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Genetic polymorphisms and adverse effects that affect the natalizumab clinical response: a review

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ABSTRACT

The clinical response to natalizumab in patients with multiple sclerosis (MS) may be significantly influenced by genetic variation. Mutations in genes related to the drug's mechanism of action or the pathological milieu of MS can contribute substantially to interindividual differences in treatment outcomes. This review aims to provide an overview of previous studies that have examined genetic polymorphisms associated with the clinical efficacy of natalizumab. A systematic literature search was conducted across the PubMed, Google Scholar, and ResearchGate databases using targeted keywords relevant to the subject matter. Several genetic loci were found to be linked to natalizumab responsiveness, including the integrin subunit alpha 4 (*ITGA4*), the nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase 1 (*NQO1*), the glutathione S-transferase pi 1 (*GSTP1*), the glycoprotein VI platelet (*GP6*), and the alpha serine/threonine-protein kinase (*AKT1*) genes. Further research is warranted in order to explore the influence of genetic factors on treatment response across diverse populations. By synthesizing existing evidence, this review underscores the role of pharmacogenomics in optimizing the use of natalizumab and highlights its efficacy and safety in improving clinical outcomes.

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1. Introduction

Natalizumab, a recombinant humanized monoclonal antibody targeting the α4-integrin (ITGA4) component of the cell adhesion molecule, is among the most effective therapies for active relapsing-remitting multiple sclerosis (RRMS)[1] and has also been approved for the treatment of inflammatory bowel disease[2]. In addition to previously identified factors, emerging research indicates that

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genetic variation may significantly influence therapeutic response in patients with multiple sclerosis (MS). Mutations in genes associated with natalizumab's mechanism of action or the pathological features of MS can substantially modulate treatment efficacy. This review aimed at synthesizing prior research investigating genetic polymorphisms that affect the clinical responsiveness to natalizumab.

2. Methodology

A comprehensive and systematic literature search was conducted using the PubMed, Google Scholar, and ResearchGate databases. Search keywords included "natalizumab", "genetic polymorphism", "multiple sclerosis", and "response". The initial query identified fifteen distinct publications. Two of the authors independently reviewed the titles and the abstracts of these studies, excluding those deemed irrelevant. Search results were subsequently imported into Mendeley, and articles were selected based on the following inclusion criteria: (i) studies examining associations between clinical response to natalizumab and genetic variation, (ii) availability of sufficient extractable data, and (iii) reporting of genotype or allele frequencies in patient cohorts. Exclusion criteria included duplicate publications, case studies, book chapters, letters to the editor, and conference proceedings. A standardized data extraction checklist was used in order to compile relevant information, including the first author's name, journal and year of publication, location, age range or mean age, genotyping method, and genotype frequencies in case and control groups. To ensure reliability, the three authors independently extracted the data. Discrepancies were resolved by consensus.

3. Response to natalizumab in MS

The integration of pharmacogenetics and pharmacogenomics into MS therapy aims to identify genetic markers that can predict drug toxicity and treatment response. Recent studies suggest that genetic diversity may play a critical role in interindividual variability in natalizumab efficacy. Variants affecting either the drug's mechanism of action or MS pathology are of particular relevance.

A point mutation in exon 24 of the ITGA4 gene results in a substitution of arginine (CGG) with glutamine (CAG) at position 3061. This 3061G variant may alter the conformation of the subunit, thereby increasing its affinity for vascular cell adhesion molecule 1 in MS patients[3].

Genetic polymorphisms have also been associated with differential drug response and increased risk of adverse reactions (Table 1). A study from Iraq has linked natalizumab response to the presence of the +3061 (G>A) missense mutation in *ITGA4*. The AG genotype was identified as a potential biomarker for non-responsiveness among Iraqi MS patients, thereby predicting ineffectiveness prior to treatment initiation[4].

In contrast, a different study involving 60 healthy individuals and 66 Iraqi MS patients has found no significant association between natalizumab responsiveness and the *ITGA4* polymorphism rs113276800 (−269C/A)[5]. Residues Gln-152, Lys-201, and Lys-256 of the *ITGA4*-encoded subunit are considered critical for natalizumab binding[6]. Moreover, in a cohort of 62 MS patients, no associations were found between natalizumab response and the rs200000911 (A/T) missense mutation, intronic mutation rs936587744 (T/C), and rs2305588 (T/C)[7].

Another potential mechanism by which natalizumab exerts its effects is through the reduction of oxidative stress. Antioxidant activity may correlate with improved clinical outcomes following treatment. The detoxifying enzyme nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase 1 (NQO1), which inhibits reactive oxygen species generation, was studied for its rs1800566 C/A polymorphism. Similarly, the rs1695 A/G polymorphism in the gene of the phase II detoxification enzyme glutathione S-transferase pi 1 (GSTP1) was examined for its role in treatment response[8]. Alexoudi *et al.*[8] have analysed the impact of *NQO1* and *GSTP1* genotypes on natalizumab efficacy in 130 MS patients. The study also examined correlations with clinical subtypes and evaluated the combined effects of the *GSTP1* 313 A/G (rs1695) and *NQO1* 609

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Table 1. Overview of studies that assess the clinical response of multiple sclerosis (MS) patients to natalizumab, based on genetic variations. Abbreviations used: AKT1, alpha serine/threonine-protein kinase; GP6, glycoprotein VI platelet; GSTP1, glutathione S-transferase pi 1; ITGA4, integrin subunit alpha 4; NQO1, nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase 1.

