Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Meta-analysis

Association between BANK1 polymorphisms and susceptibility to autoimmune diseases: A meta-analysis

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Received February 4, 2016; **Accepted** March 25, 2017; **Published** March 31, 2017

Doi: http://dx.doi.org/10.14715/cmb/2017.63.3.6

Abstract:
This study aimed to explore whether BANK1 polymorphisms are associated with susceptibility to autoimmune diseases. We conducted a meta-analysis on the associations between the BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms and autoimmune diseases. Twenty-two articles with a total of 22,684 patients and 36,437 controls were included in the meta-analysis. Meta-analysis revealed a significant association between autoimmune diseases and the BANK1 rs10516487 T allele (OR = 1.161, 95% CI = 1.092–1.275, $p = 1.9 \times 10^{-6}$, heterogeneity $p < 0.001$). The analysis also revealed an association between autoimmune diseases and the BANK1 rs3733197 A allele (OR = 1.178, 95% CI = 1.105–1.256, $p = 4.5 \times 10^{-7}$, heterogeneity $p = 0.002$) and the rs17266594 T allele (OR = 1.189, 95% CI = 1.073–1.315, $p = 0.001$, heterogeneity $p < 0.001$). Meta-analysis by autoimmune disease type revealed an association between both systemic lupus erythematosus and systemic sclerosis and the BANK1 rs10516487 T allele (OR = 1.294, 95% CI = 1.232–1.360, $p < 1.0 \times 10^{-8}$, heterogeneity $p = 0.556$; OR = 1.102, 95% CI = 1.027–1.183, $p = 0.017$, heterogeneity $p = 0.048$). However, meta-analysis failed to indicate an association between the BANK1 rs10516487 T allele and rheumatoid arthritis (RA; OR = 1.006, 95% CI = 1.956–1.058, $p = 0.819$). This meta-analysis demonstrates that BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms are associated with susceptibility to autoimmune diseases.

Key words: Autoimmune diseases; BANK1; Polymorphism; Meta-analysis.

Introduction

Autoimmune diseases are a diverse group of complex diseases characterized by the loss of self-tolerance, leading to immune-mediated tissue destruction (1,2). These diseases are multifactorial, involving interactions between various genetic and environmental factors. They share a number of characteristics that suggest common etiologic mechanisms. In particular, their pathophysiologies and their co-occurrence in families have prompted the hypothesis that autoimmune diseases share a genetic background (3).

B-cell scaffold protein with ankyrin repeats 1 (BANK1) is a B-cell adaptor protein that functions in B-cell receptor-induced calcium mobilization from intracellular stores (4). BANK1 is a signaling molecule expressed exclusively in B-cells. Binding of BANK1 to the IP3 receptors type 1 (IP3R-1) and 2 (IP3R-2) promotes their LYN-mediated phosphorylation to induce Ca2+ mobilization from endoplasmic reticulum stores (5,6). Interaction of BANK1 with downstream targets may lead to B-cell activation, which may be necessary for activation of antigen-induced immune responses (5). Changes in BANK1 expression and function have profound effects on the modulation of B-cell activity. For example, BANK1-deficient mice had higher levels of mature B-cells and spontaneous germinal center B-cells than their wild-type counterparts (7). The *BANK1* gene maps to chromosome 4q24 and exhibits polymorphisms in its exon region that appear to correlate with transcription variants (6). Three polymorphisms of *BANK1* have been studied in detail (8). The *BANK1* rs10516487 T/C polymorphism leads to a substitution of arginine by histidine at amino acid position 61 (R61H) in exon 1 of BANK-1, within the region essential for IP3R binding. The *BANK1* rs3733197 G/A polymorphism results in an alanine to threonine substitution at amino acid position 383 (A383T) in exon 7, which encodes the ankyrin repeat–like motif. The *BANK1* rs17266594 T/C polymorphism is a branch-point variant in exon 3 that may affect the relative splicing efficiency of its transcript. These three polymorphisms have functional significance, affecting *BANK1* regulatory sites and contributing to sustained B-cell receptor signaling and subsequent B-cell hyperactivity that are characteristic of autoimmune disease (8).

