The Relationship between CYP4A11 and CYP4F2 Gene Polymorphisms and Coronary Heart Disease in Chinese: A Metaanalysis

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Abstract

Aim: To investigate the correlation between CYP4A11 and CYP4F2 polymorphisms and coronary heart disease in Chinese. Methods: The related research data of CYP4A11 and CYP4F2 gene polymorphism and coronary heart disease were searched through the Internet and analyzed by Review Manager 5.3 software. Results: A total of 6 articles were included. Meta-analysis shows that there is heterogeneity between CYP4A11 gene rs3890011 genotype and coronary heart disease risk research. The CC and GG genotypes of CYP4A11 gene rs3890011 had statistical significance with the occurrence of coronary heart disease. The AA and AG genotypes of CYP4A11 gene rs9332978 had statistical significance with the occurrence of coronary heart disease. TT, CT and CC genotypes of CYP4A11 gene rs1126742 had no statistical significance with coronary heart disease. Heterogeneity exists in studies on CC and TT genotypes of CYP4F2 gene rs2108622 and the risk of coronary heart disease. The CC and TT genotypes of CYP4F2 gene rs2108622 had statistical significance with the occurrence of coronary heart disease, while the CC, CT and TT genotypes of CYP4F2 gene rs1558139 had no statistical significance with the occurrence of coronary heart disease. Conclusion: Based on the results of this paper, CYP4A11 and CYP4F2 gene polymorphisms are associated with coronary heart disease in Chinese.

Keywords

CYP4A11; CYP4F2; Gene Polymorphism; Coronary Heart Disease; Meta-analysis.

1. Introduction

Coronary heart disease (CHD) is a heart disease caused by narrowing or obstruction of vascular lumen caused by atherosclerotic lesions in coronary arteries, resulting in myocardial ischemia, hypoxia or necrosis. According to the investigation report of the World Health Organization, coronary heart disease is one of the main causes of human death, and the incidence rate is increasing year by year, and its treatment, especially prevention, is extremely important.

Cytochrome 450 is a heme thioferrin enzyme system that exists widely in organisms, and it plays a very important role in the metabolism of exogenous and endogenous compounds [1]. Studies [2-3] confirmed that CYP catalyzed arachidonic acid (AA) to produce epoxy eicosatrienoic acid (EETs), 20-hydroxy 24 enoic acid (20-HETEs) and prostacyclin. 20-HETEs plays an important role in regulating vascular dynamics by mediating vasoconstriction and vascular remodeling caused by angiotensin II, norepinephrine and Pituitrin. Among them, CYP4A11 and CYP4F2 gene polymorphisms can affect the metabolism of AA to produce 20-HETEs. There are many mutation sites in CYP4A11 and CYP4F2, such as rs9332978, rs3890011, rs1126742, rs2108622, rs1558139 and so on. Studies have found that these loci may be associated with coronary heart disease, but do not come to a consistent conclusion, so it is of important scientific value and extensive social benefits to study the relationship between CYP4A11 and CYP4F2 gene polymorphism and coronary heart disease in Chinese population. The purpose of this study is to

enlarge the sample size by summarizing the literature on the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease in Chinese, hoping to find out the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease in Chinese more accurately.

2. Materials and Methods

2.1 Search Strategy

The five researchers conducted a comprehensive search of Chinese (CNKI, VIP, wanfang) and English (PubMed, Web of Science) databases to find relevant Chinese and English research articles published before December 15, 2020 (the date of completion of the search). A literature review was performed using the terms "CYP4A11", "CYP4F2", "Gene polymorphism" AND " coronary heart disease ".

2.2 Study selection

Inclusion criteria: (1) Literature on the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease; (2)Each article reported the distribution of genotype frequency in coronary heart disease group and control group;(3)The genotypic distribution of each was in accordance with the genetic balance of Hardy-Weinberg.

Exclusion criteria: (1) Literature that cannot provide valid data;(2)Literature published with duplicate data; (3) Non-Chinese and English literature.

Completed independently by 5 researchers, they searched the literature by title or key word respectively to obtain the full text. By reading the abstract, the documents that did not meet the standard were excluded, and the full text was read to further exclude the literature that did not meet the standards and the research quality was low.

2.3 Quality assessment

Potential risks of bias were evaluated, using the Cochrane tool developed for this purpose [4]. This tool assesses bias in different domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and study staff (performance bias); blinding of outcome assessors (detection bias); incomplete results data (attrition bias); selective reporting of results (reporting bias); and other sources of bias. Each domain was rated as "High", "Low" or "Unclear" depending on the judgment of each author following the recommendations.[5]

2.4 Literature data analysis

Make Excel table and extract relevant data from the final included literature: author, publication time, nationality, sex, number of genotypes, distribution of genotypes in cases and controls.

