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The Variant rs7665090 Is Associated With Interferon-Beta Response in Multiple Sclerosis Patients

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ABSTRACT

Background: GG homozygosity for the risk gene variant rs7665090 has been reported to enhance nuclear factor kappa B (NFκB) activity in T cells from multiple sclerosis (MS) patients. Here, we investigated the association between this polymorphism and the response to different disease-modifying therapies in MS.

Methods: The rs7665090 polymorphism was genotyped in 558 MS patients treated with injectable therapies [IFNβ ($n = 213$) and glatiramer acetate ($n = 55$)], oral therapies [dimethylfumarate ($n = 97$), teriflunomide ($n = 41$), and fingolimod ($n = 37$)], and natalizumab ($n = 115$). Treatment response was assessed after 1 year for injectable therapies using the Rio Score, which considers relapses, EDSS progression, and radiological activity on MRI. For oral therapies and natalizumab, response was evaluated after 2 years based on clinical and radiological disease activity. Univariable and multivariable logistic regression analyses were performed to assess treatment response for each therapy independently.

Results: GG homozygosity was associated with a favorable response outcome in patients treated with IFNβ in the multivariable analysis after adjusting for age and EDSS at treatment onset [OR 0.42 (0.18–0.94); $p = 0.037$]. This finding was restricted to MS patients carrying the GG risk genotype and seemed specific for IFNβ treatment, since the rs7665090 polymorphism did not influence the response to the other MS therapies.

Conclusion: The polymorphism rs7665090 is associated with a favorable response to IFNβ. This study illustrates how genotyping this polymorphism could serve as a useful biomarker in clinical practice to help identify MS patients who are likely to respond favorably to treatment, and encourages further replication in larger cohorts.

1 | Introduction

The treatment landscape for patients with multiple sclerosis (MS) has changed dramatically over the last two decades and currently includes a number of injectable therapies, oral therapies, and monoclonal antibodies [1]. Injectable therapies embrace interferon-beta (IFNβ) and glatiramer acetate. IFNβ was the first therapy approved in 1993 for the treatment of patients

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with relapsing–remitting MS (RRMS) whose beneficial effects are most likely related to its anti-inflammatory and immunomodulatory properties [2]. Glatiramer acetate is a random polymer of four amino acids antigenically similar to myelin basic protein [2], which was the second therapy approved in 1996 for the prevention of MS relapses in patients with RRMS. Oral therapies include, among others: (i) dimethyl fumarate, an immunomodulatory therapy approved in 2013 for the treatment of RRMS patients with antioxidant properties via upregulation of the transcription factor Nrf-2 [3]; (ii) teriflunomide, an oral therapy approved in 2012 for the treatment of RRMS patients that acts by reversibly inhibiting mitochondrial dihydroorotate dehydrogenase, the rate limiting enzyme in the de novo pyrimidine synthesis [4]; (iii) sphingosine 1-phosphate (S1P) receptor modulators, which include fingolimod, ozanimod, ponesimod, and siponimod. They correspond to a category of drugs that block the egress of lymphocytes from lymph nodes and differ in their affinities for S1P1 and S1P5 receptors [5]. Fingolimod was the first orally administered drug approved in 2010 for the treatment of RRMS patients [5]. Monoclonal antibodies comprise natalizumab, alemtuzumab, and anti-CD20 therapies. Natalizumab is a humanized recombinant monoclonal antibody directed against the α4 subunit of the α4β1 integrin, which mediates lymphocyte migration through the blood–brain barrier [6]. Although there are many different options to treat MS patients, treatment response is highly heterogeneous and varies significantly among patients. In this setting, identifying biomarkers with the potential to predict the response to the different therapeutic options is crucial for developing personalized medicine in MS.

