Associations between polymorphisms of TNFSF13B and Primary Sjögren's Syndrome susceptibility in Primary Sjögren's Syndrome Patients: a Meta-analysis

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Abstract

Objective B cell activating factor (BAFF) is a key regulator of Primary Sjögren's Syndrome (pSS), which is characterized by B lymphocyte hyperactivity. BAFF is also known as TNF ligand superfamily member 13B (TNFSF13B). This study aimed to explore whether five single nucleotide polymorphisms (SNPs) of the TNFSF13B gene (rs9514827, rs1041569, rs9514828, rs1224141, and rs12583006) are related to pSS susceptibility. Methods We searched Pubmed, Cochrane, Elsevier, Web of Science, CNKI, CQVIP, and WanFang databases (up to January 2023). In a population with pSS, the odds ratios (ORs) with 95% confidence intervals (CIs) of genotypes and each allele were provided to investigate relationships between the polymorphisms of the BAFF (TNFSF13B) gene and pSS. Results The meta-analysis in question contains three studies. In the group of pSS patients and randomly selected health controls (HCs), there was a statistically significant relationship between rs1041569 and rs12583006 and pSS susceptibility, respectively. In fixed models, there were statistical differences in pSS patients and randomly chosen HCs. Conclusions There were relationships of rs1041569 and rs12583006 in the pSS group and HC group. BAFF(TNFSF13B) genes, particularly rs1041569 and rs12583006, were related to pSS susceptibility in pSS patients.

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Abstract

Objective

B cell activating factor (BAFF) is a key regulator of Primary Sjögren's Syndrome (pSS), which is characterized by B lymphocyte hyperactivity. BAFF is also known as TNF ligand superfamily member 13B (TNFSF13B). This study aimed to explore whether five single nucleotide polymorphisms (SNPs) of the TNFSF13B gene (rs9514827, rs1041569, rs9514828, rs1224141, and rs12583006) are related to pSS susceptibility.

Methods

We searched Pubmed, Cochrane, Elsevier, Web of Science, CNKI, CQVIP, and WanFang databases (up to January 2023). In a population with pSS, the odds ratios (ORs) with 95% confidence intervals (CIs) of genotypes and each allele were provided to investigate relationships between the polymorphisms of the BAFF (TNFSF13B) gene and pSS.

Results

The meta-analysis in question contains three studies. In the group of pSS patients and randomly selected health controls (HCs), there was a statistically significant relationship between rs1041569 and rs12583006 and pSS susceptibility, respectively. In fixed models, there were statistical differences in pSS patients and randomly chosen HCs.

Conclusions

There were relationships of rs1041569 and rs12583006 in the pSS group and HC group. BAFF(TNFSF13B) genes, particularly rs1041569 and rs12583006, were related to pSS susceptibility in pSS patients.

Key Words

Sjögren's Syndrome, Meta-analysis, Polymorphism, BAFF, TNFSF13B

1. Introduction

Primary Sjogren's syndrome (pSS) is a chronic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, most notably the salivary and lacrimal glands, resulting in oral and ocular dryness. The syndrome is identified by B-cell hyperactivity, which is characterized by hypergammaglobulinemia and a variety of autoantibodies, with BAFF or BLyS, a B cell survival factor, playing a significant role.[1] However, the pathogenesis and etiology of pSS are yet unknown. As a result of ongoing research, anti-Ro/SSA autoantibody has emerged as one of the most well-established risk factors for pSS, with a high correlation. Whereas, anti-Ro/SSA autoantibodies lack specificity, and studies are increasingly showing that high expression of the B-cell activating factor (BAFF) gene is also responsible for pSS.[1–36]

TNF ligand superfamily member 13B (TNFSF13B) is a cytokine that belongs to the TNF ligand family. It is also known as B-cell activating factor (BAFF) or B Lymphocyte Stimulator (BLyS). BAFF aids B cell

proliferation, maturation, differentiation, and immunoglobulin synthesis.[2] This cytokine is encoded by the TNFSF13B gene, and various single-nucleotide polymorphisms have been linked to vulnerability to various autoimmune diseases.[8]