Review Manager 5.3 (http://ims.cochrane.org/revman/download) was used for Meta analysis, and the combined effect amount of each genotype combination and 95% confidence interval (95% CI) were calculated. Using I² statistics for heterogeneity test, when I² < 50%, it is considered that there is no heterogeneity among the studies, and the fixed effect model is used to analyze the literature data; when I² > 50%, it is considered that there is heterogeneity. Random effect model is used. P \leq 0.05 means that the difference is statistically significant, and forest map is used for statistical description. Publication bias was evaluated by funnel chart.

3. Result

3.1 Literature screening results and quality evaluation results

A total of 70 articles were obtained from each literature database. After reading the full text to exclude the literature that did not meet the requirements, lack of inter-group data and duplicated data, 6 articles and 5535 subjects were obtained. As shown in Figure 1.

The basic characteristics of the literature are included. As shown in Table 1.

Included in the quality evaluation of the literature, see the quality evaluation chart. As shown in Figure 2.

					CAD		Con	trol	
Name	Time	Nation	Sex	Genotype	E E E E E E		Energe		
				0000070 + (+	Events	Iotal	Events	Iotal	
				rs9332978 A/A	172	276	120	180	
		Han	Men	rs9332978 A/G	90	276	54	180	
				rs9332978 G/G	14	276	6	180	
				rs9332978 A/A	51	85	94	135	
		Han	Vomen	rs9332978 4/G	28	85	38	135	
		man	"Onen	ma0220070 A/G	<u> </u>	00	~ ~	125	
				189332978 6/6	0	00	 	100	
				rs9332978 A/A	210	277	97	132	
		Uigur	Men	rs9332978 A/G	61	277	29	132	
				rs9332978 G/G	6	277	6	132	
				rs9332978 A/A	35	54	36	50	
		11: 71.17	Wanan	ma0222070 #/C	10	54	12	50	
		UISUL	women	159002970 A/G	10	54	10	50	
				rs9332978 G/G	1	34	1	50	
				<u>rs3890011 C/C</u>	78	276	46	180	
		Han	Men	<u>rs3890011 C/G</u>	121	276	102	180	
				rs3890011 G/G	77	276	32	180	
				rs3890011 C/C	19	85	42	135	
		Han	Women	re3890011 C/C	45	85	66	135	
		IIaII	"Onen	130000011 0/0		05	00	105	
Zhenvan Fu	2012			rs3890011 G/G	21	85	27	135	
				<u>rs3890011 C/C</u>	107	277	53	132	
		Uigur	Men	<u>rs3890011 C/G</u>	122	277	60	132	
				rs3890011 G/G	48	277	19	132	
				rs3890011 C/C	17	54	21	50	
		ILian	Wanan	ne3990011 C/C	21	54	20	50	
		orgur	"omen		40	4	20	50	
				rs3890011 G/G	16	54	у	50	
				<u>rs1126742 T/T</u>	186	276	118	180	
		Han	Men	rs1126742 T/C	72	276	56	180	
				rs1126742 C/C	18	276	6	180	
				re1126742 T/T	59	85	84	135	
			117		10	00	40	105	
		Han	women	rs1126/42 1/C	19	85	43	135	
			rs1126742 C/C	7	85	8	135		
			rs1126742 T/T	183	277	93	132		
	Uigur	Men	rs1126742 T/C	85	277	35	132		
		-		rs1126742 C/C	9	277	4	132	
				me1126742 T/T	22	54		50	
			217	1100742 1/1		54		50	
		Ulgur	women	rs1120/42 1/C	1/	54	14	50	
				rs1126742 C/C	4	54	3	50	
				rs3890011 C/C	338	637	404	686	
				rs3890011 C/G	244	637	236	686	
				rs3890011 G/G	55	637	46	686	
Svetlana Sirotina	2018	Russia		rc9332978 #/#	477	637	526	696	
				155332570 A/A	4()	037	150	080	
				rs9332978 A/G	160	637	158	080	
				rs9332978 G/G	0	637	0	686	
				rs9332978 A/A	111	168	225	297	
				rs9332978 A/G	53	168	68	297	
	_			rs9332978 C/C	4	168	4	297	
LIU Junhua	2012	Han		re1126742 T/T	100	162	150	207	
				ma1106740 T/C		140	100	207	
				<u>rs1120742 1/C</u>	1 23	108	123	291	
				<u> rs1126742 C/C</u>	15	168	24	297	
A.Basic characteri	stics of	CYP4A11 gene	e polymorphism an	nd coronary heart	: disease.				
				CAD		Cont	trol		
Name	Time	Nation	Genotype	Evente	Total	Evente	Total	1	
			ma2109622 C/C	2501103	420	102			
DATE OF 11	0000		<u>rszi08622 U/U</u>	404	420	193	412		
DAN San-li	2009	Han	rs2108622 C/T	152	420	186	412		
			<u>rs2108622 T/T</u>	16	420	33	412		
			rs1558139 C/C	58	168	105	297		
LIU Junhua	2012	Han	rs1558139 C/T	85	168	148	297		
			rs1558130 T/T	25	168	44	297		
			ma0100400 0/0	20	100	104	100		
			rs2108622 C/C	300	514	104	198		
WANG Xiao-huan	2017	Han	<u>rs2108622 C/T</u>	183	514	78	198		
			<u>rs2108622 T/</u> T	25	514	16	198		
			rs1558139 C/C	81	285	76	264		
		Han	rs1558139 C/T	137	285	135	264		
			re1558120 T/T	67	200	52	264		
ZHAO Ping	2016		121000108 1/1	120	200	00	204		
Ĭ		Mongolian	rs2108622 C/C	1/3	285	128	204		
			<u>rs2108622 C/T</u>	97	285	115	264		
			rs2108622 T/T	l 15	285	10	264		