The interindividual variability observed in drug response is most likely explained by variants in the patient DNA, which are probably associated with changes in the expression, activity, and substrate specificity of the corresponding gene products. One of the gene variants associated with MS risk, rs7665090 [7, 8], has been found to modulate nuclear factor kappa B (NFκB) responses. NFκB serves as a master regulator of both innate and adaptive immunity, and it is also involved in the activation of astrocytes, which play a key role in the formation of MS lesions [9]. In fact, astrocyte-specific inhibition of NFκB activation has been shown to ameliorate MS-like disease in animal models, such as experimental autoimmune encephalomyelitis (EAE) [10]. Interestingly, NFκB activation in response to TNFα and IL-1β stimulation was significantly higher in astrocytes derived from induced pluripotent stem cells of GG carriers compared to those with the AA genotype [9]. Regarding the relationship between NFκB activation and MS risk, patients carrying the rs7665090*GG genotype showed enhanced NFκB activity in T cells [11]. In MS autopsy cases, the number of perivascular CD3+ T cells in the rims of chronic active lesions was significantly higher in GG homozygotes [9]. Additionally, the NFκB rs7665090*G risk variant has been associated with enhanced astroglial NFκB signaling, leading to increased lymphocyte recruitment, CNS infiltration by the peripheral immune system, and greater neurotoxicity, resulting in larger lesion sizes [9].

Considering the role that NFκB plays as a central regulator of inflammation [12], in the present study, we aimed to investigate the relationship between the rs7665090 polymorphism and the response to a number of disease-modifying therapies in a well-characterized cohort of MS patients.

2 | Materials and Methods

2.1 | Patients and Criteria of Treatment Response

We included patients with a diagnosis of RRMS according to the current McDonald MS criteria [13] recruited at the Multiple Sclerosis Center of Catalonia (Cemcat; Barcelona) and the Hospital Clínico San Carlos (Madrid) who were receiving treatment with IFNβ, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, or natalizumab.

Each type of treatment was evaluated independently. Response to the injectable therapies IFNβ and glatiramer acetate was assessed after 1 year of treatment using the Rio Score [14]. The Rio Score classifies patients according to the following criteria: (i) presence of 1 or more relapses; (ii) confirmed increase at 6 months of 1 or more points in the Expanded Disability Status Scale (EDSS) score; (iii) presence of 3 or more active lesions (gadolinium enhancing lesions or new or enlarging T2 lesions) on the 1-year brain magnetic resonance imaging (MRI). Patients with Rio Score ≥ 2 were considered nonresponders, and patients with scores of 0 or 1 were considered responders. Response criteria for patients treated with the oral therapies dimethyl fumarate, teriflunomide, fingolimod, or the intravenously administered monoclonal antibody natalizumab were applied after 2 years of treatment, taking into account their response over this period [15]. Patients were labeled as responders when there was no evidence of disease activity (NEDA) defined by the absence of relapses, EDSS progression, and MRI activity during the follow-up period. On the other hand, nonresponders were patients with evidence of disease activity (EDA) defined by the presence of ≥ 1 relapses, sustained increase of at least 1 point in the EDSS score, or presence of active lesions (either new or enlarging T2 lesions compared with baseline MRI scan or gadolinium-enhancing lesions) during the follow-up period.

2.2 | Genotyping

Genomic DNA from peripheral blood samples was obtained using standard methods. Genotyping of rs7665090 was performed by means of the 5′ nuclease assay technology for allelic discrimination using fluorogenic TaqMan probes, commercially available from Applied Biosystems through the made to order service. In brief, a 1x Taqman Genotyping Master Mix (Applied Biosytems) was used for a PCR reaction with 10 ng of genomic DNA in a total volume of 5 μL. Amplification was performed using QuantStudio 7 Pro (Applied Biosystems) following the recommended protocol. Endpoint reading was performed on the same QuantStudio 7 Pro (Applied Biosystems) instrument, and subsequent analysis was carried out with QuantStudio 7 Pro Design and Analysis Software (Applied Biosystems). After the analysis, patients were classified according to the polymorphism as AA, GG, and AG. All patients included in the study were genotyped in a single center (Cemcat). Hardy–Weinberg equilibrium was studied for the different cohorts (Table S1);

however, the observed genotype distribution could depart from the one theoretically expected as an MS-risk polymorphism, especially when a pharmacogenetic effect is claimed in some of the cohorts, and their small size should also be considered.