Previous data suggested that TNFSF13B genotype and allele polymorphisms are involved in pSS. A study showed that the same genotype influences pSS vulnerability in both the co-dominant and recessive models. The TTTAC haplotype was discovered to enhance pSS susceptibility.[2] The other showed that TNFSF13B mRNA expression was observed to be higher in rheumatoid arthritis (RA) and pSS patients. RA patients had 2.43-fold higher TNFSF13B mRNA expression than HC patients, while pSS patients had 5.04-fold higher TNFSF13B mRNA expression.[3] Another research suggested that the CTAT haplotype increases disease susceptibility for Ro/La-positive pSS, but is not linked with high serum BAFF (s-BAFF) levels. Elevated s-BAFF levels in pSS are linked to the TTTT genotype and could be a secondary effect in Ro/La-positive pSS.[25] In addition, the research has shown that distinct haplotypes of the BAFF gene give greater susceptibility to pSS development, and the importance of genetic polymorphisms in the BAFF gene in the development of pSS and the development of pSS-related lymphomagenesis was also highlighted.[1]

Although research concluded that both a genetic propensity to pSS and a specific pattern of antibody production are unrelated to the polymorphism in the BAFF gene; the study only looked at the BAFF -871 T/C polymorphism.[37] Therefore, in this work, we attempted to conduct a meta-analysis for the first time to assess the relationship between pSS susceptibility and TNFSF13B gene polymorphisms.

2. Materials and Methods

2.1. Literature collection strategy

The databases Pubmed, Cochrane, Embase, Web of Science, CNKI, WanFangData, and Cqvip were all thoroughly searched. Without regard to language or location, the search was carried out from the beginning through January 2023. The search was conducted using the terms "Sjögren's Syndrome," "TNFSF13B," and "BAFF" along with associated nouns. To find other studies that were not indexed by our initial search, the bibliographies of other pertinent research were also searched. Articles in the full text were retrieved from Shandong University's library. The author was contacted if the library did not have access to the complete text.

2.2. Inclusion and exclusion criteria

Studies that qualify must satisfy each of the following criteria for inclusion: (1) The study's design was a case-control study; (2) It examined the association between pSS and TNFSF13B gene polymorphisms; (3) It provided information on the frequencies of TNFSF13B genotypes and alleles for both pSS patients and health controls; and (4) Its subjects were TNFSF13B gene positive. The following were the exclusion requirements: (1) duplicate data were found in the studies; (2) completely irrelevant to the theme of this meta-analysis; (3) the research was a family study; (4) the research direction was not consistent with this article; (5) reviews; (6) abstracts only; (7) the recording method of phenotype for TNFSF13B gene was different from this paper; (8) without health controls; and (9) inapplicable statistical data.

2.3. Data extraction

The first author, the publication year, the research population's ethnicity, the number of cases and controls, and the frequencies of TNFSF13B genotypes and alleles were all information that two reviewers independently acquired from each article.

2.4. Methodological quality assessment

Using the Newcastle-Ottawa Scale (NOS), two reviewers independently evaluated the methodological quality of each included study. The NOS rating goes from 0 to 9 stars. Studies that received six stars or more (> 6 stars) were regarded as being of high quality.

2.5. Statistical analysis

The statistical analysis was done using STATA 16.0 (Stata Corp LP, College Station, TX, USA). TNFSF13B gene polymorphisms and pSS susceptibility were shown to have associations using odds ratios (OR) and 95% confidence intervals (CI).

The STATA16.0 method was used to compute the Hardy-Weinberg equilibrium (HWE). There was an HWE divergence if p¡0.05. The fixed effects model and the random effects model, respectively, were used to obtain the pooled ORs. When heterogeneity is significant, the random effects model should be chosen. Using I^2 statistics, the heterogeneity between studies was identified. The fixed-effects model was appropriate for I^2 statistics when I^2¡50%. If not, the random-effects model would be appropriate. By looking at funnel plots, publication bias was evaluated. All statistical tests used in this study were two-sided, and a study was deemed statistically significant when p¡0.05.

