Association of polymorphisms in MALAT1 with risk of coronary atherosclerotic heart disease in a Chinese population

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Abstract

Background: Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) plays an important role in vascular remodeling. Down-regulation of MALAT1 can inhibit the proliferation of vascular endothelial cells and vascular smooth muscle cells, reduce cardiomyocyte apoptosis and improve left ventricular function, which is closely linked to numerous pathological processes such as coronary atherosclerotic heart disease (CAD). The aim of this study was to investigate whether polymorphisms in MALAT1 were associated with the susceptibility to CAD.

Methods: A total of 508 CAD patients and 562 age-, gender-, and ethnicity-matched controls were enrolled in this study. Four polymorphisms in MALAT1 (i.e., rs11227209, rs619586, rs664589, and rs3200401) were genotyped using a TaqMan allelic discrimination assay.

Results: The rs619586 AG/GG genotypes and G allele were associated with a reduced risk of CAD (AG/GG vs. AA: adjusted OR = 0.66, 95% CI: 0.48–0.91; G vs. A: adjusted OR = 0.68, 95% CI: 0.51–0.90). Stratification analyses showed that CAD patients with rs11227209 CG/GG, rs619586 AG/GG, and rs3200401 CT/TT genotypes exhibited lower levels of TCH (P = 0.02, 0.04, and 0.02, respectively). Moreover, CGCC haplotype was associated with a decreased risk of CAD (OR = 0.28, 95% CI: 0.16–0.48). Multivariate logistic regression analysis identified some independent risk factors for CAD, including rs619586 and rs664589. Subsequent combined analysis showed that the combined genotypes of rs619586AG/GG and rs664589CC were associated with a reduced risk of CAD (OR = 0.29; 95%CI, 0.16–0.53).

Conclusions: These findings indicate that rs619586AG/GG genotypes in MALAT1 may protect against the occurrence of CAD.

Keywords: Metastasis associated lung adenocarcinoma transcript 1, Polymorphism, Coronary atherosclerotic heart disease
8000 nucleotides in length [11]. It is located at the long arm of chromosome 11 (11q13.1) and is highly conserved in mammals [11]. Since its discovery in 2007, growing evidence has shown that MALAT1 plays a crucial role in the initiation of various cancers, such as lung cancer [12], bladder cancer [13], and prostate cancer [14]. Currently, MALAT1 has been demonstrated to implicate to the balance of vascular endothelial cell [15]. In patients with acute myocardial infarction, MALAT1 is highly expressed [16], and down-regulation of MALAT1 can decrease cardiomyocyte apoptosis and improve left ventricular function in diabetic rats [17]. These findings indicate that MALAT1 appears important not only in cancer development but also in the progression of cardiovascular diseases.

Previous studies have shown that single nucleotide polymorphisms (SNPs) in lncRNA contribute to the risk of CAD [18–24]. We therefore hypothesized that SNPs in MALAT1 may be related to the individuals’ susceptibility to CAD. To date, SNPs in MALAT1 have been investigated in colorectal cancer [25], lung cancer [26, 27], HBV-related hepatocellular carcinoma [28], as well as pulmonary arterial hypertension [29]. However, no data about the association of SNPs in MALAT1 with the risk of CAD was reported. We carried out a case-control study to analyze the association between SNPs in MALAT1 and CAD risk in a Chinese Han population.

Methods

Study population

The study population comprised individuals of Chinese Han origin examined by coronary angiography at the Yan’An Hospital Affiliated to Kunming Medical University. A total of 508 CAD patients and 562 controls were enrolled consecutively in this study between August 2011 and October 2016. CAD diagnosis was established by angiographic evidence of significant coronary stenosis (≥ 50%) in at least one major coronary artery or a history of coronary artery bypass surgery. Patients with congenital heart disease, valvular heart disease, and infectious heart disease were excluded. The controls were selected from the physical examination program during the same period at the same hospital. They were judged to be free of CAD by clinical examination and electrocardiogram. We excluded the individuals who were not Chinese Han ethnicity or had a history of heart dysfunction. All individuals enrolled lived in the southwest of China. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg at least on two distinct occasions [30]. Diabetes mellitus was defined as two fasting plasma glucose level ≥ 7.0 mmol/L. The following information was collected: age, gender, living area, ethnicity, hypertension, diabetes, total cholesterol (TCH), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The study was approved by the Institutional Review Board of the Yan’An Hospital Affiliated to Kunming Medical University. After informed consent was signed, the study subjects were allowed to donate 2–3 ml of peripheral venous blood for DNA genotyping.

