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Genetic variants in *CYP11B1* influence the susceptibility to coronary heart disease

Xiaoli Huang¹, Yimin Cheng² and Na Wang^{1*}

Abstract

Background: Genetic factors are important risk factors to develop coronary heart disease (CHD). In this study, we mainly explored whether *CYP11B1* mutations influence CHD risk among Chinese Han population.

Methods: Six variants were genotyped using Agena MassARRAY system from 509 CHD patients and 509 healthy controls. The correlations between *CYP11B1* mutations and CHD risk were assessed using odds ratio (OR) and 95% confidence interval (95% CI) by logistic regression. The haplotype analysis and were ultifactor dimensionality reduction (MDR) were conducted.

Results: In the overall analysis, *CYP11B1* polymorphisms were not correlated with CHD susceptibility. In the stratified analysis, we found that rs5283, rs6410, and rs4534 are significantly associated with susceptibility to CHD dependent on age and gender ($p < 0.05$). Moreover, we also observed that rs5283 and rs4534 could affect diabetes/hypertension risk among CHD patients ($p < 0.05$). In addition, the $C_{rs4736312}A_{rs5017238}C_{rs5301}G_{rs5283}T_{rs6410}C_{rs4534}$ haplotype of *CYP11B1* reduce the susceptibility to CHD ($p < 0.05$).

Conclusions: We found that rs4534, rs6410 and rs5283 in *CYP11B1* gene influence the susceptibility to CHD, which depend on age and gender.

Keywords: Coronary heart disease, *CYP11B1*, Polymorphisms, Susceptibility, Gene

Introduction

Coronary heart disease (CHD) is a heart disease caused by coronary artery atherosclerosis that causes stenosis or occlusion of the lumen, leading to myocardial ischemia, hypoxia, or necrosis. Epidemiological research showed that more than 8.14 million people died of CHD in 2013, accounting for 50% of the total deaths from cardiovascular disease (CVD) [1]. CHD is considered to be one of the leading causes of death in people worldwide. The World health organization (WHO) predicts that CHD will account for 13.1% of all deaths by 2030 [2]. In China, CHD is the second leading cause of death from CVD,

accounting for 22% of urban and 13% of rural mortality. Moreover, the medical costs for CHD are expected to increase by 100%, posing a severe socio-economic burden on individuals and society [3]. Therefore, it is urgent to explore the pathogenesis and etiology of CHD.

It is widely known that CHD is a complex disease that is influenced by environmental and genetic factors [4]. Genetic factors are important risk factors to develop CHD, accounting for as 30~60% of the variation in the risk of CHD [5]. Large-scale studies have documented that genetic polymorphisms are significantly associated with CHD at genome-wide significance [6]. Moreover, previous studies also have reported that a significant association between candidate gene polymorphism and CHD susceptibility [7–9]. These results underscored the crucial role of genetic factors in the pathogenesis of CHD.

*Correspondence: wangna20210527@163.com

¹The Department of Cardiovascular, Xi'an Hospital of Traditional Chinese Medicine, No. 69, Fengcheng Eighth Road, Weiyang District, Xi'an 710021, People's Republic of China

Full list of author information is available at the end of the article



The 11 β -hydroxylase (*CYP11B1*) gene is located on chromosome 8q24.3, contains 9 exons and 8 introns, and consists of 503 amino acids [10]. It is a key enzyme responsible for the final step in cortisol biosynthesis [11]. At present, studies have found that the genetic variation of *CYP11B1* was involved in the occurrence and development of various diseases. Rs6410 was significantly related to the secretion of aldosterone in the Chinese population [11]. However, rs4534, rs5283, rs4736312, rs5017238 and rs5301 in *CYP11B1* have not been reported to be related to disease in the literature. The *CYP11B* family is involved in the synthesis of important steroid hormones. The genotypes of the *CYP11B1/CYP11B2* loci are in strong linkage disequilibrium [12]. The two synthesize 11 β hydroxylase and aldosterone synthase, and then synthesize steroids, which play an important role in myocardial fibrosis, hypertension and arteriosclerosis [10, 13]. Studies have shown that steroid metabolism induces the development of coronary artery disease [14]. *CYP11B1* activates the pituitary-adrenal axis by synthesizing 11 β hydroxylase, promoting the accumulation of adrenal cortical hormones, and affecting the production of aldosterone [11], which can damage cardiac or renal organs and induce hypertension [15]. Aldosterone synthase inhibitors can efficiently regulate aldosterone levels [16] by targeting *CYP11B1* with high selectivity. In addition, hypertension and diabetes are major risk factors for cardiovascular disease [15]. Based on the above studies, we hypothesized that *CYP11B1* may play a vital role in the occurrence of CHD.

Therefore, we explored the associations of *CYP11B1* polymorphisms with CHD susceptibility. These genetic variants may provide a new screening strategy for CHD among Chinese Han population.

