



Systematic Review IL10 Gene and Neurodegenerative Sclerosis: A Systematic Review and Meta-Analysis

Ismael Duarte Machado de Almeida¹, Pedro Luiz de Paiva¹, Kamilla de Faria Santos¹, Angela Adamski da Silva Reis^{1,2,*} and Rodrigo da Silva Santos^{1,2,*}

- ¹ Laboratory of Molecular Pathology, Biological Sciences Institute, Federal University of Goiás, Goiânia 74690-900, GO, Brazil; ismaeldma03@gmail.com (I.D.M.d.A.); pedro.luizpaiva@gmail.com (P.L.d.P.); kamillafaria1@gmail.com (K.d.F.S.)
- ² Department of Biochemistry and Molecular Biology, Biological Sciences Institute, Federal University of Goiás, Goiânia 74690-900, GO, Brazil
- * Correspondence: angela@ufg.br (A.A.d.S.R.); rdssantos@ufg.br (R.d.S.S.)

Abstract: Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) are incurable degenerative scleroses with unclear etiology. Neuroinflammation is an important factor in the neurodegeneration characteristic of these diseases. Additionally, Interleukin 10 (IL10) can inhibit the synthesis of inflammatory cytokines and plays a protective role against neurodegeneration associated with neuroinflammation. Thus, we developed a systematic review and meta-analysis in order to clarify the relationship between polymorphisms in the *IL10* gene and MS and/or ALS. We searched for observational studies in four international databases without time restrictions. Seventeen studies were added to the systematic review and six polymorphisms were observed: *IL10*₋₅₉₂ (rs1800872; C>A), *IL10*₋₈₁₉ (rs1800871; C>T), *IL10*₋₁₀₈₂ (rs1800896; A>G), *IL10*₋₂₇₆₃ (rs6693899; A>C), *IL10*₋₂₈₄₉ (rs6703630; A>G) and *IL10*₋₃₅₇₅ (rs1800890; A>T). In the meta-analysis, we used odds ratio (OR) and 95% confidence interval (CI) to evaluate the association of *IL10*₋₁₀₈₂, *IL10*₋₈₁₉ and *IL10*₋₅₉₂ polymorphisms and MS. We found a positive association of MS with the *IL10*₋₁₀₈₂ SNP in genotypic comparison (AG+GG vs. AA) (OR = 1.23; 95% CI = 1.01–1.51; p = 0.04). Our search did not find any article relating polymorphisms in the *IL10* gene SNPs in the development and progression of MS.

Keywords: Interleukin 10; neurodegenerative diseases; polymorphisms; systematic review; metaanalysis

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) are neurodegenerative diseases. ALS is the most frequent of the motor neuron diseases, and it affects mostly people over 40 years old. On the other hand, MS is often related to disability in younger adults, affecting sensory and motor neurons. Both diseases are incurable, and together they affect a significant portion of the population worldwide [1–3].

Advanced age seems to be the main risk factor for ALS due to natural neuronal death associated with aging. However, the pathogenesis of ALS is influenced by environmental factors and genetic conditions associated with neurodegeneration and oxidative stress. As neurodegeneration progresses, the symptoms become apparent, which may include muscle weakness, spasms, dysphagia and weight loss [1,4–6].

Similarly, MS is correlated to multiple factors, such as age, gender, ethnicity, diet and genetics factors. MS is an autoimmune disease influenced mainly by human leukocyte antigen (HLA) genes, characterized by inflammation and demyelination of neurons in different parts of the central nervous system (CNS), which leads to different clinical presentations depending on the affected areas. Symptoms of MS include muscle weakness, speech impediments, blurred vision and cognitive impairment [7–9].



Citation: de Almeida, I.D.M.; de Paiva, P.L.; Santos, K.d.F.; Reis, A.A.d.S.; Santos, R.d.S. *IL10* Gene and Neurodegenerative Sclerosis: A Systematic Review and Meta-Analysis. *J. Mol. Pathol.* **2023**, 4, 213–224. https://doi.org/10.3390/ jmp4040019

Academic Editors: Flavio Pisani and Valerio Pisani

Received: 6 August 2023 Revised: 22 September 2023 Accepted: 27 September 2023 Published: 29 September 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). Neuroinflammation is an important factor in neurodegeneration. The constant stimuli from inflammatory mediators can increase neuron excitability, cause cell damage and dysfunction of the blood–brain barrier [10,11]. Thus, the neuron death that occurs in both ALS and MS has been associated with neuroinflammation [12–14]. In both cases, the inflammatory process is complex and involves microglial cells, astrocytes and resident leukocytes [12,15,16].