2.3 | Statistical Analysis

Baseline characteristics were collected, and the Shapiro–Wilk test confirmed a normal distribution for each variable within each treatment group. Similarly, age and EDSS were normally distributed according to the Shapiro–Wilk test in each treatment group. Two comparisons were considered for genotype association analysis: GG homozygotes versus the combination of AG heterozygotes and AA homozygotes, and the combination of GG and AG versus AA. Comparison of genotype frequencies between responders and nonresponders for each treatment was performed with univariable and multivariable logistic regression analyses. The multivariable analysis included variables that had a p value <0.1 in the univariable logistic regression analysis. p values <0.05 were considered significant. STATA/BE version 17 for Windows (StataCorp. Stata Statistical Software: Release 17. StataCorp LLC, 2021. Software) was used for statistical analysis.

2.4 | Ethical Issues

The study was approved by the local ethics committees and written informed consent was obtained from all patients. All patient data were anonymized prior to analysis. Each participant was assigned a unique identification code, and all personal identifiers were removed from the dataset to prevent any direct or indirect identification of individuals. Access to the data was restricted to authorized members of the research team only. This study followed all recommendations from the "World Medical Assembly" approved in Helsinki 1964 and subsequently modifications, and from the EU-ISO 14155.

3 | Results

3.1 | rs7665090 Polymorphism

The MS-risk single nucleotide polymorphism (SNP) rs7665090 is located on chromosome 4 at position 103,551,603 between the NFκB subunit 1 (*NFKB1*) (Chr4: 103,422,486-103,538,459) and the mannosidase beta (*MANBA*) genes (Chr4: 103,552,660-103,682,151). The frequency of the rs7665090*G allele varies among ethnic groups, ranging from 66% in African populations to 41% in South Asian populations, with 49% in European populations. Previous studies have confirmed the presence of different linkage disequilibrium (LD) blocks in the region of rs7665090 (chr4:103551603) (Hitomi et al., 2019; González-Jiménez et al., 2022). In this context, we used the LDproxy Tool (https://ldlink.nih.gov/?tab=ldproxy) to search for SNPs in LD (Figure 1). We identified 74 additional SNPs in LD ($r^2>0.9$) and only six of them were ranked as 1f and could act as eQTLs in different tissues according to RegulomeDB (Table S2). Importantly, only rs7665090 exhibited the highest regulatory scores according to RegulomeDB, and acted not only as an eQTL for *NKFB1* but also for other genes such as CDGSH iron sulfur domain 2 (*CISD2*), *MANBA*, 3-hydroxybutyrate dehydrogenase 2 (*BDH2*), and keratin 8 pseudogene 46 (*KRT8P46*).

3.2 | Association Between the rs7665090 Variant and the Response to Therapies

As shown in Table 1, a total of 558 MS patients were included in the study. Patients were categorized based on treatment received: IFNβ ($n=213$), glatiramer acetate ($n=55$), dimethyl fumarate ($n=97$), teriflunomide ($n=41$), fingolimod ($n=37$), and natalizumab ($n=115$). In patients receiving injectable therapies, 23.5% and 12.7% were considered nonresponders to IFNβ and glatiramer acetate, respectively. Regarding the oral therapies, 39.2% of patients were nonresponders to dimethyl fumarate, 58.5% to teriflunomide, and 40.5% to fingolimod. As for natalizumab, 28.7% of patients were labeled as nonresponders (Table 2). Baseline characteristics such as age, sex, and EDSS scores did not differ significantly between responders and nonresponders in each treatment group, except for older age in responders receiving IFNβ ($p=0.006$) and glatiramer acetate ($p=0.024$), and lower EDSS scores at treatment onset in IFNβ responders ($p<0.001$; Table 1).

Table 2 depicts the distribution of genotype frequencies for rs7665090 in responders and nonresponders to the different treatments. Differences in genotype frequencies between responders and nonresponders were only significant for IFNβ (in Bold). As shown in Table 2, 32.5% of responders were GG homozygotes versus 14% of nonresponders. Among patients treated with IFNβ, 88.3% of those with the GG genotype were responders, compared to 69.6% of those with the AG genotype and 78.9% of those with the AA genotype. In comparison, for patients treated with glatiramer acetate, 88.2% of those with the GG genotype were responders, similar to 84.6% of those with the AG genotype and 91.7% of those with the AA genotype. In univariable logistic regression analysis, GG homozygosity was associated with a favorable response to IFNβ [odds ratio—OR (95% confidence interval) 0.35 (0.15–0.82); $p=0.014$] (Table 2; Figure 2). The association with the response outcome remained significant in multivariable analysis after the inclusion of age and EDSS at treatment onset as covariates [OR 0.42 (0.18–0.94); $p=0.037$]. In contrast, GG homozygosity was not associated with the response to glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, or natalizumab. Similarly, the combination of GG and AG versus AA was not associated with the response to any of the treatments included in the study (Table 2; Figure 2).

