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*Original Article*

# Association of IL-8 -251A/T and +781C/T polymorphisms with the susceptibility to coronary artery disease in a population of China

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**Abstract:** Coronary artery disease is the most common type of cardiovascular disease and is caused by atherosclerosis. The pathological process of coronary artery disease is involved in a long-term process, involving in many genetic and environmental factors. We investigated the association between IL-8 -251A/T and +781C/T genetic polymorphism and development of coronary artery disease in a Chinese population. Between March 2013 and March 2015, a total of 264 coronary artery disease patients confirmed by coronary angiography examination and 286 control subjects were collected into our study. The genotyping of IL-8 -251A/T and +781C/T was carried out through polymerase chain reaction coupled with restriction fragment length polymorphism method. There was statistically significant difference in the genotype distributions of IL-8 -251A/T between coronary artery disease patients and control subjects (chi-square=13.101, P<0.001). Multiple logistic regression analysis revealed that the TA (OR=1.633, OR=1.072-2.493) and AA (OR=2.329, 95% CI=1.421-3.820) genotypes of IL-8 -251A/T contributed to a higher risk of coronary artery disease in comparison to the TT genotype. The TA+AA genotype of IL-8 -251A/T was associated with an increased risk of developing coronary artery disease when compared with the TT genotype (OR=1.845, 95% CI=1.248-2.736) in dominant model. The AA genotype of IL-8 -251A/T had a 1.722 fold risk of developing coronary artery disease when compared with the TT+TA genotype (OR=1.722, 95% CI=1.140-2.608). However, no association was observed between the IL-8 +781C/T polymorphism and development of coronary artery disease. In conclusion, our study suggests that the IL-8 -251A/T polymorphism is an independently risk factor for the development of coronary artery disease.

**Keywords:** IL-8 -251A/T, IL-8 +781C/T, coronary artery disease, polymorphism

## Introduction

Cardiovascular disease is associated with high mortality and morbidity worldwide, and this incidence of this disease shows an increasing trend in China recently [1]. Coronary artery disease is the most common type of cardiovascular disease and is caused by atherosclerosis. The pathological process of coronary artery disease is involved in a long-term process, many dietary and lifestyle factors and their interactions, such as hypertension, hypercholesterolemia, diabetes, obesity, tobacco smoking, alcohol consumption and lack of physical activity [2-5]. However, individuals would not suffer from coronary artery disease even when they are exposure to the same etiological factor of this disease. Therefore, it is hypothesis that hereditary factors contribute to the pathological process of coronary artery disease. The author of a recent study has indicated that the hereditary factors account for about 40% and 60% in the onset of coronary artery disease [6].

Interleukin-8 is a cytokine, and belongs to the chemotactic super-family. IL-8 is mainly pro-

duced by neutrophils, mononuclear cells and epithelial cells that stimulated by lipopolysaccharide and tumor necrosis factors [7]. IL-8 gene locates on chromosome 4q13-q21, and this protein is comprised of four exons, three introns, a proximal promoter region, and encodes a 99 amino acid polypeptide [8]. IL-8 belongs to modulate inflammatory medium, and it has an important role in regulating in the process of inflammation and immunity [9, 10]. IL-8 expression contributes to the pathogenesis of atherosclerosis, and polymorphisms in IL-8 could influence the expression and quantity of this protein, and ultimately affect the function of genes. Currently, two studies have reported the association between interleukin-8 gene polymorphisms and development of coronary artery diseases [11, 12], but only one study investigated the role of IL-8 -251A/T polymorphism in the risk of developing coronary artery disease [12]. Therefore, we conducted a study to investigate the association between IL-8 -251A/T (rs4073) and +781C/T (rs2227306) genetic polymorphisms and risk of developing coronary artery disease in a Chinese population.

## Material and methods

### *Subjects*

Between March 2013 and March 2015, a total of 264 patients with coronary artery disease were collected from the first people's hospital of Wenling, and all patients were confirmed by coronary angiography examination. The coronary artery disease was defined as the individual with above 50% luminal stenosis in any of the main vessels, including left main coronary artery, left anterior descending, left circumflex and right coronary artery. Patients who had a history of coronary myocardial bridge, congenital heart disease, peripheral artery disease, end-stage liver or kidney disease, or malignant tumors were excluded from this study.

During the same time period, a total of 286 control subjects were randomly recruited into our study, and the control subjects were collected from individuals who visited the outpatient clinics and health check-up examination. All the control subjects were confirmed to be free of coronary artery diseases through coronary angiography examination. Controls were confirmed to be lack of serious infection disease, severe heart failure, malignant tumor, dilated cardiomyopathy, hypertrophic cardiomyopathy, and end-stage kidney and liver diseases.

