Clin Pharmacol Ther.* 2005;78:635-646. [CrossRef]
28. Kulakova O, Bashinskaya V, Kiselev I, et al. Pharmacogenetics of glatiramer acetate therapy for multiple sclerosis: the impact of genome-wide association studies identified disease risk loci. *Pharmacogenomics.* 2017;18:1563-1574. [CrossRef]
29. Carlson RJ, Doucette JR, Nazarali AJ. Current developments in pharmacogenomics of multiple sclerosis. *Cell Mol Neurobiol*. 2014;34:1081-1085. [CrossRef]
30. Ayatollahi SA, Ghafouri-Fard S, Taheri M, Noroozi R. The efficacy of interferon-beta therapy in multiple sclerosis patients: investigation of the RORA gene as a predictive biomarker. *Pharmacogenomics J*. 2020;20:271-276. [CrossRef]
31. Alvarez-Lafuente R, Blanco-Kelly F, Garcia-Montojo M, et al. CD46 in a Spanish cohort of multiple sclerosis patients: genetics, mRNA expression and response to interferon-beta treatment. *Mult Scler*. 2011;17:513-520. [CrossRef]
32. Torbati S, Karami F, Ghaffarpour M, Zamani M. Association of CD58 polymorphism with multiple sclerosis and response to interferon β therapy in a subset of Iranian population. *Cell J*. 2015;16:506-513. [CrossRef]
33. Bustamante MF, Morcillo-Suárez C, Malhotra S, et al. Pharmacogenomic study in patients with multiple sclerosis: responders and nonresponders to IFN-β. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e154. [CrossRef]
34. Martínez-Aguilar L, Pérez-Ramírez C, Maldonado-Montoro MDM, et al. Effect of genetic polymorphisms on therapeutic response in multiple sclerosis relapsing-remitting patients treated with interferon-beta. *Mutat Res Rev Mutat Res.* 2020;785:108322. [CrossRef]
35. Weber MS, Hohlfeld R, Zamvil SS. Mechanism of action of glatiramer acetate in treatment of multiple sclerosis. *Neurotherapeutics.* 2007;4:647-653. [CrossRef]
36. Dhib-Jalbut S, Marks S. Interferon-beta mechanisms of action in multiple sclerosis. *Neurology.* 2010;74:S17-24. [CrossRef]
37. Dhib-Jalbut S, Valenzuela RM, Ito K, Kaufman M, Ann Picone M, Buyske S. HLA DR and DQ alleles and haplotypes associated with clinical response to glatiramer acetate in multiple sclerosis. *Mult Scler Relat Disord.* 2013;2:340-348. [CrossRef]
38. Sahbaz A, Selcuk BO, Domac FM, et al. Effects of HLA-DRA, HLA-DQA1 and IL-6 gene variations to glatiramer acetate resistance in multiple sclerosis patients. *Biochem Genet.* 2026;64:1161-1173. [CrossRef]
39. Tsareva EY, Kulakova OG, Boyko AN, et al. Allelic combinations of immune-response genes associated with glatiramer acetate treatment response in Russian multiple sclerosis patients. *Pharmacogenomics.* 2012;13:43-53. [CrossRef]
40. Ristić S, Starčević Čizmarević N, Lavtar P, et al. Angiotensin-converting enzyme insertion/deletion gene polymorphism and interferon-β treatment response in multiple sclerosis patients: a preliminary report. *Pharmacogenet Genomics.* 2017;27:232-235. [CrossRef]
41. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and its mechanism of action in multiple sclerosis. *Drugs.* 2014;74:659-674. [CrossRef]
42. Pawlik A, Herczynska M, Kurzawski M, Safranow K, Dziedziejko V, Drozdzik M. The effect of exon (19C>A) dihydroorotate dehydrogenase gene polymorphism on rheumatoid arthritis treatment with leflunomide. *Pharmacogenomics.* 2009;10:303-309. [CrossRef]
43. Linker RA, Lee DH, Ryan S, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the NRF2 antioxidant pathway. *Brain.* 2011;134:678-692. [CrossRef]
44. Scannevin RH, Chollate S, Jung MY, et al. Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway. *J Pharmacol Exp Ther.* 2012;341:274-284. [CrossRef]
45. Spencer CM, Crabtree-Hartman EC, Lehmann-Horn K, Cree BA, Zamvil SS. Reduction of CD8(+) T lymphocytes in multiple sclerosis patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm.* 2015;2:e76. [CrossRef]
46. Amin NS, Abd El-Aziz MK, Hamed M, Moustafa RR, El Tayebi HM. Rs205764 and rs547311 in linc00513 may influence treatment responses in multiple sclerosis patients: a pharmacogenomics Egyptian study. *Front Immunol.* 2023;14:1087595. [CrossRef].
47. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol.* 2009;158:1173-1182. [CrossRef]
48. Ayzenberg I, Hoepner R, Kleiter I. Fingolimod for multiple sclerosis and emerging indications: appropriate patient selection, safety precautions, and special considerations. *Ther Clin Risk Manag.* 2016;12:261-272. [CrossRef]
49. Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov.* 2010;9:883-897. [CrossRef]
50. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol.* 2010;33:91-101. [CrossRef]
51. Moheghi N, Sasannezhad P, John Walley A. No association between single-nucleotide polymorphisms of the *S1PR1* gene or interleukin-17 levels with fingolimod response in a small group of Iranian relapsing-remitting multiple sclerosis patients: a case-control study. *Cell J.* 2024;26:185-193. [CrossRef]
52. Ramagopalan SV, Knight JC, Ebers GC. Multiple sclerosis and the major histocompatibility complex. *Curr Opin Neurol.* 2009;22:219-225. [CrossRef]
53. Dilara RM, Alper B, Turkish Familial MS Consortium, et al. Pharmacogenomic analysis in Turkish familial multiple sclerosis cohort: associations between HLA alleles and disease-modifying therapies [PP-009]. In: 6th International Molecular Immunology and Immunogenetics Congress (MIMIC-VI 2025). [CrossRef]
54. Khoy K, Mariotte D, Defer G, Petit G, Toutirais O, Le Mauff B. Natalizumab in multiple sclerosis treatment: from biological effects to immune monitoring. *Front Immunol.* 2020;11:549842. [CrossRef]
55. Clarelli F, Corona A, Pääkkönen K, et al. Pharmacogenomics of clinical response to Natalizumab in multiple sclerosis: a genome-wide multi-centric association study. *J Neurol.* 2024;271:7250-7263. Erratum in: *J Neurol.* 2025;272:423. [CrossRef]
56. Auricchio F, Scavone C, Cimmaruta D, et al. Drugs approved for the treatment of multiple sclerosis: review of their safety profile. *Expert Opin Drug Saf.* 2017;16:1359-1371. [CrossRef]
57. Cotte S, von Ahsen N, Kruse N, et al. ABC-transporter gene-polymorphisms are potential pharmacogenetic markers for mitoxantrone response in multiple sclerosis. *Brain.* 2009;132:2517-2530. [CrossRef]
58. Grey Née Cotte S, Salmen Née Stroet A, von Ahsen N, et al. Lack of efficacy of mitoxantrone in primary progressive multiple sclerosis irrespective of pharmacogenetic factors: a multi-center, retrospective analysis. *J Neuroimmunol.* 2015;278:277-279. [CrossRef]

59. Whirl-Carrillo M, Huddart R, Gong L, et al. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2021;110:563-572. [CrossRef]
60. Yalın OÖ, Gökdoğan Edgünlü T, Karakaş Çelik S, et al. Novel SNARE complex polymorphisms associated with multiple sclerosis: signs of synaptopathy in multiple sclerosis. *Balkan Med J.* 2019;36:174-178. [CrossRef]
61. Koç S, Şen S, Terzi Y, et al. Clinical, demographic, and radiological characteristics of patients demonstrating antibodies against myelin oligodendrocyte glycoprotein. *Balkan Med J.* 2024;41:272-279. [CrossRef]