SNPs selection

Using dbSNP database (https://www.ncbi.nlm.nih.gov/snp/), we selected SNPs within the region of lncRNA MALAT1 according to the criteria of minor allele frequency more than 5% in Chinese Han population. Four SNPs (i.e., rs11227209C > G, rs619586A > G, rs664589C > G, and rs3200401C > T) in lncRNA MALAT1 were identified.

Genotyping

Genomic DNA was extracted from peripheral blood using the DNA extraction Kit (Tiangen, Beijing, China) according to the manufacturer's protocol. SNPs genotyping was analyzed using the TaqMan allelic discrimination assay on an ABI 7500 Fast Real-Time System (Applied Biosystems Inc., Foster, CA, USA). The probe ID for the rs11227209, rs619586, rs664589, and rs3200401 was C_32062431_10, C_1060479_10, C_1060482_20, and C_3246069_10, respectively. The genotyping data was read blindly by two personnel. For quality control, about 5% samples were genotyped repeatedly by Sanger sequencing, and the results from the two methods were in excellent agreement.

Statistical analysis

SPSS for Windows version 19.0 was used for statistical analysis (SPSS, Chicago, IL). Categorical data was expressed as number (percentage) and analyzed using χ² test. Continuous data was expressed as mean ± standard deviation (SD) and analyzed using Student’s t test. Hardy Weinberg equilibrium (HWE) was tested by using a χ² goodness-of-fit test. Genotype and allele associations between lncRNA MALAT1 polymorphisms and CAD risk were evaluated by calculating odds ratios (ORs) and 95% confidence intervals (CIs). The ORs were adjusted for age, gender, hypertension, and diabetes mellitus. In multiple comparisons, P value was corrected with the Bonferroni correction and significance was defined as P < 0.0125 (0.05/4). Linkage disequilibrium (LD) and haplotype analysis were performed using SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). Multivariate logistic regression analysis was performed with independent variables, such as age, gender, hypertension, diabetes mellitus, TCH, TG, HDL-C, LDL-C, and MALAT1 polymorphisms. Differences were considered statistically significant at a P value < 0.05.

Results

Characteristics of the study population

The general characteristics of the study population are shown in Table 1. There was no significant difference of
Table 1 Characteristics of the study population

| Variables          | Controls, n = 562 | Patients with CAD, n = 508 | P value |
|--------------------|------------------|-----------------|---------|
| Age (years, mean ± SD) | 60.22 ± 10.73 | 61.29 ± 11.27 | 0.11    |
| Gender (%): Male:Female | 359 (63.90):203 (36.10) | 336 (66.10):172 (33.90) | 0.44 |
| Hypertension (%): Yes:No | 118 (21.00):444 (79.00) | 315 (62.00):193 (38.00) | < 0.001 |
| Diabetes mellitus (%): Yes:No | 84 (14.90):478 (85.10) | 107 (21.10):388 (79.00) | 0.01 |
| TCH (mmol/L, mean ± SD): 4.18 ± 0.59 | 4.90 ± 0.77 | < 0.001 |
| TG (mmol/L, mean ± SD): 1.38 ± 0.48 | 1.95 ± 1.06 | < 0.001 |
| HDL-C (mmol/L, mean ± SD): 1.55 ± 0.35 | 1.33 ± 0.37 | < 0.001 |
| LDL-C (mmol/L, mean ± SD): 2.50 ± 0.76 | 2.71 ± 0.70 | < 0.001 |

CAD coronary atherosclerotic heart disease, SD standard deviation, TCH total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

age and gender distribution between CAD cases and controls (P > 0.05). The frequency of hypertension and diabetes mellitus in CAD group was significantly higher than controls. Plasma levels of TCH, TG, and LDL-C were significantly higher in CAD patients, whereas HDL-C expression was significantly lower in CAD patients (P < 0.001).

Association between lncRNA MALAT1 polymorphisms and CAD risk

The distributions of the four polymorphisms in lncRNA MALAT1 among CAD patients and controls were in HWE (P > 0.05, Additional file 1: Table S1). As shown in Table 2, the rs619586 AG/GG genotypes were associated with a reduced risk of CAD compared to AA genotype (adjusted OR = 0.66, 95% CI: 0.48–0.91, P = 0.01). The lower risk of CAD was also observed in allele comparison (G vs. A: adjusted OR = 0.68, 95% CI: 0.51–0.90, P = 0.007). However, no significant association of rs11227209, rs664589, and rs3200401 with CAD risk was found. After stratification analyses according to TCH, TG, HDL-C, and LDL-C, we found that CAD patients with rs11227209 CG/GG, rs619586 AG/GG, and rs3200401 CT/TT genotypes exhibited lower levels of TCH (P = 0.02, 0.04, and 0.02, respectively) (Table 3).