Table 1. Incorporate into the basic characteristics table of literature.

B. Basic characteristics of CYP4F2 gene polymorphism and coronary heart disease.











B. Summary bias assessment of included studies.

Figure 2. Risk of bias summary.

	CHD		Control		Risk Ratio				Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		n n	1-H, Fixed, 95% Cl			
1.1.1 CC	220	0.07			22.400	0.00.00.00.000						
Svetiana Sirotina2018	338	037	404	080	32.1%	0.90 [0.82, 0.99]			1			
Zhenyan Fu2012a Zhenyan Fu2012b	/0	270	40	100	4.070	0.7210.45.1.451						
Zhenyan Fu2012p Zhenyan Fu2012c	107	277	42 60	100	2.7.70	0.72 [0.40, 1.10]			-			
Zhenyan Fu20120 Zhenyan Fu2012d	107	54	21	50	1.9%	0.50 [0.74, 1.24]						
Subtotal (95% CI)	1.0	1329	21	1183	47.0%	0.91 [0.84, 0.99]			٠			
Total events	559	1020	566			0101 [0101, 0100]						
Heterogeneity: Chi ² = 3.0	25 df= 4	(P = 0)	52): P= 0	%								
Test for overall effect: $Z = 2.10$ (P = 0.04)												
1001101 0101011 011001.2	2.10 ()	0.0 1,										
1.1.2 CG												
Svetlana Sirotina2018	244	637	236	686	18.7%	1.11 [0.97, 1.28]			+			
Zhenyan Fu2012a	121	276	102	180	10.2%	0.77 [0.64, 0.93]			+			
Zhenyan Fu2012b	45	85	66	135	4.2%	1.08 [0.83, 1.41]			+			
Zhenyan Fu2012c	122	277	60	132	6.7%	0.97 [0.77, 1.22]			+			
Zhenyan Fu2012d	21	54	20	50	1.7%	0.97 [0.60, 1.57]			+			
Subtotal (95% CI)		1329		1183	41.5%	1.00 [0.91, 1.10]			•			
Total events	553		484									
Heterogeneity: Chi ² = 9.9	39, df = 4	(P = 0.0	04); I² = 6	0%								
Test for overall effect: Z =	= 0.04 (P =	= 0.97)										
1.1.3 GG												
Svetlana Sirotina2018	55	637	46	686	3.7%	1.29 [0.88, 1.88]						
Zhenyan Fu2012a	77	276	32	180	3.2%	1.57 [1.09, 2.27]						
Zhenyan Fu2U12b	21	85	27	135	1.7%	1.24 [0.75, 2.04]						
Zhenyan Fu2012c	48	277	19	132	2.1%	1.20 [0.74, 1.96]						
Znenyan FuZU1Zd Subtotal (05% Cl)	16	1320	9	1103	0.8%	1.65 [0.80, 3.38]			▲			
Subtotal (95% CI)	247	1529	400	1185	11.5%	1.37 [1.12, 1.07]			•			
Hotorogonoity: Chiž – 1 3	217 21 df - 4	/P = 0 (551 0 – ≊i√ac	o <u>/</u>								
Tect for overall effect: 7 -	ວ I, UI — 4 - ວ ດ ວ / D -	(F = 0.) - 0.000	50), I – U N	70								
resciul overall ellect. Z =	- 3.03 (F -	- 0.002	9									
Total (95% CI)		3987		3549	100.0 %	1.00 [0.94, 1.06]						
Total events	1329		1183									
Heterogeneity: Chi² = 28	.75, df = 1	4 (P =	0.01); I ^z =	= 51%			L 0.01			100		
Test for overall effect: Z =	= 0.00 (P =	= 1.00)					0.01	0.1	1 10 CHD control	100		
Test for subaroup differe	ences: Ch	i ² = 13	25. df = 2	2 (P = 0	.001). I ² =	84.9%			CHD CONGO			



