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Relationship between polymorphism of *DC-SIGN (CD209)* gene and the susceptibility to pulmonary tuberculosis in an eastern Chinese population

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ABSTRACT

Dendritic cell–specific intracellular adhesion molecule–3–grabbing nonintegrin *(DC-SIGN)* is an important receptor for *Mycobacterium tuberculosis* on human dendritic cells. Previous studies have shown that the variation, especially the −871A/G and −336A/G in *DC-SIGN* promoter influenced the susceptibility to tuberculosis. We therefore investigated whether polymorphisms in the *DC-SIGN* gene were associated with susceptibility to tuberculosis in an eastern Chinese population. A total of 237 culture-positive pulmonary tuberculosis case patients and 244 controls were genotyped for −871A/G and −336A/G by pyrosequencing. Our results suggested that the 2 promoter variants of *DC-SIGN* gene were not associated with susceptibility to tuberculosis in Chinese. Further analysis showed that the allele -336G was associated with a protective effect against fever in pulmonary tuberculosis patients, but not against cavity formation. In addition, we compared the allelic frequencies of −871A/G and −336A/G in African, Caucasian, and Asian groups. The results showed that the tw forms of allelic frequencies detected Chinese individuals in our study were similar to the reported frequencies in other Asian populations but differed significantly from those in the African and Caucasian groups studied.

1. Introduction

The innate immune receptors, such as Toll-like receptors, C-type lectins receptors, and Nod-like receptors, probably play a crucial role in effective immune responses to *Mycobacterium tuberculosis* (*M tuberculosis*) [1]. When the bacillus encounters the host, the specific pattern-recognition receptors on human macrophage and dendritic cell (DC) recognize the *M tuberculosis* and trigger phagocytic cell and then induce specific signaling pathways that lead to the induction of immune responses against the pathogens. Dendritic cell–specific intracellular adhesion molecule–3–grabbing nonintegrin (*DC-SIGN*), encoded by CD209, is a C-type lectin that is primarily expressed on DC and alveolar macrophage [2,3]. As a major recognition receptor on human DCs, *DC-SIGN* may influence the pathogenesis of tuberculosis. *M tuberculosis* interacts with *DC-SIGN* to activate an intracellular signaling pathway with a central role for the serine/threonine kinase Raf-1. The Raf-1-acetylation–dependent signaling pathway, which induces specific gene transcription profiles, is involved in the regulation of adaptive immune response to tuberculosis [4–6].

Genetic studies on tuberculosis have revealed that the genetic polymorphisms, potentially involved in the immune response to tuberculosis, could lead to susceptibility or resistance to tuberculosis. *DC-SIGN* might be a crucial part in host immunity to tuberculosis and one of the candidate genes for susceptibility to tuberculosis. In addition, it has been reported that the variants of *DC-SIGN* have been linked to susceptibility to several other infectious diseases, such as HIV-1 [7], Dengue [8], and severe acute respiratory syndrome (SARS) [9]. The research on *DC-SIGN* genetic variability and its association with tuberculosis mainly focused on two regions: promoter and neck. Particularly, the −336A/G loci in promoter in African populations have been studied by several groups. Barrerio et al. first reported that -336A and -871G conferred protection against tuberculosis in South African cohort [10]. Vannberg et al. further observed that -336G allele had protective effect against tuberculosis in populations from four different sub-Saharan African countries [11]. In contrast, Olesen et al., in the north African city of Tunis and Ben-Alim in the west African city of Guinea-Bissau found no association of -336 SNP polymorphism with tuberculosis [12,13]. In non-African individuals from northwestern Colombia, Gómez et al. reported that -336 SNP did not play a protective role against tuberculosis [14]. Some of these variants may affect the function of *DC-SIGN*. The variant −336A/G in the *DC-SIGN* gene promoter region was found to regulate promoter activity by affecting a Sp1-like binding site [8].

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To date, little has been known about the association of the *DC-SIGN* gene variants and tuberculosis in Asian populations. Therefore, we initiated a case-control study to investigate the relationship between *DC-SIGN* gene variants (−871A/G and −336A/G) and susceptibility to tuberculosis in China, where the incidence and mortality rates of tuberculosis have increased in the past decade.

2. Subjects and methods

2.1. Patients and controls

The samples were comprised of 237 patients with pulmonary tuberculosis and 244 healthy controls. All blood samples were collected in Shanghai Pulmonary Hospital located in Eastern China from December 2007 to November 2008. The diagnosis of tuberculosis case depended on clinical radiological evidences (such as X-ray or computed tomography [CT] scan) and sputum culture positivity. All patients were human immunodeficiency virus (HIV) negative. A body temperature greater than 37.5°C was defined as indicating fever in the pulmonary tuberculosis patients. The average age of the 237 patients was 46.6 years (SE, 17.74 years); 155 subjects (65.4%) were male and 82 subjects (34.6%) were female. Control subjects were healthy individuals and were matched to patients by gender, age, ethnicity, and socioeconomic status. The study was approved by the Ethics Committees of the Shanghai Pulmonary Hospital affiliated with Tongji University, Shanghai China.