Haplotype analysis

LD analysis showed that there was strong or moderate LD among the four polymorphisms. Six common haplotypes were detected: CACC, GGGT, CGCC, CAGC, GAGT, and CACT. Compared to the CACC haplotype, the CGCC haplotype was associated with a decreased risk of CAD (OR = 0.28, 95% CI: 0.16–0.48, P < 0.001) (Table 4).

Table 2 Association between lncRNA MALAT1 polymorphisms and CAD risk

| Genotypes | Controls, n = 562 (%) | CAD, n = 508 (%) | Adjusted OR (95% CI) a | Adjusted P value a |
|-----------|-----------------------|-----------------|------------------------|-------------------|
| rs11227209 | CC 438 (77.94) | 404 (79.53) | 1.00 |
|           | CG 118 (21.00) | 100 (19.69) | 1.02 (0.74–1.43) | 0.88 |
|           | CG/GG 124 (22.06) | 104 (20.47) | 1.01 (0.73–1.39) | 0.97 |
|           | C allele 994 (88.43) | 908 (89.37) | 1.00 |
|           | G allele 130 (11.57) | 108 (10.63) | 0.99 (0.74–1.33) | 0.95 |
| rs619586  | AA 404 (71.89) | 410 (80.71) | 1.00 |
|           | AG 144 (25.62) | 94 (18.50) | 0.69 (0.50–0.95) | 0.02 |
|           | AG/GG 152 (28.01) | 98 (19.29) | 0.66 (0.48–0.91) | 0.01 |
|           | A allele 952 (84.70) | 914 (89.96) | 1.00 |
|           | G allele 172 (15.30) | 102 (10.04) | 0.68 (0.51–0.90) | 0.007 |
| rs664589  | CC 410 (72.95) | 358 (70.47) | 1.00 |
|           | CT/TT 140 (24.91) | 146 (28.74) | 1.31 (0.97–1.77) | 0.07 |
|           | CT 126 (22.42) | 132 (25.98) | 1.36 (0.99–1.85) | 0.05 |
|           | CT 126 (22.42) | 132 (25.98) | 1.36 (0.99–1.85) | 0.05 |
|           | C allele 970 (86.30) | 856 (84.25) | 1.00 |
|           | T allele 154 (13.70) | 160 (15.75) | 1.23 (0.94–1.60) | 0.13 |

CAD coronary atherosclerotic heart disease, OR odds ratio, CI confidence interval. aAdjusted by age, gender, hypertension, and diabetes mellitus

Multivariate logistic regression analysis

Some variables were taken into consideration to identify if they are independent risk factors for CAD. As shown in Table 5, the risk factors were hypertension (OR = 6.14; 95%CI, 2.32–16.5; 95%CI, 1.65–2.57; P = 0.03), TCH (OR = 3.83; 95%CI, 2.96–4.96; P < 0.001), TG (OR = 3.63; 95%CI, 2.77–4.76; P < 0.001), diabetes mellitus (OR = 1.65; 95%CI, 1.06–2.57; P = 0.03), CAD risk. As shown in Table 6, the combined genotypes of rs619586 AG/GG and rs664589 CC were associated with CAD risk. As shown in Table 6, the combined genotypes of rs619586 AG/GG and rs664589 CC were associated with CAD risk.
with a reduced risk of CAD compared to the combined genotypes of rs619586AA and rs664589CC (OR = 0.29; 95%CI, 0.16–0.53, \( P < 0.001 \)).

**Discussion**

In silico analysis predicted that SNPs in *MALAT1* might have potential function. The rs619586 A allele can bind to nuclear erythroid-related factor 2 (Nrf2), and the rs11227209 C allele and rs664589 G allele can bind to transcriptional factor SP1, whereas rs619586 G, rs11227209 G, and rs664589 C allele can not. In patients with stable coronary artery disease, Nrf2/antioxidant-related element gene expression was significantly higher than controls [31]. Nrf2 knock out mice not only had a left ventricular diastolic dysfunction, but also had an accelerated progression to heart failure and a higher mortality rate [32, 33]. SP1 is an important regulator in the differentiation of vascular smooth muscle cell, which is linked to CAD development [34]. Based on the potential function, we investigated the association of SNPs in *MALAT1* with CAD risk in a Chinese population, and we found that participants with rs619586 AG/GG genotypes had a 0.66-fold decreased risk for CAD. Stratification analyses showed that CAD patients with rs11227209 CG/GG, rs619586 AG/GG, and rs3200401 CT/TT genotypes yielded lower levels of TCH. Haplotype analysis showed that CGCC haplotype was associated with a decreased risk of CAD. Multivariate logistic regression analysis identified some risk factors for CAD, including hypertension, diabetes mellitus, TCH, TG, HDL-C, LDL-C, rs619586 and rs664589. These findings suggest rs619586 AG/GG in *MALAT1* being a protective factor against CAD.