Interleukin 10 (IL10) is a cytokine produced by a homonymous gene located at 1q32.1 that can inhibit the synthesis of inflammatory cytokines by microglial cells and plays a protective role against neurodegeneration associated with neuroinflammation. Moreover, IL10 was associated with greater survival of neurons and regulation of neurogenesis in adult individuals [17].

Single nucleotide polymorphisms (SNPs) present in the promoter region of the *IL10* gene are capable of negatively regulating the expression of this cytokine. This can lead to neuroinflammation and result in neurodegeneration [14]. Therefore, *IL10* is a gene potentially associated with the risk of neurodegenerative diseases.

We hypothesized that some SNPs of the *IL10* gene may confer risk for MS or ALS. Thus, we performed a systematic review that aimed to identify polymorphisms in the *IL10* gene involved in the development of ALS or MS, to elucidate the pathophysiological mechanisms involved and assist in the elaboration of new diagnostic and prognostic criteria and personalized therapies. When applicable, we used meta-analysis to verify this association.

2. Materials and Methods

2.1. PROSPERO Record and Searching Strategy

This protocol was registered in the international Prospective Register of Ongoing Systematic Reviews (PROSPERO) with the number CRD42021284650 in 5 November 2021 following the guiding question "What are the implications of polymorphic variants in the *interleukin 10* gene in the pathological mechanisms of Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS)?" Aiming at a better description of the data, we used the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [18].

We conducted the database search between November 2021 and November 2022 in the Virtual Health Library (VHL), PubMed/NCBI, Scientific Electronic Library Online (SciELO) and Web of Science databases. Terms present in the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) were selected for "amyotrophic lateral sclerosis", "multiple sclerosis", "Interleukin 10" and "Single Nucleotide Polymorphism". The operators "AND" and "OR" were employed to isolate terms and expand the results found.

2.2. Study Screening, Quality Assessment and Data Extraction

We searched observational studies that investigated the involvement of *IL10* SNPs in the pathophysiology of ALS and/or MS. For inclusion criteria, we defined observational studies in humans that address polymorphisms in the *IL10* gene related to ALS and/or MS, studies fully available online and written in English, Portuguese or Spanish. For exclusion criteria, we defined duplicate records, studies in non-humans, SNPs in other genes and studies with unavailable data.

We used the Rayyan[®] platform [19] to organize the records found and for duplicate removal. Two independent reviewers performed the selection at all stages of the review. Firstly, we selected studies by titles and abstracts according to predefined inclusion and exclusion criteria. Subsequently, we read the full papers and excluded any unfitting material according to the exclusion criteria.

The Joanna Briggs Institute (JBI) [20] critical assessment tools were applied to each study design in order to assess the methodological quality. Only studies that responded positively to at least 70% of the questions were included and classified as low risk of bias. Discrepancies were resolved by consensus.

After the final selection, we extracted the data from the articles to Excel[®] spreadsheets. The following information was described: authors and year of publication; country of study; study design; sample size; gender; average age and the genotypic and allelic frequencies when it was possible.

2.3. Statistical Analysis

To develop the meta-analysis, the same polymorphism must be described in at least two different studies. The calculation of the odds ratio (OR) and 95% confidence interval (CI) was used, with the results presented in a forest plot. The ORs were evaluated in dominant (heterozygous + mutant genotypes vs. wild) and allelic (mutant vs. wild) genetic models for each SNP. The dominant model was preferred because it more clearly reflects the comparison of the minor or mutant allele with the major or wild-type allele. Additionally, we used Higgins inconsistency tests (I²) to evaluate heterogeneity between studies.

The selection of the model used in the meta-analysis was based on the results of the heterogeneity test among the studies. The fixed effect model (Mantel–Haenszel method) was applied when $I^2 < 25\%$ (low heterogeneity), and the random effects model (DerSimonian– Laird method) was applied when I^2 25–75% (moderate heterogeneity). Values > 75% were defined as high heterogeneity.

For the analysis of publication bias, Egger's regression asymmetry test was used [21], and the results visually displayed in funnel plots. A *p*-value < 0.05 indicates possible publication bias. All statistical analyses were performed using the RStudio[®] software (version 4.1.0).