Materials and methods

Study population

This study recruited 509 patients with CHD and 509 healthy controls from Xi'an Hospital of Traditional Chinese Medicine. The patients were diagnosed as CHD by two experienced imaging specialists according to coronary angiography examination. CHD was defined as more than 1 (\geq) atherosclerotic plaque in a major coronary artery (≥ 1.5 mm lumen diameter) causing $\geq 50\%$ luminal diameter stenosis by coronary angiography examination. Patients suffered from congenital heart disease, cardiomyopathy, malignancy, chronic inflammatory disease, and liver or kidney disease were excluded. The healthy controls were selected from the same hospital during the same period. The subjects without cardiovascular disease, autoimmune disease, malignancy, and other known disease were included in this study. The study got approval of the ethics committee of the hospital

and the experimental procedures were in accordance with the Declaration of Helsinki. Meanwhile, the informed consent signed by the subjects was obtained. Dyslipidemia is a key factor leading to the development of coronary heart disease, and coronary heart disease is related to various indicators such as triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL) and high density lipoprotein (HDL) in blood lipids [17]. There is an association between elevated serum UA levels and cardiovascular diseases such as coronary heart disease and stroke [18]. In addition, WBC often serves as an effective marker of inflammation, and elevated WBC counts are associated with common risk factors for coronary heart disease, including hypertension. An automatic blood analyzer was used to detect TC, TG, LDL, HDL and other indicators at 4 degrees Celsius. EDTA-treated anticoagulated samples are used to measure blood rheology parameters such as red blood cells (RBC) and white blood cells (WBC).

SNP selection and genotyping

According to the criteria of minor allele frequency (MAF) ≥ 0.05 , six SNPs (rs4534, rs5283, rs6410, rs4736312, rs5017238 and rs5301) of *CYP11B1* gene were selected from dbSNP database (<https://www.ncbi.nlm.nih.gov/SNP/>). Genomic DNA from peripheral blood was isolated using the DNA Extraction Kit (GoldMag, Co, Ltd, Xi'an, China). The concentration and purity of DNA were measured by NanoDrop 2000 (Thermo Scientific, USA). The selected SNPs were genotyped using Agena MassARRAY system (Agena, San Diego, CA, U.S.A.) as described previously [19, 20] and data was managed using Agena Typer 4.0 software.

Statistical analysis

Student t-test and χ^2 test were used to assess the difference in age and gender of study population. The Hardy-Weinberg equilibrium (HWE) in controls was evaluated by χ^2 test. The associations between *CYP11B1* SNPs and CHD susceptibility was analyzed using odds ratio (OR) and 95% confidence interval (CI) by logistic regression. In addition, linkage disequilibrium (LD) and haplotype analysis were evaluated by the Haploview software and the PLINK software. Multifactor dimensionality reduction (MDR) was conducted to assess the SNP-SNP interactions in the risk of CHD. The differences in clinical parameters in CHD patients were tested by one-way analysis of variance (ANOVA). Statistical power and false positive report probability (FPRP) values were calculated by the Excel spreadsheet which was offered on Wacholder's website [21]. A $p < 0.05$ was used as the threshold of significance.

Table 1 Primary characteristics of the cases and controls

Variants	Case (N = 509)	Control (N = 509)	p value
Age, years	62.16 ± 10.30	61.14 ± 9.02	0.094 ^a
> 60 (N, %)(N, %)	283 (55.6%)	284 (55.8%)	
≤ 60 (N, %)	226 (44.4%)	225 (44.2%)	
Gender			1.000 ^b
Male (N, %)	335 (65.8%)	335 (65.8%)	
Female (N, %)	174 (34.2%)	174 (34.2%)	
TG (mmol/L)	1.62 ± 1.00	1.84 ± 1.46	0.006^a
TC (mmol/L)	4.08 ± 1.08	4.76 ± 0.91	< 0.001^a
LDL (mmol/L)	3.83 ± 1.92	2.60 ± 0.73	0.157 ^a
HDL (mmol/L)	1.12 ± 0.26	1.17 ± 0.36	0.016^a
UA (μ mol/L)	300.90 ± 92.21	320.41 ± 79.40	0.001^a
Urea	5.37 ± 2.14	5.15 ± 1.31	0.056 ^a
RBC	4.82 ± 0.46	4.22 ± 0.97	< 0.001^a
WBC	10.75 ± 4.52	5.81 ± 1.51	< 0.001^a
Platelet (10 ⁹ /L)	183.04 ± 74.38	213.73 ± 59.60	< 0.001^a
HGB	129.73 ± 28.98	147.39 ± 16.33	< 0.001^a
Hypertension (N, %)	318 (62.5%)		
Diabetes (N, %)	147 (28.9%)		

Numbers in **bold** mean statistical significance

TG triglyceride; TC total cholesterol; LDL low-density lipoprotein; HDL high-density lipoprotein; UA uric acid; RBC red blood cells; WBC white blood cells; HGB hemoglobin

p^a and p^b values were calculated by t-test and χ² test, respectively

Results

General characteristics of CHD patients and healthy controls

A total of 509 CHD patients (335 males and 174 females) and 509 healthy controls (335 males and 174 females) included in this study were of Han Chinese ethnicity. The basic characteristics of participants were summarized in Table 1. No significant difference was observed in terms of age ($p=0.094$), gender ($p=1.000$), low-density lipoprotein (LDL, $p=0.157$), urea ($p=0.056$) between the case and control groups, with their mean age being 62.16 ± 10.30 and 61.14 ± 9.02 years, respectively. Among all the CHD patients, 318 patients had hypertension, and 147 patients had diabetes. Compared with the normal control group, the levels of TG, TC, HDL, UA, RBC, WBC, HGB and Platelet were significantly decreased in the CHD group.

