Lipids in Health and Disease

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FTO rs1121980 polymorphism contributes to coronary artery disease susceptibility in a Chinese Han population

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Abstract

Background The fat mass and obesity-associated protein (FTO) has been showed to be involved in the pathogenesis and progression of coronary artery disease (CAD). However, the effects of *FTO* variants on CAD risk remain poorly understood. We herein genotyped three SNPs (rs1121980, rs72803657, and rs4783818) in *FTO* to investigate the influence of *FTO* polymorphisms on individual susceptibility to CAD.

Methods Genotyping for the three SNPs (rs1121980, rs72803657, and rs4783818) was conducted in a cohort of 712 CAD cases with 349 myocardial infarction (MI) cases and 701 control participants, utilizing the polymerase chain reaction-ligation detection reaction (PCR-LDR) technique. The associations of these SNPs with CAD were analyzed using multivariate logistic regression, and the associations with lipid profiles were assessed by the Kruskal-Wallis or Wilcoxon-Mann-Whitney tests.

Results The A allele (OR = 1.26, 95% CI = 1.01–1.57, and $P = 0.044$) and the AA genotype (OR = 3.13, 95% CI = 1.53–6.38, and $P = 0.002$) of *FTO* rs1121980 were significantly associated with an elevated risk of CAD. Similarly, the A allele (OR = 1.54, 95% CI = 1.18–2.02, and $P = 0.002$) and the AA genotype (OR = 5.61, 95% CI = 2.57–12.27, and $P < 0.001$) of rs1121980 exhibited increased MI risk. This SNP also showed significant associations under recessive genetic models for both CAD and MI (OR = 3.09, 95% CI = 1.52–6.27, $P = 0.002$ for CAD; OR = 5.40, 95% CI = 2.49–11.71, $P < 0.001$ for MI). However, the other two SNPs did not show significant associations with CAD or MI risks under any genetic model tested. Stratified analyses indicated a more pronounced association of the A allele with increased CAD/MI risk among younger participants, non-smokers, and non-drinkers. Interestingly, A allele carriers in younger subjects exhibited higher triglyceride (TG) levels and lower high-density lipoprotein cholesterol (HDL-C) levels compared to non-carriers ($P < 0.05$).

Conclusions Our data provides the first evidence that the *FTO* rs1121980 polymorphism is associated with an increased risk of CAD in the Chinese population. This association is more significant in younger subjects, likely due to the elevated TG levels and reduced HDL-C levels.

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Keywords *FTO*, Single nucleotide polymorphism, Lipids, Coronary artery disease, Myocardial infarction, Risk

Introduction

Coronary artery disease (CAD) and its major complication, myocardial infarction (MI), are leading causes of morbidity and mortality in worldwide populations [1]. Both are complex disorders influenced by multiple risk factors including smoking, alcohol consumption, abnormal lipid levels, obesity, hypertension, and diabetes [2, 3]. In addition to these environmental risk factors, increasing evidence has revealed close associations of genetic variants in candidate genes with the risk of CAD and MI [4, 5]. Single nucleotide polymorphisms (SNPs), the most common form of genetic variation, have been shown to exert crucial roles in the pathogenesis of CAD/MI [6, 7].

Fat mass and obesity-associated protein (FTO) was the first identified RNA demethylase capable of removing m6A from RNA in a manner dependent on α-Ketoglutarate (α-KG) and Fe(II) [8]. It is located on chromosome 16q12.2, spans more than 400 Kb, and contains nine exons [9]. FTO was initially found to be a critical regulator in obesity and type 2 diabetes mellitus (T2DM) [10–12]. Subsequent studies have also uncovered a close association of FTO with the development of cardiovascular diseases such as atherosclerosis [13–15], coronary artery disease [16–18], and MI [19–21]. Atherosclerosis is the main cause of CAD, and FTO regulates different pathways involved in atherosclerotic progression in different cell types [13–15]. Mo et al. found that FTO reduces lipid uptake and promotes cholesterol efflux by inhibiting peroxisome proliferator-activated receptor gamma (PPARγ) and activating AMP-activated protein kinase (AMPK), respectively, thereby ameliorating macrophage foam cell formation and atherosclerosis development [13]. Besides, FTO influences endothelial cell inflammatory responses by regulating Kruppel-like factor 2 (KLF2) and endothelial NO synthase (eNOS) expression in an m6A-dependent and YT521-B homology m6A RNA-binding protein 3 (YTHDF3)-mediated manner [14]. Sun et al. found that FTO can suppress vascular smooth muscle cell senescence and thereby slow the progression of atherosclerotic plaques by stabilizing the MIS12 Kinetochore Complex Component (MIS12) protein [15]. Moreover, decreased expression of FTO has been observed in infarcted hearts [19]. Overexpression of FTO not only improves cardiac contractile function by targeting contractile protein Sarcoplasmic/Endoplasmic Reticulum Ca^{2+}-ATPase 2a (SERCA2a), but also reduces cardiac fibrosis and induces angiogenesis in the ischemic myocardium [20]. Therefore, FTO plays crucial roles in the pathophysiology of CAD and MI.

Previously, several groups demonstrated an association of *FTO* rs9939609 with the risk of CAD and MI [16–18, 21]. However, the contribution of genetic variants in *FTO* to the risk of CAD and MI remains largely unknown. In this study, we conducted a case-control study to investigate the association of the three other SNPs in the *FTO* gene (rs1121980, rs72803657, and rs4783818) with the risk of CAD/MI. Our findings revealed that the A allele of rs1121980 conferred an increased risk of CAD/MI in the Chinese Han population.