3. Results

3.1. Selection and Characteristics of Included Studies

We found 364 records; after removing duplicates, 248 articles remained. Subsequently, a total of 178 articles were selected by reading the titles and abstracts. Of the 158 articles excluded for not meeting the inclusion criteria, the main exclusion reasons were (1) unrelated to IL10; (2) unrelated to ALS or MS and; (3) wrong study design. After full-text reading, 17 articles with publication dates between 1999 and 2021 were included in this systematic review (Figure 1).

The articles relating the presence of polymorphisms in the *IL10* gene and the progression or development of ALS/MS were read completely, and we identified articles related to MS only. Six SNPs were identified in those articles: *IL10*₋₅₉₂ (rs1800872; C>A), *IL10*₋₈₁₉ (rs1800871; C>T), *IL10*₋₁₀₈₂ (rs1800896; A>G), *IL10*₋₂₇₆₃ (rs6693899; A>C), *IL10*₋₂₈₄₉ (rs6703630; A>G) and *IL10*₋₃₅₇₅ (rs1800890; A>T). The *IL10*₋₁₀₈₂ SNP was mentioned in 16 articles, while the other most frequently mentioned polymorphisms were *IL10*₋₈₁₉ and *IL10*₋₅₉₂.

Twelve case–control studies [22–33] and two cohort articles [34,35] on the association between $IL10_{-1082}$ SNP and MS were identified. Six case–control studies [24,25,27,29–31] and one cohort article [34] were identified for the $IL10_{-819}$ SNP, and five case–control studies [24,27,29,30,33] and one cohort [34] studies addressed the $IL10_{-592}$ SNP. We also included one review [36] and two meta-analyses [37,38] among the selected articles (Table 1).

England, Germany, Norway, Spain, Finland, Italy, Greece, Poland and India had one study each. Five studies were performed in Iran and two in Bulgaria. Not all studies specified the ethnicities or nationalities of their population, and all studies were about MS. Our search did not find any article relating polymorphisms in the *IL10* gene with ALS.

There was considerable variability in case sample size across studies, ranging from 55 to 336 individuals. Controls ranged from 85 to 454 subjects. The selected studies included a total of 2396 MS cases and 2770 controls. The percentage between genders could not be compared due to a lack of specification in some studies. However, all observational studies reported pairing between groups. In studies with known information, the case group showed a predominance of female patients. The mean age of MS cases ranged from 27 ± 8 to 49 ± 11.5 years.



Figure 1. PRISMA flowchart detailing the selection of the articles included and excluded in this systematic review and meta-analysis. Adapted from [18].

Study	Year	Country	Multiple Sclerosis				Healthy C	Controls	Dolymounhiomo	
			n	Female (%)	Mean Age (year)	n	Female (%)	Mean Age (year)	Analyzed	
Pickard et al. [33]	1999	England	185	74.0	41.7 ± 10.6	211	NA	NA	IL10-592, IL10-1082	
Mäurer et al. [32]	1999	Germany	181	NA	NA	85	NA	NA	IL10-1082	
Myhr et al. [34]	2002	Norway	168	64.9	NA	87	NA	NA	IL10-592, IL10-819, IL10-1082	
Jong et al. [31]	2002	Iran	251	59.3	49 ± 11.5	321	47.3	39 ± 17	IL10 ₋₈₁₉ , IL10 ₋₁₀₈₂ IL10 ₋₂₇₆₃ , IL10 ₋₂₈₄₉ , IL10 ₋₃₅₇₅	
Doncel et al. [30]	2002	Spain	300	67.0	NA	357	NA	NA	IL10-592, IL10-819, IL10-1082	
Luomala et al. [35]	2003	Finland	116	57.7	46 ± 10	400	NA	46 ± 10	IL10-1082	
Mihailova et al. [29]	2005	Bulgaria	55	56.3	32.3 ± 9.5	86	NA	NA	IL10-592, IL10-819, IL10-1082	
Forte et al. [28]	2006	Italy	91	NA	NA	220	NA	NA	IL10-1082	
Azarpira et al. [27]	2010	Iran	110	70.9	32.2	100	51.0	33.41	IL10-592, IL10-819, IL10-1082	
Nikolopoulos et al. [37] *	2011	Greece	-	-	-	-	-	-	IL10-819, IL10-1082	
Mirowska-Guzel et al. [26]	2011	Poland	224	73.1	38.11 ± 10.94	195	66.3	$40.09{\pm}\ 10.19$	IL10-1082	
Karimabad et al. [36] *	2012	Iran	-	-	-	-	-	-	IL10-592	
Shahbazi et al. [25]	2015	Iran	336	71.1	27 ± 8	454	NA	35.45 ± 6.9	IL10-819, IL10-1082	
Ramakrishnan et al. [38] *	2017	India	-	-	-	-	-	-	IL10-592, IL10-819, IL10-1082	
Al-Naseri et al. [24]	2019	Iraq	68	66.1	33.3± 2.3	158	77.8	32.7 ± 0.8	IL10-592, IL10-819, IL10-1082	
Trenova et al. [23]	2020	Bulgaria	159	71.7	40.08 ± 8.48	154	77.3	39.29 ± 9.454	IL10-1082	
Asgharzadeh et al. [22]	2021	Iran	152	NA	32.18 ± 6.52	242	NA	31.02 ± 7.44	IL10-1082	