The demographic, environmental and clinical variables of investigated patients and control subjects were collected from a structure questionnaires and medical records, including sex, age, family history of coronary artery disease, tobacco smoking, alcohol consumption, body mass index, diabetes, hypertension, total cholesterol (TC), triglyceride (TG), high-density lipoproteincholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c).

The performance of this study obtained the permission of the Institutional Review Board of the first people's hospital of Wenling. All coronary artery disease patients and control subjects signed the written informed consents prior to enrollment. Ethical approval for our study were in line with the standards of the Declaration of Helsinki.

### *Genotyping methods*

Five ml blood sample was obtained from each included subject, and blood samples were kept in EDTA-containing tube for total genomic DNA extraction. The isolation of genomic DNA was carried out by the TIANamp Blood DNA Kit (Tiangen, Beijing, China). The genotyping of IL-8 -251A/T and +781C/T was carried out through polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism (RFLP) method. The primers of IL-8 -251A/T for PCR reaction were as follows: 5'-ATTGGCTGGCTTATCTTCA-3' (forward) and 5'-CAAATACGGAGTATGACGAAAG-3' (reverse). The forward and reverse primers for IL-8 +781C/T were 5'-GTGGTATCACAGAGGATTATGC-3' and 5'-CAGTCATAACTGACAACATTGATC-3', respectively. The PCR reaction was carried out in a 15 μl of reaction mixture, comprising of 11 μl $ddH_2O$, 1.5 μl 10×PCR Buffer, 1.2 μl 25 mmol/L $Mg^{2+}$, 0.3 μl dNTP, 0.2 μl forward primer, 0.2 μl reverse primer, 0.1 μl Taq DNA Polymerase, and 0.5 μl template DNA. The PCR reaction was carried out as follows: initial denaturation at 95°C for 5 minutes, and then 20 cycles of denaturation at 95°C for 30 seconds, annealing at 58°C for 30 seconds, extension at 72°C for 40 seconds, extension at 72°C for 40 seconds, and a final extension at 72°C for 6 minutes. The PCR frag-

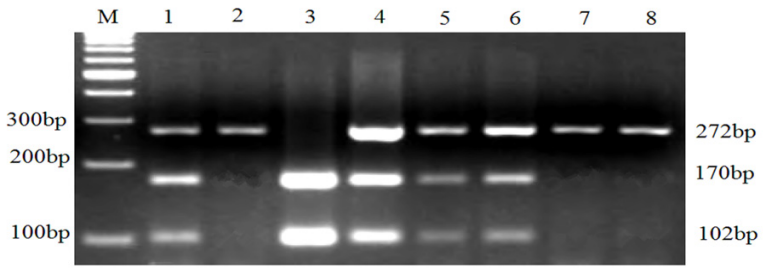


**Figure 1.** Agarose gel electrophoresis images for IL-8 -251A/T. 3 lane: AA genotype; 1, 4, 5 and 6 lanes: AT genotype: 2, 7 and 8 lanes: TT genotype.

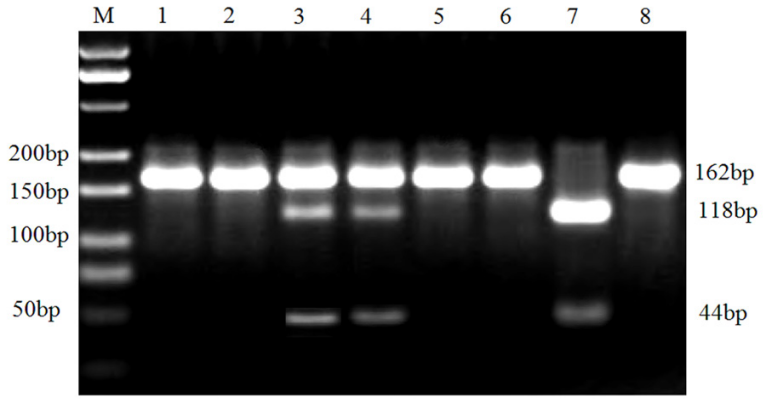


**Figure 2.** Agarose gel electrophoresis images for IL-8 +781C/T. 1, 2, 5, 6 and 8 lanes: CC genotype; 3 and 4 lanes: CT genotype: 7 lane: TT genotype.

ments of the IL-8 -251A/T and +781C/T polymorphisms were subsequently digested with the restriction enzyme of MunI and BclI, respectively. Digestion products of IL-8 -251A/T and +781C/T were separated by electrophoresis on ethidium bromide stained 2% agarose gel and visualized under UV light.