4 | Discussion

In this study, we evaluated the association between the rs7665090 polymorphism and the response to MS therapies. This variant has been previously described to enhance NFκB activity, which is a prototypical proinflammatory signaling pathway [11], and we expected that it would be most likely associated with a lack of response to therapies. Surprisingly, GG homozygosity was more represented in MS patients responding to IFNβ and was associated with a favorable response to this treatment after 1 year of treatment. This finding was restricted to MS patients under

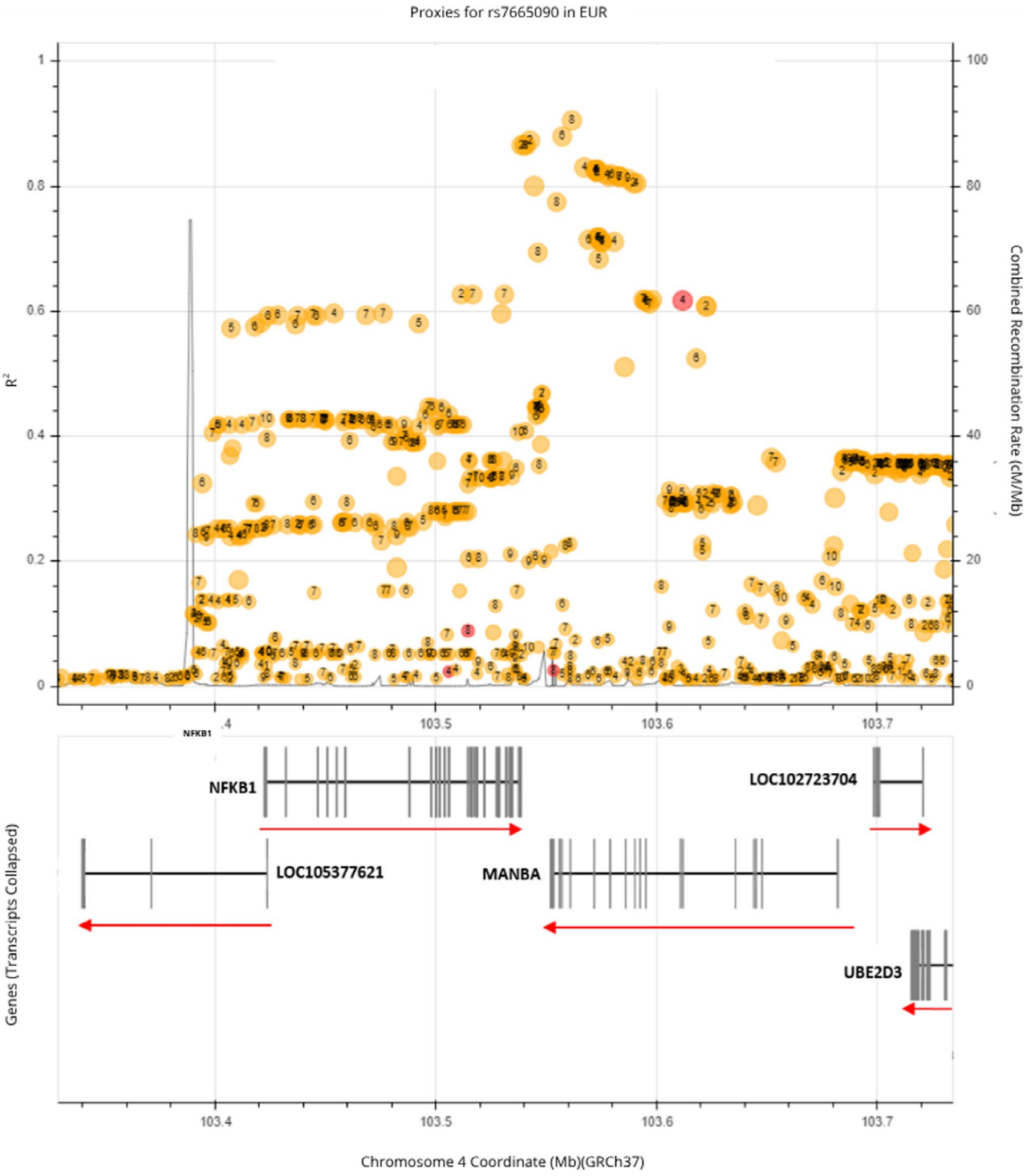

FIGURE 1 | Proxies for rs7665090 in European (EUR) populations (NIH LD proxy tool). In orange noncoding and in red coding variants, numbers and circle sizes represent the regulatory potential (FORGEdb) and the minor allele frequency of the polymorphisms, respectively. R^2 on the Y-axis refers to the correlation coefficient, which measures the linkage disequilibrium between the rs7665090 variant and other proxies. Arrows indicate the transcriptional direction of the genes. LOC depicts ncRNAs.

IFNβ treatment, since the rs7665090 polymorphism did not influence the response to the other MS therapies included in the study, such as glatiramer acetate, oral therapies, or natalizumab.

The association between the variant rs7665090 and the response to IFNβ is probably related to its mechanism of action. IFNβ is a type 1 IFN that binds to a unique heterodimeric receptor of the cell surface composed of the IFN receptor 1 (IFNAR1) and 2 (IFNAR2) subunits. Through activation