Some studies have shown that BANK1 polymorphisms are associated with several autoimmune diseases; on the other hand, other reports have found no such associations (9-29). These disparities are probably caused by small sample sizes, low statistical power, and/or clinical heterogeneity (30). Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we performed a meta-analysis (31-34). The aim

of the present study was to determine by meta-analysis whether the BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms are associated with susceptibility to autoimmune diseases.

Materials and Methods

Identification of eligible studies and data extraction

We performed a search of studies that examined associations between BANK1 polymorphisms and autoimmune diseases. The literature was searched using PubMed and EMBASE databases to identify articles in which BANK1 polymorphisms were analyzed in patients with autoimmune diseases. Combinations of keywords, such as, 'BANK1,' 'polymorphism,' 'autoimmune diseases,' and the names of individual diseases, were entered as Medical Subject Headings (MeSH) and text words. References cited in these studies were also investigated to identify additional studies not indexed by electronic databases. No restrictions were placed on language, race, ethnicity, or geographic area. Autoimmune diseases were diagnosed according to recognized classification criteria. Studies were included if (1) they were published before September 2015, (2) contained original data, and (3) provided sufficient genotype or allele data to calculate odds ratios (ORs). The following were excluded: (1) studies containing overlapping data, (2) studies in which the number of null and wild genotypes or alleles could not be ascertained, and (3) studies in which family members had been studied, for example, transmission disequilibrium tests, because the analyses conducted were based on linkage considerations. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics of subjects, and numbers of cases and controls. Frequencies of alleles were calculated from genotype distributions.

Evaluations of statistical associations

A chi-square test was used to determine whether observed genotype frequencies conformed to the Hardy-Weinberg equilibrium (HWE). Meta-analyses were performed using allelic contrast of the BANK1 rs10516487 T/C, rs3733197 G/A, and rs17266594 T/C polymorphisms. Subgroup analyses were performed for ethnicity and disease type to evaluate ethnic- and disease-specific effects. Point estimates of risks, ORs, and 95% confidence intervals (CI) were determined for each analysis. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test allowed an assessment of the null hypothesis that all studies evaluated the same effect. I^2 values were used to quantify the effect of heterogeneity, with values ranging between 0% and 100% and representing the proportion of between-study variability attributable to heterogeneity rather than chance (35). I^2 values of 25%, 50%, and 75% were nominally defined as low, moderate, and high estimates. The fixed effects model assumes a genetic factor has the same effect on disease susceptibility across all studies investigated, and that observed variations between studies are caused by chance alone. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. When study groups are homogeneous, the two models are similar, but if this is not the case, the random effects model usually provides wider CIs than the fixed effects model. The random effects model is used in the presence of significant between-study heterogeneity (36). If the significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effect model was used for meta-analysis. Otherwise fixed effect model was used (35,36). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To examine potential sources of heterogeneity observed in the meta-analysis, a meta-regression was performed. A sensitivity analysis was also performed to assess the influence of each individual study on the pooled OR by omitting each study individually and to determine whether results from this meta-analysis were statistically robust. Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which requires a range of studies of varying sizes and involves subjective judgments, publication bias was evaluated using Egger's linear regression test (37), which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Results

