Evidence for Genetic Association of CARD9 and SNAPC4 with Ankylosing Spondylitis in a Chinese Han Population

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ABSTRACT. ***Objective.*** A genome-wide association study and 2 replication studies identified 2 single-nucleotide polymorphisms (SNP) of caspase recruitment domain-containing protein 9 (CARD9) and small nuclear RNA-activating complex polypeptide 4 (SNAPC4) at Chr 9q34.3 associated with ankylosing spondylitis (AS) in whites. We explored a possible association of SNP in CARD9 and SNAPC4 and AS in a Chinese Han population from Shandong.

Methods. The study included 1150 patients with AS and 1120 healthy controls who underwent genotyping for 4 SNP of CARD9 and 2 of SNAPC4; we replicated the results in another 490 patients and 380 healthy controls of Ningxia Han Chinese during the same time. We used quantitative real-time PCR (qRT-PCR) to measure CARD9 and SNAPC4 mRNA expression in peripheral leukocytes from 44 patients and 36 controls and allele-specific mRNA expression of CARD9 and SNAPC4 in leukocytes from 130 controls.

Results. We validated that an SNP in SNAPC4, rs11145835, was significantly associated with AS in our Chinese Han population ($p = 0.001$) and replicated the association in samples from the Chinese Ningxia Han population ($p = 0.002$). Carrying the G allele of rs11145835 was associated with increased risk of AS (OR 1.34, 95% CI 1.12–1.59) and with decreased expression of CARD9 ($p = 0.001$) and SNAPC4 ($p = 0.02$) in leukocytes. SNAPC4 mRNA expression was lower in leukocytes from patients than from controls ($p = 0.0002$).

Conclusion. Our study confirmed that an SNP rs11145835 in 9q34.3 that harbors CARD9 and SNAPC4 is associated with AS in a Chinese Han population, and rs11145835 in SNAPC4 is a potential causal variant. (J Rheumatol First Release Dec 15 2013; doi:10.3899/jrheum.130519)

Key Indexing Terms:
CASPASE RECRUITMENT DOMAIN-CONTAINING PROTEIN 9
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SINGLE NUCLEOTIDE POLYMORPHISMS ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis (AS) is an autoimmune disorder with a complex genetic etiology[1]. The prevalence of AS in China is similar to that in whites, about 5 in 1000 people[2,3]. AS is clinically characterized by arthritis of the spine and sacroiliac joints, which initially causes pain and reversible stiffness and evolves into progressive joint fusion and irreversible deformity, with extraarticular lesions also closely involved in disease progression[4]. The pathogenesis of AS remains to be further elucidated.

Risk of AS is considered largely determined by genetic factors. Although HLA-B27 makes a major genetic contribution, it explains only about 16% to 40% of the overall genetic risk, which suggests that (non-MHC) genes are involved in the disease pathogenesis[5,6]. A recent genome-wide association study (GWAS) by the Wellcome Trust Case Control Consortium (WTCCC) identified an association of 2 non-synonymous single nucleotide polymorphisms (SNP), rs4077515 and rs3812571, on 9q34.3 (previously linked to AS) with AS ($p < 0.004$ and

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$p < 0.005$, respectively)[7]. The first SNP lies in a functional candidate gene, caspase recruitment domain-containing protein 9 (CARD9), and the latter in an adjacent gene, small nuclear RNA-activating complex polypeptide 4 (SNAPC4).

A replication study supported that CARD9 is a plausible susceptibility gene for AS[8]. Another GWAS by the WTCCC found strong evidence of an association for an SNP across CARD9 (rs10781500; $p = 1.1 \times 10^{-6}$)[9]. CARD9 has a vital role in mediating the innate immune response. It functions as an intracellular signal transduction protein that acts downstream of the antifungal pattern recognition receptor (PRR), dectin 1, and cytoplasmic PRR of the NOD family[10,11,12,13]. As well, CARD9 can couple innate to adaptive immunity by modulating the Th17 pathway, which was previously linked to AS pathogenesis[7,14]. Considerable evidence supports some degree of overlap between AS and inflammatory bowel disease (IBD) pathogenesis, and a study validated an association of CARD9 (rs1080077) and ulcerative colitis and Crohn disease[15,16]. SNAPC4 is the largest subunit of the SNAP complex, a multisubunit complex of proteins that promotes basal levels of transcription of RNA polymerase II and III small nuclear RNA[17]. A role of SNAPC4 in autoimmune disorders has yet to be clarified, so SNAPC4 SNP are likely in strong linkage disequilibrium (LD) with CARD9-associated SNP[8].