Materials and methods

Study subjects

A total of 712 patients with CAD (including 349 MI patients) and 701 control individuals were enrolled in the study from the Affiliated Hospital of Guangdong Medical University (Zhanjiang, China) and the First People's Hospital of Foshan (Foshan, China) between March 2013 and February 2021. All study subjects were genetically unrelated Han Chinese who lived in southern China. Each participant was interviewed to collect detailed information on demographic data and CAD-related risk factors. Informed consent was obtained from all participants. This study received ethical approval from the Medical Ethics Committees of both hospitals.

The diagnosis of CAD and MI was made by two independent expert cardiologists based on the coronary angiography results. CAD was defined angiographically as luminal stenosis ≥ 50% in any of the three major coronary arteries (left anterior descending artery, left circumflex artery, or right coronary artery) or in their main branches with a diameter of ≥ 2 mm [22]. The diagnosis of MI was based on clinical symptoms and characteristic electrocardiographic patterns of acute MI, along with increases in the serum levels of cardiac biomarkers (such as troponin T and creatinine kinase) [23]. Coronary angiography further supported the diagnosis by identifying the culprit lesion in any of the major coronary arteries or in the left main trunk. Patients with rheumatic heart disease, congestive heart failure, peripheral vascular disease, pulmonary heart disease, hepatic disease, chronic kidney disease, or any malignancy were excluded. Ultimately, a total of 712 patients with CAD (including 349 with MI) were included (Fig. 1). The CAD patients were newly diagnosed and previously untreated. Control subjects were also from the same hospitals for routine physical examinations during the period of case collection and were judged to be free of CAD by medical history, electrocardiography and clinical examination.

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, or the patient was under antihypertensive treatment [24]. Diabetes was diagnosed according

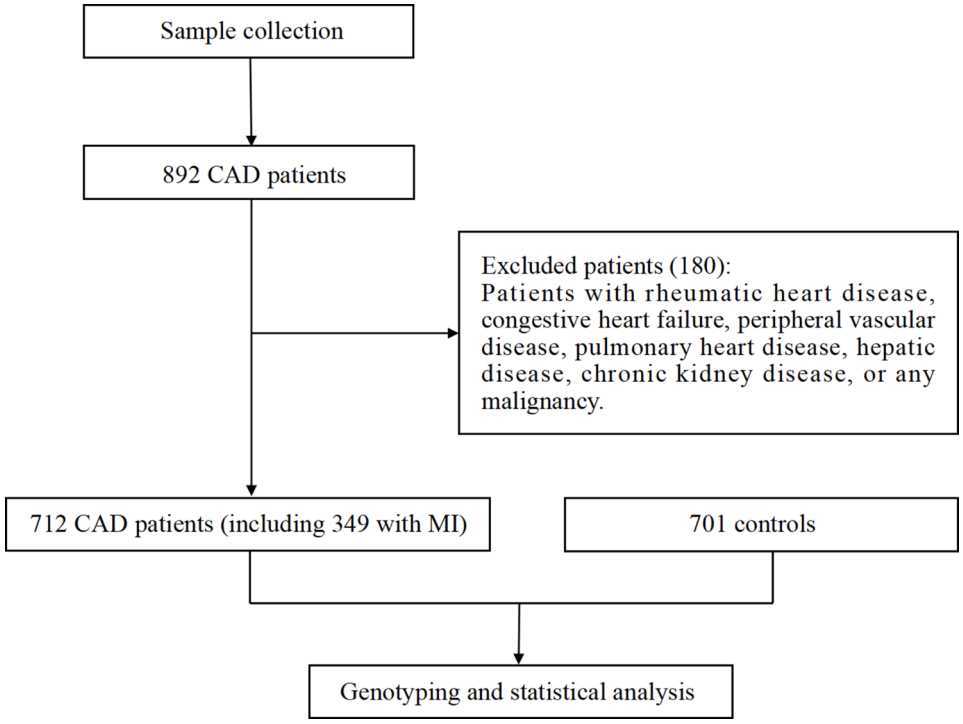

Fig. 1 Flow chart of this study

to any of the following criteria: (1) fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL); (2) 2-h PG ≥ 11.1 mmol/L (200 mg/dL) during oral glucose tolerance test (OGTT); (3) random plasma glucose ≥ 11.1 mmol/L (200 mg/dL); (4) HbA_{1c} ≥ 6.5% (48 mmol/mol) [25]. Individuals with triglyceride (TG) levels ≥ 2.3 mmol/L, total cholesterol (TC) levels ≥ 6.2 mmol/L, low-density lipoprotein cholesterol (LDL-C) levels ≥ 4.1 mmol/L, or high-density lipoprotein cholesterol (HDL-C) levels < 1.0 mmol/L were diagnosed with dyslipidemia [26]. Smoking and drinking were defined according to the criteria outlined in a previous study [27].

Analysis of biochemical parameters

Venous blood samples were obtained from each participant after at least 12 h of fasting. These samples were then centrifuged at 2000×g for 15 min after collection. Plasma glucose levels (mmol/L) were analyzed by the glucose oxidase method with an Abbott V/P Analyzer (Abbott Laboratories, USA). Enzymatic measurements of serum triglyceride (TG, mmol/L), total cholesterol (TC, mmol/L), high density lipoprotein cholesterol (HDL-C, mmol/L), and low density lipoprotein cholesterol (LDL-C, mmol/L) were performed using a chemistry analyzer (Olympus, Japan).

DNA extraction and genotyping

Genomic DNA was isolated from EDTA anticoagulated peripheral blood using a blood DNA extraction kit (TianGen Biotech, Beijing, China) according to the manufacturer's instructions. The extracted DNA was then dissolved in water and stored at -80 °C for future analysis.

