ORIGINAL RESEARCH

Common Polymorphisms in the CD43 Gene Region Are Associated with Tuberculosis Disease and Mortality

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Abstract

CD43, a surface glycoprotein, regulates *Mycobacterium tuberculosis* macrophage binding, replication, and proinflammatory cytokine induction in a murine model. We hypothesized that single-nucleotide polymorphisms (SNPs) in the CD43 gene region are associated with human tuberculosis (TB) susceptibility. We performed a case-population study in discovery (352 TB cases and 382 control subjects) and validation cohorts (339 TB cases and 376 control subjects). We examined whether 11 haplotype-tagging SNPs in the CD43 gene region were associated with tuberculous meningitis (TBM) and pulmonary TB (PTB) in Vietnam. Three SNPs from the CD43 gene region were associated with TB susceptibility with a genotypic model. The association fit a recessive genetic model and was greater for TBM than for PTB (for TBM: rs4788172, odds ratio [OR], 1.64; 95% confidence interval [CI], 1.04–2.59, rs17842268 [OR, 2.20; 95% CI, 1.29–3.76, and rs12596308 [OR, 2.38; 95% CI, 1.47–3.89]). Among TBM cases, rs17842268 was associated with decreased survival (hazard ratio, 2.7; 95% CI, 1.1–6.5; $P = 0.011$). In addition, rs12596308 and rs17842268 were associated with focal neurologic deficit at TBM presentation. Our data suggest that CD43 polymorphisms are associated with TB susceptibility, disease manifestations, and worse outcomes. To our knowledge, this is the first report that links CD43 genetic variants with susceptibility and outcome from a disease.

Keywords: tuberculosis; CD43; mortality; single-nucleotide polymorphism; tuberculous meningitis

Clinical Relevance

This is the first study on CD43 and tuberculosis in humans. We found that a common variation in CD43 that is associated with susceptibility to tuberculosis is also associated with increased mortality. This has potential for translational impact due to the high frequency of death and disability caused by tuberculous meningitis.

In 2011, tuberculosis (TB) caused over 1.4 million deaths, and there were 8.7 million new cases of TB disease (1). Tuberculous meningitis (TBM) is the most severe form of the disease, with mortality around 25% in HIV-uninfected and 60% in HIV-infected adults (2). The genetic determinants of susceptibility to the most severe forms of TB, such as TBM, and their pathogenesis are not well understood.

Studies of the host genetic susceptibility to TB encompass twin (3, 4), linkage, candidate gene association, and genome-wide association studies (5–12). We and others have identified associations between common polymorphisms in innate immunity genes and susceptibility to TB and clinical phenotypes (6, 8, 11, 13). Most of this work

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has focused on macrophage receptors that initiate phagocytosis and mediate specific host immune responses. Numerous macrophage receptors that recognize MTB have been described, including Toll-like receptors (TLR1, -2, -4, -6, -8, and -9) (14), nucleotide binding oligomerization domain protein 2 (NOD2) (15), RIG-I–Like receptors (STING), C-type lectin receptors (DC-SIGN and CLEC4E/Mincle) (16, 17), and CD43 (18–20). The details of how human genetic variation of receptors modulates mycobacterium TB (MTB) uptake and subsequent signaling events are largely unknown.

The gene for CD43 has two exons (21) encoding one 381-amino acid polypeptide (22) that functions as a cell surface sialoglycoprotein, abundantly expressed on monocytes and T cells. Although CD43 is associated in the development of several types of cancer (23–25), it is also involved in the immune response to several pathogens, such as *Trypanosoma cruzi*, HIV, and MTB (26–28). CD43 may bind specifically to *Mycobacteria* but not to other types of bacteria (18, 19, 29). Moreover, Hickey and colleagues described the MTB molecular chaperone Cpn60.2 as a mycobacterial surface ligand that interacts with CD43 to stabilize the interaction between the mycobacteria and the macrophage (30). CD43 has also been shown to regulate intracellular MTB growth and TNF secretion (19), reducing TNF secretion in response to infection and shifting macrophage's cell death away from apoptosis to necrosis (20). Together, these findings indicate that CD43 binds Mycobacterial species and regulates macrophage signaling and mechanisms of cell death. However, it is not known if CD43, or its genetic variants, regulate susceptibility to human TB.