Table 1. Clinical characteristics of the 17 studies included.

* Review/meta-analyses. NA = Not available.

3.2. Results of Individual Studies

In summary, most studies showed an association between *IL10* polymorphisms and progression or susceptibility to MS. Mirowska-Guzel et al. [26], Mäurer et al. [32], Azarpira et al. [27], Pickard et al. [33], Myhr et al. [34] and Forte et al. [28] found no significant association for alleles or genotypes with the development of MS (p > 0.05). Data from Doncel et al. [30] indicate that *IL10* is not a major susceptibility locus in MS but can have a minor role in the development of the disease.

However, Jong et al. [31] revealed that carrying the A allele for the *IL10*₋₂₈₄₉ SNP is significantly associated with susceptibility for relapse–onset MS among non-HLA-DR2 carriers, providing further evidence that *IL10* polymorphisms can be associated with MS susceptibility. Furthermore, Al-Naseri et al. [24] reported a significantly increased frequency of CC genotype (*IL10*₋₅₉₂ SNP) in patients and demonstrated that the G (*IL10*₋₁₀₈₂), C (*IL10*₋₈₁₉) and C (*IL10*₋₅₉₂) haplotypes were associated with increased risk to develop MS.

Mihailova et al. [29] found an association of CC ($IL10_{.819}$ SNP) genotype and discussed the possibility that both SNPs ($IL10_{.592}$ and $IL10_{.819}$) play a role in MS susceptibility. Shahbazi et al. [25] found the same association; the CC ($IL10_{.819}$ SNP) genotype was significantly more frequent among MS patients compared to controls and was associated with a higher risk of developing the disease.

Shahbazi et al. [25] also showed that the GG ($IL10_{-1082}$ SNP) genotype and the HLA-DRB1*15 allele were associated with susceptibility to MS. The polymorphisms studied were not associated with MS susceptibility in the article by Luomala et al. [35]; however, the results suggest that IL10 production levels may be a factor in the progression of MS. The AG genotype of the $IL10_{-1082}$ polymorphism discussed by the authors is known to produce low levels of IL10.

Trenova et al. [23] reported that the AA genotype (SNP *IL10*₋₁₀₈₂) may be a risk factor for susceptibility to relapsing–remitting MS (RRMS) in Bulgarian patients and that it may be associated with impaired cognitive functions in these patients. Data from Trenova et al. [23] contradict those shown by Asgharzadeh et al. [22] and suggested by Al-Naseri et al. [24], in which they identify a possible protective role of the AA genotype of *IL10*₋₁₀₈₂ SNP in MS. As shown in the study, this contradiction may be related to environmental factors and population differences.

The data from the included studies in this review, when combined with the review by Ramakrishnan et al. [38], revealed that the *IL10*-592, *IL10*-819 and *IL10*-1082 SNPs might not be risk factors for the development of MS in Asian and Caucasian populations, and Karimabad et al. [36] show that there is no consensus among studies on the association between the *IL10*-592 SNP and MS.

3.3. Meta-Analysis

Only three of the six polymorphisms identified in this systematic review allowed meta-analysis to be performed: $IL10_{-592}$, $IL10_{-819}$ and $IL10_{-1082}$ SNPs, applied only for MS. Regarding the other polymorphisms, it was not possible to reach the minimum number of two studies. The total number of subjects identified in each SNP was 358 cases and 431 controls for $IL10_{-592}$, 1177 cases and 1415 controls for $IL10_{-819}$, and 2100 cases and 2714 controls for $IL10_{-1082}$.