Studies included in the meta-analysis

One hundred and ten reports were identified by electronic and manual searching, and 32 were selected for full-text review based on title and abstract details. Ten reports were excluded because they contained other polymorphisms, duplicate data, or family data. Thus, 22 reports met the inclusion criteria (9-29). In addition, four of these reports contained data on two different groups (17,21,24,27,38) and one on three different groups (12), and we analyzed these studies independently. Therefore, a total of 28 separate studies were considered in the meta-analysis, which, in total, evaluated 22,684 patients and 36,437 controls. Twenty-five studies, corresponding to 19,924 patients and 30,650 controls, examined the BANK1 rs10516487 polymorphism; 17 studies, corresponding to 13,773 patients and 16,036 controls, examined the BANK1 rs3733197 polymorphism; and 12 studies, corresponding to 10,719 patients and 13,766 controls, examined the BANK1 rs17266594 polymorphism. These studies encompassed systemic lupus erythematosus (SLE; n = 12), rheumatoid arthritis (RA; n = 5), systemic sclerosis (SSc; n = 3), type 1 diabetes (T1D; n = 1), autoimmune thyroid disease (AITD; n = 1), primary Sjogren's syndrome (pSS; n = 1), inflammatory bowel disease (IBD; n = 1), multifocal motor neuropathy (MMN; n = 1), psoriasis (n = 1), giant cell arteritis (GCA; n = 1), and antiphospholipid antibody syndrome (APS; n = 1). From the available data, disease-specific meta-analyses were performed for SLE, RA, and SSc, and ethnicity-specific meta-analyses were also conducted for Caucasian, Asian, African, and Tunisian populations. Selected characteristics of these studies related to the association between BANK1 polymorphisms and diseases are summarized in Table 1.

Meta-analysis of BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms in autoimmune disease

A summary of findings on the associations between BANK1 polymorphisms and autoimmune diseases is provided in Table 2. Meta-analysis revealed a significant association between autoimmune disease and the BANK1 rs10516487 T allele (OR = 1.161, 95% CI = 1.092–1.275, $p = 1.9 \times 10^{-6}$) (Fig. 1, Table 2), and stratification by ethnicity indicated an association between this allele and autoimmune diseases in Caucasians, Asians, and Africans (OR = 1.143, 95% CI = 1.053–1.239, $p = 0.001$; OR = 1.147, 95% CI = 1.002–1.313, $p = 0.046$; OR = 1.285, 95% CI = 1.156–1.428, $p = 3.3 \times 10^{-6}$), but not in Tunisians. Meta-analysis showed a significant association between autoimmune disease and the rs3733197 A allele (OR = 1.178, 95% CI = 1.105–1.256, $p = 4.5 \times 10^{-7}$) (Fig. 2, Table 2), and stratification by ethnicity indicated an association between this allele and autoimmune diseases in Caucasians, Asians, and Tunisians (OR = 1.177, 95% CI = 1.088–1.273, $p = 4.8 \times 10^{-7}$; OR = 1.142, 95% CI = 1.033–1.263, $p = 0.009$; OR = 1.517, 95% CI = 1.127–2.044, $p = 0.006$). Meta-analysis showed an association between autoimmune disease and the rs17266594 T allele (OR = 1.189, 95% CI = 1.073–1.315, $p = 0.001$) (Fig. 3, Table 2), and stratification by ethnicity indicated an association between this allele and autoimmune diseases in Caucasians (OR = 1.157, 95% CI = 1.043–1.285, $p = 0.006$), but not in Asians and Tunisians.

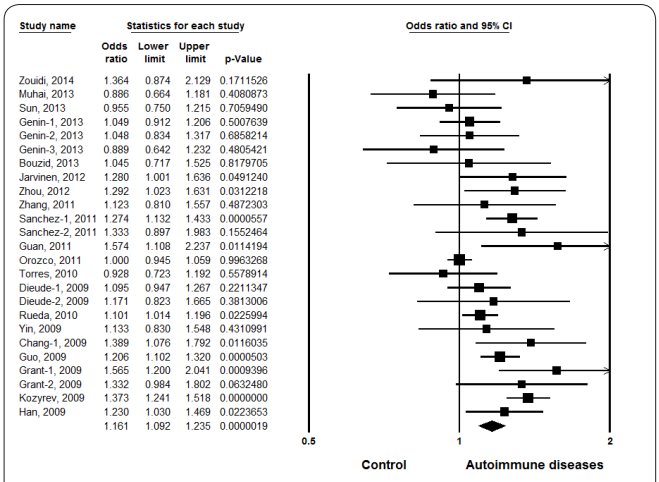

Figure 1. Forest plot of odd ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data indicating the association between the BANK1 rs10516487 T allele and autoimmune diseases.