Genotypes of *FTO* SNPs were determined using the polymerase chain reaction-ligase detection reaction (PCR-LDR) method (Shanghai Biowing Applied Biotechnology Company), as previously described [28]. To ensure quality control, approximately 10% of the samples were randomly selected for repeated testing and the results were 100% concordant. The sequences of primers and probes are listed in Supplementary Table S1.

Statistical analysis

Genotype frequencies in the control group were checked for the Hardy-Weinberg equilibrium (HWE) using the goodness-of-fit χ^2 test. Quantitative variables were expressed as medians with interquartile ranges, while qualitative variables were presented as percentages. Differences in demographic and clinical characteristics between the case and control groups were analyzed using the χ^2 test for categorical variables or the Wilcoxon-Mann-Whitney test for continuous variables. Risk factors for CAD, including age, gender, smoking, drinking, hypertension, diabetes, and dyslipidemia, were analyzed as covariates using logistic regression analysis. The association between genotypes and serum lipid profiles was tested by the Kruskal-Wallis test or the Wilcoxon-Mann-Whitney test. All statistical analyses were performed using SPSS (version 21), with a two-sided $P < 0.05$ was

Table 1 The characteristics of CAD, MI and controls

Variable	Controls (*n* = 701)	CAD (*n* = 712)	MI (*n* = 349)	*P*[a] vs. controls	
				CAD	MI
Age (years)	63.00 (55.00–73.00)	65.00 (56.00–73.00)	62.0 (53.50–71.0)	0.290	**0.038**[b]
Sex (male)	410 (58.5%)	495 (69.5%)	268 (76.8%)	**< 0.001**	**< 0.001**
Smoking	135 (19.3%)	330 (46.3%)	189 (54.2%)	**< 0.001**	**< 0.001**
Drinking	57 (8.1%)	134 (18.8%)	73 (20.9%)	**< 0.001**	**< 0.001**
Hypertension	264 (37.7%)	457 (64.2%)	209 (59.9%)	**< 0.001**	**< 0.001**
Diabetes	111 (15.8%)	349 (49.0%)	180 (51.6%)	**< 0.001**	**< 0.001**
Dyslipidemia	254 (36.2%)	452 (63.5%)	229 (65.6%)	**< 0.001**	**< 0.001**
SBP (mm Hg)	132.00 (120.00-145.00)	138.00 (126.00-155.00)	136.00 (125.00-153.00)	**< 0.001**	**< 0.001**
DBP (mm Hg)	73.00 (66.00–80.00)	76.00 (70.00–83.00)	74.00 (68.00–80.00)	**< 0.001**	0.397
FPG (mM)	5.35 (4.85–6.27)	6.22 (5.20–7.58)	6.23 (5.20–7.57)	**< 0.001**	**< 0.001**
TG (mM)	1.30 (0.97–1.75)	1.77 (1.18–2.45)	1.77 (1.23–2.44)	**< 0.001**	**< 0.001**
TC (mM)	4.76 (3.96–5.45)	4.77 (3.82–5.67)	4.77 (3.90–5.59)	0.952	0.927
HDL-C (mM)	1.30 (1.05–1.57)	1.15 (0.96–1.39)	1.10 (0.93–1.37)	**< 0.001**	**< 0.001**
LDL-C (mM)	2.62 (2.07–3.29)	2.91 (2.11–3.54)	2.82 (2.12–3.63)	**0.003**	**0.009**

SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

Data were presented as number (percentage) or median (interquartile range)

[a] *P* values obtained in the comparison between CAD or MI patients and controls. MI was a subgroup of CAD. The differences between the two groups were determined by the $\chi 2$ test or the Wilcoxon-Mann-Whitney test

[b] *P* values under 0.05 were indicated in bold font

Table 2 Primary information for rs1121980, rs72803657 and rs4783818 SNPs

Genotyped SNPs	rs1121980	rs72803657	rs4783818
Chr Pos (GRCh38)	16:53775335	16:53702971	16:53704371
Pos in FTO gene	Intron 1	Promoter	Intron 1
MAF[a] for Chinese (CHB and CHS)	0.185	0.173	0.125
MAF in our controls (*n* = 701)	0.168	0.180	0.133
P value for HWE[b] test in controls	0.190	0.060	0.409

[a] MAF: minor allele frequency

[b] HWE: Hardy-Weinberg equilibrium

considered statistically significant. Statistical power was assessed using the PS program (Power and Sample Size Calculations, Version 3.0.43). In our study, the statistical power is 97.6%, 97.3%, and 66.4% at a Type I error rate of 0.05 in the homozygous, recessive, and allelic models, respectively.

Results

Clinical characteristics of the study population

A total of 712 CAD cases (including 349 MI patients) and 701 control subjects were included in this study. Clinical characteristics are shown in Table 1. Compared with control subjects, CAD and MI patients had a higher proportion of males, smokers, and drinkers. A higher incidence of hypertension, diabetes, and dyslipidemia was observed in CAD and MI patients. Additionally, the CAD and MI patients had higher levels of FPG, TG, and LDL-C, but lower HDL-C levels versus control participants. Overall, these data indicated that male gender, smoking, drinking, hypertension, diabetes and dyslipidemia are pivotal risk factors for CAD/MI development in the Chinese Han population.