Association of CYP11B1 polymorphisms and CHD risk

Additional File 1: Table S1 exhibited the primary information of CYP11B1 polymorphisms. The genotype frequency distributions of the selected polymorphisms of CYP11B1 were in line with HWE ($p>0.05$).

We investigated the association between CYP11B1 polymorphisms and CHD risk among Chinese Hans. As shown in Table 2, CYP11B1 polymorphisms were not

correlated with CHD susceptibility in total population under five inheritance models ($p>0.05$).

Stratification analyses

The correlation between CYP11B1 polymorphisms and CHD risk was further analyzed in different subgroups (age, gender, hypertension and diabetes). Table 3 showed that the TC (OR=1.80, 95% CI=1.19–2.74, $p=0.006$) and TT+TC genotypes (OR=1.68, 95% CI=1.13–2.50, $p=0.011$) of rs4534 was related to a significantly increased risk of CHD in younger population (age ≤ 60 years). However, the T allele (OR=0.72, 95% CI=0.53–0.96, $p=0.026$), TC genotype (OR=0.67, 95% CI=0.45–0.99, $p=0.042$), TT+TC genotype (OR=0.65, 95% CI=0.45–0.94, $p=0.023$) and the additive model (OR=0.70, 95% CI=0.52–0.95, $p=0.022$) of rs6410 showed a decreased risk of CHD patients with age ≤ 60 years.

The results of gender stratification were presented in Table 3. In females, except for the recessive model, rs6410 was correlated with a lower-risk of CHD in other models (allele: OR=0.68, 95% CI=0.51–0.92, $p=0.011$; homozygote: OR=0.44, 95% CI=0.20–0.95, $p=0.036$; heterozygote: OR=0.67, 95% CI=0.45–0.99, $p=0.044$; dominant: OR=0.63, 95% CI=0.43–0.92, $p=0.017$; additive: OR=0.66, 95% CI=0.49–0.90, $p=0.009$). However, rs4583 could elevate the susceptibility to CHD in the allele (OR=1.37, 95% CI=1.01–1.85, $p=0.040$), heterozygote (OR=1.98, 95% CI=1.32–2.97, $p=0.001$), dominant (OR=1.80, 95% CI=1.23–2.64, $p=0.003$), and additive model (OR=1.40, 95% CI=1.03–1.91, $p=0.034$).

Stratified analyses by diabetes revealed that rs5283 increased the risk of diabetes in CHD patients (allele: OR=1.45, 95% CI=1.09–1.93, $p=0.012$; heterozygote: OR=1.79, 95% CI=1.19–2.70, $p=0.006$; dominant: OR=1.78, 95% CI=1.20–2.64, $p=0.004$; additive: OR=1.47, 95% CI=1.09–1.98, $p=0.011$, Table 4). While rs4534 could reduce the risk of diabetes in CHD subjects (allele: OR=0.74, 95% CI=0.56–0.98, $p=0.032$; homozygote: OR=0.53, 95% CI=0.28–0.99, $p=0.048$; additive: OR=0.73, 95% CI=0.54–0.98, $p=0.036$). In addition, we found rs4534 was associated with a higher risk of hypertension in CHD patients (homozygote: OR=1.97, 95% CI=1.08–3.59, $p=0.026$; recessive: OR=1.84, 95% CI=1.07–3.16, $p=0.028$; additive: OR=1.33, 95% CI=1.01–1.75, $p=0.044$). There were no significant associations between rs4736312, rs5017238, and rs5301 and CHD susceptibility.

Clinical characteristics and SNPs

We also investigated the correlation between clinical characteristics and SNPs (Additional File 1: Table S2).