3. Results

3.1. Literature search and study characteristics

Seven hundred and thirty-seven items satisfied the search criteria based on the search technique. Other sources did not turn up any new research. Due to duplicate content, two hundred and fifty-eight articles were removed. Four hundred and thirty-eight articles were then removed since they didn't follow our instructions. Forty-one articles were chosen for thorough publishing assessment. Thirty-eight articles were excluded for a variety of reasons. As a result, three case-control studies from three articles were examined in our study (Figure 1). All of the studies that were included were of high quality.

The relevant studies were published between 2014 and 2022. For one particular study, the size of the sample ranged from 101 to 193 for pSS patients and 137 to 309 for health controls. Athenian, Mexican, and Caucasian Greek ethnicities were represented in the studies. The meta-analysis comprised 646 health controls and 442 pSS patients. The SNPs TNFSF13B were studied. SNPs were found in HWE in the health control group (p¿0.05). Table 1 shows the features of each eligible study.

3.2. The relationship between rs9514827 and pSS susceptibility in random health controls and pSS patients

There were no statistical differences in rs9514827 in pSS patients and health controls (Table 2). Because of heterogeneity (Figures 2a, 2b, 2c, 2d and 2e), the genotype of TT and CC chose the fixed model, and the genotype of TC and the allele of T and C chose the random model. For rs9514827, OR values, 95% CIs and P values for each genotype and allele are shown in Table 2. There was no relationship between rs9514827 and pSS susceptibility (OR [95% CI], p-value: TT=0.92[0.62-1.37], p=0.70, TC=1.14[0.88-1.47], p=0.33, CC=0.81[0.50-1.31], p=0.39, T=0.95[0.60-1.51], p=0.84, and C=1.05[0.66-1.67], p=0.84) (Table 2, Figures 2a, 2b, 2c, 2d and 2e).

3.3. The relationship between rs1041569 and pSS susceptibility in random health controls and pSS patients

There was a statistical difference in rs1041569 in pSS patients and health controls (Table 2). Because of heterogeneity (Figures 3a, 3b, 3c, 3d and 3e), the genotype of AA, AT and TT and the allele of A and T chose the fixed model. For rs1041569, OR values, 95% CIs and P values for each genotype and allele are shown in Table 2. There was a relationship between the genotype of TT in rs1041569 and pSS susceptibility (OR [95% CI], p-value: AA=0.96[0.74-1.26], p=0.78, AT=0.91[0.70-1.20], p=0.52, TT=4.62[1.59-13.43], p=0.00, A=0.95[0.70-1.27], p=0.72, and T=1.06[0.78-1.42], p=0.72) (Table 2, Figures 3a, 3b, 3c, 3d and 3e).

3.4. The relationship between rs9514828 and pSS susceptibility in random health controls and pSS patients

There were no statistical differences in rs9514828 in pSS patients and health controls (Table 2). Because of heterogeneity (Figures 4a, 4b, 4c, 4d and 4e), the genotype of CT and TT and the allele of C and T chose the fixed model, and the genotype of CC chose the random model. For rs9514828, OR values, 95% CIs and P values for each genotype and allele are shown in Table 2. There was no relationship between

rs9514828 and pSS susceptibility (OR [95% CI], p-value: CC=0.99[0.63-1.56], p=0.98, CT=0.83[0.64-1.07], p=0.15, TT=1.33[0.94-1.87], p=0.10, C=0.88[0.70-1.12], p=0.31, and T=1.13[0.89-1.43], p=0.31) (Table 2, Figures 4a, 4b, 4c, 4d and 4e).

3.5. The relationship between rs1224141 and pSS susceptibility in random health controls and pSS patients

There were no statistical differences in rs1224141 in pSS patients and health controls (Table 2). Because of heterogeneity (Figures 5a, 5b and 5c), the genotype of GG, GT and TT chose the fixed model. For rs1224141, OR values, 95% CIs and P values for each genotype and allele are shown in Table 2. There was no relationship between rs1224141 and pSS susceptibility (OR [95% CI], p-value: TT=0.75[0.53-1.05], p=0.09, GT=1.24[0.88-1.75], p=0.22 and GG=2.32[0.77-7.00], p=0.14) (Table 2, Figures 5a, 5b and 5c).