of the JAK–STAT signaling pathway, it leads to the assembly of an IFN-stimulated gene factor 3 (ISGF3) complex that translocates to the nucleus, binds to IFN-stimulated response elements (ISREs), and initiates the transcription of type I IFN-responsive genes [16]. IFNβ has been reported to modulate

TABLE 1 | Baseline characteristics of patients included in the study.

	Responders	Nonresponders	Total ($n = 558$)	p
IFNβ, *n* (%)	163 (76.5)	50 (23.5)	213 (38.2)	
Age	32.0 (0.7)	27.3 (1.2)	30.9 (0.6)	**0.006**
Sex (female), *n* (%)	115 (70.6)	35 (70.0)	150 (70.4)	0.858
EDSS	1.8 (0.1)	2.5 (0.2)	2.0 (0.1)	**< 0.001**
Glatiramer acetate, *n* (%)	48 (87.3)	7 (12.7)	55 (9.9)	
Age	34.2 (1.1)	27.0 (2.2)	33.2 (1.1)	**0.024**
Sex (female), *n* (%)	33 (68.8)	4 (57.1)	37 (67.3)	0.585
EDSS	1.9 (0.2)	1.8 (0.4)	1.9 (0.2)	0.814
Dimethyl fumarate, *n* (%)	59 (60.8)	38 (39.2)	97 (17.4)	
Age	40.2 (1.7)	40.0 (1.2)	40.1 (1.0)	0.952
Sex (female), *n* (%)	38 (64.4)	20 (52.6)	58 (59.8)	0.154
EDSS	1.9 (0.8)	1.4 (0.4)	1.6 (0.4)	0.522
Teriflunomide, *n* (%)	17 (41.5)	24 (58.5)	41 (7.3)	
Age	41.7 (1.7)	40.6 (2.0)	41.1 (1.3)	0.696
Sex (female), *n* (%)	10 (58.8)	16 (66.7)	26 (63.4)	0.505
EDSS	1.7 (0.8)	1.6 (0.4)	1.6 (0.5)	0.899
Fingolimod, *n* (%)	22 (59.5)	15 (40.5)	37 (6.6)	
Age	39.4 (2.5)	33.3 (2.5)	36.7 (1.8)	0.095
Sex (female), *n* (%)	14 (63.6)	12 (80.0)	26 (70.3)	0.379
EDSS	2.3 (0.5)	2.0 (0.4)	2.2 (0.3)	0.622
Natalizumab, *n* (%)	82 (71.3)	33 (28.7)	115 (20.6)	
Age	37.5 (1.2)	38.3 (1.9)	37.8 (1.0)	0.711
Sex (female), *n* (%)	53 (64.6)	23 (69.7)	76 (66.1)	0.274
EDSS	2.7 (1.0)	2.9 (1.1)	2.8 (0.8)	0.978