The meta-analysis for the *IL10*₋₅₉₂ SNP and MS included four studies, and the results showed no association between the polymorphism and disease in both the genotypic (CA+AA vs. CC) (OR = 0.80; 95% CI = 0.37–1.72; p = 0.56) and allelic comparisons (A vs. C) (OR = 0.79; 95% CI = 0.44–1.42; p = 0.43) (Figure 2).

For the $IL10_{-819}$ SNP and MS, seven studies were included, and the meta-analysis did not demonstrate an association between the polymorphism and the disease in the genotypic (CT+TT vs. CC) (OR = 0.88; 95% CI = 0.71–1.10; p = 0.25) and allelic comparisons (T vs. C) (OR = 0.89; 95% CI = 0.76–1.04; p = 0.14) (Figure 3).

		Case	C	ontrol				
Author, Year	CA+AA	Total	CA+AA	Total	Odds Ratio	OR	95%-CI	Weight
Al-Naseri et al., 2019	32	68	98	158	—_∎ _∔	0.54	[0.31; 0.97]	25.5%
Azarpira et al., 2010	41	67	38	100	i ∎	- 2.57	[1.36; 4.86]	24.7%
Mihailova et al., 2005	24	55	58	86		0.37	[0.19; 0.75]	23.8%
Myhr et al., 2002	65	168	39	87		0.78	[0.46; 1.31]	26.1%
Random effects model	- 0 5122	358	01	431		0.80	[0.37; 1.72]	100.0%
Heterogeneity. $I = 64\%, \tau$	- 0.5123	, p = 0	.01	C	0.2 0.5 1 2	5		
	С	ase	Contro	1				
Author, Year	AT	otal	A Tota	I	Odds Ratio	OR	95%-CI	Weight
Al-Naseri et al., 2019	37	136 1	31 316	3 -	<u>+</u>	0.53	[0.34; 0.82]	25.5%
Azarpira et al., 2010	49	134	49 200	0	· · · · · · · · · · · · · · · · · · ·	1.78	[1.10; 2.86]	24.9%
Mihailova et al 2005	27	110	71 17	>		0 46	[0 27 0 79]	23.9%
Myhr et al., 2002	75	336	42 17	4	— —	0.90	[0.59; 1.39]	25.7%
Random effects mod Heterogeneity: $I^2 = 84\%$,	el τ ² = 0.2	716 950, p	86 2 < 0.01	2		0.79	[0.44; 1.42]	100.0%
					0.5 1 2			

Figure 2. Forest plot for the genotypic and allelic comparison of *IL10*₋₅₉₂ SNP (CA+AA vs. CC and A vs. C). CI = confidence interval; OR = odds ratio. Al-Naseri et al., 2019 [24]; Azarpira et al., 2010 [27]; Mihailova et al., 2005 [29]; Myhr et al., 2002 [34].



Figure 3. Forest plot for the genotypic and allelic comparison of *IL10*₋₈₁₉ SNP (CT+TT vs. CC, and T vs. C). CI = confidence interval; OR = odds ratio. Al-Naseri et al., 2019 [24]; Azarpira et al., 2010 [27]; Jong et al., 2002 [31]; Mihailova et al., 2005 [29]; Myhr et al., 2002 [34]; Pickard et al., 1999 [33]; Shahbazi et al., 2015 [25].

Meta-analysis for the *IL10*₋₁₀₈₂ SNP and MS included 13, studies and the forest plot revealed an association between the polymorphism and the disease in the genotypic

