



Interleukin (IL)-8 polymorphisms contribute in suicide behavior

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ABSTRACT

Previous studies have highlighted the role of immune dysregulation in suicide behavior. Interleukin (IL)-8 is a chemokine with neuroprotective effects whose lower serum concentrations have been detected in individuals committed suicide. In the present study, we genotyped three single nucleotide polymorphisms (SNPs) within *IL-8* gene (rs4073, rs2227306 and rs1126647) in 229 individuals who attempted suicide with soft suicide methods, 235 suicide victims and 290 individuals without any history of psychiatric disorders or suicide attempt. The T allele of rs4073 was significantly over-represented in suicide attempt group compared with both control and completed suicide groups (adjusted P values of 8.3E-7 and 9.8E-8 respectively). This SNP was associated with suicide attempt in both dominant and co-dominant models (P values of 6.2E-9 and 4.3 E-8 respectively). The genotype and allele frequencies of other SNPs were not significantly different among the three study groups. The T C A haplotype (rs4073, rs2227306 and rs1126647 respectively) were significantly less prevalent in completed suicide group compared with suicide attempt group (OR (95% CI) = 0.63 (0.46–0.86), adjusted P value = 0.03). Besides, the A T A haplotype has significant lower frequency in individuals who attempted soft suicide compared with controls (OR (95% CI) = 0.44 (0.26–0.75), adjusted P value = 0.02). However, this haplotype was significantly more prevalent in individuals attempted hard methods compared with those attempted soft methods (OR (95% CI) = 2.21 (1.26–3.87), adjusted P value = 0.04). The present study provided further evidence for the role of IL-8 in suicide behavior.

1. Introduction

Based on the statistics provided by world health organization (WHO), suicides account for 1.4% of total mortality and 15% of injury mortality [1]. Several lines of evidence obtained from post-mortem studies, genetic association studies and as well as structural and functional assessments support a biological source for this mental problem [2]. A pilot study searching for candidate gene regions associated with suicide behavior has identified a number of single nucleotide polymorphisms (SNPs) among them were immune system related genes whose expression has been changed in suicide attempters compared with controls [3]. Further studies have shown altered levels of cytokines in individuals attempted suicide as compared with controls or depressed patients without suicide ideation [4,5]. Moreover, the elevated expression of type 2 T-helper cytokines has been demonstrated in the orbitofrontal cortex suicide victims [6]. Interleukin (IL)-8 is a pro-

inflammatory chemokine whose neuroprotective effect has been demonstrated *in vitro* [7]. This chemokine is secreted by microglia, astrocytes and endothelial cells [8]. Its expression in human astrocytes after Fas stimulation probably protects these cells from Fas-mediated death [9]. Its contribution in suicide risk has been suggested through detection of lower plasma and cerebrospinal fluid (CSF) levels of this chemokine in suicide attempters with anxiety compared with healthy controls. Moreover, a certain polymorphism (rs4073) within its promoter region was associated with suicide behavior in female subjects [10]. In addition to this functional SNP, the rs2227306 intronic variant of this gene has been shown to alter IL-8 expression at both mRNA and protein levels [11]. Besides, the rs1126647 SNP is located in the 3' untranslated region of the *IL-8* gene and is expected to contribute in its posttranscriptional regulation [12]. Consequently, in the present study we genotyped the rs4073, rs2227306 and rs1126647 SNPs of *IL-8* in suicide attempter and control subjects to reveal their contribution in

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Table 1

The nucleotide sequence of primers used in the study.

SNP	Primer sequence	Tm	Annealing temperature	PCR product size (bp)
rs4073	Forward inner primer (A allele): 5'-AAAGTCATCTAGCAATAAAAAAGCATAGAA	58 °C	61 °C	146 bp (A allele)
	Reverse inner primer (T allele): 5'-AATCTCCACAATTTGGTGAATTATCTAA	57 °C		102 bp (T allele)
	Forward outer primer: 5'-ATACCTGCCACTCTTGTACTATATCTG	60 °C		190 bp (two outer primers)
	Reverse outer primer: 5'-CTATCTGTTACTTATCAAATACGGAGT	62 °C		
rs2227306	Forward inner primer (C allele): 5'-ACAGAACTCTAACTCTTATATAGGAACCTC	59 °C	62 °C	222 bp (C allele)
	Reverse inner primer (T allele): 5'-ACAATCATAACTGACAACATTGAGCA	59 °C		148 bp (T allele)
	Forward outer primer: 5'-TATCTTGCCTACTATAAATAACACTGTG	59 °C		314 bp (two outer primers)
	Reverse outer primer: 5'-AAGTGATTAAGGAATGATTTTATCAAC	60 °C		
rs1126647	Forward inner primer (T allele): 5'-GTACCCAGTTACATTTTCATTTCCAGATAT	60 °C	58 °C	181 bp (T allele)
	Reverse inner primer (A allele): 5'-TGACTTTACTAAAGAATTATTTGTTATT	61 °C		233 bp (A allele)
	Forward outer primer: 5'-ATGTATTATTAAAGCATCGAATATTTGT	60 °C		358 bp (two outer primers)
	Reverse outer primer: 5'-GTTTTGATAGTTCTAACTCATTATTCGG	60 °C		