Note: Age and EDSS are expressed as mean (standard deviation) and referred to treatment onset. Variables significantly associated with the outcome ($p < 0.05$) were shown in bold.
Abbreviations: EDSS, Expanded Disability Score Scale; IFNβ, interferon-beta.

cellular gene-expression programs related to antiviral activity, apoptosis, Th1 differentiation, and cell cycle, among others [17]. A potential explanation of our results would be that the increased NFκB activity conferred by the GG genotype is boosting this type 1 IFN pathway that mediates the IFNβ effect [18]. NFκB activation has been reported to enhance the STING signaling pathway (cyclic guanosine monophosphate (GMP)-AMP synthase (cGAS) stimulator of interferon genes, STING), which via activation of tank-binding kinase 1 (TBK1) and IFN regulatory factor 3 (IRF3) promotes the transcription of genes encoding type I IFNs [19]. Furthermore, NFκB induces tumor necrosis factor (TNF) alpha, which was shown to operate cooperatively with type I IFNs to increase the expression of IFN-responsive genes [20]. In this context, in a previous study conducted by our group, upregulated genes predominantly or selectively induced by type I IFNs driven by the action of IFNβ were associated with a better response to this treatment in RRMS patients, whereas nonresponders seemed to have an already activated type I IFN pathway in blood cells that was refractory to exogenous administration of IFNβ [21]. Therefore, the expected response to IFNβ observed in patients with the GG genotype is likely attributable to the aforementioned mechanisms, and patients with the AG or AA genotypes exhibited a poorer response to IFNβ treatment. Being the rs7665090 polymorphism in the intergenic promoter region between *NFKB1* and *MANBA* genes and given the existing linkage disequilibrium blocks [22], the possible implication of additional nearby genes to *NFKB1* can not be strictly ruled out.

Despite the demonstrated association between the rs7665090 polymorphism and treatment response to IFNβ, our results indicate that the response to other disease-modifying therapies does not appear to be significantly influenced by this polymorphism. However, these findings require further validation in larger cohorts, particularly for teriflunomide and fingolimod, given the limited sample sizes available for these treatments. This study contributes to the growing body of

TABLE 2 | Distribution of genotype frequencies for rs7665090 in responders and nonresponders to the different treatments.

Treatment	Genotypes	Total *n* (%)	Responders *n* (%)	Nonresponders *n* (%)	OR (95% CI)[a] GG versus AG/AA	*p*	GG/AG versus AA	*p*
Interferon-β	AA	38 (17.8)	30 (18.6)	8 (16.0)	**0.35 (0.15–0.82)**	**0.014**	0.86 (0.37–2.03)	0.541
	AG	115 (54.0)	80 (49.1)	35 (70.0)				
	GG	60 (28.2)	53 (32.5)	7 (14.0)				
Glatiramer acetate	AA	12 (21.8)	11 (22.9)	1 (14.3)	0.88 (0.15–5.06)	0.886	0.56 (0.06–5.17)	0.334
	AG	26 (47.3)	22 (45.8)	4 (57.1)				
	GG	17 (30.9)	15 (31.3)	2 (28.6)				
Dimethyl fumarate	AA	27 (27.8)	14 (25.5)	13 (34.2)	0.93 (0.38–2.31)	0.988	1.56 (0.63–3.85)	0.361
	AG	40 (41.2)	26 (44.1)	14 (36.8)				
	GG	30 (30.9)	19 (32.2)	11 (29.0)				
Teriflunomide	AA	10 (24.4)	5 (31.3)	5 (20.8)	1.97 (0.33–11.63)	0.497	0.63 (0.15–2.65)	0.456
	AG	24 (58.5)	10 (58.8)	14 (58.3)				
	GG	7 (17.1)	2 (12.5)	5 (20.5)				
Fingolimod	AA	4 (10.8)	1 (5.3)	3 (20.0)	0.88 (0.22–3.48)	0.741	5.25 (0.49–56.26)	0.206
	AG	20 (54.1)	13 (59.1)	7 (46.7)				
	GG	13 (35.1)	8 (36.4)	5 (33.3)				
Natalizumab	AA	25 (21.7)	20 (24.4)	5 (15.2)	0.65 (0.24–1.70)	0.379	0.55 (0.19–1.62)	0.277
	AG	59 (51.3)	38 (47.5)	21 (63.6)				
	GG	31 (27.0)	24 (29.3)	7 (21.2)				