Multivariate associations of three SNPs in *FTO* with the risk of CAD

Three *FTO* SNPs (rs1121980, rs72803657, and rs4783818) were genotyped in CAD (n=701) and control subjects (n=712). Representative examples of the genotyping are shown in Supplementary Figure S1. Essential information for the three variants is presented in Table 2. Genotype frequency distributions for all three SNPs in the control group did not deviate from the HWE (all *P* values ≥ 0.05, Table 2), indicating no population stratification in this study. After adjusting for traditional CAD risk factors, only rs1121980 showed statistical significance, and the A allele was associated with an increased risk of CAD (OR=1.26, 95% CI=1.01–1.57, P=0.044) and MI (OR=1.54, 95% CI=1.18–2.02, P=0.002, Table 3). Consistently, the AA genotype was also associated with an increased risk of CAD (OR=3.13, 95% CI=1.53–6.38, P=0.002 for AA vs. GG; OR=3.09, 95% CI=1.52–6.27,

Table 3 Multivariate associations of three SNPs in FTO with the risk of CAD or MI

Type		Controls	Cases		OR (95% CI) [a] vs. controls		*P*[a] vs. controls	
		Number (%) *n* = 701	CAD (%) *n* = 712	MI (%) *n* = 349	CAD	MI	CAD	MI
rs1121980								
Allele	G	1166 (83.2)	1148 (80.7)	632 (79.8)	1.00	1.00	-	-
	A	236 (16.8)	274 (19.3)	160 (20.2)	1.26 (1.01–1.57)	1.54 (1.18–2.02)	**0.044**[b]	**0.002**
Genotype	GG	480 (68.5)	467 (65.6)	213 (61.0)	1.00	1.00	-	-
	AG	206 (29.4)	214 (30.1)	112 (32.1)	1.04 (0.80–1.36)	1.13 (0.81–1.59)	0.769	0.468
	AA	15 (2.1)	31 (4.4)	24 (6.9)	3.13 (1.53–6.38)	5.61 (2.57–12.27)	**0.002**	**< 0.001**
Dominant	GG	480 (68.5)	467 (65.6)	213 (61.0)	1.00	1.00	-	-
	AG + AA	221 (31.5)	245 (34.5)	136 (39.0)	1.16 (0.90–1.50)	1.37 (0.99–1.88)	0.259	0.056
Recessive	AG + GG	686 (97.9)	681 (95.7)	325 (93.1)	1.00	1.00	-	-
	AA	15 (2.1)	31 (4.4)	24 (6.9)	3.09 (1.52–6.27)	5.40 (2.49–11.71)	**0.002**	**< 0.001**
rs72803657								
Allele	T	1150 (82.0)	1189 (83.5)	572 (81.9)	1.00	1.00	-	-
	G	252 (18.0)	235 (16.5)	126 (18.1)	0.84 (0.67–1.05)	0.88 (0.67–1.17)	0.131	0.380
Genotype	TT	479 (68.3)	501 (70.4)	235 (67.3)	1.00	1.00	-	-
	TG	192 (27.4)	187 (26.3)	102 (29.2)	0.89 (0.68–1.18)	0.97 (0.69–1.38)	0.419	0.880
	GG	30 (4.3)	24 (3.4)	12 (3.4)	0.59 (0.30–1.15)	0.57 (0.24–1.34)	0.121	0.198
Dominant	TT	479 (68.3)	501 (70.4)	235 (67.3)	1.00	1.00	-	-
	TG + GG	222 (31.6)	211 (29.7)	114 (32.7)	0.85 (0.65–1.11)	0.92 (0.66–1.28)	0.232	0.606
Recessive	TG + TT	671 (95.7)	688 (96.6)	337 (96.6)	1.00	1.00	-	-
	GG	30 (4.3)	24 (3.4)	12 (3.4)	0.61 (0.31–1.19)	0.58 (0.25–1.34)	0.143	0.201
rs4783818								
Allele	A	1215 (86.7)	1211 (85.0)	604 (86.5)	1.00	1.00	-	-
	T	187 (13.3)	213 (15.0)	94 (13.5)	1.13 (0.88–1.44)	0.98 (0.71–1.35)	0.337	0.907
Genotype	AA	529 (75.5)	518 (72.8)	261 (74.8)	1.00	1.00	-	-
	AT	157 (22.4)	175 (24.6)	82 (23.5)	1.05 (0.79–1.40)	0.95 (0.66–1.37)	0.745	0.793
	TT	15 (2.1)	19 (2.7)	6 (1.7)	1.71 (0.77–3.83)	1.13 (0.36–3.53)	0.190	0.831
Dominant	AA	529 (75.5)	518 (72.8)	261 (74.8)	1.00	1.00	-	-
	AT + TT	172 (24.5)	194 (27.3)	88 (25.2)	1.10 (0.83–1.45)	0.96 (0.68–1.37)	0.515	0.840
Recessive	AT + AA	686 (97.9)	693 (97.3)	343 (98.3)	1.00	1.00	-	-
	TT	15 (2.1)	19 (2.7)	6 (1.7)	1.69 (0.76–3.77)	1.14 (0.37–3.56)	0.198	0.815

[a] Adjusted for age, gender, smoking, drinking, hypertension, dyslipidemia and diabetes

[b] *P* values under 0.05 were indicated in bold font

P=0.002 for AA vs. AG/GG, Table 3) and MI (OR=5.61, 95% CI=2.57–12.27, *P*<0.001 for AA vs. GG; OR=5.40, 95% CI=2.49–11.71, *P*<0.001 for AA vs. AG/GG, Table 3). Collectively, our data indicate that the *FTO* SNP rs1121980 is associated with CAD and MI risk, and that individuals carrying the A allele might have significantly increased CAD and MI susceptibility. However, no significant associations were observed between rs72803657 or rs4783818 and CAD/MI risk under the allelic and established genetic models.