In our present study, we sought to investigate the possible relationship of CARD9 and SNAPC4 polymorphisms and AS and the potential functional variants.

MATERIALS AND METHODS

Subjects. From 2008 to 2011, we recruited 1150 patients (750 males) with AS from Qilu Hospital and Shandong Provincial Hospital at Jinan, Shandong, a coastal province of eastern China. All patients (mean age 27 ± 9.1 yrs, range 16–42 yrs) fulfilled the modified New York criteria for AS, and sacroiliitis was confirmed by computed tomography or magnetic resonance imaging. The duration of disease was from 0.8 to 18 years. We also recruited 1120 unrelated, random-sampled healthy controls (700 males; mean age 25 ± 6.5 yrs, range 19–45 yrs) from a health checkup center at the hospital within the same period. All controls were matched to cases by age, ethnicity, and geographic region and underwent comprehensive medical screening by at least 2 experienced rheumatologists before recruitment. They had no symptoms or history of AS, and had no first-degree relatives with symptoms or history of AS at the time of recruitment. Only patients were HLA-B27–positive. The clinical characteristics of patients with AS are summarized in Table 1. The replication samples for 490 patients and 380 controls from Ningxia (a province in northwestern China) were provided by Prof. Ze Yang, with detailed information[18].

Table 1. Clinical characteristics of patients with ankylosing spondylitis (AS). Data are n (%) except where indicated.

Characteristics	Patients with AS, n = 1150
Back pain	1054 (91.7)
Morning stiffness > 30 min	594 (51.7)
Back pain at night	772 (67.1)
Peripheral joint involvement	922 (80.2)
Duration, yrs	0.8–18
Uveitis	285 (24.8)

All subjects provided written informed consent for the use of samples. Flow cytometry was used for typing HLA-B27 in patients and controls. The study was approved by the ethics review committee for human studies at the School of Medicine, Shandong University.

SNP selection and genotyping. Genomic DNA was extracted from peripheral blood leukocytes by a standard phenol-chloroform method. We analyzed the LD situation of 9q34.3 region containing CARD9 and SNAPC4 gene (chr9: 138375k–138420k) using the HapMap HCB data (HapMap3 genome browser release #3) by Haploview 4.2, and 4 SNP (rs11145750, rs3812555, rs11145835, and rs3812556) were selected, with a minor allele frequency ≥ 5% in HCB population from different LD blocks. The LD situation of this region is shown in Figure 1A. Also, rs3812571 and rs4077515 were selected because they were reported to have positive association with disease in previous studies. Among the 6 selected SNP, rs11145750, rs3812555, rs3812556, and rs4077515 were located in the CARD9 gene. All SNP were genotyped by the Taqman SNP genotyping method with assay-on-demand probes and primers (C_27225718_10 for rs11145750, C_353877_10 for rs3812555, C_25956930_20 for rs4077515, C_27487601_10 for rs3812556, C_25592346_20 for rs3812571, and C_32127993_10 for rs11145835, Applied Biosystems). All genotyping involved the Applied Biosystems 7500 real-time PCR (RT-PCR) system and SDS 1.4 Automation controller software. Genotyping accuracy was confirmed by direct sequencing of PCR products for a 5% randomly chosen sample.

RT-PCR analysis. Total RNA was extracted from peripheral leukocytes of subjects by the TRIZOL reagent method. We used RT-PCR to analyze differences in mRNA expression of CARD9 and SNAPC4 in 44 patients with AS and 36 controls and the effect of carriage of the SNP rs3812571 and rs11145835 on CARD9 and SNAPC4 mRNA expression in 130 healthy controls with 3 different genotypes. RT-PCR involved use of the ABI 7500 RT-PCR system, with human GAPDH mRNA as an internal control. The comparative cycle of the threshold (CT) method was used for quantification. Four duplicate wells were used for each subject.