3.6. The relationship between rs12583006 and pSS susceptibility in random health controls and pSS patients

There were statistical differences in rs12583006 in pSS patients and health controls (Table 2). Because of heterogeneity (Figures 6a, 6b and 6c), the genotype of AA, TA and TT chose the fixed model. For rs12583006, OR values, 95% CIs and P values for each genotype and allele are shown in Table 2. There was a relationship between the genotype of AA and TT in rs12583006 and pSS susceptibility, respectively (OR [95% CI], p-value: TT=0.73[0.54-0.99], p=0.04, TA=1.08[0.79-1.49], p=0.63 and AA=2.55[1.34-4.86], p=0.00) (Table 2, Figures 6a, 6b and 6c).

3.7. Publication bias

There was no discernible publication bias found (Table 2). Egger's test did not show publication bias in each genotype and allele of rs9514827, rs1041569, rs9514828, rs1224141 and rs12583006.

4. Discussion

There are many studies on pSS and TNFSF13B, mostly focusing on rs9514828, rs1041569, rs9514827, rs12583006 and rs1224141. Most of them have been associated with increased susceptibility to pSS in the literature, but there are subtle differences in opinion. Kintrilis et al. concluded that genotype TT of rs1041569, a variant of the TNFSF13B gene, had a significantly increased prevalence in the pSS patient group compared to healthy controls. It was also demonstrated that genotype TT of rs1041569 was a risk factor for pSS, altering susceptibility to pSS, and that haplotype TTAC was found to increase susceptibility to pSS. The article also concluded that haplotypes TATTT and TTCTT were only detected in pSS patients with thickened arterial walls.[2] Santillan-Lopez et al. demonstrated that the expression of TNFSF13B mRNA was increased in pSS patients compared to healthy controls, with a 5.04-fold increase. They also investigated the relationship between soluble BAFF (sBAFF) and TNFSF13B gene expression and found that elevated gene expression levels were consistent with sBAFF protein levels. However, they concluded that TNFSF13B transcript levels in pSS patients were not associated with the gene polymorphism of rs9514828.[3] Nezos et al. concluded that the TNFSF13B gene polymorphism increased susceptibility to pSS in both the high-risk group (type I) pSS patients and the low-risk group (type II) pSS patients compared to healthy controls. In the high-risk group of pSS patients, the CC genotype of rs9514828 and the TT genotype of rs9514827 were statistically different from those of healthy controls. In the low-risk group of pSS patients, the minor A allele of rs12583006 and the AA genotype of rs12583006 were statistically different from those of healthy controls.[1] Another study identified the TT genotype of the TNFSF13B rs9514828 gene variant as a protective factor against fatigue in patients with pSS.[38]

As seen in this article, our results demonstrated that the TT genotype of rs1041569, the TT genotype of rs12583006 and the AA genotype of rs12583006 could increase the susceptibility of pSS. These genotypes were statistically significantly related to pSS. On the one hand, we suggested that the TT genotype of rs1041569 and the AA genotype of rs12583006 are risk factors from OR and 95% CI (OR [95% CI], p-value: 4.62[1.59-13.43], p=0.00 and 2.55[1.34-4.86], p=0.00 in the fixed-effects model). On the other hand, we also

considered that the TT genotype of rs12583006 is a protective factor from OR and 95% CI (OR [95% CI], p-value: 0.73[0.54-0.99], p=0.04 in the fixed-effects model).

