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ORIGINAL ARTICLE

Association between the *BANK1* rs3733197 polymorphism and polymyositis/dermatomyositis in a Chinese Han population

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Abstract

The aim of our study was to investigate the association between single nucleotide polymorphisms (SNPs) in the *BANK1* gene and polymyositis/dermatomyositis (PM/DM) in a Chinese Han population. In total, 363 PM patients, 654 DM patients, and 1280 healthy controls were recruited and genotyped using the Sequenom MassArray system. A significant allele association was observed in rs3733197 among the PM/DM patients (OR 0.81, 95%CI 0.70–0.94, $Pc = 1.83 \times 10^{-2}$). Notably, rs3733197 was associated with DM and PM/DM patients with ILD involvement ($Pc = 0.026$; $Pc = 6.0 \times 10^{-3}$, respectively). However, no statistically significant difference was observed in the allele or genotype frequencies of three SNPs (rs4522865, rs17266594, and rs10516487) among the DM, PM, and PM/DM patients and healthy controls (all $Pc > 0.05$). This study was the first to demonstrate that a *BANK1* gene SNP (rs3733197) could confer genetic predisposition in PM/DM patients and PM/DM patients with ILD in a Chinese Han population.

Keywords Association · *BANK1* · Dermatomyositis · Polymyositis · rs3733197

Introduction

Idiopathic inflammatory myopathies (IIMs), including polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), and myositis overlapping with other connective tissue diseases, comprise a heterogeneous group of rare autoimmune diseases characterized by the presence of symmetrical, proximal muscle weakness, inflammatory infiltrates in skeletal muscle tissue, and elevated levels of skeletal muscle enzymes. In addition, patients with IIMs may also present with extra-muscular features, such as skin rashes, interstitial lung disease (ILD), and malignancy, that are often related to the serum antibody status [1, 2]. Thus, IIMs are complex genetic diseases initiated by immune activation following specific environmental trigger events in genetically predisposed individuals. However, the exact cause of these diseases remains unclear.

To date, the strongest genetic associations in the IIMs have consistently been shown to be within the major histocompatibility complex (*MHC*), although candidate gene studies have identified shared genetic susceptibility with other autoimmune diseases [3]. *BANK1* (B cell scaffold protein with ankyrin repeats 1) is a B cell adaptor protein that is highly expressed in B cells [4, 5]. B cell activation via the B cell receptor leads to the tyrosine phosphorylation of *BANK1*, which, in turn, promotes its association with the tyrosine kinase Lyn and the calcium channel IP3R and facilitates the phosphorylation and activation of IP3R by Lyn and the release of Ca2+ from endoplasmic reticulum stores [6, 7]. Recently, polymorphisms of the *BANK1* gene have been confirmed as susceptibility factors in multiple autoimmune diseases. In addition, according to recent genome-wide association studies (GWAS), IIMs share non-MHC genetic regions with other autoimmune diseases

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[8–10]. In prior studies, the branch-point-site single nucleotide polymorphism (SNP) rs17266594 and the nonsynonymous SNP rs10516487 (R61H) in the *BANK1* gene have been shown to be associated with systemic lupus erythaematous (SLE) [11–14], systemic sclerosis (SSc) [15, 16], rheumatoid arthritis (RA) [17], and psoriasis [18]. In addition, the SNP rs4522865, which is located in the first intron of *BANK1*, is also associated with SLE [19, 20]. In addition, the polymorphic SNP rs3733197, which causes an alanine to threonine substitution at amino acid position 383 (A383T) in exon 7, encodes an ankyrin repeat-like motif, and rs3733197 is also associated with SLE [11, 13], SSc [15, 16], RA [17], and psoriasis [18].

However, whether these SNPs in the *BANK1* gene contribute to the development of PM/DM in a Chinese Han population has not been explored. Because the *BANK1* gene is involved in the activation and function of B cells, we analyzed the potential associations between four SNPs (rs4522865, rs17266594, rs10516487, and rs3733197) in the *BANK1* gene region and the susceptibility to PM/DM in a Chinese Han population. The SNP rs3733197 in the *BANK1* gene is a risk factor for the development of PM/DM in this population.