Stratification analysis of rs1121980 with the risk of CAD

The association between the rs1121980 alleles and CAD susceptibility was assessed by stratifying the participants based on age, gender, smoking, or drinking status. As shown in Table 4, the increased risk of CAD was more notable among younger individuals (≤60 years old, OR=1.55, 95% CI=1.07–2.24, *P*=0.020), non-smokers (OR=1.38, 95% CI=1.06–1.79, *P*=0.018) and non-drinkers (OR=1.30, 95% CI=1.03–1.64, *P*=0.030) carrying the A allele. No significant associations were observed between rs1121980 alleles and CAD risk when stratified by gender. In addition, the increased risk of MI for individuals carrying the A allele was more pronounced among younger individuals (OR=1.76, 95% CI=1.14–2.73, *P*=0.011), female (OR=1.90, 95% CI=1.21-3.00, *P*=0.006), non-smokers (OR=1.74, 95% CI=1.24–2.45, *P*=0.001) and non-drinkers (OR=1.59, 95% CI=1.19–2.13, *P*=0.002).

Association analysis between *FTO* rs1121980 polymorphism and serum lipid levels

To investigate the potential explanation for the enhanced effects of the *FTO* rs1121980 polymorphism on CAD/MI risk among younger individuals, non-smokers and non-drinkers, we further analyzed the association between

Table 4 Multivariate associations of the FTO rs1121980 with the risk of CAD or MI by further stratification analysis

Variable	Allele	Controls	Cases		OR (95% CI)		*P* vs. controls	
		Number (%)	CAD (%)	MI (%)	CAD	MI	CAD	MI
Age [a]								
≤60	G	483 (84.7)	412 (79.2)	412 (79.2)	1.00	1.00	-	-
	A	87 (15.3)	108 (20.8)	108 (20.8)	1.55 (1.07–2.24)	1.76 (1.14–2.73)	**0.020**[e]	**0.011**
>60	G	683 (82.1)	736 (81.4)	294 (77.0)	1.00	1.00	-	-
	A	149 (17.9)	168 (18.6)	88 (23.0)	1.12 (0.85–1.49)	1.42 (1.00-2.02)	0.417	**0.049**
Gender [b]								
Male	G	677 (82.6)	807 (81.5)	423 (78.9)	1.00	1.00	-	-
	A	143 (17.4)	183 (18.5)	113 (21.1)	1.16 (0.87–1.55)	1.39 (0.99–1.96)	0.300	0.059
Female	G	489 (84.0)	341 (78.6)	115 (71.0)	1.00	1.00	-	-
	A	93 (16.7)	93 (21.4)	47 (29.0)	1.39 (0.97-2.00)	1.90 (1.21-3.00)	0.069	**0.006**
Smoking [c]								
Yes	G	220 (81.5)	539 (81.7)	297 (78.6)	1.00	1.00	-	-
	A	50 (18.5)	121 (18.3)	81 (21.4)	1.02 (0.67–1.54)	1.22 (0.78–1.93)	0.935	0.381
No	G	945 (83.6)	609 (79.7)	241 (75.3)	1.00	1.00	-	-
	A	185 (16.4)	155 (20.3)	79 (24.7)	1.38 (1.06–1.79)	1.74 (1.24–2.45)	**0.018**	**0.001**
Drinking [d]								
Yes	G	94 (82.5)	221 (82.5)	115 (78.8)	1.00	1.00	-	-
	A	20 (17.5)	47 (17.5)	31 (21.2)	0.78 (0.36–1.66)	1.01 (0.45–2.28)	0.515	0.975
No	G	1071 (83.3)	927 (80.2)	423 (76.6)	1.00	1.00	-	-
	A	215 (16.7)	229 (19.8)	129 (23.4)	1.30 (1.03–1.64)	1.59 (1.19–2.13)	**0.030**	**0.002**

[a] Adjusted for gender, smoking, drinking, hypertension, dyslipidemia, and diabetes

[b] Adjusted for age, smoking, drinking, hypertension, dyslipidemia, and diabetes

[c] Adjusted for age, gender, drinking, hypertension, dyslipidemia, and diabetes

[d] Adjusted for age, gender, smoking, hypertension, dyslipidemia, and diabetes

[e] *P* values under 0.05 were indicated in bold font

rs1121980 and serum lipid levels, including TG, TC, HDL-C, and LDL-C. As shown in Fig. 2, the TG levels and HDL-C levels in younger subjects were different among the GG, AG and AA genotypes ($P<0.05$). Specifically, younger individuals carrying the A allele exhibited higher TG levels and lower HDL-C levels compared to the A allele non-carriers ($P<0.05$). However, none of the above lipid profiles showed a significant association with rs1121980 in non-smokers and non-drinkers (Supplementary Table S2). These findings suggest that in younger individuals, the increased CAD risk associated with the FTO rs1121980 polymorphism may be partially mediated by lipid profiles, particularly elevated TG levels and decreased HDL-C levels. However, in non-smokers and non-drinkers, this risk is independent of lipid changes, indicating potential differences in the underlying mechanisms among these subgroups.

Discussion

CAD, as a complex multifactorial disease, is characterized by interactions between various environmental factors and genetic changes. Obesity is a well-established risk factor for CAD. It is reasonable to postulate that FTO as an obesity related locus, may confer the risk of CAD. In this study, a genetic association analysis was conducted for three *FTO* SNPs (rs1121980, rs72803657, and rs4783818) in 712 CAD patients (including 349 MI patients) and 701 controls in a Chinese Han population. Our findings revealed that the *FTO* rs1121980 polymorphism is significantly correlated with CAD risk under the allelic, homozygous and recessive models, suggesting that this polymorphism contributes to the risk of CAD.