As research has progressed, the role of TNFSF13B in pSS has been explored. Nossent et al. suggested that susceptibility of Ro/La-positive pSS increases with CTAT haplotype and that elevated serum BAFF levels in pSS patients are associated with TTTT haplotype.[25]Carrillo-Ballesteros et al. concluded that pSS patients with elevated serum BAFF levels had a longer disease duration and the highest levels of anti-La/SSB antibodies. In addition, they found that the duration of the disease was associated with anti-Ro/SSA antibodies and SSDAI scores.[6] Loureiro-Amigo et al. determined that BAFF, CXCL13 and PD-L2 showed the highest accuracy in identifying patients with pSS, with significant differences between patients and controls. The most accurate score was obtained by applying BAFF, CXCL13 and PD-L2 levels to the formula [ln(CXCL13) + ln(BAFF)]/ln(PD-L2), which had an Area Under Curve (AUC) value of 0.854, with a sensitivity of 77.2% and specificity of 86.4%, using a cut-off value of 1.7.[5] Another research showed that eight of the nine optimal immune-related genes (IRGs) (IL-18, JAK2, TBK1, EED, TNFSF10, TNFSF13B, CYSLTR1, and ICOS) were significantly overexpressed in pSS patients and were defined as key genes by qRT-PCR. ROC analysis showed high sensitivity and specificity for TNFSF13B and CYSLTR1.[4]

In conclusion, our meta-analysis of the published data demonstrated that polymorphisms in the TNFSF13B gene were related to vulnerability to pSS in the pSS group and healthy controls. The TT genotype of rs1041569 and the AA genotype of rs12583006 were risk factors from OR and 95% CI in pSS patients, and the TT genotype of rs12583006 was a protective factor from OR and 95% CI in pSS patients. As a result, more investigation into the relationship between TNFSF13B, serum BAFF levels, levels of autoantibodies, sensitivity and specificity may shed light on the process by which genetic polymorphisms affect autoantibodies production in patients with pSS, aiding in the clinical diagnosis and therapy of the condition.

Table 1. Basic information of literature included in pSS patients and healthy controls). pSS primary Sjögren's Syndrome patients, HC Healthy Countrols, SNP Single Nucleotide Polymorphism, HWE Hardy–Weinberg equilibrium

HWE	Yes	Yes	Yes	
SNPs	rs9514827 rs1041569 rs9514828 rs1224141 rs12583006	rs9514827 rs1041569 rs9514828	rs9514827 rs1041569 rs9514828 rs1224141 rs12583006	
HC No	200	309	137	
pSS No	148	101	193	
Ethnicity	Athenian	Mexican	Caucasian	
Country	Athens	Mexico	Greek	
1st author	Nikolaos Kintrilis	Enrique Santillán-López	Adrianos Nezos	
Year	2022	2022	2014	

Table 2. Summary of odds ratios (95%CI) in the analysis of the relationship of TNFSF13B with pSS susceptibility in pSS patients and Healthy Controls.

			0.79 0.91	0.74 0.88	0.28 0.91		
	Publication bias	p	0.23 0.38 0.38	0.90 0.69 0.69	0.92 0.18 0.18	0.95 0.78 0.31	0.18 0.31 0.90
		Egger's test	0.27 -0.11 -1.20 0.88 -0.88	0.34 0.16 -0.12 0.39 -0.39	-2.10 -0.12 0.10 1.35 -1.35	-0.06 -0.27 1.03	-1.33 1.02 -0.12
	Heterogeneity	I^2(%)	56.74 46.94 -24.32 65.61 65.61	-718.34 -1592.91 5.43 -545.45 -545.45	57.36 -2.99 -7819.51 44.84 44.84	-27360.62 -1229.40 8.74	43.21 3.43 -6574.89
		p	0.10 0.15 0.45 0.09 0.09	0.88 0.94 0.35 0.69 0.69	0.10 0.38 0.99 0.18 0.18	0.95 0.78 0.30	0.18 0.31 0.90
		Q	4.62 3.77 1.61 2.91 2.91	0.24 0.12 2.11 0.15 0.15	4.69 1.94 0.03 1.81 1.81	0.00 0.08 1.10	1.76 1.04 0.01
	Random effects	p	0.70 0.84 0.84		0.98		
		OR [95%CI]	0.92 [0.62-1.37] 0.95 [0.60-1.51] 1.05 [0.66-1.67]		0.99 [0.63-1.56]		
	Fixed effects	p	0.33 0.39	0.78 0.52 0.00 0.72 0.72	0.15 0.10 0.31 0.31	0.09 0.22 0.14	0.04 0.63 0.00
		OR (95%CI)	1.14[0.88-1.47] 0.81[0.50-1.31]	0.96 [0.74-1.26] 0.91 [0.70-1.20] 4.62 [1.59-13.43] 0.95 [0.70-1.27] 1.06 [0.78-1.42]	0.83 [0.64-1.07] 1.33 [0.94-1.87] 0.88 [0.70-1.12] 1.13 [0.89-1.43]	0.75 [0.53-1.05] 1.24 [0.88-1.75] 2.32 [0.77-7.00]	0.73 [0.54-0.99] 1.08 [0.79-1.49] 2.55 [1.34-4.86]
	Genotype/Allele	Genotype/Allele	TT TC CC T C	AA AT TT A T	CC CT TT C T	TT GT GG	TT TA AA