Materials and methods

Subjects

The PM ($n = 363$) and DM patients ($n = 654$) were predetermined to have probable or definite myositis according to the criteria proposed by Bohan and Peter [21, 22]. The patients were recruited from the Peking Union Medical College Hospital between February 2013 and May 2015 ($n = 596$; PM, $n = 184$; DM, $n = 385$) and several additional centers in China that cooperated on a grant from the Research Special Fund for Public Welfare Industry of Health ($n = 448$; PM, $n = 179$; DM, $n = 269$). ILD in patients was identified with high-resolution chest computed tomography (HRCT) [23]. Patients with myositis-connective tissue disease (CTD) overlap syndrome were excluded if they met either the following published criteria (American College of Rheumatology (ACR) criteria for SLE [24], ACR criteria for RA [25], ACR criteria for SSc [26], and American and European consensus criteria for Sjogren's disease (SS) [27] or the criteria for mixed CTD by Sharp et al. [28]. And we also excluded amyopathic dermatomyositis (ADM), who could not meet the traditional criteria of Sontheimer [29]. Patients with myasthenia gravis, myasthenia syndrome, muscular dystrophy, inherited, metabolic, or infectious myopathies or muscle diseases caused by other factors were systematically excluded. Ethnically matched healthy controls ($n = 1280$) were enrolled from the Peking Union Medical College Hospital during their physical examinations. There is overlap between these samples and previous PM/DM genetic studies [30–33]. Approval for this study was obtained from the Ethics Committee of the Peking Union Medical College Hospital (Beijing, China). Informed consent was obtained from all individuals participating in this study.

DNA extraction and genotyping

Peripheral blood (2 mL) was collected from all subjects and genomic DNA was extracted using a kit (Tiangen; Beijing, China) according to the manufacturer's instructions. The four SNPs of the *BANK1* gene were genotyped using the MassArray iPLEX system (Sequenom; San Diego, USA) according to the manufacturer's instructions. Briefly, after the multiplex polymerase chain reaction (PCR) amplifications, the products were used for locus-specific single-base extension reactions. The final products were desalted and transferred to 384-element SpectroCHIP arrays. The allele detection was performed using matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS). The resultant mass spectrograms and genotype data were analyzed using MassArray Typer 4.0 software.

Statistical analysis

The four SNPs were examined for deviation from Hardy–Weinberg equilibrium (HWE) in the healthy controls by performing a chi-square (χ^2) test. Any SNPs that significantly departed from HWE ($P < 0.05$ in the control groups) were excluded from further analyses. In the analysis of the association between the *BANK1* polymorphisms and IIM patients, the statistical analyses were performed using PLINK v1.07 software (Shaun Purcell; Boston, MA, USA) [34]. The differences in the genotype and allele frequencies between the patients and controls were analyzed by performing a χ^2 test. The odds ratio (OR) and 95% confidence interval (95%CI) were calculated, and P values (corrected for multiple testing by Bonferroni adjustment) < 0.05 were considered statistically significant. In addition, the genotype frequencies were further analyzed using the following three logistic regression genetic models: additive, dominant, and recessive. In addition, a subphenotype stratification analysis of the association between the *BANK1* polymorphisms and the presence of ILD was performed.

Results

Clinical characterization of subjects

The clinical characteristics of the patients and controls are shown in Table 1. In total, 1017 PM/DM patients (74.3% female) were enrolled, including 363 PM patients and 654

Table 1 Clinical data of the PM/DM patients and controls

Characteristic	Patients	Controls
Number of subjects (DM/PM)	1017 (654/363)	1280
Female ratio (%)	74.3	87.1
Average age	46.1 ± 15.2	41.8 ± 12.7
DM with ILD, no/total (%)	390/654 (59.6)	–
PM with ILD, no/total (%)	195/363 (53.7)	–

PM, polymyositis; *DM*, dermatomyositis; *ILD* interstitial lung disease

DM patients. The mean age of the PM/DM patients was 46.1 ± 15.2 years. The healthy controls included 1280 subjects (87.1% female; mean age 41.8 ± 12.7 years). The success rate of genotyping all subjects was greater than 97%, and all SNPs were in HWE in the healthy controls ($P_{HWE} > 0.05$).

Genetic analysis

The risk allele and genotype frequencies among the PM and DM patients were compared to those among the healthy controls (Table 2). A significant allele association in rs3733197 was observed among the PM/DM patients (OR 0.81, 95%CI 0.70–0.94, $Pc = 1.83 \times 10^{-2}$). However, no statistically significant difference was observed in the allele or genotype frequencies of three SNPs (rs4522865, rs17266594, and rs10516487) among the DM, PM, and PM/DM patients and the healthy controls (all $Pc > 0.05$; Table 2). Similar results were obtained in the statistical analysis using genetic additive, dominant, and recessive logistic regression models (Table 3). Significant associations were observed between rs3733197 and the PM/DM patients in the additive and dominant models.