Statistical analysis. SNP were tested for adherence to Hardy-Weinberg equilibrium by chi-squared test. Categorical variables were compared by Fisher's exact test and allelic expression level by 1-way ANOVA. Association analysis involved use of Plink 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/). OR and 95% CI were calculated. Pairwise LD was measured by use of Haploview 4.2. A $p < 0.05$ was considered statistically significant.

RESULTS

Association study. The distribution of the 6 SNP were in Hardy-Weinberg equilibrium ($p > 0.05$) for both patients and controls in the Shandong Chinese Han population. SNP rs4077515 and rs11145750 of CARD9 showed minimal association with AS. The SNP rs3812571 and rs11145835 of SNAPC4 were significantly associated with AS [(OR 1.21, 95% CI 1.06-1.38) and 1.34 (1.12–1.59), allelic p = 0.005 and 0.001, respectively]. In addition, rs3812555 was associated with AS in Shandong population, with a p = 0.006 (Table 2). However, we confirmed only the association of rs11145835 and AS in the Ningxia Chinese Han population [joint p = 0.0008, OR 1.43 (1.24-1.65)]. Subjects carrying the G allele of rs11145835 showed increased risk of AS (Table 3).

LD evaluation. The SNP rs11145750, rs3812556, and rs4077515 of CARD9 and rs3812571 of SNAPC4 were in

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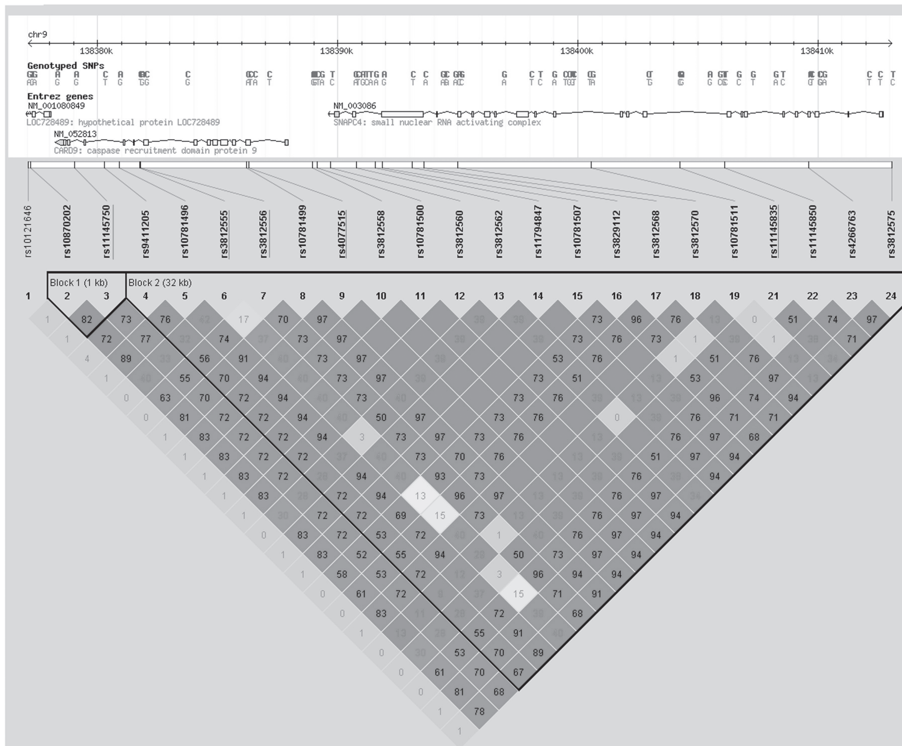