Table 2

Exact test for Hardy-Weinberg equilibrium.

	rs4073			P-value	rs2227306			P-value	rs1126647			P-value
	TT	TA	AA		CC	CT	TT		AA	AT	TT	
Case	183	214	67	0.77	173	207	84	0.11	185	209	70	0.39
Control	83	158	49	0.07	111	125	54	0.08	123	121	46	0.08

suicide behavior.

2. Material and methods

2.1. Study participants

In the current study, *IL-8* SNPs were genotyped in blood samples gathered from 229 individuals who attempted suicide with soft suicide methods (male/female ratio = 66%/34% age (mean \pm SD) = 36.2 \pm 1.3), 235 suicide victims (male/female ratio = 67%/33% age (mean \pm SD) = 37.01 \pm 0.53) and 290 individuals without any history of psychiatric disorders or suicide attempt. In the cases of suicide victims, blood samples were collected through cardiopuncture while in other cases peripheral blood was used for genotyping. The control group were matched with cases in both sex and age parameters. The study protocol was approved by local ethic committee. Written informed consent was obtained from study participants or their guardians.

2.2. SNP genotyping

DNA was extracted from blood samples using the standard salting out method. The rs4073, rs2227306 and rs1126647 variants within *IL-8* gene were genotyped using tetra-primer ARMS-PCR technique and the results were confirmed by Sanger sequencing of 10% of samples in ABI 3730xl DNA analyzer (Macrogen, Korea). The PCR program was started with a denaturation step at 94 °C for 5 min followed by 35 cycles of 94 °C for 30 s, specific annealing temperatures for 35 s, and 72 °C for 35 s and an ultimate extension stage in 72 °C for 10 min. Table 1 shows the nucleotide sequence of primers used in the study.

2.3. Statistical analysis

All statistical analyses including Hardy-Weinberg Equilibrium, haplotype estimation, linkage disequilibrium (LD) blocking and association analysis were performed using SNPAnalyzer 2.0 [13]. D' and r^2 parameters were calculated for assessment of between pairwise SNPs. Association between SNPs and suicide behavior were assessed in co-dominant, dominant and recessive models. The results of association analysis were stated as Odds ratios (OR) and 95% confidence interval of

OR (95% CI), P-value and Bonferroni adjusted P-values. The Bonferroni corrected P values were measured by multiplying the P values by the number of SNPs. P-values less than 0.05 were considered statistically significant.

3. Results

The genotype frequencies of all three SNPs in cases and controls were in accordance with HWE. Table 2 shows the results of assessment of accordance with HWE in cases and controls.

The T allele of rs4073 was significantly over-represented in the suicide attempt group compared with both control and completed suicide groups (adjusted P values of 8.3E-7 and 9.8E-8 respectively). This SNP was associated with suicide attempt in both dominant and co-dominant models (P values of 6.2E-9 and 4.3 E-8 respectively). The genotype and allele frequencies of other SNPs were not significantly different among the three study groups. Table 3 shows the details of association study of *IL-8* polymorphisms and suicide behavior.

The T C A haplotype (rs4073, rs2227306 and rs1126647 respectively) were significantly less prevalent in the completed suicide group compared with the suicide attempt group (OR (95% CI) = 0.63 (0.46–0.86), adjusted P value = 0.03). Besides, the A T A haplotype has significant lower frequency in individuals who attempted soft suicide compared with controls (OR (95% CI) = 0.44 (0.26–0.75), adjusted P value = 0.02). However, this haplotype was significantly more prevalent in individuals attempted hard methods compared with those attempted soft methods (OR (95% CI) = 2.21 (1.26–3.87), adjusted P value = 0.04). Table 4 shows the frequencies of estimated haplotype blocks in the three study groups.

Based on the r^2 and D' statistics, there were no strong LD between the three assessed SNPs in either cases or controls (data not shown).

4. Discussion

The presence of a genetic basis for suicide behavior has been suggested by several studies. For instance, a genome wide association study and meta-analysis of the European ancestry discovery samples have shown significant association between a locus adjacent to *MRAP2* (*melanocortin 2 receptor accessory protein 2*) and suicide behavior. The expression of this gene in brain and adrenal cortex and its participation

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