Table 2 Association of *CYP11B1* polymorphisms and CHD risk

SNP	Model	Genotype	Case (N, %)	Control (N, %)	OR (95% CI)	p value ^a
rs4534	Allele	C	592 (58.50%)	610 (60.04%)	1.00	0.480
		T	420 (41.50%)	406 (39.96%)	1.07(0.89–1.27)	
	Codominant	CC	165 (32.61%)	181 (35.63%)	1.00	0.582
		TT	79 (15.61%)	79 (15.55%)	1.11 (0.76–1.62)	
	Heterozygote	TC	262 (51.78%)	248 (48.82%)	1.16(0.88–1.53)	0.279
		CC	165 (32.61%)	181 (35.63%)	1.00	
	Dominant	TT+TC	341 (67.39%)	327 (64.37%)	1.15 (0.89–1.49)	0.290
		TC+CC	427 (84.39%)	429 (84.45%)	1.00	
	Recessive	TT	79 (15.61%)	79 (15.55%)	1.02(0.72–1.43)	0.928
		–	–	–	1.08(0.90–1.29)	
rs5283	Allele	G	703 (69.33%)	717 (70.71%)	1.00	0.497
		A	311 (30.67%)	297 (29.29%)	1.07(0.88–1.29)	
	Codominant	GG	240 (47.33%)	257 (50.69%)	1.00	0.978
		AA	44 (8.68%)	47 (9.27%)	0.99 (0.63–1.56)	
	Heterozygote	AG	223 (43.99%)	203 (40.03%)	1.18 (0.91–1.53)	0.214
		GG	240 (47.33%)	257 (50.69%)	1.00	
	Dominant	AA+AG	267 (52.67%)	250 (49.31%)	1.14(0.89–1.46)	0.286
		AG+GG	463 (91.32%)	460 (90.73%)	1.00	
	Recessive	AA	44 (8.68%)	47 (9.27%)	0.92(0.60–1.42)	0.708
		–	–	–	1.07 (0.88–1.29)	
rs6410	Allele	C	741 (73.08%)	712 (70.22%)	1.00	0.117
		T	273 (26.92%)	306 (30.18%)	0.86(0.71–1.04)	
	Codominant	CC	271 (53.45%)	245 (48.13%)	1.00	0.320
		TT	37 (7.30%)	42 (8.25%)	0.79 (0.49–1.26)	
	Heterozygote	TC	199 (39.25%)	222 (43.62%)	0.80(0.62–1.04)	0.100
		CC	271 (53.45%)	245 (48.13%)	1.00	
	Dominant	TT+TC	236 (46.55%)	264 (58.17%)	0.80(0.63–1.03)	0.080
		TC+CC	470 (92.70%)	467 (91.75%)	1.00	
	Recessive	TT	37 (7.30%)	42 (8.25%)	0.87(0.55–1.37)	0.540
		–	–	–	0.85 (0.70–1.03)	
rs4736312	Allele	C	850 (83.83%)	853 (83.96%)	1.00	0.936
		A	164 (16.17%)	163 (16.04%)	1.01(0.80–1.28)	
	Codominant	AA	356 (70.22%)	357 (20.28%)	1.00	0.888
		CC	13 (2.56%)	12 (2.36%)	1.06(0.48–2.36)	
	Heterozygote	CA	138 (27.22%)	139 (27.36%)	0.99(0.75–1.30)	0.926
		AA	356 (70.22%)	357 (70.28%)	1.00	
	Dominant	CC+CA	151 (29.78%)	151 (29.72%)	0.99(0.76–1.30)	0.957
		CA+AA	494 (97.44%)	496 (97.64%)	1.00	
	Recessive	CC	13 (2.56%)	12 (2.36%)	1.06(0.48–2.36)	0.880
		–	–	–	1.00(0.79–1.27)	
rs5017238	Allele	A	838 (83.47%)	850 (83.83%)	1.00	0.827
		G	166 (16.53%)	164 (16.17%)	1.03(0.81–1.30)	
	Codominant	AA	356 (70.92%)	357 (70.41%)	1.00	0.349
		GG	20 (3.98%)	14 (2.76%)	1.40(0.69–2.82)	
	Heterozygote	GA	126(25.10%)	136 (26.82%)	0.92(0.69–1.22)	0.573
		AA	356 (70.92%)	357 (70.41%)	1.00	
	Dominant	GG+GA	146 (29.08%)	150 (29.59%)	0.97(0.74–1.27)	0.804
		GA+AA	482 (96.02%)	493 (97.24%)	1.00	
	Recessive	GG	20 (3.98%)	14 (2.76%)	1.43(0.71–2.87)	0.315
		–	–	–	–	

Table 2 (continued)

SNP	Model	Genotype	Case (N, %)	Control (N, %)	OR (95% CI)	p value ^a
rs5301	Additive	–	–	–	1.02(0.81–1.28)	0.898
	Allele	C	841 (83.10%)	853 (83.79%)	1.00	
		T	171 (16.90%)	165 (16.21%)	1.05(0.83–1.33)	0.676
		Codominant	CC	349 (68.97%)	356 (69.94%)	1.00
	Homozygote	TT	14 (2.77%)	12 (2.36%)	1.16(0.53–2.55)	0.709
	Heterozygote	TC	143 (28.26%)	141 (27.70%)	1.03(0.78–1.36)	0.845
	Dominant	CC	349 (68.97%)	356 (69.94%)	1.00	
		TT+TC	157 (31.03%)	153 (30.06%)	1.04(0.79–1.36)	0.783
	Recessive	TC+CC	492 (97.23%)	497 (97.64%)	1.00	
		TT	14 (2.77%)	12 (2.36%)	1.15(0.53–2.52)	0.723
Additive	–	–	–	1.04(0.82–1.32)	0.726	

SNP single nucleotide polymorphism; OR odds ratio; CI confidence interval

p < 0.05 indicates statistical significance

^a Adjusted for age and gender

The results have shown that there was no significant correlation between the genetic variation of *CYP11B1* and clinical parameters ($p > 0.05$).

FPRP analysis

FPRP and statistical power were calculated for all positive results. As shown in Additional File 1: Table S3, at the prior probability of 0.1 and FPRP threshold of 0.2, the significant results of rs5283 remained noteworthy.

Haplotype analysis and MDR analysis

The haplotype analysis of *CYP11B1* polymorphisms and CHD risk was conducted. The results of Table 5 presented that the $C_{rs4736312}A_{rs5017238}C_{rs5301}G_{rs5283}T_{rs6410}C_{rs4534}$ haplotype was correlated with a decreased risk of CHD compared to $C_{rs4736312}A_{rs5017238}C_{rs5301}G_{rs5283}C_{rs6410}T_{rs4534}$ (OR = 0.72, 95%CI = 0.54–0.96, $p = 0.024$). And we observed an LD plot consisted of six SNPs (rs4736312, rs5017238, rs5301, rs5283, rs6410 and rs4534), as exhibited in Fig. 1.