The length of the PCR amplification products for IL-8 -251A/T was 272 bp (**Figure 1**). The product fragments of the AA genotype of IL-8 -251A/T were 170 bp and 102 bp, fragments were 272 bp, 170 bp and 102 bp for AT genotype, and fragment was 272 bp for TT genotype. The length of the PCR amplification products for IL-8 +781C/T was 162 bp (**Figure 2**). The product fragment of the CC genotype of IL-8 +781C/T was 162 bp, the fragments were 118 bp and 44 bp for the TT genotype, and the fragments were 162 bp, 118 bp and 44 bp the CT genotype.

*Statistical analysis*

Chi-square test or student t test were taken to compare the differences between coronary artery disease patients and control subjects in terms of demographic, lifestyle and clinical variables. Before performing the association study, the Hardy-Weinberg Equilibrium (HWE) for any deviation from expected allele frequencies of IL-8 -251A/T and +781C/T were analyzed using a Chi-square ($\chi^2$)-test with one degree of freedom. A multivariate logistic regression analyses were taken to determine the association between IL-8 -251A/T and +781C/T polymorphisms and coronary artery disease risk, and the adjusted odd ratio (OR) and 95% confidence interval (CI). Spearman correlation analysis were performed to analyze the correlation between IL-8 -251A/T and +781C/T polymorphisms and environmental factors in the risk of coronary artery disease. All statistical analyses were done by using IBM SPSS Statistics for Windows, Version 20.0. (SPSS Inc. Armonk, NY, USA). A *P*-value <0.05 at 95% confidence interval (CI) was considered as a statistically significant.

## Results

Comparison of demographic, lifestyle and clinical variables between included patients and control subjects were shown in **Table 1**. We observed that the coronary artery disease patients were more likely to be males (chi-square=4.687, P=0.030), have higher BMI (chi-square=6.074, P=0.014), be suffered from hypertension (chi-square=32.844, P<0.001) and diabetes (chi-square=6.099, *P*=0.014), have a habit of tobacco smoking (chi-square =8.099, P=0.004), and have higher levels of TC (t=4.016, P<0.001), TG (T=2.107, P=0.018) and LDL-c (t=8.422, P<0.001) and lower levels of HDL-c (t=4.621, P<0.001). However, no significant difference was observed between coronary artery disease patients and controls with respects to sex (chi-square=0.693, P=0.405), alcohol consumption (chi-square=3.328, P= 0.068) and family history of coronary artery disease (chi-square=1.282, P=0.258).

**Table 1.** The demographic, lifestyle and clinical variables of coronary artery disease patients and control subjects

| Characteristics | Patients N=264 | % | Controls N=286 | % | Chi-square test | *P* value |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Female | 96 | 36.364 | 130 | 45.455 | | |
| Male | 168 | 63.636 | 156 | 54.545 | 4.687 | 0.030 |
| Age, years | | | | | | |
| <50 | 143 | 54.167 | 165 | 57.692 | | |
| ≥50 | 121 | 45.833 | 121 | 42.308 | 0.693 | 0.405 |
| BMI, kg/m$^2$ | | | | | | |
| <24 | 108 | 40.909 | 147 | 51.399 | | |
| ≥24 | 156 | 59.091 | 139 | 48.601 | 6.074 | 0.014 |
| Hypertension | | | | | | |
| No | 125 | 47.348 | 204 | 71.329 | | |
| Yes | 139 | 52.652 | 82 | 28.671 | 32.844 | <0.001 |
| Diabetes | | | | | | |
| No | 217 | 82.197 | 256 | 89.510 | | |
| Yes | 47 | 17.803 | 30 | 10.490 | 6.099 | 0.014 |
| Tobacco smoking | | | | | | |
| No | 147 | 55.682 | 193 | 67.483 | | |
| Yes | 117 | 44.318 | 93 | 32.517 | 8.099 | 0.004 |
| Alcohol consumption | | | | | | |
| No | 176 | 66.667 | 211 | 73.776 | | |
| Yes | 88 | 33.333 | 75 | 26.224 | 3.328 | 0.068 |
| family history of coronary artery disease | | | | | | |
| No | 253 | 95.833 | 279 | 97.552 | | |
| Yes | 11 | 4.167 | 7 | 2.448 | 1.282 | 0.258 |
| TC | | 187.724±47.501 | | 171.926±44.747 | 4.016 | <0.001 |
| TG | | 128.662±41.716 | | 121.253±40.735 | 2.107 | 0.018 |
| HDL-c | | 38.542±15.525 | | 44.415±14.280 | 4.621 | <0.001 |
| LDL-c | | 121.905±18.650 | | 108.820±17.782 | 8.422 | <0.001 |

TC: total cholesterol; TG: triglyceride; HDL-c: high-density lipoproteincholesterol; LDL-c: low-density lipoprotein cholesterol.

