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Original Article

Rs2021783 polymorphism in *CYP21A2* was associated with an increased risk of coronary artery disease in a Chinese Han population

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Abstract: Objective: The aim of this study was to investigate the association between *CYP21A2, CYP17A1* and coronary artery disease (CAD) in Chinese Han. Methods: We enrolled 639 unrelated people, including 316 CAD cases and 323 controls, then used TaqMan allelic discrimination real-time PCR method to genotype thetwo polymorphisms of rs2021783 in *CYP21A2* and rs4409766 in *CYP17A1*. Results: There was significant difference in the genotypic frequencies of *CYP21A2* rs2021783 between total CAD patients and controls (P=0.026). The CC genotype of rs2021783 was associated with the risk of CAD (P=0.020). For women, the T allele might be a factor protecting from CAD (P=0.016, OR=0.558, 95% CI 0.346-0.899) and the genotype of CC was associated with the development of CAD (P=0.007). There were no significant differences in men CAD. For rs4409766 in CYP17A1, no significant differences were found in genetic distributions of CYP17A1 between CAD patients and controls. Conclusion: Our data indicate that CYP21A2 was associated with CAD and rs4409766 in *CYP17A1* was not play a crucial role in the pathogenesis of CAD in Chinese Han.

Keywords: Coronary artery disease, *CYP21A2, CYP17A1*, single nucleotide polymorphism, susceptibility

Introduction

Coronary artery disease (CAD) is one of the common disease among human, which caused by the stenosis of one or more coronary arteries or occlusion caused by coronary artery atherosclerosis. It has been one of the leading causes of morbidity and mortality globally [1, 2]. As a complex multifactorial disorder, CAD is the consequence of interactions between genetic and environment risk factors [3]. More and more studies supported that genetic factors play an important role in the development of CAD, especially the genes involved in lipoprotein and lipid metabolism are playing an important role in the susceptibility of CHD [4-6].

Furthermore, Fan et al [7] suggested that the levels of steroids hormones can affect the development of CAD. *CYP17A1* and *CYP21A2* were the genes that related to synthesis of steroids hormones. *CYP17A1* encodes the cytochrome P450 super-family, which has the activities of 17-alpha-hydroxylase and 17, 20-lyase and are the precursors of sex hormones. Furthermore, large scale genome-wide association study (GWAS) among the worldwide suggested that *CYP17A1* had been reported as susceptibility loci for CAD [18, 19] and other SNPs (rs1004467, rs4919687, rs10786712) in CYP17A1 had been validated in Chinese Han population [8]. *CYP21A2* encodes 21-hydroxylase enzyme, which plays a crucial role in the synthesis of steroid hormones, and mutations in this gene may cause congenital adrenal hyperplasia, which is characterized by hypertension, hypokalemia and sexual infantilism [9].

And a large-scale genome-wide association studies (GWAS) included a total of 80,962 subjects, which selected from Chinese Han ancestry [10], reported that rs4409766 in CYP17A1 and rs2021783 in CYP21A2 had a relationship with hypertension. The two SNPs were as susceptibility loci of hypertension, and hypertension was a risk factor for CAD [3], and a possible interaction with these variants are poorly understood in patients with CAD.

Table 1. Demographic and clinical characteristics of case and control groups

	Total			Men			Women		
	CHD	Control	P	CHD	Control	P	CHD	Control	P
Number	316	323		211	202		105	121	
Age (years)	64.27±9.62	64.14±9.91	0.873	63.17±9.36	63.81±10.68	0.524	66.46±9.81	64.71±8.47	0.150
Hypertension, n (%)	208 (65.82)	194 (60.06)	0.132	129 (61.14)	116 (57.43)	0.443	79 (75.24)	78 (64.46)	0.079
Smoking, n (%)	150 (47.47)	142 (43.96)	0.374	132 (62.56)	120 (59.41)	0.059	18 (17.14)	22 (18.19)	0.838
TG	1.65±1.11	1.71±1.19	0.554	1.68±1.21	1.69±1.19	0.920	1.59±0.91	1.61±1.04	0.909
TC	4.94±1.61	4.17±1.11	0.000	4.76±1.59	4.02±0.98	0.000	5.12±1.62	4.46±1.28	0.001

TG, triglyceride; TC, total cholesterol.

As the genes play crucial roles in steroid hormone biosynthesis and have an effect on hypertension, we hypothesized that the CYP17A1 gene and CYP21A2 gene could be candidate genes predisposing to CHD development. Therefore, we selected the two single nucleotide polymorphisms (SNPs) of rs2021783 in *CYP21A2* and rs4409766 in *CYP17A1* and designed a case-control study to explore their relationship with CAD in a Chinese Han population.