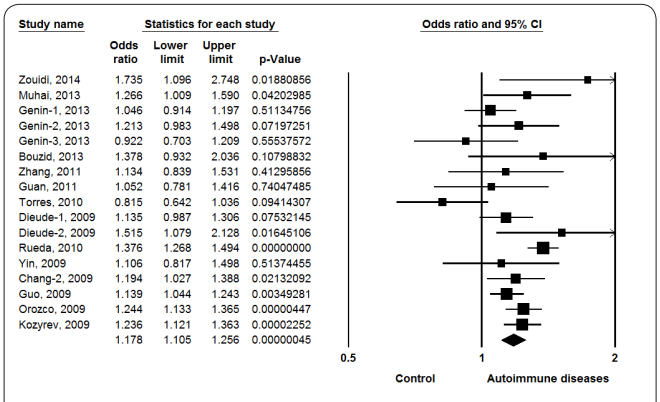

Figure 2. Forest plot of odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data indicating the association between the BANK1 rs3733197 G allele and autoimmune diseases.

Meta-analysis of BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms and autoimmune disease type

Findings on the association between BANK1 polymorphisms and SLE, RA, and SSc are summarized in Table 2. Meta-analysis revealed a significant association between SLE and the BANK1 rs10516487 T allele (OR = 1.294, 95% CI = 1.232–1.360, $p < 1.0 \times 10^{-8}$) (Table 2), and between this allele and SSc (OR = 1.102, 95% CI = 1.027–1.183, $p = 0.017$) (Table 2). However, meta-analysis failed to reveal an association between the BANK1 rs10516487 T allele and RA (OR = 1.006, 95% CI = 1.956–1.058, $p = 0.819$) (Table 2). An association was also found between the BANK1 rs3733197 A allele and SLE and SSc (OR = 1.178, 95% CI = 1.111–1.249, $p = 4.0 \times 10^{-8}$; OR = 1.299, 95% CI = 1.110–1.519, $p = 0.001$), but not RA (OR = 1.126, 95% CI = 0.993– 1.276, $p = 0.064$) (Table 2). Similarly, meta-analysis revealed an association between the BANK1 rs17266594 T allele and SLE and SSc (OR = 1.407, 95% CI = 1.215–1.628, $p = 5.0 \times 10^{-5}$; OR = 1.091, 95% CI = 1.004–1.186, $p = 0.039$), but not RA (OR = 1.092, 95% CI = 0.991–1.203, $p = 0.075$) (Table 2).

Heterogeneity, sensitivity, and publication bias

Some heterogeneity was found in the meta-analyses of the BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms (Tables 2). These heterogeneities might have been due to clinical or genetic heterogeneity, and they resolved or decreased in subgroup analyses by ethnicity and autoimmune disease type. There was no heterogeneity in the meta-analyses of the BANK1 rs10516487 polymorphism and SLE, RA, and SSc, and the BANK1 rs3733197 polymorphism and SLE (Tables 2). HWE was examined in studies where genotype frequencies were available. The distributions of genotypes in the normal control groups were not consistent with HWE in one study of the BANK1 rs17266594 polymorphism (22). Deviation from HWE among controls implies a bias during control selection or genotyping errors. However, excluding this study did not affect our results on the association of the BANK1 rs17266594 polymorphism with autoimmune diseases. Sensitivity analysis showed that no individual study significantly

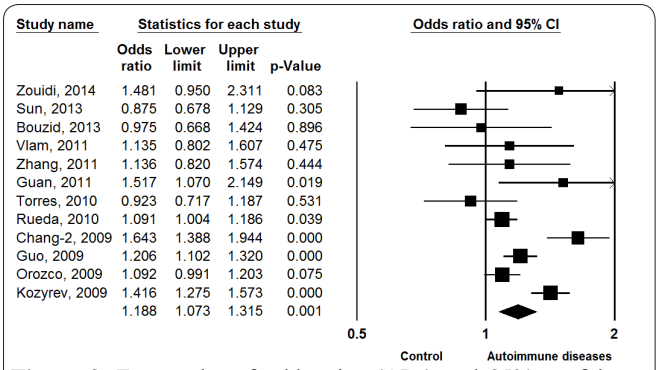

Figure 3. Forest plot of odd ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data indicating the association between the BANK1 rs17266594 T allele and autoimmune diseases.