Note: Variables significantly associated with the outcome ($p < 0.05$) were shown in bold.
Abbreviation: OR (95% CI), odds ratio (95% confidence interval).
[a]The outcome was classified as non-responsiveness following treatment.

evidence necessary to advance personalized treatment strategies in MS [23]. Regardless of the specific biological mechanisms involved, identifying predictive biomarkers such as rs7665090 is crucial for selecting the most suitable therapy for individual patients. Although the clinical relevance of assessing this polymorphism might be limited in regions where IFNβ usage has markedly declined, investigating genetic variations affecting NFκB, a critical hub gene in immunological processes [19], remains highly relevant to the scientific community. Moreover, future pharmacogenomic tools aimed at tailoring MS treatments should consider incorporating this polymorphism, as IFNβ continues to be widely used globally, particularly in resource-limited healthcare settings [24, 25].

A limitation of the study is the high variability in the number of MS patients receiving disease modifying therapies that were included. These numbers were particularly low for treatments such as glatiramer acetate, teriflunomide, and fingolimod, leading to low statistical power and a high risk of type II errors. Consequently, a significant association of the rs7665090 polymorphism with the response to these therapies cannot be totally ruled out, and studies with a larger number of patients are warranted. Therefore, future studies should aim for more balanced and larger sample sizes across all treatment groups to validate and extend our findings. An additional limitation is the lack of epidemiological diversity, as this multicenter study involved only Spanish MS centers. Another limitation is the exclusion of additional factors beyond baseline EDSS and age, as other clinical variables could also facilitate the selection of MS patients responsive to IFNβ treatment. Additionally, the absence of detailed baseline MRI data could introduce confounding bias due to unmeasured differences in radiological disease activity between responders and nonresponders. However, our analyses accounted for baseline clinical characteristics such as EDSS and were conducted separately within each treatment subgroup, inherently improving patient homogeneity and reducing potential biases arising from differences in baseline disease severity or activity. While our bioinformatics analysis suggests a potential role for the rs7665090 variant as a biomarker of IFNβ response, we acknowledge that experimental validation, not performed in this study, is necessary to confirm these findings. Future studies should focus on elucidating the biological mechanisms and validating the clinical utility of this variant.

In summary, the rs7665090 variant acts as a biomarker for the response to IFNβ treatment in MS patients, with GG homozygosity being associated with a favorable response. Our results support that genotyping of this variant in combination with additional clinical factors aids in the identification of IFNβ responders, albeit