Using a case-population design, we investigated whether CD43 genetic polymorphisms are associated with susceptibility to TB and influence clinical presentation and outcome.

Materials and Methods

Study Population

TB cases were recruited from 1997 until 2008 from study sites in Ho Chi Minh City, Vietnam, as previously described (31–33). In brief, study subjects were recruited from Pham Ngoc Thach Hospital for Tuberculosis and the Hospital for Tropical Diseases. Umbilical cord blood samples were used as control samples. Cases were divided in discovery and validation cohorts. In the discovery cohort, "Definite TBM" cases and PTB cases recruited in 2003 and 2004 were included. The validation cohort included "Definite TBM" and "Probable TBM" cases as well as inpatient and outpatient cases with PTB recruited between 2006 and 2008 (*see* Table E1 in the online supplement). Approval for human study protocols was obtained from the human subjects review boards at the Hospital for Tropical Diseases and Pham Ngoc Thach hospitals, Health Services of Ho Chi Minh City, Hung Vuong Hospital, Oxford Tropical Research Ethics Committee, and the University of Washington.

Single-Nucleotide Polymorphism Selection and Assessment of Linkage Disequilibrium

We selected haplotype-tagging single-nucleotide polymorphisms (SNPs) from the Han Chinese population using International HapMap Project data from the Genome Variation Server. We searched a region 13,000 kb upstream and downstream of the CD43 gene on the 16p11.2 chromosome for tagged SNPs using an R^2 cutoff of 0.8 for linkage disequilibrium. We selected 11 SNPs in the CD43 region, which is located between the carbonic anhydrase VA pseudogene 1 (CA5AP1) and quinolinate phosphoribosyltransferase (QPRT) genes (Figure 1). Three SNPs were intronic (rs2071420, rs12596308, and rs12599318), one was in a synonymous coding region (rs1050881), and the rest were intergenic (rs376642725, rs376642727, rs11574552, rs11859842, rs11150564, rs4788172, and rs17842268).

Genomic Techniques

Genomic DNA was purified from peripheral blood samples using the QIAamp DNA blood kit (Qiagen). In the discovery cohort, subjects were genotyped using Sequenom, a chip-based, matrix-assisted laser desorption/ionization time-of-flight mass array technique as previously described (34). For genotyping in the validation cohort, we used a TaqMan Assay (Life Technologies). Cluster plots were visually inspected to ensure accurate genotyping calls. The call rate for each SNP exceeded 94% in the discovery cohort. All candidate SNPs were in Hardy-Weinberg equilibrium ($P > 0.05$) among control subjects according to a χ^2 goodness-of-fit test and were further evaluated for association with TB.

Statistical Methods

To determine whether CD43 polymorphism frequencies in our discovery cohort were associated with TB in a genotypic model, we used Stata 11 software and the package "genass." SNP rs17842268 was also genotyped in the validation cohort.

SNPs were investigated under additional genetic models (dominant, recessive, and heterozygous advantage) for association with the clinical subtypes of TB. We used logistic regression models to estimate associations of SNPs and characteristics of disease presentation: cranial nerve palsy, hemiplegia, focal neurologic deficit, TBM British Medical Research Council Grade, and clinical outcomes (death and neurologic disability). We used Cox regression models for survival analysis.

Results

CD43 Region SNPs Are Associated With Susceptibility to TB

To determine whether polymorphisms in the CD43 gene region were associated with susceptibility to TB, we examined a discovery cohort of 352 HIV-uninfected adult subjects with TB (182 PTB, 170 TBM) and 382 population control subjects. We also examined a validation cohort of 339 patients with TB (212 PTB, 127 TBM) and 376 control subjects. The clinical characteristics of these two cohorts have been described previously (31).