Study	Country and year of the study	Study design	Studied polymorphisms	Genotype proportion		Study outcome
				Responders	Non-responders	
Ahmed *et al.*[4]	Iraq (2023)	single-centered, prospective, cross-sectional study	*ITGA4* rs1143676 (+3061, G/A) (N=59)	GG: 0 AG: 8 AA: 21 (N=29)	GG: 0 AG: 17 AA: 13 (N=30)	the AG genotype has been shown to significantly raise the likelihood of not responding to natalizumab
Khaleil *et al.*[5]	Iraq (2022)	single-centered, prospective, case-controlled study	*ITGA4* rs113276800 (−269, C/A) (N=66)	CC: 16 CA: 14 CC: 2 (N=32)	CC: 18 CA: 14 CC: 2 (N=34)	the rs113276800 polymorphism does not affect how MS patients respond to natalizumab
Ahmed *et al.*[7]	Iraq (2023)	single-centered prospective cross sectional study	*ITGA4* rs200000911 (256, A/T) (N=62) *ITGA4* rs936587744 (intronic, T/C) (N=62) *ITGA4* rs2305588 (intronic, T/C) (N=62)	AA: 23 AT: 9 TT: 0 (N=32) TT: 18 TC: 14 CC: 0 (N=32) TT: 22 TC: 10 CC: 0 (N=32)	AA: 22 AT: 8 TT: 0 (N=30) TT: 17 TC: 13 CC: 0 (N=30) TT: 23 TC: 4 CC: 3 (N=30)	no correlation was found between the missense mutation rs200000911 (A/T), rs936587744 (T/C), and rs2305588 (T/C) intronic mutations with the response to natalizumab
Alexoudi *et al.*[8]	Greece (2016)	single-centered, prospective study	*GSTP1* rs1695 (313, A/G) (N=129) *NQO1* rs1800566 (609, C/T) (N=124)	AA: 54 AG: 48 GG: 12 (N=114) CC: 63 CT: 41 TT: 5 (N=109)	AA: 6 AG: 9 GG: 0 (N=15) CC: 5 CT: 9 TT: 1 (N=15)	a significantly greater frequency of double *GSTP1* and *NQO1* mutant polymorphisms was observed when comparing non-responders to responders
Al-Mojel *et al.*[9]	Kuwait (2019)	single-centered, prospective study	*GP6* rs2304166 (940, C/G) exome cohort (N=33) replicate cohort (N=86)	GG: 7 GC: 12 CC: 4 (N=23) GG: 20 GC: 37 CC: 10 (N=67)	GG: 0 GC: 3 CC: 7 (N=10) GG: 1 GC: 4 CC: 14 (N=19)	a poor response to natalizumab is linked to the CC genotype; rs2304166 in *GP6* may be used as a genetic predictor of how MS patients respond to natalizumab
Rossi *et al.*[10]	Italy (2013)	prospective study	*AKT1* rs2498804 (G/T) (N=67)	GG: 29 GT/TT: 38 (N=67)	none	T allele carriers were shown to have a lower lymphocyte count and a lower risk of recurrence after therapy

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C/T (rs1800566) polymorphisms[8]. Given the role of these enzymes in mitigating inflammation-induced oxidative stress, genotype variation may influence disease progression. Notably, double mutant genotypes in *GSTP1* and *NQO1* were more prevalent among non-responders, while wild-type or singly mutated variants correlated with better clinical outcomes[8].

A missense mutation (rs2304166) in the glycoprotein VI platelet (GP6) gene, which is involved in collagen-induced platelet aggregation and thrombus formation, has been identified *via* exome sequencing. In MS patients, the homozygous CC genotype has been associated with poor response to natalizumab[9]. The study evaluated 33 patients *via* sequencing, and has subsequently validated findings in an expanded cohort of 86 MS patients, thereby confirming the association[9].

Finally, the rs2498804 G/T polymorphism in the AKT1 gene (encoding a serine/threonine protein kinase involved in cell proliferation) has been analysed by Rossi *et al.*[10] in 67 Italian RRMS patients. The T allele was linked to reduced lymphocyte counts and lower relapse risk following natalizumab therapy[10].

4. Conclusion

Poor responsiveness to natalizumab has been linked to the homozygous CC genotype of the rs2304166 variant in *GP6*, which may be associated with progressive MS disability. Continued research is needed in order to elucidate the relationship between specific genetic variants and natalizumab responsiveness, with a focus on identifying the most influential genes.

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Conflicts of interest

None exist.

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