Materials and methods

Subjects

We recruited age-matched 639 participants (316 CAD patients, 64.27±9.62 years; 323 controls, 64.14±9.91 years) from the Affiliated Hospital of Qingdao University between May 2014 and June 2016. Our study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University and all participants had signed the informed consent.

The inclusion criteria of CAD were the diameter stenosis of more than 50% in at least one coronary artery through coronary angiography. At least two cardiologists had judged the angiography results. The exclusion criteria of participates is people with congenital heart disease, multiple organ failure syndrome, cancer, bleeding disorders, and severe liver or kidney disease. The control group is composed of the people who had a less than 50% stenosis in the coronary artery, or did not have any atherosclerotic vascular disease. In order to further investigate the association between CYP21A2, CYP17A1 variants and CAD, were divided all CAD patients into two subgroups men CAD patients (n=211) and women CAD patients (n=105).

We also collected the demographic and clinical characteristics of all participates, such as age, hypertension, smoking, and results of laboratory examinations, which was shown in **Table 1**.

Genetic studies

Genomic DNA was extracted from 200 ml peripheral blood using the TIANamp Genomic DNA kit (Tiangen, China). The polymorphisms of rs2021783 and rs4409766 were genotyped using the TaqManallelic discrimination real-time PCR method. For rs2021783 the primers sequence were 5'-GGCAGGAGGACTGCTTGAAC-3' (forward) and 5'-AGCCTCATCATGACTTGGTT-GA-3' (reverse); for rs4409766 primers sequence were 5'-ATGTGTCTGGTCTGTTTATGTAGGA-AA-3' (forward) and 5'-AAAGGGAACATAGGCAC-TTACATCA-3' (reverse). The Taqman probes and primers were synthesized by Applied Biosystems of Life Technologies (ABI, New York, USA). The polymerase chain reaction (PCR) was concluded in 25 μL reaction mixture, which contains 20×SNP Genotyping Assay 1.25 μL, 2×PCR Master Mix 12.5 μL, and 11.25 μL DNA and DNase-free water. Then the reactions were carried out by C1000TM thermal cycler system. The reaction condition was 95°C for 3 min, followed by 45 cycles of 95°C for 15 s and 60°C for 1 min, and discrimination of genotypes was conducted using Bio-Rad CFX manager software 3.0.

Statistical analysis

Statistical analysis was performed by using SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA). Hardy-Weinberg equilibrium was used to test in the control group genotypes. The clinical characteristics of CAD patients and controls were analyzed by Pearson's χ^2 test or Student *t*-test, and were presented by the mean ± standard error (SE) or percentage. Allele and genotype frequencies were calculated using the Pearson's χ^2 test. Oddsratios (ORs) and 95% confidence intervals (CIs) were used to express

Table 2. Genotypic and allelic distributions in CAD group and control group

		CAD	Control	X^2	P	OR	95% CI
rs2021783							
Genotyping	TT	13	10				
	TC	79	112				
	CC	224	201	7.262	0.026		
Allele	T	105	132				
	C	527	514	3.085	0.079	0.766	0.584-1.030
	TT	13	10				
	TC+CC	303	313	0.477	0.490	1.343	0.580-3.109
	CC	224	201				
	TT+TC	92	122	5.374	0.020	1.478	1.061-2.057
rs4409766							
Genotyping	TT	160	156				
	TC	134	133				
	CC	22	34	2.549	0.280		
Allele	T	454	446				
	C	178	202	1.387	0.239	1.155	0.909-1.469
	TT	160	156				
	TC+CC	156	167	0.349	0.555	1.098	0.805-1.743
	CC	22	34				
	TT+TC	294	289	2.538	0.111	0.636	0.363-1.114

Table 3. Genotypic and allelic distributions in men subgroup and control group

		Men					
		CAD	Control	X^2	P	OR	95% CI
rs2021783							
Genotyping	TT	9	4				
	TC	55	65				
	CC	147	133	3.262	0.196		
Allele	T	73	73				
	C	349	331	0.084	0.722	0.948	0.663-1.356
	TT	9	4				
	TC+CC	202	198	1.768	0.184	2.205	0.668-1.278
	CC	147	133				
	TT+TC	64	69	0.692	0.405	1.192	0.788-1.801
rs4409766							
Genotyping	TT	105	92				
	TC	95	90				
	CC	11	20	3.411	0.182		
Allele	T	305	274				
	C	117	130	1.953	0.162	1.237	0.918-1.667
	TT	105	92				
	TC+CC	106	110	0.736	0.391	1.184	0.805-1.743
	CC	11	20				
	TT+TC	200	182	3.266	0.071	0.501	0.233-1.073

the risk between CAD and control groups. The level of *p* value less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Table 1 showed the comparison of demographic and clinical characteristics between total CAD patients, men CAD patients, women CAD patients and the controls. No significant differences were found in age, hypertension, smoking, the level of TG between total subjects, men subgroup and women subjects and controls (all, P>0.05). However, CAD group had higher levels of TC (P<0.001) compared with control group. The same higher levels of TC were also found in men/women subgroup.