Association between BANK1 polymorphisms and the ILD phenotype in PM/DM patients

In addition, we investigated the potential associations between these SNPs and ILD among the PM/DM patients. We compared the ILD patients with ILD-negative patients, ILD patients with all healthy controls, and PM/DM patients without ILD with all healthy controls (Table 4). Notably, rs3733197 was associated with the DM and PM/DM patients with ILD involvement ($Pc = 0.026$; $Pc = 6.0 \times 10^{-3}$, respectively). However, the other SNPs were not associated with PM or DM complicated with ILD in this cohort.

Discussion

Here, we conducted a large-scale hospital-based case-control study and investigated the associations between four SNPs (rs4522865, rs17266594, rs10516487, and rs3733197) in the *BANK1* gene and the risk of PM/DM in a Chinese Han

Table 2 Allele and genotype distribution of the *BANK1* gene markers in the PM/DM patients and controls

SNPs	Groups	Allele (%)		OR (95%CI)	*P*	*Pc*	Genotype (%)			χ^2	*P*	*Pc*
		G	A				GG	AG	AA			
rs4522865	DM	532 (40.7)	776 (59.3)	1.07 (0.93–1.22)	0.354	NS	101 (15.4)	330 (50.5)	223 (34.1)	1.54	0.464	NS
	PM	307 (42.3)	419 (57.7)	1.14 (0.96–1.35)	0.126	0.504	67 (18.4)	173 (47.7)	123 (33.9)	2.64	0.267	NS
	PM+DM	839 (41.2)	1195 (58.8)	1.09 (0.97–1.23)	0.146	0.584	168 (16.5)	503 (49.5)	346 (34.0)	2.25	0.325	NS
	Controls	1001 (39.1)	1557 (60.9)				194 (15.2)	613 (47.9)	472 (36.9)			
		C	T				CC	TC	TT			
rs17266594	DM	180 (13.8)	1124 (86.2)	0.95 (0.79–1.16)	0.624	NS	15 (2.3)	150 (23.0)	487 (74.7)	0.23	0.890	NS
	PM	101 (13.9)	625 (86.1)	0.96 (0.76–1.22)	0.747	NS	11 (3.0)	79 (21.8)	273 (75.2)	0.87	0.647	NS
	PM+DM	281 (13.8)	1749 (86.2)	0.96 (0.81–1.13)	0.600	NS	26 (2.6)	229 (22.6)	760 (74.8)	0.46	0.793	NS
	Controls	368 (14.4)	2190 (85.6)				32 (2.5)	304 (23.8)	943 (73.7)			
		A	G				AA	GA	GG			
rs10516487	DM	179 (13.7)	1129 (86.3)	0.94 (0.77–1.13)	0.497	NS	15 (2.3)	149 (22.8)	490 (74.9)	0.45	0.800	NS
	PM	100 (13.8)	626 (86.2)	0.94 (0.74–1.20)	0.626	NS	11 (3.0)	78 (21.5)	274 (75.5)	1.02	0.602	NS
	PM+DM	279 (13.7)	1755 (86.3)	0.94 (0.79–1.11)	0.454	NS	26 (2.6)	227 (22.3)	764 (75.1)	0.74	0.692	NS
	Controls	371 (14.5)	2189 (85.5)				33 (2.6)	305 (23.8)	942 (73.6)			
		A	G				AA	GA	GG			
rs3733197	DM	237 (18.1)	1071 (81.9)	0.81 (0.69–0.96)	0.016	0.064	19 (2.9)	199 (30.4)	436 (66.7)	5.93	0.052	0.208
	PM	130 (17.9)	596 (82.1)	0.80 (0.65–0.99)	0.040	0.160	10 (2.8)	110 (30.3)	243 (66.9)	4.35	0.114	0.456
	PM+DM	367 (18.0)	1667 (82.0)	0.81 (0.70–0.94)	4.58×10^{-3}	1.83×10^{-2}	29 (2.9)	309 (30.4)	679 (66.7)	8.25	0.016	0.064
	Controls	548 (21.4)	2012 (78.6)				53 (4.2)	442 (34.5)	785 (61.3)			

PM, polymyositis; *DM*, dermatomyositis; *OR*, odds ratio; *CI*, confidence interval; χ^2, chi-square test; *Pc*, *P* value corrected by the Bonferroni method; *NS*, not significant; The italics indicate statistical significance ($P < 0.05$)