Then, the SNP-SNP interaction was performed by MDR analysis. As shown in Fig. 2, the Fruchterman-Reingold (Fig. 2) described the interactions between these SNPs. The results of MDR model analysis of the SNP-SNP interactions are demonstrated in Table 6. The six-locus model including rs4736312, rs5017238, rs5301, rs5283, rs6410, rs4534 was the best model and driving the high-risk combinations for CHD (CVC = 10/10, OR = 1.51, 95% CI = 1.18–1.93, $p = 0.0011$).

Discussion

This is the first study to explore the effect of *CYP11B1* polymorphisms on CHD susceptibility. The results of overall analysis revealed that *CYP11B1* polymorphisms

were not correlated with CHD susceptibility. In the stratified analysis, we found that rs5283, rs6410, and rs4534 are significantly associated with susceptibility to CHD in females and individuals aged ≤ 60 years old. Moreover, we also observed that rs5283 and rs4534 could affect diabetes/hypertension risk among CHD patients. In addition, the $C_{rs4736312}A_{rs5017238}C_{rs5301}G_{rs5283}T_{rs6410}C_{rs4534}$ haplotype of *CYP11B1* reduce the susceptibility to CHD. These data highlight the crucial role of *CYP11B1* genetic variants in the development of CHD.

CYP11B1 gene is located on chromosome 8q24.3, containing 9 exons and 8 introns. It catalyzes the final step of cortisol biosynthesis. Some studies have documented that elevated cortisol is associated with a number of metabolic changes, such as hyperlipidaemia, diabetes, hypertension and abdominal adiposity [22, 23], which are correlated with CHD risk. Moreover, cortisol had a direct impact on the heart and blood vessels and played an important role in the process of atherogenesis and cardiovascular disease [24]. These results implied that *CYP11B1* may be involved in pathophysiology of CHD through regulating cortisol. Recently, some reports have studied the role of *CYP11B1* polymorphisms in disease. For example, Deng et al. indicated that rs4534 showed no significant association with autism in Chinese children [25]. Zhang et al. have shown that rs6410 was related to primary hyperaldosteronism, which is a common form of secondary hypertension [11]. Meanwhile, Wang et al. indicated that rs6410 and rs6387 haplotype is correlated with persistent postoperative hypertension in Chinese patients undergoing adrenalectomy with aldosterone-producing adenoma [13]. However, no study has investigated the effect of *CYP11B1* genetic variants on CHD. Rs6410 in *CYP11B1* can affect skeletal

Table 3 The association between CYP11B1 polymorphisms and CHD susceptibility stratified by age and gender

SNP	Model	Genotype	Age							
			> 60 years		≤ 60 years					
			Case (N, %)	Control (N, %)	OR(95% CI)	P	Case (N, %)	Control (N, %)	OR(95% CI)	P
rs6410	Allele	C	401 (71.10%)	402 (70.77%)	1.00		340 (75.56%)	310 (68.89%)	1.00	
		T	163 (28.90%)	166 (29.23%)	0.98(0.76–1.27)	0.904	110 (24.44%)	140 (31.11%)	0.72(0.53–0.96)	0.026
	Codominant	CC	144 (51.06%)	142 (50.00%)	1.00		127 (56.45%)	103 (45.78%)	1.00	
		TT	25 (8.87%)	24 (8.45%)	1.01(0.55–1.87)	0.970	12 (5.33%)	18 (8.00%)	0.54(0.25–1.18)	0.122
		TC	113 (40.07%)	118 (41.55%)	0.89(0.63–1.27)	0.525	86 (38.22%)	104 (46.22%)	0.67(0.45–0.99)	0.042
		CC	144 (51.06%)	142 (50.00%)	1.00		127 (56.45%)	103 (45.78%)	1.00	
		TT+TC	138(48.94%)	130 (50.00%)	0.91(0.65–1.27)	0.589	98(43.55%)	122 (54.22%)	0.65(0.45–0.94)	0.023
		TC+CC	257 (91.13%)	260 (91.55%)	1.00		213 (94.67%)	207 (92.00%)	1.00	
		TT	25 (8.87%)	24 (8.45%)	1.07(0.59–1.93)	0.836	12 (5.33%)	18 (8.00%)	0.65(0.30–1.38)	0.258
		Additive	-	-	0.96(0.74–1.24)	0.743	/	/	0.70(0.52–0.95)	0.022
rs4534	Allele	C	341 (60.68%)	337 (59.33%)	1.00		251 (55.78%)	273 (60.94%)	1.00	
		T	221 (39.32%)	231 (40.67%)	0.95(0.75–1.20)	0.644	199(44.22%)	175 (39.06%)	1.24(0.95–1.61)	0.117
	Codominant	CC	104 (37.01%)	95 (33.45%)	1.00		61 (27.11%)	86 (38.39%)	1.00	
		TT	44 (15.66%)	42 (14.79%)	0.99(0.59–1.65)	0.956	35 (15.56%)	37 (16.52%)	1.33(0.76–2.35)	0.321
		TC	133 (47.33%)	147 (51.76%)	0.82(0.56–1.18)	0.279	129(57.33%)	101 (45.09%)	1.80(1.19–2.74)	0.006
		CC	104 (37.01%)	95 (33.45%)	1.00		61 (27.11%)	86 (38.39%)	1.00	
		TT+TC	177 (62.99%)	189 (66.55%)	0.85(0.60–1.21)	0.372	164 (72.89%)	138 (61.61%)	1.68(1.13–2.50)	0.011
		TC+CC	237 (84.34%)	233 (85.21%)	1.00		190 (84.44%)	187 (83.48%)	1.00	
		TT	44 (15.66%)	42 (14.79%)	1.11(0.70–1.77)	0.658	35 (15.56%)	37 (16.52%)	0.93(0.56–1.54)	0.780
		Additive	-	-	0.95(0.74–1.22)	0.694	/	/	1.25(0.95–1.65)	0.108
Gender										
Gene SNP	Model	Genotype	Male				Female			
			Case (N, %)	Control (N, %)	OR(95% CI)	P	Case (N, %)	Control (N, %)	OR(95% CI)	P
rs5283	Allele	G	464 (69.46%)	458 (68.77%)	1.00		374 (68.00%)	259 (74.43%)	1.00	
		A	204 (30.54%)	208 (31.23%)	0.97(0.77–1.22)	0.784	176 (32.00%)	89 (25.57%)	1.37(1.01–1.85)	0.040
	Codominant	GG	163 (48.80%)	157 (47.15%)	1.00		118 (42.91%)	100 (57.47%)	1.00	
		AA	33 (9.88%)	32 (9.61%)	0.99(0.58–1.69)	0.977	19 (6.91%)	15 (8.62%)	1.08(0.52–2.24)	0.838
		AG	138 (41.32%)	144 (43.24%)	0.92(0.67–1.27)	0.629	138 (50.18%)	59 (33.91%)	1.98(1.32–2.97)	0.001
		GG	163 (48.80%)	157 (47.15%)	1.00		118 (42.91%)	100 (57.47%)	1.00	
		AA+AG	171(51.20%)	176 (52.85%)	0.94(0.69–1.27)	0.672	157 (57.09%)	74 (42.53%)	1.80(1.23–2.64)	0.003
		AG+GG	301 (90.12%)	301 (90.39%)	1.00		256 (93.09%)	159 (91.38%)	1.00	
		AA	33 (9.88%)	32 (9.61%)	1.03(0.62–1.72)	0.912	19 (6.91%)	15 (8.62%)	0.79(0.39–1.60)	0.514