In our primary analysis, we examined whether 11 haplotype-tagging SNPs in the CD43 region were associated with all forms of TB in our discovery cohort. Using a genotypic model, we identified that 3 of the 11 SNPs were significantly associated with susceptibility to TB (rs12596308 [$P = 0.003$], rs17842268 [$P = 0.004$], and rs4788172 [$P = 0.004$]) (Table 1). An additional two SNPs had a trend toward statistically significant association (rs11574552 and rs1050881). All three SNPs remained significant after a Bonferroni correction for multiple comparisons (conservative

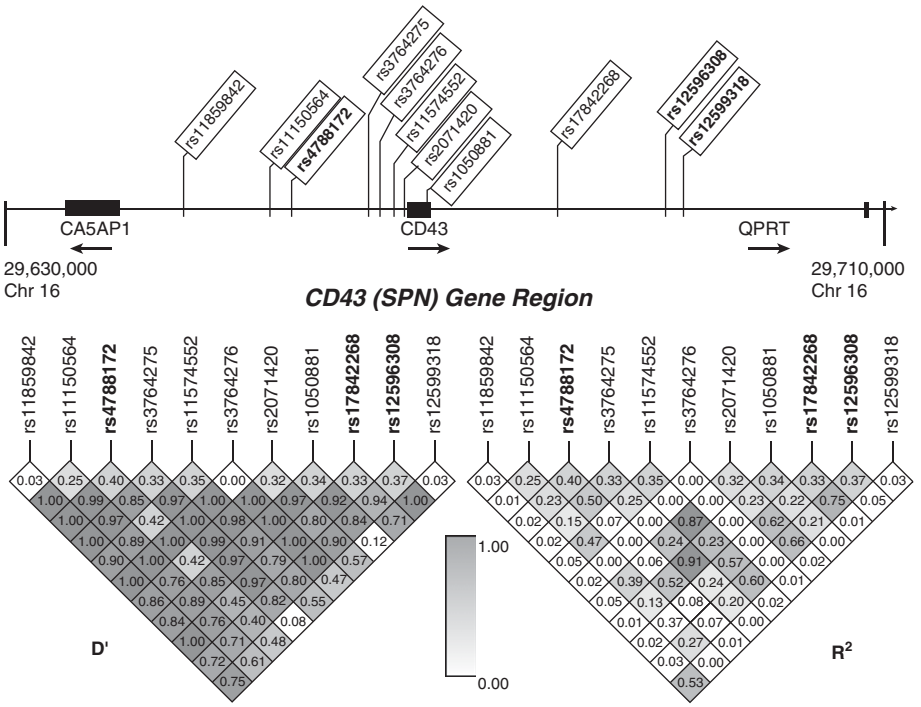

Figure 1. Linkage disequilibrium plot of CD43 gene region. Genomic positions of 11 single-nucleotide polymorphisms (SNPs) in the 5′ untranslated region and intronic regions of the CD43 gene. 2 exons are shown as black rectangles. D′ and R^2 values were calculated from control subjects in the discovery cohort. Values are shown numerically and by shading based upon the legend in the middle. The minor allele frequency is shown below each corresponding SNP. SNPs in bold type had significant associations in this study. CA5AP1, carbonic anhydrase VA pseudogene 1; QPRT, quinolinate phosphoribosyltransferase.

adjusted threshold of $P < 0.05/11 = 0.0045$). The linkage disequilibrium patterns showed moderate to high linkage disequilibrium between rs17842268 and rs12596308 ($R^2 = 0.75$) but not rs4788172 ($R^2 = 0.08$ and 0.07, respectively) in the control population (Figure 1). We replicated these results in the validation cohort for SNP rs17842268 (genotypic model $\chi^2 = 7.84$; $P = 0.02$) (Table E2). We next considered whether these associations were confounded by population admixture. All subjects were unrelated, and more than 95% were of the Vietnamese Kinh ethnicity. We previously genotyped a panel of 24 control SNPs to look for evidence of admixture and found no significant differences in genotype frequencies between cases and control subjects (31). A principal component analysis by Khor and colleagues confirmed the genetic homogeneity of this population (35).

Analysis of rs4788172, rs17842268, and rs12596308

We next performed several secondary analyses. The association of the tree significant SNPs (rs4788172, rs17842268, and rs12596308) with susceptibility to all cases of TB was consistent with a recessive model (genotype AA: odds ratio [OR], 1.58; 95% confidence interval [CI], 1.07–2.34; $P = 0.015$; genotype CC: OR, 1.88; 95% CI, 1.16–3.07; $P = 0.006$; and genotype TT: OR, 1.99; 95% CI, 1.29–3.10; $P = 0.001$, respectively) rather than a dominant, heterozygous advantage, or additive model (P = NS) (Table 2 and data not shown). When examining the two clinical phenotypes of TB, we found that the association was stronger with TBM than with PTB ($P = 0.032$, $P = 0.003$, and $P < 0.001$ versus $P = 0.061$, $P = 0.088$, and $P = 0.049$, respectively) (Table 2). These data indicate that three CD43 SNPs are associated with increased susceptibility to TB with a recessive model of inheritance and a stronger association with TBM.