Previous studies have shown that IncRNA-related polymorphisms may contribute to the susceptibility for CAD [22, 23]. Cheng et al. reported that rs10965215 G and rs10738605 C allele in the exons of antisense non-coding RNA in the INK4 locus (*ANRIL*) conferred a significantly increased risk of myocardial infarction [22]. Shanker et al. reported that *ANRIL* rs2383206 showed

**Table 3** Stratification analysis of IncRNA *MALAT1* polymorphisms and clinical features of CAD

| Genotypes   | TCH (mmol/L) Mean ± SD | TG (mmol/L) Mean ± SD | HDL-C (mmol/L) Mean ± SD | LDL-C (mmol/L) Mean ± SD |
|-------------|------------------------|-----------------------|-------------------------|-------------------------|
|             | \( P \) value          | \( P \) value         | \( P \) value            | \( P \) value            |
| rs11227209  |                        |                       |                         |                         |
| CC          | 4.95 ± 0.74            | 1.95 ± 1.07           | 1.33 ± 0.36             | 2.69 ± 0.67             |
| CG/GG       | 4.72 ± 0.86            | 0.02                  | 1.95 ± 1.02             | 0.94                    |
| rs619586    |                        |                       |                         |                         |
| AA          | 4.94 ± 0.77            | 1.98 ± 1.07           | 1.32 ± 0.36             | 2.69 ± 0.68             |
| AG/GG       | 4.76 ± 0.79            | 0.04                  | 1.85 ± 1.01             | 0.27                    |
| rs664589    |                        |                       |                         |                         |
| CC          | 4.93 ± 0.74            | 1.97 ± 1.08           | 1.32 ± 0.36             | 2.71 ± 0.70             |
| CG/GG       | 4.84 ± 0.85            | 0.28                  | 1.92 ± 1.00             | 0.67                    |
| rs3200401   |                        |                       |                         |                         |
| CC          | 4.95 ± 0.75            | 1.98 ± 1.05           | 1.33 ± 0.36             | 2.70 ± 0.69             |
| CT/TT       | 4.77 ± 0.81            | 0.02                  | 1.87 ± 1.07             | 0.29                    |

CAD coronary atherosclerotic heart disease, TCH total cholesterol, SD standard deviation, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

**Table 4** Haplotype analysis of IncRNA *MALAT1* polymorphisms with CAD risk

| Haplotypes † | Controls (%) | CAD (%) | OR (95% CI) | \( P \) value ‡ |
|--------------|--------------|---------|-------------|-----------------|
| CACC         | 871 (77.49)  | 802 (78.94) | 1.00 |                       |
| GGGT         | 103 (9.16)   | 74 (7.28)   | 0.78 (0.57–1.07) | 0.12             |
| CGCC         | 66 (5.87)    | 17 (1.67)   | 0.28 (0.16–0.48) | < 0.001          |
| CAGC         | 31 (2.76)    | 32 (3.15)   | 1.12 (0.68–1.85) | 0.66             |
| GAGT         | 27 (2.40)    | 33 (3.25)   | 1.33 (0.79–2.23) | 0.28             |
| CACT         | 23 (2.05)    | 37 (3.64)   | 1.75 (1.03–2.97) | 0.04             |

CAD coronary atherosclerotic heart disease, OR odds ratio, CI confidence interval
†Haplotype frequencies > 3% were presented
‡\( P \) value was adjusted for multiple comparisons by Bonferroni correction