2.2. Genotyping techniques

The genomic DNA was extracted from 2 ml ethylenediaminetetraacetic acid (EDTA)–treated blood by using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The *DC-SIGN* −871A/G (rs735239) and −336A/G (rs4804803) SNP assays were performed by pyrosequencing using a PSQ96MA system (Pyrosequencing AB, Uppsala, Sweden). The primers sequences were designed by PSQ Assay Design Software Version 1.1 and are presented in Table 1. The PCR reaction was performed in a total volume of 50 μl of reaction mix containing 50 ng of genomic DNA, 20 pmol of F and R primers, 0.2 mM of dNTP mixture, and 1.0 U of Taq polymerase. The PCR program amplified the *DC-SIGN* −871A/G was as follows: 5 minutes' denaturation at 95°C; 50 cycles of 30 seconds at 95°C, 30 seconds at 54°C, and 30 seconds at 72°C, with a final extension of 10 minutes at 72°C. The amplified condition of the *DC-SIGN* −336A/G was 95°C for 5 minutes, followed by 50 cycles of 95°C for 30 seconds, 58°C for 30 seconds, 72°C for 30 seconds, and then 1 cycle at 72°C for 10 minutes. Single strand separation was performed using a Vacuum Prep Tool and Vacuum Prep worktable (Biotage, Uppsala, Sweden) according to the manufacturer's recommendations. Pyrosequencing was performed in an automated PSQ96 MA system using PyroGold SNP reagent kit containing enzymes and substrates ((Biotage, Uppsala, Sweden).

Table 1
Different loci selected within *DC-SIGN* gene and their corresponding primers used by pyrosequencing

SNP	Locus	Primer sequence (5′→3′)	Temp (°C)	Product (bp)
−871	rs735239	F: bio-AAATTGGAACAACCCCGTGTC R: TTCCCATTCTGAGTCTCCTTCAAA S: TGTTTTGTGAGATTTATCTA	54	239
−336	rs4804803	F: GAGCAGTGGGATGCTTTTAATGA R: bio-AGGACAGCAGCAGCTCAAA S: CCTCCACTAGGGCAAG	58	169

F, forward primer; R, reverse primer; S, sequencing primer; SNP, single nucleotide polymorphism; Bio, biotin; Temp, temperature.

Table 2
Frequency of *DC-SIGN* −336A/G and −871A/G genotypes and alleles in tuberculosis patients and controls

Genotype/allele	Patients (n = 237)	Controls (n = 244)	p Value[a]	OR (95% CI)
SNP-871				
A/A	148 (62.4)	138 (56.6)		
G/G and A/G	89 (37.6)	106 (43.4)	0.188	1.277 (0.887–1.840)
A	376 (79.3)	374 (76.6)		
G	98 (20.7)	114 (23.4)	0.315	1.169 (0.862–1.587)
SNP-336				
A/A	208 (87.8)	209 (85.7)		
G/G and A/G	29 (12.2)	35 (14.3)	0.496	1.201 (0.708–2.037)
A	445 (93.9)	452 (92.6)		
G	29 (6.1)	36 (7.3)	0.437	1.222 (0.737–2.028)

CI, confidence interval; OR, odds ratio.
[a] χ^2 Test for genotype distribution between patients and controls.

2.3. Statistical analysis

The allele and genotype frequencies were determined by direct counting. The significant differences of allele and genotype frequencies were calculated using Pearson χ^2 test. Age was considered as quantitative variables and determined by using the Student t test. The associations of genotype and patients' clinical features of tuberculosis were carried out by χ^2 test. Further analysis was performed by using a stepwise binary logistic regression correction to adjust for the confounding factors of age and gender when the unadjusted p value was significant. The analyses were performed by using the SPSS (SPSS, Inc., Chicago, IL). The Hardy–Weinberg equilibrium of each polymorphism was determined by the program HWE. Pairwise linkage disequibilibrium (LD) between SNPs was calculated using HaploView statistical software. The power analysis was performed by Gpower3.0 software. All statistical analyses were two-tailed, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Allele and genotype frequencies of DC-SIGN gene

The allele and genotype frequencies of the *DC-SIGN* allele at -871and -336 loci in 237 tuberculosis patients and 244 controls are presented in Table 2. For the two polymorphisms tested in this study within the *DC-SIGN* gene, genotype distributions were in Hardy–Weinberg equilibrium in both patients and controls (all $p >$ 0.05). For the -336 variant, genotypes GG and GA were less frequently observed in tuberculosis patients and controls, only one variant of genotype GG being observed in controls and none in patients. For the -871 variant, genotype AA was more frequent than genotypes AG and GG in patients and controls. However, statistical analyses showed that there was no significant difference in genotype and allele frequencies between tuberculosis patients and controls at the investigated loci. With regard to the power analysis of the whole study, the study had power of 99.2% to yield a statistically significant result using *post hoc* analysis when α had been set at 0.05, effect size set at 0.2, and the total sample size was 481 for the two groups.