Table 1. Characteristics of the individual studies included in the meta-analysis.

Study(Ref)	Population	Autoimmune disease	Sample size		Studied polymorphism	Associations found
			Case	Control		
Zouidi, 2014(9)	Tunisian	T1D	76	162	rs1051648, rs3733197, rs17266594	rs1051648 (NS), rs3733197 (p = 0.006), rs17266594 (p = 0.004)
Muhai, 2013(10)	Asian	AITD	667	301	rs1051648, rs3733197	Rs1051648 (NS), rs3733197 (p = 0.042)
Sun, 2013(11)	Asian	pSS	540	577	rs1051648, rs17266594	NS
Genin-1, 2013(12)	Caucasian	RA	806	1203	rs1051648, rs3733197	NS
Genin-2, 2013(12)	Caucasian	RA	461	373	rs1051648, rs3733197	NS
Genin-3, 2013(12)	Asian	RA	634	322	rs1051648, rs3733197	NS
Bouzid, 2013(13)	Tunisian	IBD	107	162	rs1051648, rs3733197, rs17266594	Rs1051648 (NS), rs3733197 (p = 0.021), rs17266594 (NS)
Jarvinen, 2012(14)	Caucasian	SLE	275	356	rs1051648	Rs1051648 (p = 0.04)
Vlam, 2011(15)	Caucasian	MMN	92	1152	rs17266594	NS
Zhou, 2012(29)	Asian	SLE	500	1000	rs1051648	NS
Zhang, 2011(16)	Asian	Psoriasis	242	317	rs1051648, rs3733197, rs17266594	NS
Sanchez-1, 2011(17)	African	SLE	1517	1800	rs1051648	Rs1051648 ($p = 5.9 \times 10^{-5}$)
Sanchez-2, 2011(17)	African	SLE	152	122	rs1051648	NS
Guan, 2011(18)	Asian	SLE	264	268	rs1051648, rs3733197, rs17266594	Rs1051648 (p = 0.011), rs3733197 (NS), rs17266594 (p = 0.018)
Orozco, 2011(19)	Caucasian	RA	3962	9275	rs1051648	NS
Torres, 2010(20)	Caucasian	GCA	214	534	rs1051648, rs3733197, rs17266594	NS
Dieude-1, 2009(21)	Caucasian	SSc	868	936	rs1051648, rs3733197	Rs1051648 (p = 0.0046), rs3733197 (p = 0.007)
Dieude-2, 2009(21)	Caucasian	SSc	138	182	rs1051648, rs3733197	Rs1051648 (NS), rs3733197 (p = 0.01)
Rueda, 2010(22)	Caucasian	SSc	2380	3270	rs1051648, rs3733197, rs17266594	rs1051648 (p = 0.01), rs3733197 (NS), rs17266594 (p = 0.003)
Yin, 2009(23)	Caucasian	APS	133	468	rs1051648, rs3733197	NS
Chang-1, 2009(24)	Asian	SLE	314	920	rs1051648	rs1051648 (p = 0.011)
Chang-2, 2009(24)	Asian	SLE	949	1042	rs3733197, rs17266594	rs3733197 (p = 0.021), rs17266594 ($p = 4.67 \times 10^{-9}$)
Guo, 2009(25)	Caucasian	SLE	1892	2652	rs1051648, rs3733197, rs17266594	rs1051648 (p = 2.84E-05), rs3733197 (p = 5.46E-03), rs17266594 (p = 2.20E-05)
Orozco, 2009(26)	Caucasian	RA	2125	2168	rs3733197, rs17266594	rs3733197 (p = 0.0009), rs17266594 (NS)
Grant-1, 2009(27)	Caucasian	SLE	178	1808	rs1051648	rs1051648 ($p = 7.07 \times 10^{-4}$)
Grant-2, 2009(27)	African	SLE	148	1894	rs1051648	rs1051648 (p = 0.039)
Kozyrev, 2009(38)	Caucasian	SLE	2003	1968	rs1051648, rs3733197, rs17266594	rs1051648 ($p = 3.74 \times 10^{-10}$), rs3733197 ($p = 4.67 \times 10^{-5}$), rs17266594 ($p = 4.74 \times 10^{-11}$)
Han, 2009(28)	Asian	SLE	1047	1205	rs1051648	NS