Previously, several studies have reported that *FTO* rs1121980 is associated with obesity in German, Chinese, Indians, Swedish, and West African populations [29–33]. Another research in Japanese subjects found an association between rs1121980 and insulin resistance [34]. rs1121980 showed a strong correlation with plasma immunoreactive insulin (IRI) level and homeostasis model assessment insulin resistance (HOMA-IR) under additive and recessive models [34]. Kawajiri et al. have shown that rs1121980 is associated with an increased risk of metabolic syndrome risk in a cohort of Japanese workers [35]. Obesity, metabolic syndrome and cardiovascular disease are interrelated through a complex interplay of genetic and environmental factors [18]. A recent study have also shown that rs1121980 A allele is associated with increased risk of heart disease in Black participants in a cross-sectional study [36]. Analogously, our results showed that rs1121980 confers a significantly increased CAD risk to A allele carriers, which is in consistent with

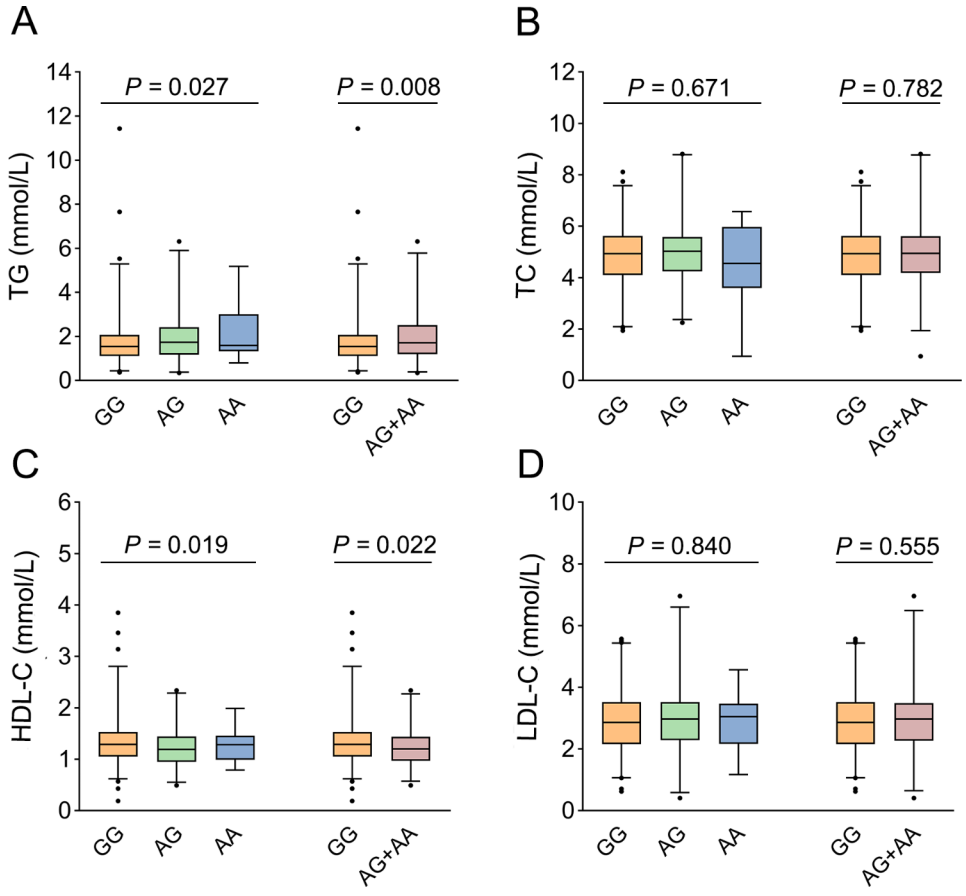

Fig. 2 Association of the FTO rs1121980 with serum lipid levels in younger subjects. The values of (**A**) triglycerides (TG), (**B**) total cholesterol (TC), (**C**) high-density lipoprotein cholesterol (HDL-C), and (**D**) low-density lipoprotein cholesterol (LDL-C) were presented as medians with interquartile ranges. The differences among the genotypes were determined by the Kruskal-Wallis test or the Wilcoxon-Mann-Whitney test

the findings from the above association analysis between rs1121980 and heart disease.

In the stratified analysis, our findings indicated that the increased risk of the rs1121980 A allele in CAD/MI was more evident among younger individuals, non-smokers and non-drinkers. The potential risk for CAD in older individuals may be more influenced by age-related factors (e.g., relative high level exposure to environmental risk factors, weak immune system) rather than direct genetic effects. Therefore, the *FTO* rs1121980 polymorphism might be more influential in premature CAD. Cigarette smoking increases inflammation, thrombosis and oxidative stress, which accelerates the progression of atherosclerosis and increases the incidence of cardiovascular dysfunction [37]. Excessive alcohol intake may be toxic to heart and contribute to the development of atherosclerosis [38]. It is plausible that smoking and alcohol consumption may mask the impact of this polymorphism on CAD risk in the present study population. Therefore, rs1121980 may have a stronger impact in individuals not exposed to these environmental risk factors, underscoring the role of genetic predisposition in CAD risk, independent of lifestyle factors.