Author, Year	AG+GG	Case Total	AG+GG	ontrol Total	Odds Ratio	OR	95%-CI	Weight
Al-Naseri et al., 2019	48	68	92	158	+	- 1.72	[0.94: 3.17]	6.3%
Asgharzadeh et al., 2021	112	152	151	242		1.69	[1.08; 2.63]	8.7%
Azarpira et al., 2010	89	110	84	100		0.81	[0.39; 1.65]	5.2%
Forte et al., 2006	62	91	153	220		0.94	[0.55; 1.58]	7.4%
Jong et al., 2002	196	251	234	324		1.37	[0.93; 2.02]	9.7%
Luomala et al., 2003	83	116	265	400		1.28	[0.81; 2.02]	8.5%
Maurer et al., 1999	130	181	56	85		1.32	[0.76; 2.30]	7.0%
Mihailova et al., 2005	36	55	45	86		- 1.73	[0.86; 3.47]	5.4%
Mirowska-Guzel et al., 2011	168	224	143	193		1.05	[0.67; 1.63]	8.7%
Myhr et al., 2002	120	168	64	87		0.90	[0.50; 1.61]	6.7%
Pickard et al., 1999	150	189	153	211		1.46	[0.92; 2.32]	8.3%
Shahbazi et al., 2015	284	336	335	454		- 1.94	[1.35; 2.79]	10.1%
Trenova et al., 2020	98	159	115	154		0.54	[0.34; 0.88]	8.0%
Random effects model Heterogeneity: $I^2 = 53\%$, $\tau^2 = 0$	0.0713, p	2100 = 0.01		2714		1.23	[1.01; 1.51]	100.0%
					0.5 1 2			
	0	Case	Contro	bl				
Author, Year	G	otal	G Tota	al	Odds Ratio	OR	95%-CI	Weight
Al-Naseri et al., 2019	60	136	119 31	6	- <u> </u>	1.31	[0.87; 1.97]	5.3%
Asgharzadeh et al., 2021	139	304	197 48	4		1.23	[0.92; 1.64]	8.5%
Azarpira et al., 2010	95	220	89 20	0		0.95	[0.64; 1.39]	5.7%
Forte et al., 2006	80	182	205 44	0		0.90	[0.64; 1.27]	6.7%
Jong et al., 2002	254	502	311 64	8		1.11	[0.88; 1.40]	11.0%
Luomala et al., 2003	104	232	353 80	0	· • • • • • • • • • • • • • • • • • • •	1.03	0.77: 1.381	8.4%
Maurer et al., 1999	168	362	75 17	0		1.10	0.76: 1.58]	6.2%
Mihailova et al. 2005	45	110	54 17	2		- 1.51	0.92 2.491	3.8%
Mirowska-Guzel et al 201	1 213	448	187 38	6		0.96	0 73: 1 271	9.2%
Myhr et al 2002	168	336	85 17	4		1.05	0 73 1 511	6.2%
Pickard et al 1999	206	378	216 42	2		1 14	0.86 1.51	9.0%
Shahbazi et al 2015	337	672	382 00	8		1 30	1 13 1 601	12 7%
Trenova et al., 2020	120	318	142 30	8		0.71	[0.52; 0.97]	7.5%
Dandam effects model		1000	F 10	•		4.00	0.00.4.041	100 00/
Heterogeneity: $l^2 = 34\% \tau^2$	4	4200	542	8	N	1.09	0.98: 1.211	100.0%
	= 0.0127	p = 0	11	- r				

comparison (AG+GG vs. AA) (OR = 1.23; 95% CI = 1.01–1.51; *p*-value = 0.04) but not in the allelic comparisons (G vs. A) (OR = 1.09; 95% CI = 0.98–1.21; *p*-value = 0.12) (Figure 4).

Figure 4. Forest plot for the genotypic and allelic comparison of $IL10_{-1082}$ SNP (AG+GG vs. AA, and A vs. G). CI = confidence interval; OR = odds ratio. Al-Naseri et al., 2019 [24]; Asgharzadeh et al., 2021 [22]; Azarpira et al., 2010 [27]; Forte et al., 2006 [28]; Jong et al., 2002 [31]; Luomala et al., 2003 [35]; Maurer et al., 1999 [32]; Mihailova et al., 2005 [29]; Mirowska-Guzel et al., 2011 [26]; Myhr et al., 2002 [34]; Pickard et al., 1999 [33]; Shahbazi et al., 2015 [25]; Trenova et al., 2020 [23].

In this meta-analysis, the OR and 95% CI were calculated using the Mantel–Haenszel test, and the random effect model was applied for all comparisons due to the value found in the test of heterogeneity (I²). The analysis of publication bias for all SNPs found no significant publication bias according to funnel plot (Figure 5) and Egger's test for allelic (*IL*10₋₅₉₂: p = 0.8561; *IL*10₋₈₁₉: p = 0.7025; *IL*10₋₁₀₈₂: p = 0.4112) and genotypic comparisons (*IL*10₋₅₉₂: p = 0.9769; *IL*10₋₈₁₉: p = 0.1646; *IL*10₋₁₀₈₂: p = 0.2883).