Table 3 Analysis of the four SNPs using three genetic models

SNPs	Groups	Additive model		Dominant model		Recessive model	
		Pc	OR (95%CI)	*Pc*	OR (95%CI)	*Pc*	OR (95%CI)
rs4522865	PM	0.504	1.14 (0.96–1.35)	NS	1.14 (0.89–1.46)	0.524	1.27 (0.93–1.72)
	DM	NS	1.07 (0.93–1.23)	0.896	1.13 (0.93–1.38)	NS	1.02 (0.79–1.33)
	PM+DM	0.575	1.09 (0.97–1.23)	0.608	1.13 (0.95–1.35)	NS	1.11 (0.88–1.39)
rs17266594	PM	NS	0.96 (0.76–1.22)	NS	0.93 (0.71–1.21)	NS	1.22 (0.61–2.44)
	DM	NS	0.95 (0.79–1.15)	NS	0.95 (0.77–1.18)	NS	0.92 (0.49–1.71)
	PM+DM	NS	0.96 (0.81–1.13)	NS	0.94 (0.78–1.14)	NS	1.02 (0.61–1.73)
rs10516487	PM	NS	0.95 (0.75–1.19)	NS	0.91 (0.69–1.19)	NS	1.18 (0.59–2.36)
	DM	NS	0.94 (0.78–1.13)	NS	0.93 (0.75–1.16)	NS	0.89 (0.48–1.65)
	PM+DM	NS	0.94 (0.80–1.11)	NS	0.92 (0.76–1.12)	NS	0.99 (0.59–1.67)
rs3733197	PM	0.150	0.80 (0.64–0.99)	0.206	0.78 (0.61–1.00)	0.912	0.66 (0.33–1.30)
	DM	0.060	0.81 (0.68–0.96)	0.086	0.79 (0.65–0.97)	0.707	0.69 (0.41–1.18)
	PM+DM	*0.0166*	0.80 (0.69–0.93)	*0.0286*	0.79 (0.66–0.94)	0.400	0.68 (0.43–1.08)

PM, polymyositis; *DM*, dermatomyositis; *OR*, odds ratio; *CI*, confidence interval; *Pc*, *P* value corrected by the Bonferroni method; *NS*, not significant; The italics indicate statistical significance ($P < 0.05$)

population. A significant association between the *BANK1* (rs3733197) polymorphism and the PM/DM patients was observed. Remarkably, this study is the first to demonstrate a significant association between a *BANK1* (rs3733197) polymorphism and susceptibility to PM/DM in a Chinese Han population.

The *BANK1* protein can also promote the Lyn-mediated tyrosine phosphorylation of inositol 1,4,5-trisphosphate receptors. The increased interaction between *BANK1* and its downstream targets may lead to a steady state characterized by B cell hyperresponsiveness or deregulated B cell activation [6]. *BANK1*-deficient mice display higher levels of mature B cells and spontaneous germinal center B cells, particularly in response to T-dependent antigens [35], leading the investigators to hypothesize that *BANK1* may attenuate CD40-mediated Akt activation, thereby preventing hyperactive B cell responses. Kozyrev et al. [11] performed a detailed analysis of *BANK1* expression and structure and observed that *BANK1* is indeed primarily expressed in CD19+ B cells, with very low expression in other cell populations. Thus, variations in *BANK1* expression and function could have profound effects on the modulation of B cell activity and immune phenotypes.

The SNP rs10516487 leads to a nonsynonymous arginine to histidine substitution at position 61 (R61H) of the *BANK1* protein, which is located within a region essential for the