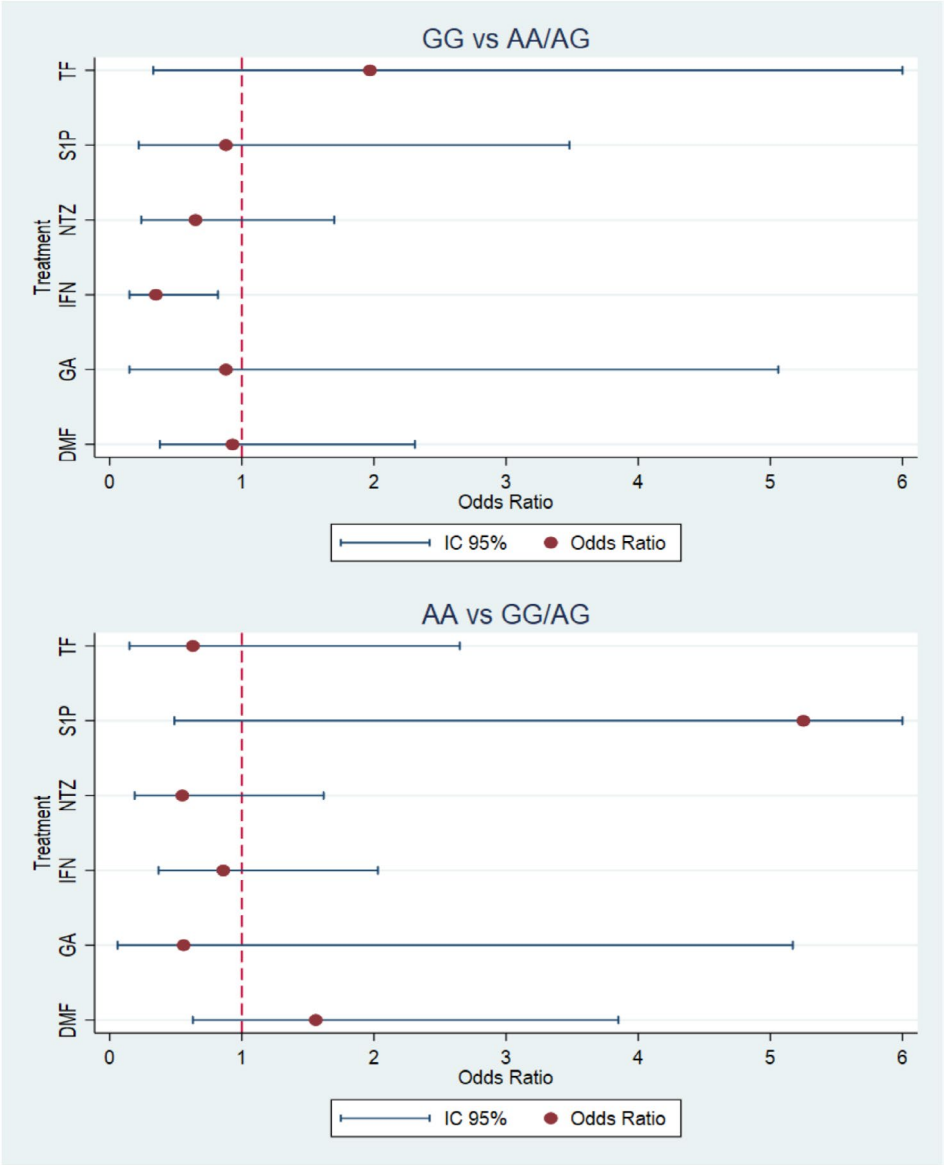

FIGURE 2 | Association between rs7665090 genotypes and response to different treatments. Data are represented as odds ratios with 95% confidence intervals. Note that confidence intervals are capped at 6 (for upper values of S1P and TF, please refer to Table 2). DMF, dimethyl fumarate; GA, glatiramer acetate; IFN, interferon-beta; NTZ, natalizumab; S1P, Fingolimod; TF, teriflunomide.

replication in an independent cohort of MS patients is encouraged to unequivocally support the utility of our results.

Author Contributions

Andreu Vilaseca: conceptualization, writing – original draft, investigation, methodology, formal analysis. **Elena Urcelay:** writing – review and editing, methodology, validation. **Sunny Malhotra:** supervision, software, investigation, writing – review and editing. **Mireia Castillo:** supervision, data curation. **Montserrat Aroca:** data curation. **Angela Vidal-Jordana:** writing – review and editing. **Agustín Pappolla:** writing – review and editing. **René Carvajal:** writing – review and editing. **Georgina Arrambide:** writing – review and editing. **Adela González-Jiménez:** methodology, investigation, writing – review and editing, validation. **Irene Gómez-Delgado:** methodology, investigation, writing – review and editing, validation. **Alvaro Cobo-Calvo:** writing – review and editing. **Neus Mongay-Ochoa:** writing – review and editing. **Breogan Rodriguez-Acevedo:** writing – review and editing. **Carmen Tur:** writing – review and editing. **Javier Villacieros-Álvarez:** writing – review and editing. **Helena Ariño:** writing – review and editing. **Joaquín Castilló:** writing – review and editing. **Ana Zabalza:** writing – review and editing. **Luciana Midaglia:** writing – review and editing. **Delon La Puma:** writing – review and editing. **Jaume Sastre-Garriga:** writing – review and editing. **Mar Tintoré:** funding acquisition, writing – review and editing. **Jordi Río:** writing – review and editing. **Xavier Montalban:** writing – review and editing, conceptualization, funding acquisition, resources, supervision. **Manuel Comabella:** conceptualization, investigation, writing – original draft, writing – review and editing, methodology, software, formal analysis, project administration, supervision, resources, visualization.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.