**Table 5** Logistic regression analysis for identifying risk factors of CAD

| Variables     | \( B \) | OR (95% CI) | \( P \) value |
|---------------|--------|-------------|--------------|
| Hypertension  | 1.82   | 6.14 (4.28–8.81) | < 0.001      |
| Diabetes mellitus | 0.50  | 1.65 (1.06–2.57) | 0.03         |
| TCH           | 1.34   | 3.83 (2.96–4.96) | < 0.001      |
| TG            | 1.29   | 3.63 (2.77–4.76) | < 0.001      |
| HDL-C         | –2.04  | 0.13 (0.08–0.22) | < 0.001      |
| LDL-C         | 0.57   | 1.77 (1.38–2.27) | < 0.001      |
| rs619586      | –0.45  | 0.64 (0.46–0.91) | 0.01         |
| rs664589      | 0.52   | 1.68 (1.21–2.32) | 0.002        |

CAD coronary atherosclerotic heart disease, OR odds ratio, CI confidence interval, TCH total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol
an increased risk of CAD with an adjusted OR of 2.55 [23]. Results from a separate study and meta-analysis showed that ANRIL rs4977574 G allele was more likely to increase the risk of CAD [19, 21]. Another meta-analysis was conducted by Wang and the colleagues who found ANRIL rs2383207 being a risk factor for CAD development [18]. Gao et al. reported that the risk rs2067051A allele in lncRNA-H19 was more frequent in CAD patients than in controls [20]. Shahmoradi et al. reported that the frequency of rs555172 GG genotype in IncRNA4 was significantly higher among female CAD patients compared to male patients [24]. In this study, we found a reduced risk of rs619586 AG/GG genotypes in MALAT1 with CAD. Although no evidence of association between rs64589 and CAD risk was observed in single site analysis, multivariate logistic regression analysis showed that rs664589 was a risk factor for CAD. We then performed combined analysis of rs619586 and rs664589. Interestingly, a reduced risk of CAD with the combined genotypes of rs619586AG/GG and rs664589CC was observed, suggesting that the protective effect of rs619586 is stronger than the risk polymorphism rs664589. Previous results together with our current data indicate that lncRNA-related SNPs are involved in the etiology of CAD. It is difficult to explain why the rs619586 was not registered as a significant effect locus in genome wide association studies, some possibilities should be considered, such as environmental exposure, sample size, and ethnicity.

Although the exact mechanism of rs619586 in MALAT1 influencing CAD risk is still not clear, genetic variants in lncRNA might affect its expression through altering its secondary structure and stability [22]. The expression of MALAT1 is abnormal in heart diseases, with high levels in acute myocardial infarction patients [16] and low levels in atherosclerotic plaques [35]. In vascular endothelial cells, MALAT1 silencing promoted migratory capacity and basal sprouting but inhibited the proliferation [15]. In vivo studies confirmed that genetic deletion or pharmacological inhibition of MALAT1 suppressed proliferation of endothelial cells and impaired vascularization [15]. In coronary vascular smooth muscle cells, MALAT1 knockdown reduced stiffness-dependent proliferation and migration [36]. In diabetic rats, down-regulation of MALAT1 reduced cardiomyocyte apoptosis and improved left ventricular function [17]. Based on this background, we speculated that the protective effect of rs619586 G allele in MALAT1 on CAD risk might be explained by the disruption of Nrf2 binding site, resulting in low expression of MALAT1. Further studies are necessary to clarify the mechanism.

Admittedly, the present study had a few limitations. The study design is hospital-based and restricted to a Chinese Han population, and thus the selection bias cannot be avoided. Additionally, due to moderate sample size, the association study might not have enough power to obtain the real effect. In the current study, we used chi-square to test the HWE, and found that the genotype distributions were in HWE, indicating that the selected subjects can be representative of the general population. Moreover, Quanto software was used to estimate the statistical power, and we found that power is >80% if the relative risk is set as 1.8 under a dominant genetic model. Therefore, it appears that the observed association of rs619586 AG/GG with CAD risk is unlikely to be achieved by chance.

Conclusion

This study provides the first evidence of the protective role of rs619586 AG/GG in MALAT1 on the susceptibility of CAD in the Chinese Han population. Further association studies in diverse ethnicities and functional analysis are warranted to confirm our findings.

Additional file

Additional file 1: Table S1. HWE test of lncRNA MALAT1 among CAD patients and controls. (DOCX 14 kb)

Abbreviations

ANKI: antisense non-coding RNA in the INK4 locus; CAD: coronary atherosclerotic heart disease; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; HDL-C: HDL-C; LDL-C: low-density lipoprotein cholesterol; lncRNAs: long noncoding RNAs; MALAT1: lung adenocarcinoma transcript 1; NEAT2: nuclear-enriched abundant transcript 2; OR: odds ratio; SD: standard deviation; SNPs: single nucleotide polymorphisms; TCH: total cholesterol; TG: triglyceride.

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