Haplotype Analysis of rs4788172, rs17842268, and rs12596308

We next constructed haplotypes of the SNPs that were significantly associated with TB (rs4788172, rs17842268, and rs12596308) to analyze whether there were additive associations using a different combination of the alleles (Table E3). We found one haplotype (001) that was associated with all types of TB combined (OR, 2.06; $P = 0.04$). In addition, we found that haplotypes 001 and 010 were associated with PTB (001: OR, 2.34; $P = 0.03$ and 010: OR, 4.31; $P = 0.02$). However, overall the haplotype analysis did not reveal that combinations of polymorphisms had a different pattern or magnitude of association with susceptibility to TB.

TBM Disease Severity in Individuals with rs17842268

Due to the stronger association with TBM, we next examined whether CD43 SNPs were associated with features of TBM disease severity, including meningitis grade, Glasgow coma scale, and focal neurologic deficit (Table 3). There was no association of SNP rs4788172 and the presence of TBM disease manifestations. Genotypes rs17842268 and rs12596308, which are in high linkage disequilibrium, were significantly associated with focal deficit (OR, 4.02; $P = 0.004$ and OR, 2.34; $P = 0.05$, respectively) (Table 3). This relationship was maintained after adjusting for age and gender. None of the SNPs was associated with TBM grade or Glasgow coma scale in the adjusted analysis. In addition, the SNPs were not associated with the median pretreatment leukocyte counts or protein in cerebrospinal fluid (data not shown).

Together, these data suggest that there are likely two independent CD43 genetic loci associated with susceptibility to TB disease but different associations with TBM disease severity and survival.

CD43 rs17842268 Is Associated with Decreased Survival

We examined whether any of the SNPs were associated with survival. We found that among TBM cases, rs17842268 genotype CC was significantly associated with decreased survival compared with genotype TT and CT, fitting a recessive model (hazard ratio, 2.82; 95% CI, 1.3–6.3; $P = 0.01$) (Figure 2). In contrast, SNPs rs4788172 and rs12596308 were not associated with decreased survival. These data suggest that SNP rs17842268 is associated with more severe presentation and survival in patients with TBM.

Table 1. CD43 Polymorphism Frequencies in Control and Tuberculosis Groups

SNP,* Group	Subjects with Genotype (*n* [%])			Genotypic Comparison		HWE *P* Value
	00	01	11	χ^2	*P* Value	
rs11859842 T/C						
Control	364 (0.953)	18 (0.047)	0 (0)			0.637
All TB†	347 (0.934)	21 (0.061)	2 (0.006)	2.883	0.237	
rs11150564 G/A						
Control	218 (0.578)	137 (0.363)	22 (0.058)			0.938
All TB	196 (0.578)	116 (0.342)	27 (0.080)	1.410	0.494	
rs4788172 G/A						
Control	126 (0.335)	187 (0.497)	63 (0.168)			0.650
All TB	122 (0.378)	123 (0.381)	78 (0.241)	10.92	0.004	
rs3764275 C/A						
Control	163 (0.429)	176 (0.463)	41 (0.108)			0.523
All TB	161 (0.491)	126 (0.384)	41 (0.125)	4.496	0.106	
rs11574552 T/C						
Control	171 (0.451)	165 (0.476)	43 (0.113)			0.738
All TB	143 (0.427)	133 (0.397)	59 (0.176)	5.753	0.056	
rs3764276 T/C						
Control	381 (0.997)	1 (0.003)	0 (0)			0.980
All TB	348 (0.997)	1 (0.003)	0 (0)	0.004	0.949	
rs2071420 A/G						
Control	179 (0.469)	165 (0.432)	38 (0.099)			0.998
All TB	154 (0.467)	132 (0.400)	44 (0.133)	2.197	0.333	
rs1050881 C/T						
Control	161 (0.429)	172 (0.459)	42 (0.112)			0.698
All TB	146 (0.465)	119 (0.379)	49 (0.156)	5.567	0.062	
rs17842268 T/C						
Control	165 (0.440)	176 (0.469)	34 (0.091)			0.181
All TB	161 (0.407)	127 (0.371)	54 (0.158)	11.02	0.004	
rs12596308 T/C						
Control	156 (0.413)	180 (0.476)	42 (0.111)			0.354
All TB	137 (0.408)	132 (0.393)	67 (0.199)	11.92	0.003	
rs12599318 G/A						
Control	361 (0.953)	18 (0.047)	0 (0)			0.636
All TB	315 (0.938)	19 (0.057)	2 (0.057)	2.581	0.275	