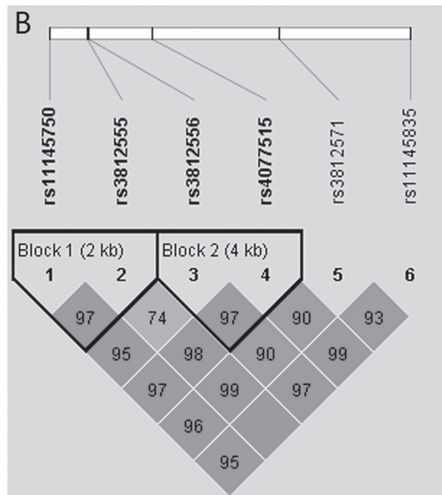

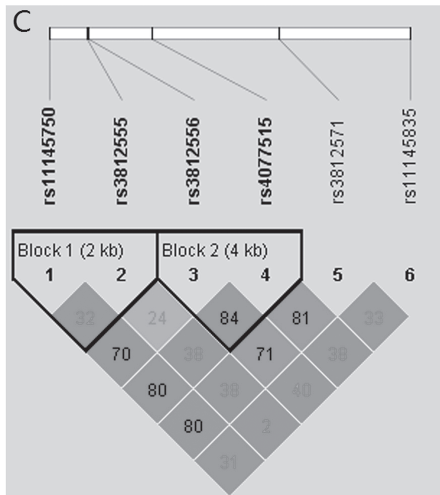

Figure 1. A. Linkage disequilibrium (LD) situation of caspase recruitment domain-containing protein 9 (CARD9) and small nuclear RNA-activating complex polypeptide 4 (SNAPC4) region. B and C: LD situation for 6 single nucleotide polymorphisms (SNP) of CARD9 and SNAPC4; left is D' and right is r^2.

strong LD ($r^2 > 0.70$; Figure 1B and 1C); however, rs3812555 and rs11145835 were in weak LD with the 4 other SNP, as expected.

Association of SNP alleles and mRNA levels of CARD9 and SNAPC4. SNAPC4 mRNA level was lower in patients than controls in the Shandong Han Chinese population ($p = 0.0002$, Figure 2). The mRNA levels of CARD9 and SNAPC4 were lower in patients with 1 or 2 copies of the risk allele of rs11145835 than in homozygote carriers of the reference allele ($p = 0.001$ and 0.02 respectively, Figure 3).

DISCUSSION

We undertook our present study to investigate the association of CARD9 and SNAPC4 variants and AS in Chinese Han population. We identified an SNP, rs11145835, in SNAPC4 that was significantly associated with AS in a

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Table 2. Genotype and allele frequencies of 6 SNP in CARD9 and SNAPC4 in cases and controls in a Chinese Han population.

SNP	Gene	Position	Genotype/allele	Controls	Cases	OR (95% CI)	p
rs11145750	CARD9	139259249	AA	501 (0.508)	472 (0.455)	1	
			AG	392 (0.398)	446 (0.431)	0.83 (0.69–1.00)	
			GG	93 (0.094)	119 (0.115)	0.74 (0.55–0.99)	0.044
			A	1394 (0.707)	1390 (0.670)	1	
			G	578 (0.293)	684 (0.330)	0.84 (0.74–0.96)	0.012
rs3812555	CARD9	139261933	TT	807 (0.743)	888 (0.787)	1	
			CT	252 (0.232)	224 (0.199)	1.24 (1.01–1.52)	
			CC	27 (0.025)	16 (0.014)	1.86 (0.99–3.47)	0.023
			T	1866 (0.859)	2000 (0.887)	1	
			C	306 (0.141)	256 (0.113)	1.28 (1.07–1.53)	0.006
rs3812556	CARD9	139261991	AA	649 (0.591)	641 (0.580)	1	
			AG	384 (0.349)	395 (0.357)	0.96 (0.80–1.15)	
			GG	66 (0.060)	70 (0.063)	0.93 (0.65–1.33)	0.861
			A	1682 (0.765)	1677 (0.758)	1	
			G	516 (0.235)	535 (0.242)	0.96 (0.84–1.10)	0.580
rs4077515	CARD9	139266496	CC	513 (0.563)	570 (0.519)	1	
			CT	334 (0.367)	439 (0.399)	0.85 (0.70–1.02)	
			TT	64 (0.070)	90 (0.082)	0.79 (0.56–1.11)	0.128
			C	1360 (0.746)	1579 (0.718)	1	
			T	462 (0.254)	619 (0.282)	0.87 (0.75–1.00)	0.046
rs3812571	SNAPC4	139275294	GG	610 (0.556)	540 (0.494)	1	
			GC	410 (0.373)	460 (0.421)	0.79 (0.66–0.94)	
			CC	78 (0.071)	93 (0.085)	0.74 (0.54–1.02)	0.015
			G	1630 (0.742)	1540 (0.704)	1	
			C	566 (0.258)	646 (0.296)	0.83 (0.72–0.95)	0.005
rs11145835	SNAPC4	139284452	AA	851 (0.776)	802 (0.721)	1	
			AG	229 (0.209)	280 (0.252)	0.77 (0.63–0.94)	
			GG	16 (0.015)	30 (0.027)	0.50 (0.27–0.93)	0.005
			A	1931 (0.881)	1884 (0.847)	1	
			G	261 (0.119)	340 (0.153)	0.75 (0.63–0.89)	0.001