Dyslipidemia, characterized by increased serum levels of TG, TC, LDL-C, combined with decreased levels of HDL-C, is a serious risk factor for CAD [39]. In addition, low level of HDL-C is an independent risk factor for CAD [40]. Here, we investigated the effect of *FTO* rs1121980 on TG, TC, HDL-C, and LDL-C levels. Our data indicated that younger individuals carrying the A allele had higher TG levels and lower HDL-C levels compared to those with the GG genotype, which offers a reasonable explanation for the enhanced effects of rs1121980 on CAD pathogenesis in younger individuals.

Several limitations should be addressed in this case-control study. First, all the subjects enrolled from hospitals may not fully represent the general population. Nonetheless, the genotype distribution of the controls adhered to Hardy-Weinberg equilibrium, indicating that the control group is genetically homogeneous and provides evidence that no significant stratification exists in this study population. Second, the study was conducted only in the Chinese Han population. Future research

involving diverse populations is essential to validate the association between the rs1121980 polymorphism and CAD risk.

Conclusions

In summary, this study demonstrated that *FTO* rs1121980 polymorphism was associated with the risk of CAD in a Chinese population, and the association was more evident in younger individuals, potentially due to the elevated TG levels and decreased HDL-C levels.

Abbreviations

FTO	Fat mass and obesity-associated protein
CAD	Coronary artery disease
MI	Myocardial infarction
T2DM	Type 2 diabetes mellitus
SNP	Single nucleotide polymorphism
PCR-LDR	Polymerase chain reaction-ligase detection reaction
OR	Odds ratio
CI	Confidence interval
HWE	Hardy-Weinberg equilibrium
TG	Triglyceride
HDL-C	High density lipoprotein cholesterol
TC	Total cholesterol
LDL-C	Low density lipoprotein cholesterol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02417-1.

Supplementary Material 1

Author contributions

X.M. and Y.-l.Z. performed the experimental work and analyzed the data statistically. X.M. drafted the manuscript. Y.-f.Q., Z.-f.L., H.L., J.C. and L.-l.L. helped to collect study subjects. H.-l.M. and Z.-g.W. provided suggestions to the study design. X.-d.X. financed the study. X.-d.X. designed this study and revised the manuscript. All authors reviewed and approved the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information.

Declarations

Competing interests

The authors declare no competing interests.

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References

1. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, et al. 2024 Heart Disease and Stroke statistics: a report of US and Global Data from the American Heart Association. Circulation. 2024;149(8):e347–913.
2. Akhabue E, Thiboutot J, Cheng JW, Vittorio TJ, Christodoulidis G, Grady KM, Lerakis S, Kosmas CE. New and emerging risk factors for coronary heart disease. Am J Med Sci. 2014;347(2):151–8.
3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937–52.
4. Zeng L, Moser S, Mirza-Schreiber N, Lamina C, Coassin S, Nelson CP, Annilo T, Franzen O, Kleber ME, Mack S, et al. Cis-epistasis at the LPA locus and risk of cardiovascular diseases. Cardiovasc Res. 2022;118(4):1088–102.
5. Domingues-Montanari S, Subirana I, Tomas M, Marrugat J, Senti M. Association between ESR2 genetic variants and risk of myocardial infarction. Clin Chem. 2008;54(7):1183–9.
6. Aherrahrou R, Guo L, Nagraj VP, Aguhob A, Hinkle J, Chen L, Yuhl Soh J, Lue D, Alencar GF, Boltjes A, et al. Genetic regulation of atherosclerosis-relevant phenotypes in human vascular smooth muscle cells. Circ Res. 2020;127(12):1552–65.
7. Jung C, Gene GG, Tomas M, Plata C, Selent J, Pastor M, Fandos C, Senti M, Lucas G, Elosua R, Valverde MA. A gain-of-function SNP in TRPC4 cation channel protects against myocardial infarction. Cardiovasc Res. 2011;91(3):465–71.
8. Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, Yi C, Lindahl T, Pan T, Yang YG, He C. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol. 2011;7(12):885–7.
9. Loos RJ, Bouchard C. FTO: the first gene contributing to common forms of human obesity. Obes Rev. 2008;9(3):246–50.
10. Dina C, Meyre D, Gallina S, Durand E, Korner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet. 2007;39(6):724–6.
11. Fischer J, Koch L, Emmerling C, Vierkotten J, Peters T, Bruning JC, Ruther U. Inactivation of the Fto gene protects from obesity. Nature. 2009;458(7240):894–8.
12. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, et al. A genome-wide association study of type 2 diabetes in finns detects multiple susceptibility variants. Science. 2007;316(5829):1341–5.
13. Mo C, Yang M, Han X, Li J, Gao G, Tai H, Huang N, Xiao H. Fat mass and obesity-associated protein attenuates lipid accumulation in macrophage foam cells and alleviates atherosclerosis in apolipoprotein E-deficient mice. J Hypertens. 2017;35(4):810–21.
14. Mo W, Chen Z, Zhang X, Dai G, Ma D, Pan J, Zhang X, Wu G, Fan W. N6-Methyladenosine demethylase FTO (Fat Mass and obesity-Associated protein) as a Novel Mediator of Statin effects in Human endothelial cells. Arterioscler Thromb Vasc Biol. 2022;42(5):644–58.
15. Sun J, Wang M, Jia F, Song J, Ren J, Hu B. FTO stabilizes MIS12 to inhibit vascular smooth muscle cell senescence in atherosclerotic plaque. J Inflamm Res. 2024;17:1857–71.
16. Gustavsson J, Mehlig K, Leander K, Lissner L, Bjorck L, Rosengren A, Nyberg F. FTO genotype, physical activity, and coronary heart disease risk in Swedish men and women. Circ Cardiovasc Genet. 2014;7(2):171–7.
17. Aijala M, Ronkainen J, Huusko T, Malo E, Savolainen ER, Savolainen MJ, Salonurmi T, Bloigu R, Kesaniemi YA, Ukkola O. The fat mass and obesity-associated (FTO) gene variant rs9939609 predicts long-term incidence of cardiovascular disease and related death independent of the traditional risk factors. Ann Med. 2015;47(8):655–63.
18. Shahid SU, Shabana, Rehman A, Hasnain S. Role of a common variant of Fat Mass and obesity associated (FTO) gene in obesity and coronary artery disease in subjects from Punjab, Pakistan: a case control study. Lipids Health Dis. 2016;15:29.
19. Vausort M, Niedolistek M, Lumley AI, Okninska M, Paterek A, Maczewski M, Dong X, Jager C, Linster CL, Leszek P, Devaux Y. Regulation of N6-Methyladenosine after Myocardial Infarction. Cells. 2022;11(15).