Definition of abbreviations: HWE, Hardy Weinberg equilibrium *P* value in control subjects; SNP, single-nucteotide polymorphism; TB, tuberculosis.
*SNPs are listed by reference SNP ID in genomic order on chromosome 16. 0, common allele; 1, minor allele.
†All TB includes pulmonary tuberculosis and tuberculous meningitis cases from the discovery cohort.

Discussion

The primary finding of our study is that CD43 polymorphisms rs4788172, rs12596308, and rs17842268 are associated with susceptibility to TB, and to TBM in particular, in Vietnam. In addition, rs12596308 and rs17842268 were associated with TBM disease severity at presentation, and rs17842268 was associated with death. To our knowledge, this is the first report demonstrating an association of common CD43 SNPs with susceptibility to, and outcome from, a human infectious disease.

In addition to overall susceptibility, one CD43 SNP was associated with disease severity and mortality. To our knowledge, only one gene (LTA4H) has a polymorphism that has been associated with TBM mortality (11). Among the limited number of studies evaluating host genetic susceptibility to TBM, our group has previously found several innate immune gene variants (TLR2, TIRAP/Mal, and LTA4H) that are associated with susceptibility to TBM (6, 8, 11). TLR2 and TIRAP regulate MTB-induced activation of NF-κB and secretion of proinflammatory cytokines, including TNF. CD43 may similarly affect TB disease manifestations by regulating proinflammatory cascades. Leukotriene (LT)A4H encodes LTA4 hydrolase, an enzyme that regulates synthesis of LTB4, a potent chemoattractant and proinflammatory eicosanoid that induces TNF production. CD43 and LTA4H regulate TNF levels, a common pathway that could lead to increased mortality from TB due to adverse effects from inflammatory sequelae. Although there is some overlap of the functional effects of CD43, TLR2, TIRAP, and LTA4H on proinflammatory pathways, the details and regulatory mechanisms of how the expression and function of each of these molecules interact are unknown.

The mechanism by which CD43 SNPs regulates human susceptibility to TB is unknown. However, CD43 has a significant role controlling the growth of MTB demonstrated not only within macrophages but also in CD43-deficient mice (18, 19). This process appears to occur via two different mechanisms: binding and uptake of mycobacteria and regulation of TNF production. TNF restricts mycobacterial growth through activation of macrophages, regulation of granuloma formation, Th1 cytokine expression (36), and the initiation of apoptosis. MTB-stimulated *Cd43−/−* macrophages had decreased TNF production and showed lower levels of Caspase-3 mediated apoptosis in