rs11145835 joint p = 0.0008, OR 1.43 (CI 1.24–1.65). rs3812571 joint p = 0.07, OR 1.13 (CI 1.01–1.32). SNP: single-nucleotide polymorphisms; CARD9: caspase recruitment domain-containing protein 9; SNAPC4: small nuclear RNA-activating complex polypeptide 4.

Table 3. Replicated results of genotype and allele frequencies of 3 SNP in CARD9 and SNAPC4 in cases and controls in a Ningxia Han population.

SNP	Gene	Position	Genotype/allele	Controls	Cases	OR (95% CI)	p
rs3812555	CARD9	139261933	TT	265 (0.718)	357 (0.732)		
			CT	92 (0.249)	123 (0.252)		
			CC	12 (0.033)	8 (0.016)		0.22
			T	622 (0.843)	837 (0.858)	1	
			C	116 (0.157)	139 (0.142)	0.89 (0.68–1.16)	0.40
rs3812571	SNAPC4	139275294	GG	212 (0.559)	251 (0.532)		
			GC	141 (0.372)	192 (0.405)		
			CC	26 (0.069)	30 (0.063)		0.59
			G	565 (0.745)	694 (0.734)		
			C	193 (0.255)	252 (0.266)	1.06 (0.85–1.32)	0.58
rs11145835	SNAPC4	139284452	AA	309 (0.824)	352 (0.730)		
			AG	61 (0.163)	122 (0.253)		
			GG	5 (0.013)	8 (0.017)		0.005
			A	679 (0.905)	826 (0.857)	1	
			G	71 (0.095)	138 (0.143)	1.60 (1.18–2.16)	0.002

SNP: single-nucleotide polymorphisms; CARD9: caspase recruitment domain-containing protein 9; SNAPC4: small nuclear RNA-activating complex polypeptide 4.

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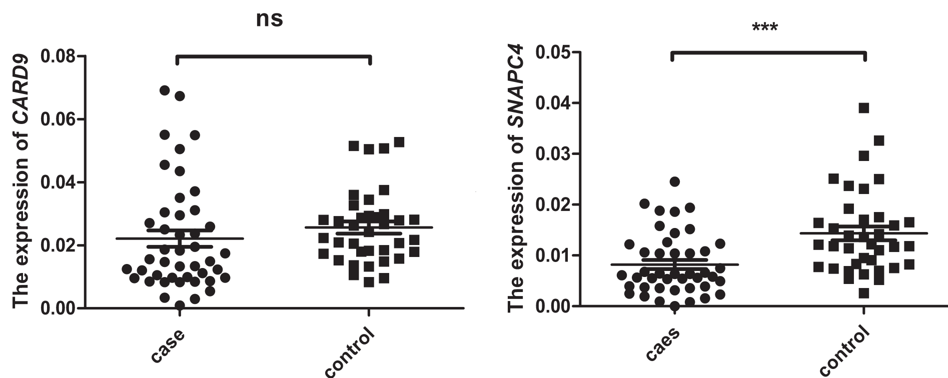

Figure 2. mRNA expression of caspase recruitment domain-containing protein 9 (CARD9) and small nuclear RNA-activating complex polypeptide 4 (SNAPC4) in patients and controls. *** p < 0.001. ns: not significant.