Table 4 Association between four SNPs and PM/DM with ILD

Disease	Groups	rs4522865		rs17266594		rs10516487		rs3733197	
		Pc	OR (95%CI)	*Pc*	OR (95%CI)	*Pc*	OR (95%CI)	*Pc*	OR (95%CI)
PM	P vs. N	NS	1.05 (0.78–1.41)	NS	1.14 (0.74–1.74)	NS	1.11 (0.73–1.70)	NS	0.87 (0.59–1.27)
	P vs. C	0.66	1.17 (0.94–1.45)	NS	1.02 (0.75–1.38)	NS	0.99 (0.73–1.34)	0.17	0.75 (0.56–0.99)
	N vs. C	NS	1.11 (0.88–1.40)	NS	0.90 (0.64–1.25)	NS	0.89 (0.64–1.24)	NS	0.86 (0.65–1.15)
DM	P vs. N	NS	1.05 (0.84–1.32)	NS	1.04 (0.76–1.44)	NS	1.09 (0.79–1.51)	0.69	0.82 (0.61–1.09)
	P vs. C	NS	1.01 (0.92–1.28)	NS	0.97 (0.77–1.22)	NS	0.97 (0.77–1.22)	*0.026*	0.75 (0.61–0.92)
	N vs. C	NS	1.04 (0.86–1.25)	NS	0.93 (0.71–1.22)	NS	0.89 (0.67–1.17)	NS	0.91 (0.72–1.15)
PM+DM	P vs. N	NS	1.05 (0.87–1.25)	NS	1.08 (0.83–1.39)	NS	1.10 (0.85–1.42)	0.50	0.84 (0.67–1.05)
	P vs. C	0.54	1.11 (0.97–1.28)	NS	0.99 (0.81–1.20)	NS	0.98 (0.80–1.19)	6.0×10^{-3}	0.75 (0.62–0.90)
	N vs. C	NS	1.06 (0.91–1.25)	NS	0.92 (0.73–1.15)	NS	0.89 (0.71–1.11)	NS	0.89 (0.74–1.08)

Group P (DM: $n = 390$; PM: $n = 195$; DM+PM: $n = 585$); group N (DM: $n = 264$; PM: $n = 168$; DM+PM: $n = 432$); group C ($n = 1280$)

DM, dermatomyositis; *PM*, polymyositis; *ILD*, interstitial lung disease; *Group P*, patients with ILD; *Group N*, patients without ILD; *Group C*, healthy controls; *Pc*, *P* value corrected by the Bonferroni method; The italics indicate statistical significance ($P < 0.05$)

binding of IP3R. In individuals carrying *BANK1* functional mutations (R61H), altered B cell activation via the B cell receptor leads to *BANK1* phosphorylation and signaling. The SNP rs17266594 is located in a branch-point site and affects the relative splicing efficiency of *BANK1*, which, in turn, could lead to a more active protein in at-risk individuals [11]. The SNP rs4522865, which was selected in our study, is an independent factor for increased susceptibility to SLE in Asians [19, 20]. However, we did not observe any significant association between the frequency of these variants (rs4522865, rs17266594, and rs10516487) and patients with PM/DM in this population. Fundamental differences may exist among these variants (rs4522865, rs17266594, and rs10516487) in terms of the susceptibility and pathogeneses of PM/DM and other autoimmune diseases.

The SNP rs3733197 causes an alanine to threonine substitution at amino acid position 383 (A383T) in exon 7, which encodes an ankyrin repeat-like motif. The importance of mutations in ankyrin motifs for interactions with IP3R has recently been highlighted by a discovery linking single amino acid substitutions in the adaptor protein ankyrin-B with cardiac arrhythmia and sudden cardiac death [36]. Although the A383 variant is associated with SLE, the minor allele, i.e., 383T, of rs3733197 might create a site for threonine kinases [37]. In the present study, significant allele association was observed between the *BANK1* (rs3733197) polymorphism and PM/DM patients. Notably, rs3733197 was associated with DM and PM/DM patients with ILD involvement. Therefore, the *BANK1*-related genetic susceptibility loci (rs3733197) were associated with PM/DM in a Han Chinese population. However, the precise role played by *BANK1* in B cell receptor-mediated signaling remains unclear. Further experiments are required to fully understand whether and how *BANK1* polymorphisms lead to B cell hyperactivity, breakage of B cell tolerance, and more precisely, the development of PM/DM.

Studies investigating IIM are difficult due to its rarity. To avoid this difficulty, in our study, we enrolled a large number of PM/DM patients from the Chinese Han population. However, our study has certain limitations. We did not test the function of these genetic variants in the development of antigen-specific B cells in the PM/DM patients. At the same time, there is no statistically significant association between ILD-positive patients with ILD-negative patients. Therefore, further studies involving a larger population and functional studies investigating B cells are warranted.

Altogether, our data are the first to indicate that the SNP rs3733197 (A383T) of the *BANK1* region, but not the *BANK1* SNPs rs10516487 (R61H), rs17266594 (branch-point variant), and rs4522865, is associated with the development of PM/DM in a Han Chinese population.

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Compliance with ethical standards

This study was approved by the Ethics Committee of the Peking Union Medical College Hospital (Beijing, China). Informed consent was obtained from all individuals participating in this study.

Disclosures None.

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