Table 3 (continued)

Gene SNP	Model	Genotype	Male			Female			OR(95% CI)	p
			Case (N, %)	Control (N, %)	OR(95% CI)	Case (N, %)	Control (N, %)	OR(95% CI)		
rs6410	Additive	-	-	-	0.97(0.77-1.22)	0.786	/	1.40(1.03-1.91)	0.034	
	Allele	C	478 (71.56%)	478 (71.34%)	1.00		234 (67.24%)	1.00		
		T	190 (28.44%)	192 (28.66%)	0.99(0.78-1.26)	0.931	114 (32.76%)	0.68(0.51-0.92)	0.011	
	Codominant	CC	176 (52.70%)	169 (50.44%)	1.00		76 (43.68%)	1.00		
		TT	32 (9.58%)	26 (7.76%)	1.17(0.67-2.06)	0.573	16 (9.20%)	0.44(0.20-0.95)	0.036	
	Heterozygote	TC	126 (37.72%)	140 (41.20%)	0.86(0.62-1.19)	0.357	82 (47.12%)	0.67(0.45-0.99)	0.044	
		CC	176 (52.70%)	169 (50.44%)	1.00		76 (43.68%)	1.00		
	Dominant	TT + TC	158 (47.30%)	166 (49.56%)	0.91(0.67-1.23)	0.539	98 (56.32%)	0.63(0.43-0.92)	0.017	
		TC + CC	302 (90.42%)	309 (92.24%)	1.00		158 (90.80%)	1.00		
	Recessive	TT	32 (9.58%)	26 (7.76%)	1.25(0.73-2.16)	0.412	16 (9.20%)	0.53(0.25-1.12)	0.096	
		Additive	-	-	0.99(0.78-1.25)	0.907	/	0.66(0.49-0.90)	0.009	

SNP single nucleotide polymorphism; OR odds ratio; 95% CI 95% confidence interval

p values were calculated by logistic regression analysis with adjustment for age and gender

Bold values indicate statistical significance (p < 0.05)

Table 4 Associations of *CYP11B1* polymorphisms and CHD risk stratified by diabetes and hypertension