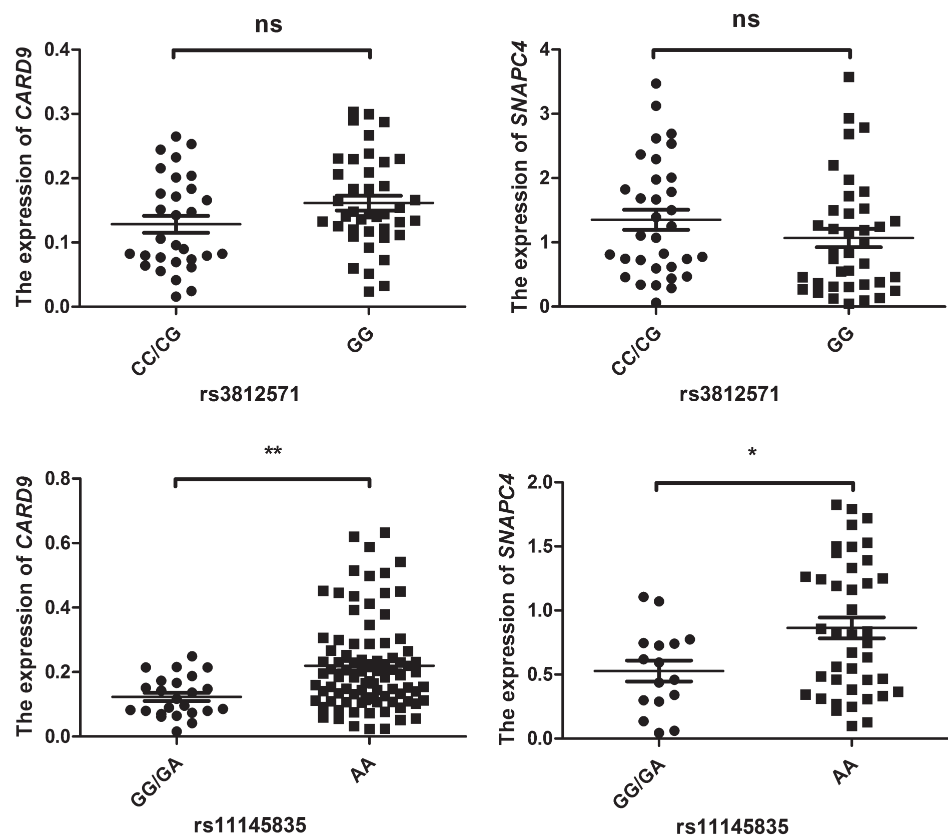

Figure 3. Allele-specific expression level of caspase recruitment domain-containing protein 9 (CARD9; left) and small nuclear RNA-activating complex polypeptide 4 (SNAPC4; right) by genotype of rs3812571 and rs11145835. * p < 0.05, ** p < 0.01. ns: not significant.

Chinese Han population. We also showed a lower expression of SNAPC4 in peripheral leukocytes from patients than controls. In addition, the risk allele for the SNP was linked to decreased mRNA level of CARD9 and SNAPC4 in leukocytes of patients. To our knowledge, we first demonstrated the association of SNAPC4 polymorphisms in 9q34.3 and AS in a Chinese Han population. Especially, we verified the association of rs11145835 and AS in 2 populations of large sample size, Chinese Shandong Han and Ningxia Han populations, supporting the credibility of our outcomes. We found no significant association of the SNP rs3812571 and rs4077515 of CARD9 and AS in our Chinese Han population, which was inconsistent with the results of previous studies, as indicated. This may be attributed to the distinct genetic background of Chinese Han and European populations and again underlines the impor-

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tance of taking racial diversities into consideration in association studies. Given the LD status within 9q34.3, it is possible that rs11145835 is in strong LD with the true disease-associated loci. Previous studies implicated CARD9 instead of SNAPC4 as a functional candidate gene in 9q34.3. The SNP rs11145835 appeared to be linked with the transcriptional activities of CARD9 and SNAPC4 but the detailed mechanisms, such as mRNA splicing, transcription factor binding, and microRNA targeting, have yet to be clearly elucidated. Because it lies in the intron region of SNAPC4, rs11145835 is more likely a marker SNP instead of a functional locus that itself influences the expression.