Ref: reference, T1D: Type 1 diabetes, AITD: Autoimmune thyroid diseases, pSS: Primary Sjogren's syndrome, RA: Rheumatoid arthritis, IBD: Inflammatory bowel disease, SLE: Systemic lupus erythematosus, MMN: Multifocal motor neuropathy, GCA: Giant cell arteritis, SSc: Systemic sclerosis, APS: Antiphospholipid antibody syndrome.

Table 2. Meta-analysis of the associations between BANK1 polymorphisms and autoimmune diseases

Polymorphism	Population	No. of studies	Sample size		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	p-value	Model	p-value	I^2
rs10516487 T vs. C	Autoimmune disease	25	19924	30650	1.161	1.092–1.275	1.9×10^{-6}	R	0.000	63.9
	Caucasian	12	13232	22130	1.143	1.053–1.239	0.001	R	0.000	74.9
	Asian	8	4688	4388	1.147	1.002–1.313	0.046	R	0.043	51.7
	African	3	1817	3816	1.285	1.156–1.428	3.3×10^{-6}	F	0.948	0
	Tunisian	2	111	158	1.169	0.876–1.558	0.289	F	0.371	0
	SLE	11	5790	12721	1.294	1.232–1.360	$<1.0 \times 10^{-8}$	F	0.674	0
	RA	4	5812	11107	1.006	0.956–1.058	0.819	F	0.786	0
	SSc	3	3368	4366	1.102	1.027–1.183	0.007	F	0.942	0
rs3733197 G vs. A	Autoimmune diseases	17	13773	16036	1.178	1.105–1.256	4.5×10^{-7}	R	0.002	57.1
	Caucasian	10	10834	13487	1.177	1.088–1.273	4.8×10^{-5}	R	0.001	69.5
	Asian	5	2756	2249	1.142	1.033–1.263	0.009	F	0.430	0
	Tunisian	2	183	300	1.517	1.127–2.044	0.006	F	0.453	0
	SLE	4	4924	5837	1.178	1.111–1.249	4.0×10^{-8}	F	0.556	0
	RA	4	4026	4066	1.126	0.993–1.276	0.064	R	0.062	59.1
	SSc	3	3390	4248	1.299	1.110–1.519	0.001	R	0.048	67.1
rs17266594 T vs. C	Autoimmune diseases	12	10719	13766	1.189	1.073–1.315	0.001	R	0.000	75.7
	Caucasian	6	8567	11310	1.157	1.043–1.285	0.006	R	0.001	76.4
	Asian	4	1973	2148	1.259	0.913–1.735	0.160	R	0.000	83.1
	Tunisian	2	179	308	1.163	0.871–1.551	0.306	F	0.161	49.2
	SLE	4	4961	5736	1.407	1.215–1.628	5.0×10^{-5}	R	0.006	75.7
	RA	1	2166	2154	1.092	0.991–1.203	0.075	NA	NA	NA
	SSc	1	2351	3198	1.091	1.004–1.186	0.039	NA	NA	NA

R: random effects model, F: fixed effects model, NA: not available, SLE: systemic lupus erythematous, RA: rheumatoid arthritis, SSc: systemic sclerosis.

affected the pooled OR, indicating statistically robust results from this meta-analysis. It was difficult to create a funnel plot, which is usually used to detect publication bias, because of the small number of studies included in this analysis. However, Egger's regression test showed no evidence of publication bias ($p > 0.1$).

Discussion

Genetic factors are considered to be strong determinants of autoimmune diseases, despite their multifactorial nature. Accumulating evidence suggests the presence of common genetic factors that predispose a person to autoimmunity (3). The BANK1 gene has been considered a candidate gene for the development of autoimmune diseases, because autoantibody formation against self-antigens is one of the key features of autoimmune disease, and BANK1 polymorphisms cause B-cell hyperactivity or activation of deregulated B-cells that contribute to the production of autoantibodies (8).