Figure 5. Funnel plots for the publication bias of the studies included in the meta-analysis. (**A**) Allelic comparison (A vs. C) for *IL10*₋₅₉₂ SNP and MS; (**B**) genotypic comparison (CA+AA vs. CC) for *IL10*₋₅₉₂ SNP and MS; (**C**) allelic comparison (T vs. C) for *IL10*₋₈₁₉ SNP and MS; (**D**) genotypic comparison (CT+TT vs. CC) for *IL10*₋₈₁₉ SNP and MS; (**E**) allelic comparison (G vs. A) for *IL10*₋₁₀₈₂ SNP and MS; (**F**) genotypic comparison (AG+GG vs. AA) for *IL10*₋₁₀₈₂ SNP and MS.

4. Discussion

There is still much to learn about the mechanisms behind neurodegenerative scleroses, as well as the influence of genetic factors on susceptibility and progression of these diseases. IL10 secretion may vary in humans according to the genetic composition of the *IL10* locus, which may increase or decrease the serum levels of this cytokine [39,40]. Therefore, our study sought to assess the influence of *IL10* gene polymorphisms on neurodegenerative scleroses, since polymorphisms in this gene could affect the balance of the immune system.

Neuroinflammation can cause undesirable effects, such as neuron damage, increased neuronal excitability and dysfunction of the blood–brain barrier [10,11]. Furthermore, this mechanism has been associated with the onset and progression of neurodegenerative diseases, including MS, ALS, Alzheimer's and Parkinson's disease [12,14,41].

Thus, due to its potent anti-inflammatory effect, IL10 has a protective role against neurodegeneration associated with neuroinflammation. Furthermore, IL10 induces the alternative microglial activation phenotype, which secretes more IL10, neurotrophic factors and other anti-inflammatory cytokines. In astrocytes, IL10 decreases pro-inflammatory signaling by inducing astrocyte inactivation [42–45]. Regarding ALS, studies in murine models (*SOD1-G*93A mice) show that overexpression of IL10 in microglial cells significantly delayed disease onset and increased survival in ALS, highlighting the importance of this cytokine in disease progression [46].

We did not find any work relating polymorphisms in the *IL10* gene with ALS. However, our data indicate that the *IL10*₋₁₀₈₂ SNP is associated with MS risk. This SNP is located in the promoter region of the *IL10* gene and is possibly linked to cytokine production [47]. Of the six polymorphisms found, three (*IL10*₋₂₇₆₃, *IL10*₋₂₈₄₉ and *IL10*₋₃₅₇₅) were described

only by Jong et al. [31]. Therefore, the lack of studies relating these polymorphisms to the susceptibility and progression of neurodegenerative diseases is highlighted.

Similar to our study, Nikolopoulos et al. [37] performed a meta-analysis of the $IL10_{-1082}$ and $IL10_{-819}$ SNPs in MS. In a recessive model, the GG genotype ($IL10_{-1082}$ SNP) was associated with MS. Furthermore, they also found that the T allele ($IL10_{-819}$ SNP) was associated with decreased risk of MS (OR = 0.841). This result corroborates the association of the AG+GG genotype of the $IL10_{-1082}$ SNP with MS found in our meta-analysis. Furthermore, in our meta-analysis, thirteen studies on the $IL10_{-1082}$ SNP and seven studies on the $IL10_{-819}$ SNP were included, while Nikolopoulos et al. [37] included only eight and five for their analysis, respectively. Nikolopoulos et al. [37] also reported difficulties regarding heterogeneity and scarcity of studies in ethnicities other than Caucasians.

Ramakrishnan et al. [38] performed another similar study, in which they found no association between *IL10*₋₁₀₈₂ SNP and MS in any of the tested genetic models. Their findings regarding this SNP were different from ours, despite having a larger number of included studies. On the other hand, we found heterogeneity issues in our expanded database, which hindered our analysis.