SNP	Model	Genotype	Diabetes				Hypertension			
			Case (N, %)	Control (N, %)	OR(95% CI)	p	Case (N, %)	Control (N, %)	OR(95% CI)	p
rs5283	Allele	G	187 (63.61%)	516 (71.67%)	1.00		439 (69.24%)	264 (69.47%)	1.00	
		A	107 (36.39%)	204(28.33%)	1.45(1.09–1.93)	0.012	195 (30.76%)	116 (30.53%)	1.01(0.77–1.33)	0.939
	Codominant	GG	55 (37.42%)	185 (51.39%)	1.00		150 (47.32%)	90 (47.37%)	1.00	
		AA	15 (10.20%)	29 (8.06%)	1.73(0.86–3.46)	0.123	28 (8.83%)	16 (8.42%)	1.06(0.54–2.08)	0.868
	Dominant	AG	77 (52.38%)	146 (40.55%)	1.79(1.19–2.70)	0.006	139 (43.85%)	84 (44.21%)	0.98(0.67–1.44)	0.921
		GG	55 (37.42%)	185 (51.39%)	1.00		150 (47.32%)	90 (47.37%)	1.00	
	Recessive	AA + AG	92 (62.58%)	175 (48.61%)	1.78(1.20–2.64)	0.004	167 (52.68%)	100 (52.63%)	0.99(0.69–1.4)	0.972
		AG + GG	132 (89.08%)	331 (91.94%)	1.00		289 (91.17%)	174 (91.58%)	1.00	
	Additive	–	–	–	1.29(0.67–2.49)	0.450	28 (8.83%)	16 (8.42%)	1.07(0.56–2.05)	0.842
rs4534	Allele	C	186 (63.70%)	406 (56.39%)	1.00		356 (56.33%)	236 (62.11%)	1.00	
		T	106 (36.30%)	314 (43.61%)	0.74(0.56–0.98)	0.032	276 (43.67%)	144 (37.89%)	1.27(0.98–1.65)	0.071
	Codominant	CC	57 (39.04%)	108 (30.00%)	1.00		98 (31.01%)	67 (35.26%)	1.00	
		TT	17 (11.64%)	62 (17.22%)	0.53(0.28–0.99)	0.048	58 (18.35%)	21 (11.05%)	1.97(1.08–3.59)	0.026
	Heterozygote	TC	72 (49.32%)	190 (52.78%)	0.74(0.48–1.13)	0.157	160 (50.63%)	102 (53.69%)	1.12(0.75–1.68)	0.581
		CC	57 (39.04%)	108 (30.00%)	1.00		98 (31.01%)	67 (35.26%)	1.00	
	Dominant	TT + TC	89 (60.96%)	252 (70.00%)	0.69(0.46–1.03)	0.068	218 (68.99%)	123 (64.74%)	1.26(0.86–1.87)	0.238
		TC + CC	129 (88.36%)	298 (82.78%)	1.00		258 (81.65%)	169 (88.95%)	1.00	
	Recessive	TT	17 (11.64%)	62 (17.22%)	0.64(0.36–1.14)	0.126	58 (18.35%)	21 (11.05%)	1.84(1.07–3.16)	0.028
–		–	–	0.73(0.54–0.98)	0.036	/	/	1.33(1.01–1.75)	0.044	

CHD coronary heart disease; SNP single nucleotide polymorphism; OR odds ratio; 95% CI 95% confidence interval

p values were calculated by logistic regression analysis with adjustment for age and gender

Bold values indicate statistical significance (p < 0.05)

Table 5 Haplotype analysis of *CYP11B1* polymorphisms and CHD risk

Haplotypes	Frequency in case	Frequency in control	Without adjustment		With adjustment	
			OR(95% CI)	p value	OR(95% CI)	p value
C _{rs4736312} A _{rs5017238} C _{rs5301} G _{rs5283} C _{rs6410} T _{rs4534}	0.414	0.400	1.00		1.00	
C _{rs4736312} A _{rs5017238} C _{rs5301} A _{rs5283} C _{rs6410} C _{rs4534}	0.304	0.289	1.00 (0.81–1.24)	0.99	1.00 (0.81–1.24)	1.000
A _{rs4736312} G _{rs5017238} T _{rs5301} G _{rs5283} T _{rs6410} C _{rs4534}	0.159	0.157	0.95 (0.74–1.24)	0.73	0.95 (0.73–1.23)	0.690
C _{rs4736312} A _{rs5017238} C _{rs5301} G _{rs5283} T _{rs6410} C _{rs4534}	0.107	0.144	0.72 (0.54–0.96)	0.027	0.72 (0.54–0.96)	0.024

CHD coronary heart disease; OR odds ratio; 95% CI, 95% confidence interval

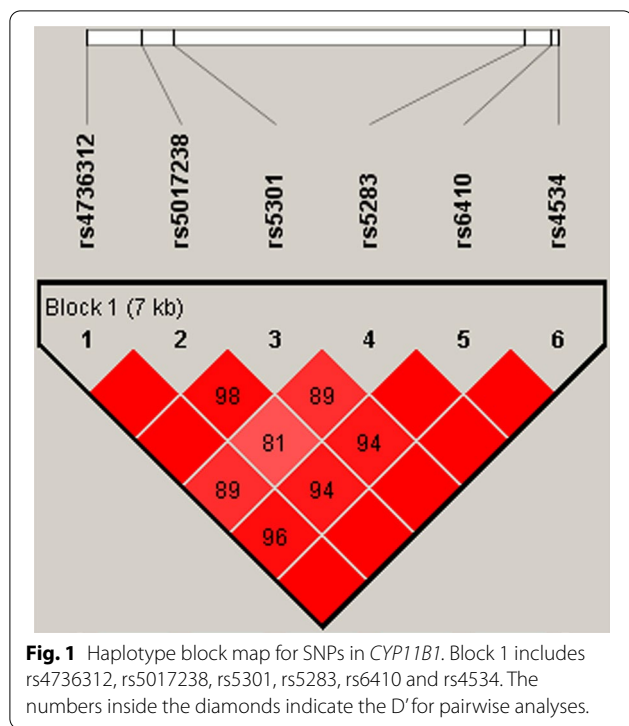
Bold values indicate statistical significance (p < 0.05)

