

## Letter to the Editor

**Interleukin 8 Gene Polymorphisms Are Not Associated with Tuberculosis Susceptibility in the Chinese Population\***

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**Interleukin 8 (IL8) is an important chemokine that elicits host immune response against tuberculosis (TB). However, whether there is an association between *IL8* gene polymorphism and TB susceptibility in the Chinese population is unknown. *IL8* gene was amplified and sequenced to search for nucleotide polymorphisms among the Chinese population. Four single nucleotide polymorphisms (SNPs) were identified, selected, and analyzed in a cohort of 438 patients with TB and 536 healthy controls. Allelic, genotypic, and haplotypic analysis demonstrated that the distribution of the four *IL8* SNPs between patients with TB and healthy controls was not significantly different ( $P>0.05$ ). The four *IL8* SNPs detected in this study were not associated with TB susceptibility in the Chinese population. Secretion of IL8 by peripheral blood cells was greatly stimulated upon exposure to *Mycobacterium tuberculosis* whole cell extract, but such enhanced secretion was not associated with the *IL8* rs4073 alleles.**

Tuberculosis (TB) is a worldwide threat that passively infects one-third of the world population and kills approximately two million people each year. As one of the most important cytokine, IL8 is essential to control *Mycobacterium tuberculosis* (*M. tuberculosis*) infection in humans. However, whether there is an association between *IL8* gene polymorphism and TB susceptibility is not clear, especially in the Chinese population, presenting a high TB burden.

Ma et al. reported that rs4073 polymorphism in

the *IL8* promoter region was associated with TB susceptibility in two ethnic groups in the United States<sup>[1]</sup>. In contrast, Cooke et al. reported that this polymorphism was not a true factor affecting TB susceptibility in Gambia<sup>[2]</sup>. Debates<sup>[3]</sup> on conflicting results raise the question whether there is an association between *IL8* gene polymorphism and TB susceptibility, especially in countries with high TB burden. In this study, we evaluated the association between *IL8* genetic polymorphisms and TB susceptibility in a large Chinese population. The effect of *IL8* rs4073 polymorphism on IL8 expression level was also determined.

To identify single nucleotide polymorphisms (SNPs) among a Chinese population, *IL8* gene (including the promoter region, but excluding most of the first intron) was sequenced using 60 DNA samples from 30 TB patients and 30 healthy controls. Five genetic polymorphisms, rs56090111, rs4073, rs2227541, rs2227543, and rs188973626, were detected (Table 1). Two of the polymorphisms were located in the promoter region and the other three were located in the introns. No SNP was detected in exons. Further analysis showed that two SNPs rs2227541 and rs2227543 were in perfect linkage disequilibrium (LD) (Table 1). Thus, rs2227541 SNP was not used for further genotyping.

The genotypic distributions in patients with TB and controls were checked separately for Hardy-Weinberg equilibrium (HWE) test. No deviation was observed with all 4 polymorphism sites ( $P>0.05$ ). The frequencies of the four SNPs

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(rs56090111, rs4073, rs2227543, and rs188973626) in 438 patients with TB and 536 healthy controls were evaluated. No statistically significant allelic, genotypic, or haplotypic difference was observed

between the patients and the control groups (Table 2). These results suggest that the four polymorphisms are not associated with TB risk or resistance in the Chinese population.

**Table 1.** *IL-8* Gene Polymorphisms Identified by Sequencing

SNP rs Number	Allele (frequency)	Genotype (frequency)
rs56090111	- (0.05) / TTAA (0.95)	-- (0.00) / -TTAA (0.10) / TTAA TTAA (0.90)
rs4073	A (0.48) / T (0.52)	AA (0.22) / AT (0.53) / TT (0.25)
rs2227541 <sup>a</sup>	- (0.48) / A (0.52)	-- (0.20) / -A (0.57) / AA (0.23)
rs2227543 <sup>a</sup>	C (0.52) / T (0.48)	CC (0.23) / CT (0.57) / TT (0.20)
rs188973626	A (0.01) / G (0.99)	AA (0.00) / AG (0.02) / GG (0.98)

**Note.** <sup>a</sup>These two SNPs presented perfect LD.

**Table 2.** *IL-8* Gene Allele, Genotype, and Haplotype Association with TB

Item	TB (%)	Control (%)	$\chi^2$	P	OR (95% CI)	
<b>Allele</b>						
rs56090111	TTAA	850 (97.0)	1046 (97.6)	0.546	0.460	0.813 (0.468-1.410)
	-	26 (3.0)	26 (2.4)			
rs4073	A	369 (42.1)	436 (40.7)	0.419	0.517	1.062 (0.886-1.273)
	T	507 (57.9)	636 (59.3)			
rs2227543	C	523 (59.7)	647 (60.4)	0.085	0.770	0.973 (0.811-1.168)
	T	353 (40.3)	425 (39.6)			
rs188973626	A	4 (0.5)	2 (0.2)	1.145	0.285	2.454 (0.448-13.431)
	G	872 (99.5)	1070 (99.8)			
<b>Genotype</b>						
rs56090111	TTAA TTAA	413 (94.3)	510 (95.1)	1.428	0.490	
	-TTAA	24 (5.5)	26 (4.9)			
	--	1(0.2)	0 (0.0)			
rs4073	AA	75 (17.1)	88 (16.4)	0.522	0.770	
	AT	219 (50.0)	260 (48.5)			
	TT	144 (32.9)	188 (35.1)			
rs2227543	CC	148 (33.8)	192 (35.8)	0.736	0.692	
	TC	227 (51.8)	263 (49.1)			
	TT	63 (14.4)	81 (15.1)			
rs188973626	AA	0 (0.0)	0 (0.0)	1.149	0.284	
	AG	4 (0.9)	2 (0.4)			
	GG	434 (99.1)	534 (99.6)			
<b>Haplotype<sup>*</sup></b>						
	TTAA/A/C/G	24.47 (2.8)	17.02 (1.6)	-	-	-
	TTAA/A/T/A	0.11 (0.0)	1.94 (0.2)	-	-	-
	TTAA/A/T/G	318.43 (36.4)	391.69 (36.5)	0.176	0.675	1.041 (0.862-1.258)
	TTAA/T/C/A	3.89 (0.4)	0.06 (0.0)	-	-	-
	TTAA/T/C/G	491.72 (56.1)	629.84 (58.8)	0.176	0.675	0.960 (0.795-1.160)
	TTAA/T/T/G	11.37 (1.3)	5.45 (0.5)	-	-	-
	-/A/C/G	2.90 (0.3)	0.07 (0.0)	-	-	-
	-/A/T/G	23.08 (2.6)	25.28 (2.4)	-	-	-
	-/T/T/G	0.00 (0.0)	0.65 (0.0)	-	-	-
	-/T/C/G	0.02 (0.0)	0.00 (0.0)	-	-	-

**Note.** <sup>\*</sup>Frequencies lower than 3% both in TB and control groups were not evaluated by  $\chi^2$  test.

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