In addition, we performed the analyses at the haplotype level. A χ^2 test first revealed that the global distribution of haplotype frequencies was not significantly different between PTB patients and controls ($p = 0.36$). The analysis of haplotypes containing the two SNPs −336A/G and −871A/G showed no significant difference between the patients and controls (Table 3).

3.2. DC-SIGN and clinical features of tuberculosis

The *DC-SIGN* −871A/G and −336A/G SNP were further examined in the patients for association with clinical features of tuberculosis; results are presented in Table 4. A χ^2 test first revealed a

Table 3
Haplotype distribution of −871A/G and −336A/G in tuberculosis patients and controls

Haplotype	Haplotype frequency		*p* Value	OR (95% CI)
	Patients ($n = 237$)	Controls ($n = 244$)		
AA	0.7321	0.6926	0.81	1.20 (0.808–1.781)
GA	0.2068	0.2336	0.23	1.22 (0.880–0.680)
AG	0.0612	0.0738	0.33	1.30 (0.770–2.200)

significant association between the *DC-SIGN* -336G variant and fever in PTB patients (Pearson's test $\chi^2 = 6.626$, $p = 0.010$, odds ratio [OR] = 0.209, 95% confidence interval [CI] = 0.058 – 0.758). Adjusting for the potential confounding factor of age and gender, analysis of logistic regression demonstrated there was significant difference between *DC-SIGN* -336G and fever ($p = 0.037$). The fever rate was 17% and 49% in -336G allele carriers and A allele carriers, respectively. The fever rate of G allele carriers decreased 32% compared with A allele carriers. In *post hoc* analysis, the study had power of 95% to yield a significant effect if α had been set at 0.05, effect size set at 0.3, and the total sample size was 149 for patients with and without fevers. However, the significant association between *DC-SIGN*-336GG genotype and cavity formation described in previously study had not been observed in our research. There was no significant difference between the polymorphism of *DC-SIGN* −871A/G and clinical features (data not shown).

3.3. Allelic distribution of DC-SIGN -871 and -336 among different populations

To find whether allelic distribution was different among various ethnic origins, we compared the allelic frequencies between African populations, Caucasian populations reported by Barreiro et al., and the Chinese populations in the control group in our study, and found a significant difference in the distribution of *DC-SIGN* allelic frequencies among these ethnic groups. The allele -336G had the lowest frequencies in Asians compared with Africans and Caucasians (Table 5). The frequencies of -871G in Asians were higher than in Africans and lower than in Caucasians. The allelic frequencies of two forms detected in our study were similar to the frequencies of Asian populations previously reported by Barreiro et al. and Sakuntabhai et al. [8,10].

4. Discussion

DC-SIGN is a type II transmembrane lectin receptor and has gained great attention in recent years because of its involvement in multiple aspects of immune-related function. *DC-SIGN* is involved not only in various DC functions, such as differentiation, migration, antigen capture and T-cell priming, but also in induction of intracellular signaling pathways via several motifs [15,16] that can cause extensive modulation of immune responses [6]. In addition, *DC-SIGN* recognizes several pathogens, such as viruses (HIV-1, dengue, West Nile virus, and measles virus) [17,18,19,20], bacteria (*Helicobacter pylori*, *Streptococcus pneumoniae*) [15,21], fungi (*Candida albicans* and *Aspergillus fumigatus*) [22] and parasites (*Leishmania* and *Schistosoma mansoni*) [23] contributing to generation of pathogen-tailored immune responses [24], induces immunosuppressive response by disarming the MAPK pathway in DCs [25], and enhances TH1 differentiation.