Table 2. CD43 Polymorphisms, Genetic Models, and Tuberculosis Phenotypes

SNP*	Group	Subjects with Genotype (*n* [%])			Genotypic Model			Recessive Model			Dominant Model	
		00	01	11	χ^2	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
rs4788172	Control	126 (0.335)	187 (0.497)	63 (0.168)								
G/A	All TB	122 (0.378)	123 (0.381)	78 (0.241)	10.92	0.004	1.58	1.09–2.29	0.015	1.38	0.88–1.64	0.241
	PTB	58 (0.341)	72 (0.424)	40 (0.235)	4.21	0.122	1.53	0.98–2.39	0.061	0.02	0.70–1.51	0.889
	TBM	64 (0.418)	51 (0.333)	38 (0.248)	12.32	0.002	1.64	1.04–2.59	0.032	2.80	0.97–2.10	0.094
rs17842268	Control	165 (0.440)	176 (0.469)	34 (0.091)								
T/C	All TB	161 (0.471)	127 (0.371)	54 (0.158)	11.02	0.004	1.88	1.34–2.63	0.006	0.68	0.94–1.36	0.409
	PTB	85 (0.470)	71 (0.392)	25 (0.138)	4.46	0.107	1.61	0.93–2.79	0.088	0.43	0.79–1.61	0.511
	TBM	76 (0.472)	56 (0.348)	29 (0.180)	11.77	0.003	2.20	1.29–3.76	0.003	0.37	0.79–1.65	0.542
rs12596308	Control	156 (0.413)	180 (0.476)	42 (0.111)								
T/C	All TB	137 (0.408)	132 (0.393)	67 (0.199)	11.92	0.003	1.99	1.48–2.69	0.001	0.01	1.60–2.43	0.893
	PTB	69 (0.394)	76 (0.434)	30 (0.171)	3.90	0.143	1.65	1.00–2.75	0.049	0.17	0.64–1.34	0.682
	TBM	68 (0.422)	56 (0.348)	37 (0.230)	15.13	0.001	2.39	1.47–3.89	<0.001	1.04	0.72–1.51	0.835

Definition of abbreviations: CI, confidence interval; OR, odds ratio; PTB, pulmonary tuberculosis; SNP, single-nucleotide polymorphism; TB, tuberculosis; TBM, tuberculous meningitis.
*SNPs are listed by reference SNP ID. For OR calculations, each group was compared with the control group. 0, common allele; 1, minor frequency allele.

comparison to wild-type cells. By adding recombinant TNF to *Cd43−/−* macrophages, apoptosis levels increased, and growth of MTB was controlled to levels seen in CD43-expressing cells (20). In addition to decreased production of TNF, *Cd43−/−* macrophages also had decreased production of proinflammatory cytokines, such as IL-12 (which is involved in TH1 T cell differentiation and restricting mycobacterial growth *in vivo* in mice) (37) and IL-6 (which is involved in the acute response to MTB) (38). These findings provide evidence that CD43 regulates the immune response to MTB not only through direct binding of the mycobacteria but also by regulating of the production of proinflammatory and T cell–polarizing cytokines.

In addition to innate immune mechanisms, previous studies suggest that CD43 is involved primarily in three main functions: (*1*) cellular adhesion due to structural characteristics of the extracellular domain, which has O-glycosylated mucin-like aminoacids and sialic acid residues (39, 40); (*2*) T cell activation and migration via cleavage of the CD43 extracellular domain, which interacts with endogenous lectin coreceptors (41) and proteins of the cytoskeleton (42) (CD43 uses E-selectin as a ligand on endothelial cells to regulate migration to sites of inflammation [41, 43]); and (*3*) CD43 regulates T cell trafficking to lymph nodes via phosphorylation of a specific serine residue in the CD43 intracellular domain (42, 44, 45). Moreover, CD43 forms clusters via thiol group oxidation on lymphocytes. These clusters are recognized by macrophages as early apoptotic cells (46). In a mouse model of infection with lymphocytic choriomeningitis virus, CD43 regulated generation of virus-specific CD8 T cells as well as trafficking of T cells to the central nervous system (45). It is possible that CD43 genetic variants modulate susceptibility to TB in humans by regulating generation and trafficking of MTB-specific T cell responses in the brain.

Table 3. CD43 Single-Nucleotide Polymorphisms and Tuberculous Meningitis Disease Presentation

SNP	Unadjusted Model			Adjusted for Age and Gender		
	OR*	95% CI	*P* Value	OR	95% CI	*P* Value
rs4788172 G/A, *n* = 147						
TBM grade	1.49	1.04–2.12	0.03	1.19	0.81–1.77	0.37
Glasgow coma scale	1.74	1.17–2.60	0.01	1.53	0.99–2.37	0.06
Focal deficit	0.91	0.47–1.75	0.77	0.91	0.47–1.77	0.78
rs17842268 T/C, *n* = 155						
TBM grade	1.72	1.05–2.81	0.03	1.33	0.76–2.33	0.32
Glasgow coma scale	1.49	0.92–2.43	0.11	1.01	0.59–1.74	0.96
Focal deficit	4.02	1.58–10.2	0.004	4.46	1.71–11.6	0.002
rs12596308 T/C, *n* = 100						
TBM grade	1.65	1.02–2.68	0.04	1.39	0.77–2.33	0.31
Glasgow coma scale	1.46	0.91–2.36	0.12	0.99	0.58–1.71	0.98
Focal deficit	2.34	0.99–5.50	0.05	2.59	1.06–6.33	0.04

Definition of abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism; TBM, tuberculous meningitis.
*Odds ratio estimated following recessive model.