Table 6 MDR analysis of SNP-SNP interactions

Model	Training Bal. Acc	Testing Bal. Acc	CVC	OR (95% CI)	p
rs6410	0.527	0.518	7/10	1.24 (0.97–1.58)	0.091
rs5017238,rs6410	0.542	0.492	7/10	1.39 (1.08–1.79)	0.009
rs5017238,rs6410,rs4534	0.550	0.500	7/10	1.46 (1.14–1.87)	0.003
rs5017238,rs5301,rs5283,rs4534	0.554	0.503	6/10	1.51 (1.18–1.93)	0.0011
rs4736312,rs5017238,rs5301,rs5283,rs4534	0.554	0.503	6/10	1.51 (1.18–1.93)	0.0011
rs4736312,rs5017238,rs5301,rs5283,rs6410,rs4534	0.554	0.497	10/10	1.51 (1.18–1.93)	0.0011

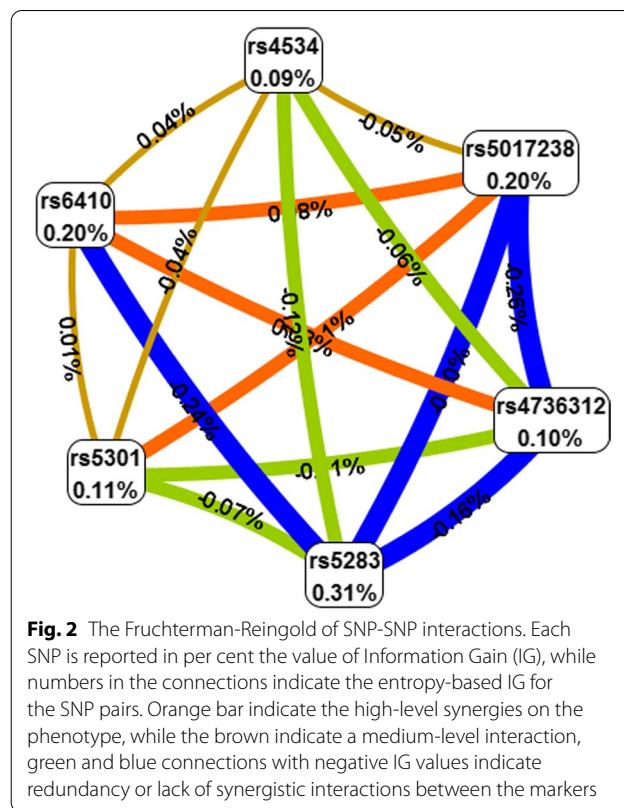
MDR multifactor dimensionality reduction; Bal. Acc. balanced accuracy; CVC cross-validation consistency; OR, odds ratio; CI, confidence interval

p < 0.05 indicates statistical significance, which was indicated in bold



maturation through variable shearing [26] and was significantly associated with trabecular bone mineral density and cross-sectional area in Caucasian elderly men [27]. However, rs5283, rs4736312, rs5017238 and rs5301 in *CYP11B1* have not been reported to be related to disease in the literature.

In the present study, we found that rs6410 reduced the susceptibility to CHD individuals aged ≤ 60 years old and females. Rs5283 not only increased the susceptibility to CHD in females, but also enhanced the risk of diabetes among CHD patients. Rs4534 also correlated with increased risk of CHD subjects younger than 60 years. Besides, in CHD patients, rs4534 enhanced the susceptibility to diabetes, whereas reduced the risk of hypertension. The rs4534 polymorphism is a missense variant located in exon 9 of the *CYP11B1* gene. Rs5283 and rs6410 are, synonymous nucleotide polymorphisms, located on the exon region. Missense and synonymous mutations have been widely studied in the development of disease by causing changes in protein expression, conformation and function [28–31]. Therefore, we presumed that these three polymorphisms can affect *CYP11B1* gene mRNA and protein by altering translation, mRNA stability or protein folding, thereby affecting CHD susceptibility. However, it should be confirmed in further functional studies.



Conclusions

To sum up, we found that a missense mutation (rs4534) and two synonymous variants (rs6410 and rs5283) in *CYP11B1* gene influence the susceptibility to CHD, which depend on age and gender. It indicated that *CYP11B1* gene variant plays an important role in the development of CHD. These mutations may provide new ideas for exploring the pathogenesis of CHD.

Abbreviations

CHD: Coronary heart disease; FPRP: False positive report probability; OR: Odds ratio; CI: Confidence intervals; MAF: Minor allele frequency; HWE: Hardy-Weinberg equilibrium; MDR: Multifactor dimensionality reduction.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12920-022-01307-8>.

Additional file 1: Basic information on SNPs of *CYP11B1*, clinical characteristics of participants with different SNPs, and false-positive reporting probability of susceptibility.

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Author contributions

NW designed, conceived, and supervised the study; XH drafted the manuscript; XH performed the DNA extraction and genotyping; YC performed the data analysis. NW polished the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the zenodo repository (<https://zenodo.org/record/6562820#YoXyqPnISUK>).

Declarations**Ethics approval and consent to participate**

This research received approval from the Ethics committee of Xi'an Hospital of Traditional Chinese Medicine, and conformed to the Declaration of Helsinki. Informed consent was acquired from each participant at recruitment after fully describing our research to them.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹The Department of Cardiovascular, Xi'an Hospital of Traditional Chinese Medicine, No. 69, Fengcheng Eighth Road, Weiyang District, Xi'an 710021, People's Republic of China. ²The Department of Obstetrics and Gynecology, The Hospital of Xi'an Shiyong University, Xi'an 710065, People's Republic of China.

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