Table 2. Summary of odds ratios (95%CI) in the analysis of the relationship of TNFSF13B with pSS susceptibility in pSS patients and Healthy Controls.

			0.79 0.91	0.74 0.88	0.28 0.91		
	Publication bias		0.23 0.38	0.90 0.69	0.92 0.18	0.95 0.78	0.18 0.31
		p	0.38	0.69	0.18	0.31	0.90
	Study(n) Comparison	Study(n) Comparison	3 rs9514827	3 rs1041569	3 rs9514828	2 rs1224141	2 rs12583006

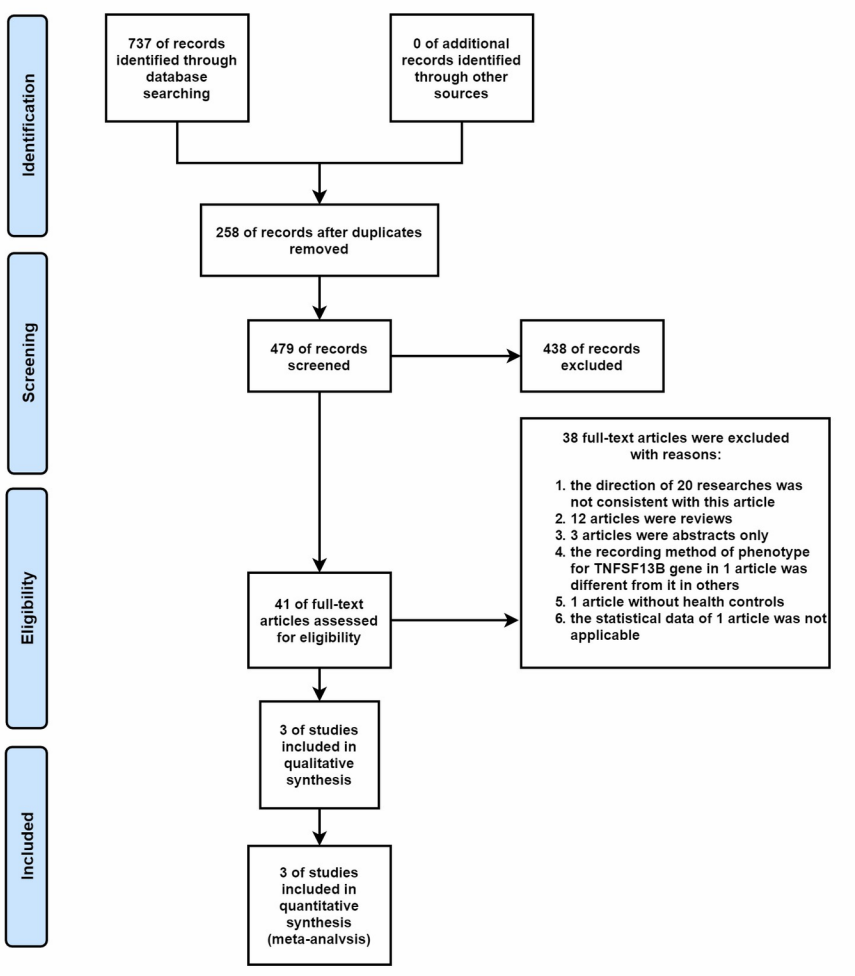

Fig. 1. The flow chart of search results.