As for the *IL10*₋₅₉₂ SNP, Ramakrishnan et al. [38] found that the AA genotype presents an OR of 0.76 when compared to CC individuals. Our analysis also did not associate *IL10*₋₅₉₂ SNP genotypes and alleles with MS. Ramakrishnan et al. [38] also investigated the association between MS and the *IL10*₋₈₁₉ SNP. Their analysis indicated that the CC genotype is negatively associated with MS risk (OR = 0.80) compared to the TT genotype, which could represent a protective factor. Our findings revealed an OR of 0.88 for the CT+TT genotypes, demonstrating the non-association with MS. However, the scarcity of studies on this particular SNP is still an obstacle to any robust association, highlighting the importance of further studies.

Trenova et al. [23] also found associations of the AG genotype of the *IL10*₋₁₀₈₂ SNP and highlighted that this genetic variant may be associated with cognitive decline in Bulgarian patients with RRMS. Another study by Trenova et al. [48] suggest that pro-inflammatory cytokines IL17A and TNF-alpha in combination with IL10 decrease are involved in cognitive deterioration in RRMS, which corroborates to the hypothesis that low levels of IL10 in serum may cause risks when associated with other factors. Polymorphisms in the *IL10* gene promoter have a direct impact on the serum levels of the cytokine. Several studies try to relate the low levels of this cytokine with the risk for several diseases and the high production with protective factors. For example, the AA genotype of the SNP *IL10*₋₁₀₈₂ (rs1800896) is recognized for its associated with the risk of prostate cancer [49].

Therefore, our meta-analysis shows an association in the genotypic comparison for the $IL10_{-1082}$ SNP (OR = 1.23) with the risk of MS. Nevertheless, our data must be interpreted with caution. As described in the literature, it is still not possible to arrive at precise answers due to the low number of studies in the same populations. Additionally, due to the rarity of these neurodegenerative scleroses, research with larger samples is necessary to obtain more precise answers.

A large number of studies would also be necessary to perform analysis by subgroups (gender or ethnicities for example) or meta-regression, which would enable the obtaining of lower heterogeneity between studies. In our study, one obstacle was the lack of published data on specific characteristics of the participants, such as the exact number of males and females genotyped in each group (Table 1). Furthermore, the dominant model was preferred because it more clearly reflects the comparison of the minor or mutant allele with the major or wild-type allele; however, further analyses with different models of inheritance may clarify the relationship of SNPs with MS.

The study of genetic factors related to the susceptibility or progression of diseases helps to create tools for precision medicine and can lead to an improved quality of life for patients. It was not possible to fulfill the objective of verifying the relationship of polymorphisms in the *IL10* gene with ALS due to the lack of studies. However, this fact reveals the need for research aimed at better investigating the immunogenetic mechanisms of ALS.

In conclusion, this systematic review and meta-analysis reveals that carriers of the AG+GG genotype of the *IL10*₋₁₀₈₂ SNP have an approximately 1.23-fold higher risk for MS. Our results indicate that *IL10* SNPs can represent susceptibility factors for MS. This study may provide important information about the immunogenetic mechanisms related to the susceptibility and progression of neurodegenerative diseases. Our results may contribute to the development of therapeutic technologies for MS as well as influence future genetic research, in addition to revealing the need for more research in ALS.

Author Contributions: Conceptualization, R.d.S.S. and A.A.d.S.R.; Methodology, I.D.M.d.A., P.L.d.P., K.d.F.S., R.d.S.S. and A.A.d.S.R.; Software, K.d.F.S., R.d.S.S. and A.A.d.S.R.; Validation, R.d.S.S. and A.A.d.S.R.; Formal Analysis, I.D.M.d.A., P.L.d.P. and K.d.F.S.; Investigation, I.D.M.d.A., P.L.d.P., K.d.F.S., R.d.S.S. and A.A.d.S.R.; Data Curation, I.D.M.d.A., P.L.d.P., and K.d.F.S.; Writing—Original Draft Preparation, I.D.M.d.A., P.L.d.P., R.d.S.S. and A.A.d.S.R.; Writing—Review and Editing, I.D.M.d.A., P.L.d.P., K.d.F.S., R.d.S.S. and A.A.d.S.R.; Supervision, R.d.S.S. and A.A.d.S.R.; Project Administration, R.d.S.S.; Funding Acquisition, R.d.S.S. and A.A.d.S.R. All authors have read and agreed to the published version of the manuscript.

Funding: Coordination for the Improvement of Higher Education Personnel (CAPES) with financial support to K.d.F.S. and the National Council for Scientific and Technological Development (CNPq) with financial support to I.D.M.d.A.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

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