Our study has several limitations. First, the association findings may not be due to genetic variants within the CD43 gene. The haplotype-tagging SNPs span a region that includes two flanking genes: (*1*) QPRT, which encodes a key enzyme in catabolism of quinolate, a potent neurotoxin linked to neurodegenerative disorders (47), and (*2*) CA5AP1, which encodes a liver enzyme that catalyzes rapid conversion of carbon dioxide and water to bicarbonate and protons (48). Although we cannot exclude these as candidate genes, there is substantial evidence that CD43 plays a crucial role in the host immune response to TB, whereas the functions of CA5AP1 and QPRT are primarily related to metabolic pathways. Therefore, it is likely that these three SNPs of interest are in linkage disequilibrium with functional SNPs localized in the CD43 gene. Second, we chose cord-blood subjects as controls to

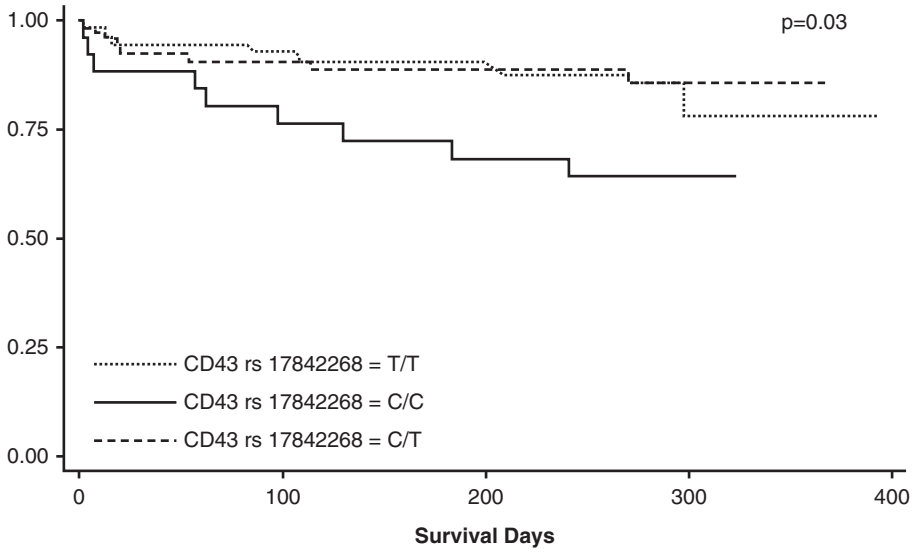

Figure 2. CD43 SNP and survival estimates in patients with tuberculosis meningitis. A Kaplan-Meier curve shows the association between rs17842268 genotype CC and decreased mortality among 156 tuberculous meningitis cases. The log-rank *P* value is 0.028 for the genotypic model and 0.0079 for the recessive model.

be able to compare background population genotype frequencies with the adult cases. These cord blood subjects may develop TB later in life, which may represent a misclassification of controls, leading to an underestimation of the genetic risk of SNPs. We expect that the misclassification rate would be low given that only 10% of individuals progress from latent to active disease and that an even lower number develop meningitis (6, 31). Lastly, population substructure acts as a confounder in candidate gene association studies. Our study population, the Vietnamese Kinh, is a relatively homogenous population in Southeast Asia in which we previously found no evidence of population stratification using control genomic SNPs (34).

In conclusion, we found that three common genetic variants localized within the CD43 gene region are associated with susceptibility to developing TB. Furthermore, among patients with TBM, individuals with genotype CC for rs17842268 had decreased survival. These results support a role for human CD43 in the immunopathogenesis of TB. Further studies are needed to dissect the mechanism by which CD43 increases susceptibility to TB disease. ■

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