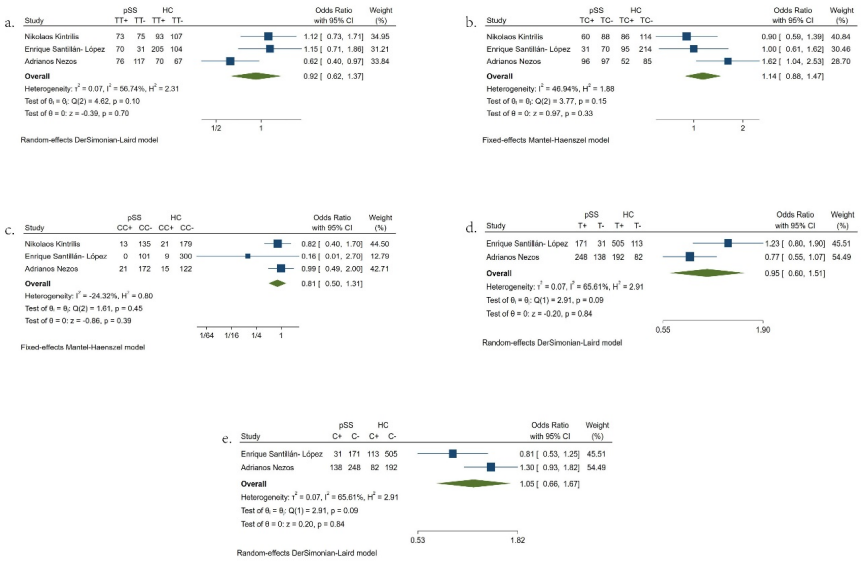

Fig. 2. Forest maps of rs9514827 between pSS patients and healthy controls. Abbreviations: pSS: primary Sjogren's Syndrome patients; HC: Healthy Controls.

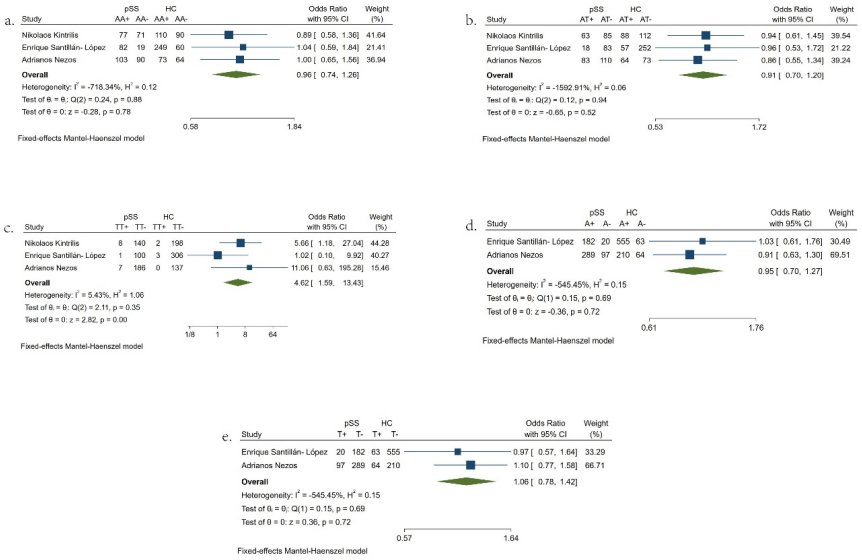

Fig. 3. Forest maps of rs1041569 between pSS patients and healthy controls. Abbreviations: pSS: primary Sjogren's Syndrome patients; HC: Healthy Controls.