In this meta-analysis, we addressed the association between the functional BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms and susceptibility to autoimmune diseases. We found an association between the risk of autoimmune diseases and the BANK1 rs10516487 T allele (OR = 1.161, 95% CI = 1.092–1.275, $p = 1.9 \times 10^{-6}$). After stratification by ethnicity, a subgroup meta-analysis indicated an association between the BANK1 rs10516487 T allele and autoimmune diseases in Caucasians, Asians, and Africans. We also found associations between autoimmune diseases and the BANK1 rs3733197 A allele and rs17266594 T allele. Meta-analysis by autoimmune disease type revealed an association between SLE and SSc and the BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms. However, no association was found between RA and these BANK1 polymorphisms.

The BANK1 rs10516487 polymorphism is within the region essential for binding of IP3R, a downstream protein that mediates *BANK1* activity (6). BANK1 rs17266594 is located in a branch-point site and affects the relative splicing efficiency of BANK1. The BANK1 rs3733197 polymorphism, causing an alanine to threonine substitution at position 383 in exon 7, could affect the B-cell signaling process (8). Individuals carrying the BANK1 functional polymorphisms have been reported to show altered B-cell activation through the B-cell receptor that leads to BANK1 phosphorylation and signaling that may contribute to the production of autoantibodies (7). Sustained B-cell receptor signaling and B-cell hyperactivity are characteristic of autoimmune diseases (39). Disease-specific autoantibodies are produced in autoimmune diseases, including SLE and SSc (8).

Our meta-analysis failed to reveal an association between the BANK1polymorphisms and RA, which conflicts with results of functional studies conducted on BANK1 polymorphisms (8). However, it is not uncommon that epidemiological results fail to agree with the results of functional studies, since multiple genes, different genetic backgrounds, and different environmental factors contribute to the development of this

complex disease. Conversely, it is also possible that our meta-analysis results demonstrated a type II error (false-negative), because a relatively small number of studies were included. Our findings suggest that further investigations will be required to determine the nature of the association between these BANK1 polymorphisms and autoimmune diseases. Our findings also suggest that BANK1 polymorphisms are disease-specific and also support the notion that different pathogenic mechanisms are involved in the development of polygenic disorders, such as autoimmune diseases.

This meta-analysis differs from a previous meta-analysis on the relationship between BANK1 polymorphisms and SLE risk performed by Fan et al. (40), in that the present study included eighteen more studies on BANK1 polymorphisms and autoimmune diseases (9-23,26,27,29). Studies included in our meta-analysis were not limited to those focused on SLE. We included available data on all autoimmune diseases, including SLE. However, the results of this meta-analysis regarding the contribution of the BANK1 polymorphisms to the development of SLE are in agreement with the previous study.

The present study has some limitations that require consideration. First, heterogeneity and confounding factors may have distorted the analysis. Second, we did not stratify and analyze certain factors, such as sex or clinical or environmental variables, because of a lack of data, and BANK1 polymorphisms may be associated with clinical manifestations in addition to disease susceptibility. Third, study and subject numbers in the disease-specific subgroup analyses were relatively small; thus, our analysis may have been underpowered in these analyses. Fourth, several autoimmune diseases, such as T1D, AITD, IBVD, MMN, psoriasis, GCA, and APS, were not analyzed in the present study. Thus, additional studies are warranted to explore the associations between these autoimmune diseases and BANK1 polymorphisms.

In conclusion, this meta-analysis shows that the BANK1 rs10516487, rs3733197, and rs17266594 polymorphisms are associated with susceptibility to autoimmune diseases, especially SLE and SSc. This meta-analysis provides further evidence that the BANK1 gene plays a role in the etiology of autoimmune diseases. Given what is known about the importance of BANK1 in autoimmunity, our findings suggest that BANK1 polymorphisms may modulate the development of autoimmune diseases. Further studies are required to clarify the role of the BANK1 gene in autoimmune pathogenesis.

Acknowledgements

This study was supported in part by a grant of the Korea Healthcare technology R&D Project, Ministry for Health and Welfare, Republic of Korea (HI15C2958).

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