Analysis of genotypic and allelic frequencies

The genotypic distributions of the two SNPs in control groups were in accordance with the Hardy-Weinberg equilibrium (for rs2021783, χ^2=1.423, P=0.233; for rs4409766, χ^2=0.502, P=0.478). The genotypic and allelic frequencies of CYP17A1 (rs4409766) and CYP21A2 (rs2021783) polymorphisms were shown in (**Tables 2**-**4**).

There was significant difference in the genotypic frequencies of CYP21A2 rs2021783 between total CAD patients and controls (χ^2= 7.262, P=0.026). Then subdividing these genotypes into TT/TC+CC group and CC/

Table 4. Genotypic and allelic distributions in women subgroup and control group

	Women					
	CAD	Control	X^2	P	OR	95% CI
rs2021783						
Genotyping	4	6				
	24	47				
	77	68	7.313	0.026		
Allele	32	59				
	178	183	5.844	0.016	0.558	0.346-0.899
	4	6				
	101	115	0.176	0.675	0.759	0.208-2.766
	77	68				
	28	53	7.178	0.007	2.143	1.222-3.761
rs4409766						
Genotyping	55	64				
	39	43				
	11	14	0.104	0.952		
Allele	149	171				
	61	71	0.005	0.946	1.014	0.675-1.523
	55	64				
	50	57	0.006	0.939	0.980	0.580-1.654
	11	14				
	94	107	0.068	0.794	0.894	0.387-2.065

TC+TT group, we found a significant difference between total CAD patients and controls in CC/TC+TT group (χ^2=5.374, P=0.020, OR=1.478, 95% CI 1.061-2.057). The CC genotype of rs2021783 was associated with the risk of CAD. To further investigate the association between the variants of CYP21A2 and CAD, we divided total CAD patients into men and women CAD groups. For women CAD group, the distribution of genotypic and allelic frequencies showed significant difference between women CAD patients and controls (P=0.026 by genotype; P=0.016 by allele). For women, the T allele might be a factor protecting from CAD (OR=0.558, 95% CI 0.346-0.899) and the genotype of CC was associated with the development of CAD (P=0.007). But for men, neither genotypes nor alleles was found significant difference between two groups (all, P>0.05).

No significant differences were found in the genotype and allele frequencies of rs4409766 in *CYP17A1* between total CAD cases and controls (χ^2=2.549, P=0.280 by genotype; χ^2=1.387, P=0.239, OR=1.155, 95% CI 0.909-1.469 by allele; TT vs. TC+CC, χ^2=0.349, P=0.555, OR=1.098, 95% CI 0.805-1.743; CC vs. TT+TC, χ^2=2.538, P=0.111, OR=0.636, 95% CI 0.363-1.114). Furthermore, no significant differences were found in two subgroups (For men subgroup, χ^2=3.411, P=0.182 by genotype; χ^2=1.953, P=0.162, OR=1.237, 95% CI 0.918-1.667 by allele; TT vs. TC+CC, χ^2=0.736, P=0.391, OR=1.184, 95% CI 0.805-1.743; CC vs. TT+TC, χ^2=3.266, P=0.071, OR=0.501, 95% CI 0.233-1.073; For women subgroup, χ^2=0.104, P=0.952 by genotype; χ^2=0.005, P=0.946, OR=1.014, 95% CI 0.675-1.523 by allele; TT vs. TC+CC, χ^2=0.006, P=0.939, OR=0.98, 95% CI 0.580-1.654; CC vs. TT+TC, χ^2=0.068, P=0.794, OR=0.894, 95% CI 0.387-2.065).

Discussion

CAD is one of the most common types of heart disease. Even though the dramatic advances in the use of diagnosing and curing CAD, the death rate of CAD and its complications is still a leading cause of morbidity and mortality among the worldwide, especially in developing countries [1, 2]. As we all know, many factors can affect the development of CAD, such as the age, gender, smoking, hypertension, BMI, diabetes mellitus (DM), especially the genetic factors [3]. Increasing evidences supported that sex hormones had critical roles in the maintenance of cardiovascular health [4, 5], the levels of sex hormones can affect the development of cardiovascular diseases[6]. CYP17A1 and CYP21A2 gene were known to play an important role in the metabolic pathways of steroid hormones.