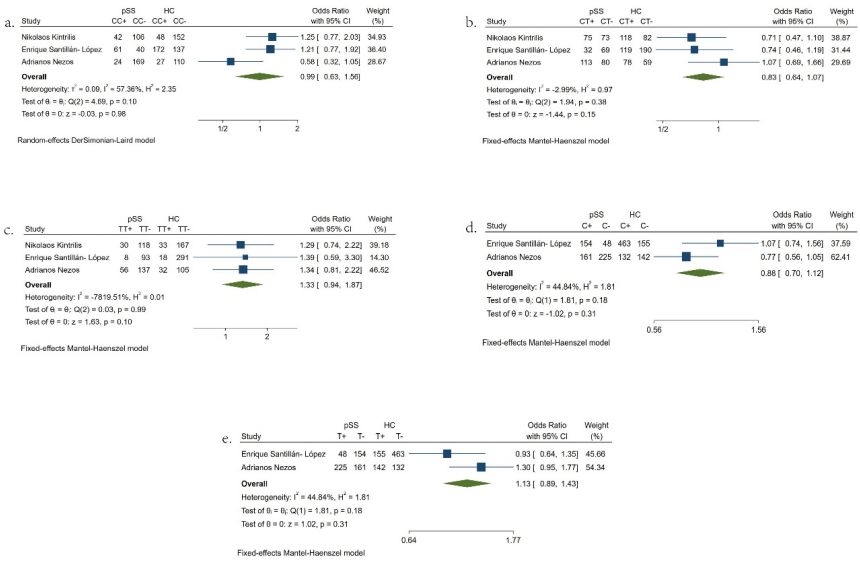

Fig. 4. Forest maps of rs9514828 between pSS patients and healthy controls. Abbreviations: pSS: primary Sjogren's Syndrome patients; HC: Healthy Controls.

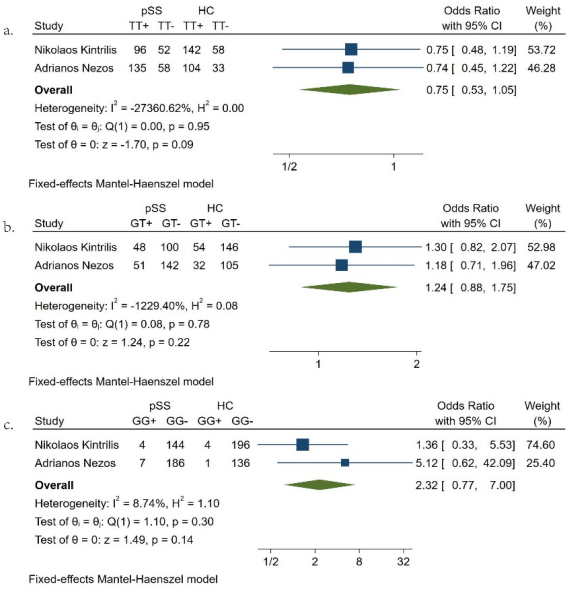

Fig. 5. Forest maps of rs1224141 between pSS patients and healthy controls. Abbreviations: pSS: primary Sjogren's Syndrome patients; HC: Healthy Controls.

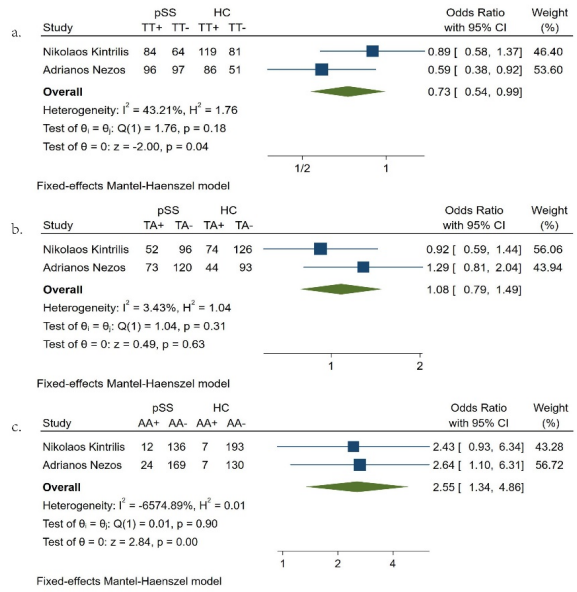

Fig. 6. Forest maps of rs12583006 between pSS patients and healthy controls. Abbreviations: pSS: primary Sjogren's Syndrome patients; HC: Healthy Controls.

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