**Table 2.** Genotype distribution of IL-8 -251A/T and +781C/T between the two study groups

| | Patients N=264 | % | Controls N=286 | % | Chi-square test | *P* value | Patients | | Controls | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Chi-square for HWE | P for HWE | Chi-square for HWE | P for HWE |
| IL-8 -251A/T | | | | | | | | | | |
| TT | 61 | 23.106 | 102 | 35.664 | | | | | | |
| TA | 125 | 47.348 | 128 | 44.755 | | | | | | |
| AA | 78 | 29.546 | 56 | 19.580 | 13.101 | <0.001 | 0.636 | 0.425 | 1.882 | 0.170 |
| IL-8 +781C/T | | | | | | | | | | |
| CC | 107 | 40.53 | 126 | 44.06 | | | | | | |
| CT | 121 | 45.83 | 117 | 40.91 | | | | | | |
| TT | 36 | 13.64 | 43 | 15.03 | 1.359 | 0.507 | 0.037 | 0.847 | 3.248 | 0.072 |

The genotype distributions of IL-8 -251A/T and +781C/T were presented in **Table 2**. Using Pearson Chi-square test, we observed a significant difference between the two study groups in terms of the genotype frequencies of IL-8 -251A/T (chi-square=13.101, P<0.001), but no significant difference in the genotype distributions of IL-8 +781C/T (chi-square=1.359,

**Table 3.** Association between IL-8 -251A/T and +781C/T gene polymorphism and development of coronary artery disease by multiple logistic regression analysis

| IL-8 | Patients N=264 | % | Controls N=286 | % | OR (95% CI)[1] | *P* value |
|---|---|---|---|---|---|---|
| -251A/T | | | | | | |
| Co-dominant model | | | | | | |
| TT | 61 | 23.106 | 102 | 35.664 | 1.0 (Reference) | - |
| TA | 125 | 47.348 | 128 | 44.755 | 1.633 (1.072-2.493) | 0.016 |
| AA | 78 | 29.545 | 56 | 19.580 | 2.329 (1.421-3.820) | <0.001 |
| Dominant model | | | | | | |
| TT | 61 | 23.106 | 102 | 35.664 | 1.0 (Reference) | - |
| TA+AA | 203 | 76.894 | 184 | 64.336 | 1.845 (1.248-2.736) | 0.001 |
| Recessive model | | | | | | |
| TT+TA | 186 | 70.455 | 230 | 80.420 | 1.0 (Reference) | - |
| AA | 78 | 29.545 | 56 | 19.580 | 1.722 (1.140-2.608) | 0.007 |
| +781C/T | | | | | | |
| Co-dominant model | | | | | | |
| CC | 107 | 40.53 | 126 | 44.06 | 1.0 (Reference) | - |
| CT | 121 | 45.83 | 117 | 40.91 | 1.218 (0.834-1.778) | 0.286 |
| TT | 36 | 13.64 | 43 | 15.03 | 0.986 (0.571-1.700) | 0.957 |
| Dominant model | | | | | | |
| CC | 107 | 40.53 | 126 | 44.06 | 1.0 (Reference) | - |
| CT+TT | 157 | 59.47 | 160 | 55.94 | 1.155 (0.812-1.645) | 0.403 |
| Recessive model | | | | | | |
| CC+CT | 228 | 86.36 | 243 | 84.97 | 1.0 (Reference) | - |
| TT | 36 | 13.64 | 43 | 15.03 | 0.892 (0.536-1.479) | 0.640 |

[1]Adjusted for sex, age, BMI, hypertension, diabetes, tobacco smoking, TC, TG, HDL-c and LDL-c.

**Table 4.** Spearman correlation analysis between IL-8 -251A/T and environmental factors

| Variables | Spearman correlation coefficient | *P* value |
|---|---|---|
| Sex | 0.039 | 0.294 |
| Age | 0.024 | 0.390 |
| BMI | 0.035 | 0.314 |
| Hypertension | 0.059 | 0.052 |
| Diabetes | 0.013 | 0.673 |
| Tobacco smoking | 0.044 | 0.075 |
| Alcohol drinking | 0.038 | 0.106 |

P=0.507). The genotype distributions of IL-8 -251A/T and +781C/T were in agreement with the Hardy-Weinberg Equilibrium in both coronary artery disease patients and control subjects.