AS is considered to represent a multifactorial disorder orchestrated by a complex interplay between genetic predisposition and environmental factors. Apart from the well-known HLA-B27 association, a recent genome-wide scan by the WTCCC identified an association of CARD9 and SNAPC4 expression and AS[7]. A followup study independently replicated these associations ($p = 3 \times 10^{-4}$ for rs3812571 and $p = 4 \times 10^{-4}$ for rs4077515 of CARD9). In a metaanalysis of the replication, the associations strengthened to $p = 5 \times 10^{-6}$ and $p = 6 \times 10^{-6}$, respectively. The study also identified novel associations of 5 tag SNP of CARD9 and AS with nominal significance. More importantly, the SNP most strongly associated with AS (or in strong LD) were those most associated with CARD9 expression[8]. Another GWAS by the WTCCC found strong evidence of an association for an SNP across CARD9 (rs10781500, $p = 1.1 \times 10^{-6}$)[9]. Given its central regulatory role in the innate immunity, CARD9 might be associated with disease pathogenesis.

CARD9 is crucial in mediating signal transduction of the innate immune response. Central to the integration of signals downstream of PRR, CARD9 functions as an adaptor protein to relay receptor-proximal events to core transcription factors[10]. CARD9 acts downstream of immunoreceptor tyrosine-based activation motif (ITAM)-bearing or ITAM-coupled receptors. Its pivotal role downstream of the antifungal PRR, dectin 1 and splenic tyrosine kinase (SYK), is the best characterized. Activation of SYK results in signaling through CARD9, which interacts with BCL-10 and MALT1 to induce the canonical nuclear factor-κB pathway and also p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathways for proinflammatory responses[12,19,20]. As well, CARD9 is involved in signal transduction downstream of cytoplasmic sensors including the NOD family of PRR. CARD9-dependent activation of p38 MAPK and JNK has been implicated in NOD2 signal transduction in the innate immune response against certain intracellular pathogens[10,13]. In addition, CARD9 signaling contributes to the activation and modulation of adaptive immunity. Stimulation of CARD9 signaling induces the maturation of dendritic cells into full effector antigen-presenting cells that can prime naive T cells for the differentiation of interferon γ-producing Th1 cells and the generation of interleukin 17 (IL-17)-producing Th17 cells[14]. Thus CARD9 can couple innate to adaptive immunity and favor a Th17 bias that has been previously linked to AS with the identification of the association of IL-23R with AS and IBD[7,21]. AS was long considered to be triggered by exposure to a ubiquitous environmental pathogen in a genetically susceptible person. Of note, dectin 1 recognizes β-glucan, a component of fungus and some bacterial cell walls, exposure to which induces spondyloarthritis in *skg* mice[14,22]. Our current understanding of AS pathogenesis may be extended with the knowledge that CARD9 can link innate immunity stimuli with activation of the Th17 pathway[23].

The mechanisms of action of SNAPC4 in immunity and autoimmune disorders have not been clearly elucidated. Our study was limited in that more SNP in 9q34.3 need to be selected for possible haplotype analysis in disease risk assessment. Moreover, CARD9 and SNAPC4 polymorphisms may be involved in the mechanisms of gene expression modulation such as mRNA splicing, transcription factor binding, and microRNA targeting, which need further investigation.

Despite successful identification of common variants associated with various complex diseases, GWAS are inadequate in confirming disease-associated or function-relevant SNP. Our study suggests that CARD9 and also SNAPC4 may be causal genes of functional significance in AS. Given the LD situation in 9q34.3, verification of the true functional loci/genes that independently contribute to the disease susceptibility is challenging. Further clarifying the associations with stringent levels in multiple ethnic groups and the mechanisms of 9q34.3 variants conferring AS susceptibility would be beneficial.

Our replication study revealed an SNP in 9q34.3, rs11145835, significantly associated with AS in a group of Chinese Han people. This variant affects CARD9 and SNAPC4 gene expression, with the presence of the risk allele decreasing the expression. Future association studies and functional investigation will help elucidate potential genetic polymorphisms that play a role in the pathogenesis of AS.

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