The *CYP17A1* located on chromosome 10q24.3 and encoded the cytochrome P450 proteins, which had 17alpha-hydroxylase and 17, 20-lyase activities. They converted pregnenolone to 17α-OH-pregnenolone and 17α-OH-progesterone, then converted these into dehydroepiandros-terone (DHEA) and androstenedione [11], which were involved in the synthesis of steroid hormones (estrogen, testosterone, and androgens). Accumulating evidence indicated that CYP17A1 played a role in multiple complex

diseases, such as prostate cancer [12], breast cancer [13], ovarian cancer [14] and endometrial cancer [15, 16]. The CYP21A2 gene located on chromosome 6p21.3, encodes 21-hydroxylase enzyme. The enzyme had the activity that could convert 17-hydroxyprogesterone to 11-deoxycortisol, and progesterone to deoxycorticosterone, which were precursors for cortisol and aldosterone [17]. Deficiency of these enzyme caused congenital adrenal hyperplasia (CAH), which characterized by hypertension, hypokalaemia and sexual infantilism [17]. Therefore, the mutations in gene of CYP17A1 and CYP21A2 could loss the enzyme activity then affect the synthesis of steroid hormones. Some studies have suggested that the levels of steroid hormones could affect the development of cardiovascular diseases [7]. As we all know, the relationship between CYP genetic polymorphism and CAD has been reported [5], Dai et al [9] found that rs1004467, rs4919687, rs10786712 of CYP17A1 gene are associated with CAD in Han population of China, which recruited 490 CAD patients and 507 controls. However, no study about CYP21A2 has been suggested that the gene is associated with CAD.

With the development of the society, genome-wide association studies (GWAS) had become a powerful method in identifying genetic variants that predispose individuals to diseases. Lu et al found the strongest association with rs4409766 in CYP17A1 ($P=7.33\times10^{-13}$) and rs2021783 in CYP21A2 ($P=3.53\times10^{-11}$) in a large-scale GWAS of hypertension, which included a total of 80,962 subjects with Chinese Han ancestry [10]. And, in addition to genetic factors, other metabolic factors includedBody-mass index (BMI), obesity and steroid metabolism imbalance that substantially increase the risk for the occurrence of CAD [18, 19].

As the genes associated with the synthesis of steroid, CYP17A1 and CYP21 A2 may play a role in the development of CAD. Therefore, we selected rs4409766 (CYP17A1) and rs2021783 (CYP21A2) to explore the associations with CAD, which had been identified by several genome-wide association study (GWAS) as the genetic variant associated with hypertension in Chinese population [10, 20]. As tag-SNPs of CYP gene, rs4409766 and rs2021783 locate in the intron variant of the related gene. We evaluated the two SNPs that had relationship with the synthesis of steroid hormones, whether were associated with the development of CAD. To the best of our knowledge, this is the first study that provides data on association of SNPs with CAD risk in Chinese Han population.

In our study, we conducted the genotypes of 316 CAD patients (221 men and 105 women) and 323 age-matched controls. There was significant difference in the genotypic frequencies of *CYP21A2* rs2021783 between total CAD patients and controls. Compared with TC+TT, people with genotype of CC showed a 1.478 fold risk of developing CAD. For women CAD group, the T allele might be a factor protecting from CAD (OR=0.558, 95% CI 0.346-0.899) and the genotype of CC was associated with the development of CAD. However, the significant differences were not found in men CAD group. For rs4409766, we did not find any significant in genotypic and allelic frequencies in *CYP17A1* between CAD and control groups, even in the men or women subgroups.

There were several limitations that should be noted. Firstly, all the participants were recruited from Shandong province in North of China; the results may have regions or ethnics limitation. Secondly, the size of our sample is not large enough. Finally, CAD is a complex multifactorial disease and was the consequence of interaction between genetic and environment risk factors and their interaction. Therefore, studies with more SNPs and functional are needed to be verified in different races and regions to explore the association between *CYP17A1* polymorphisms and CAD.

In conclusion, our data suggest that CYP21A2 was associated with CAD and the genotype of CC was associated with the risk of CAD. For women, the T allele might be a factor protecting from CAD and the genotype of CC was associated with the development of CAD. rs4409766 in CYP17A1 didnot play a crucial role in the risk of CAD in Chinese Han.

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Disclosure of conflict of interest

None.

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