Multiple logistic regression analysis revealed that the TA (OR=1.633, OR=1.072-2.493) and AA (OR=2.329, 95% CI=1.421-3.820) genotypes of IL-8 -251A/T contributed to a higher risk of coronary artery disease in comparison to the TT genotype (**Table 3**). The TA+AA genotype of IL-8 -251A/T was associated with an increased risk of developing coronary artery disease when compared with the TT genotype (OR=1.845, 95% CI=1.248-2.736) in dominant model. The AA genotype of IL-8 -251A/T had a 1.722 fold risk of developing coronary artery disease when compared with the TT+TA genotype (OR=1.722, 95% CI=1.140-2.608). However, no association was observed between the IL-8 +781C/T polymorphism and development of coronary artery disease in co-dominant, dominant and recessive models.

We further analyze the interaction between IL-8 -251A/T and environmental factors, including sex, age, BMI, hypertension, diabetes, tobacco smoking and alcohol drinking, in the risk of coronary artery disease (**Table 4**). However, we did not find any interaction of IL-8 -251A/T with sex, age, BMI, hypertension, diabetes, tobacco smoking and alcohol drinking in the risk of coronary artery disease.

## Discussion

It is widely accepted that coronary artery disease is a multifactorial disease, and the pathogenesis of coronary artery disease can be promoted through a single dominant mutation leading to altering the expression of susceptibility genes. It is of importance to capture targeted genetic variations that is responsible for the functional changes of susceptibility gene. Genetic polymorphisms in coding regions can alter amino acids that might change the protein's function and influence the susceptibility to disease. In the present study, we investigate the association between IL-8 -251A/T and +781C/T polymorphisms and development of coronary artery disease, and we observed that the IL-8 -251A/T was correlated with the development of coronary artery disease risk.

IL-8 is a source of cytokines. IL-1, TNF-α, LPS and PMA could induce the synthesis of monocyte, macrophage, fibroblasts and endothelial cells and secret IL-8 [13-15]. Rus et al. reported that the IL-8 was induced by complement activation and this may contribute to increased IL-8 levels found in the atherosclerotic wall [16], and IL-8 is involved in the inflammatory event in initiation and progression of atherosclerosis [16]. The IL-8 production remains a long time in acute inflammation, and other inflammation cytokines were cleared within a few hours [17, 18]. Liu et al. has reported that the IL-8 may contribute to the recruitment of T lymphocytes and smooth muscle cells into the subendothelial space, and has an important role in the formation of atherosclerotic lesions [19]. Nair et al. reported that expression of IL-8 genes is a predictor for cardiovascular risk [20]. Therefore, the expression of IL-8 may play a role in the pathogenesis of atherosclerosis, and thus is associated with development of coronary artery disease.

Genetic polymorphism means the conversion of single-base transversion in a single base insertion/deletion, and other forms of performance [21]. The genetic polymorphism of IL-8 can change the structure of the gene expression product and quantity, and ultimately affect the function of this gene. Previous studies have reported that IL-8 gene polymorphisms are associated with development of coronary artery disease, but the results are inconsistent [11, 12, 22, 23]. Vogiatzi et al. conducted a study to investigate the role of common polymorphisms of the IL-8 gene in the development of coronary artery disease, and they showed that combination of IL-8 -251A/T and -781C/T genes is associated with the susceptibility to coronary artery disease [11]. However, He et al. did not find that the IL-8 -251A/T genetic variation could influence the development of coronary artery disease [22]. Ren et al. reported that the IL-8-251T/A gene polymorphism was not associated with the risk of coronary artery disease [12]. Yang et al. also did not find a significant association between IL-8 gene polymorphism and coronary artery disease risk [23]. In our study, we reported that IL-8 -251A/T polymorphism is independently associated with an increased risk of coronary artery disease. Such discrepancies between the results of these studies may be induced by differences in populations, selection of patients and control subjects, and sample sizes.

Several limitations in this study should be addressed. First, the subjects were recruited from one hospital, which may not have properly represented the general population. Second, the sample size was relatively small in this study, which may have reduced the statistical power to evaluate differences between the groups. Third, there may have been some interaction between the IL-8 polymorphisms and environmental factors. Therefore, further large sample size studies are required to verify the association between IL-8 polymorphisms and susceptibility to coronary artery disease.

In conclusion, our study suggests that the IL-8 -251A/T polymorphism is an independently risk factor for the development of coronary artery disease in the Chinese population. Further studies with large samples and more ethnicities are greatly needed to confirm our findings.

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## Disclosure of conflict of interest

None.

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