In this study, we detected the polymorphisms at -871 and -336 loci situated in the promoter region of the *DC-SIGN* gene in total 481 individuals. The two variants and haplotype of −871A/G and −336A/G in the *DC-SIGN* gene were not associated with the susceptibility to pulmonary tuberculosis in Chinese population, although the frequency of A allele in patients for both SNPs increased somewhat. The association between *DC-SIGN* polymorphisms and susceptibility to tuberculosis has been described in many studies, which showed positive association in South African and sub-Saharan African populations [10,11], whereas no association was observed in the Tunisian and Colombian populations studied [12,14]. The host genetic background might be an explanation for this discrepancy [26,27]. Our results showed that the allelic distribution of *DC-SIGN* gene in Asian populations differed from that of African and Caucasian populations and the difference between African and Asian groups was more prominent. The highest -336G allelic frequency was found in African populations and lowest was observed

Table 5
Analysis of *DC-SIGN* −336A/G and clinical features of tuberculosis

Characteristic	Genotype frequency (%)		*p* Value	OR (95% CI)
	AA	AG+GG		
Gender				
Male	138 (89.0)	17 (11.0)	0.413	1.392 (0.630–3.075)
Female	70 (85.4)	12 (14.6)		
Age (y)				
0–19	11 (100)	0 (0)	0.439	
20–49	105 (86.8)	16 (13.2)		
50–99	92 (87.6)	13 (12.4)		
Fever				
No	67 (81.7)	15 (18.3)	0.01	0.209 (0.058–0.758)
Yes	64 (95.5)	3 (4.5)		
Hemoptysis				
No	101 (87.8)	14 (12.2)	0.878	0.902 (0.240–3.389)
Yes	24 (88.9)	3 (11.1)		
Cacitation				
No	115 (90.6)	12 (9.4)	0.323	1.533 (0.654–3.592)
Yes	75 (86.2)	12 (13.8)		
Treatment				
Initial treatment	129 (89.0)	16 (11.0)	0.909	1.052 (0.442–2.504)
Retreatment	69 (88.5)	9 (11.5)		
Zones affected				
1–3	78 (88.6)	10 (11.4)	0.914	0.949 (0.365–2.465)
4–6	74 (89.2)	9 (10.8)		

CI, confidence interval; OR, odds ratio.

Table 4
Allelic distribution of *DC-SIGN* −871A/G and −336A/G among different populations

Variant	Population allelic frequencies (%)							
	Chinese $n = 244$	Zimbabwean $n = 200$	Sub-Saharan African $n = 82$	South African black $n = 1422$	Caucasian Canadian $n = 200$	Caucasian European $n = 86$	Thai $n = 80$	Asian $n = 86$
SNP-871								
A	76.6	95	100	88.4	58	61.6	78.8	79.1
G	23.4	5	0	11.6	42	38.4	21.2	20.9
p^a		<0.001	<0.001	0.041	0.004	0.021	0.733	0.733
SNP-336								
A	92.6	55	62.2	57.2	82	79.1	92	94.2
G	7.3	45	37.8	42.8	18	20.9	8	5.8
p^a		<0.001	<0.001	<0.001	0.019	0.004	0.788	0.774

[a]Difference between the Chinese subjects and other populations determined by χ^2 test.

in Asians. Of our 481 samples, the genotype -336 GG was detected only in 1 sample. In the control group, the frequency of the -336G allele was 7.3%, whereas a high frequency (35–45%) was observed in African populations. Similarly, the allele -871G was absent in sub-Saharan African populations, whereas it had a frequency of 23.4% in our study [8,10,28,29]. Although the two SNPs might be associated with resistance to TB in Africans, we failed to duplicate this association in the Chinese population. We speculated that for the two SNPs to take effect, other genes or combination of genes need to be involved.

Further analysis about the relationship of the 2 variants in *DC-SIGN* gene promoter and the clinical features of the cases suggested a significant association between G allele in -336 loci and protection against fever in PTB patients in a Chinese population. Fever is a typical symptom of active tuberculosis. The potential role of *DC-SIGN* on fever tuberculosis disease is novel and warrants further investigation. *M tuberculosis* infection induces fever, and this symptom is attributed to an increased production of predominant endogenous pyrogen, such as interleukin (IL)–6, IL-1, and interferon (INF)–γ. Moreover, *M tuberculosis* Manose-dependent binding to *CD209* leads to Raf-1–dependent upregulation of IL-6 [15]. However, the *DC-SIGN* -336G variant affects a Sp1 binding site and decreases the expression of *DC-SIGN* resulting in less efficient cytokine and chemokine secretion [8,30]. It is hypothesized that individuals homozygous for the -336G allele may, in part, be protected from expressing low levels of *DC-SIGN* and therefore less prone to the IL-6 secretion induced by Manose-dependent binding to *DC-SIGN*.

In conclusion, no significant association with tuberculosis was observed for the two variants of −871A/G and −336A/G in *DC-SIGN* gene in a Chinese population. However, the -336G allele was weakly associated with PTB patients' fever. In addition, our results offered the SNP frequencies in an eastern Chinese population, which might be useful for the study in ethnic groups.

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