20. Mathiyalagan P, Adamiak M, Mayourian J, Sassi Y, Liang Y, Agarwal N, Jha D, Zhang S, Kohlbrenner E, Chepurko E, et al. FTO-Dependent N(6)-Methyladenosine regulates cardiac function during remodeling and repair. Circulation. 2019;139(4):518–32.
21. Doney AS, Dannfald J, Kimber CH, Donnelly LA, Pearson E, Morris AD, Palmer CN. The FTO gene is associated with an atherogenic lipid profile and myocardial infarction in patients with type 2 diabetes: a Genetics of Diabetes Audit and Research Study in Tayside Scotland (Go-DARTS) study. Circ Cardiovasc Genet. 2009;2(3):255–9.
22. Knuuti J, Ballo H, Juarez-Orozco LE, Saraste A, Kolh P, Rutjes AWS, Juni P, Windecker S, Bax JJ, Wijns W. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. Eur Heart J. 2018;39(35):3322–30.
23. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Executive Group on behalf of the Joint European Society of Cardiology / American College of Cardiology /American Heart Association /World Heart Federation Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138(20):e618–51.
24. Joint Committee for Guideline R. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. J Geriatr Cardiol. 2019;16(3):182–241.
25. American Diabetes Association Professional Practice C. 2. Diagnosis and classification of diabetes: standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S20–42.
26. Joint committee for guideline r. 2016 Chinese guidelines for the management of dyslipidemia in adults. J Geriatr Cardiol. 2018;15(1):1–29.
27. Zhou YL, Wu WP, Cheng J, Liang LL, Cen JM, Chen C, Liu X, Xiong XD. CircFOXO3 rs12196996, a polymorphism at the gene flanking intron, is associated with circFOXO3 levels and the risk of coronary artery disease. Aging. 2020;12(13):13076–89.
28. Tang SS, Xu S, Cheng J, Cai MY, Chen L, Liang LL, Yang XL, Chen C, Liu XG, Xiong XD. Two tagSNPs rs352493 and rs3760908 within SIRT6 gene are Associated with the severity of coronary artery disease in a Chinese Han Population. Dis Markers. 2016;2016:1628041.
29. Hinney A, Nguyen TT, Scherag A, Friedel S, Bronner G, Muller TD, Grallert H, Illig T, Wichmann HE, Rief W, et al. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS ONE. 2007;2(12):e1361.
30. Chiang KM, Chang HC, Yang HC, Chen CH, Chen HH, Lee WJ, Pan WH. Genome-wide association study of morbid obesity in Han Chinese. BMC Genet. 2019;20(1):97.
31. Reddy A, Venkatesh K, Sahu S, Roy PS, Datta K, Pearlin, Reddy LVK, Moghal ETB, Mullick M, Rao GHR, Sen D. Intron-specific single nucleotide polymorphisms of Fat Mass and obesity- Associated Gene in obese and overweight individuals of the Indian Adult Population- A Pilot Study. Curr Diabetes Rev. 2019;16(1):84–94.
32. Renstrom F, Payne F, Nordstrom A, Brito EC, Rolandsson O, Hallmans G, Barroso I, Nordstrom P, Franks PW, Consortium G. Replication and extension of genome-wide association study results for obesity in 4923 adults from northern Sweden. Hum Mol Genet. 2009;18(8):1489–96.
33. Adeyemo A, Chen G, Zhou J, Shriner D, Doumatey A, Huang H, Rotimi C. FTO genetic variation and association with obesity in West africans and African americans. Diabetes. 2010;59(6):1549–54.
34. Shimaoka I, Kamide K, Ohishi M, Katsuya T, Akasaka H, Saitoh S, Sugimoto K, Oguro R, Congrains A, Fujisawa T, et al. Association of gene polymorphism of the fat-mass and obesity-associated gene with insulin resistance in Japanese. Hypertens Res. 2010;33(3):214–8.
35. Kawajiri T, Osaki Y, Kishimoto T. Association of gene polymorphism of the fat mass and obesity associated gene with metabolic syndrome: a retrospective cohort study in Japanese workers. Yonago Acta Med. 2012;55(2):29–40.
36. Yu H, Armstrong N, Pavela G, Kaiser K. Sex and race differences in obesity-related genetic susceptibility and risk of Cardiometabolic Disease in older US adults. JAMA Netw Open. 2023;6(12):e2347171.
37. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43(10):1731–7.
38. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. J Am Coll Cardiol. 2007;50(11):1009–14.
39. Berberich AJ, Hegele RA. A Modern Approach to Dyslipidemia. Endocr Rev. 2022;43(4):611–53.
40. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease–the Framingham Heart Study. Can J Cardiol. 1988;4(Suppl A):A5–10.

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