3.2 Gene polymorphism and risk analysis and heterogeneity analysis of coronary heart disease **3.2.1.**Genetic polymorphism of CYP4A11 and risk analysis and heterogeneity analysis of coronary heart disease

Comparing the CC, CG and GG genotypes of CYP4A11 gene rs3890011 between the coronary heart disease group and the control group, the results showed that there was heterogeneity between patients with CG genotype and the risk of coronary heart disease ($I^2=60\%$). Patients with CC genotype had a lower risk of coronary heart disease (OR = 0.91,95% CI: 0.84-0.99, P = 0.04), while patients with GG genotype had an increased risk of coronary heart disease (OR = 1.37,95% CI: 1.12-1.67, P = 0.002). As shown in Figure 3.

The TT, CT and CC genotypes of CYP4A11 gene rs1126742 in the coronary heart disease group and the control group were compared. the results showed that there was no correlation between patients with TT, CT and CC genotypes and the risk of coronary heart disease (OR = 1.04,95% CI: 0.97-1.12, P = 0.27; OR = 0.787,95% CI: 0.75-1.01, P = 0.07). OR = 1.31,95% CI: 0.88-1.96, P = 0.19). As shown in Figure 4.

The genotypes of AA, AG and GG of CYP4A11 gene rs9332978 in coronary heart disease group and control group were compared. The results showed that patients with AA genotype had a lower risk of coronary heart disease (OR = 0.95,95% CI: 0.91-1.00, P = 0.03), while patients with AG genotype had an increased risk of coronary heart disease (OR = 1.13,95% CI: 1.00-1.28, P = 0.04). The risk of developing coronary heart disease in patients with GG allele did not exist in correlation (OR = 1.31,95% CI: 0.77-2.24, P = 0.32). As shown in Figure 5.

	CHD		Contr	ol		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl					
2.1.1 TT												
LIU Junhua2012	100	168	150	297	14.1%	1.18 [1.00, 1.39]	-					
Zhenyan Fu2012a	186	276	118	180	18.6%	1.03 [0.90, 1.18]	†					
Zhenyan Fu2012b	59	85	84	135	8.5%	1.12 [0.92, 1.35]	+					
Zhenyan Fu2012c	183	277	93	132	16.4%	0.94 [0.82, 1.08]	1					
Zhenyan Fu2012d	33	54	33	50	4.5%	0.93 [0.69, 1.24]	-					
Subtotal (95% CI)		860		794	62.1%	1.04 [0.97, 1.12]	1					
Total events	561		478									
Heterogeneity: Chi ² = 5.44, df = 4 (P = 0.25); l ² = 26%												
Test for overall effect: Z = 1.10 (P = 0.27)												
2.1.2 TC												
LIU Junhua2012	53	168	123	297	11.6%	0.76 (0.59, 0.99)						
Zhenyan Fu2012a	72	276	56	180	8.8%	0.84 [0.62, 1.13]	-+					
Zhenyan Fu2012b	19	85	43	135	4.3%	0.70 [0.44, 1.12]						
Zhenyan Fu2012c	85	277	35	132	6.2%	1.16 [0.83, 1.62]						
Zhenyan Fu2012d	17	54	14	50	1.9%	1.12 [0.62, 2.04]						
Subtotal (95% CI)		860		794	32.8%	0.87 [0.75, 1.01]	•					
Total events	246		271									
Heterogeneity: Chi ² =	5.38, df=	4 (P =	0.25); l² :	= 26%								
Test for overall effect:	Z=1.79 ((P = 0.0	17)									
2.1.3 CC												
LIU Junhua2012	15	168	24	297	2.3%	1.10 [0.60, 2.05]	_ 					
Zhenyan Fu2012a	18	276	6	180	0.9%	1.96 [0.79, 4.83]	+					
Zhenyan Fu2012b	7	85	8	135	0.8%	1.39 [0.52, 3.69]						
Zhenyan Fu2012c	9	277	4	132	0.7%	1.07 [0.34, 3.42]						
Zhenyan Fu2012d	4	54	3	50	0.4%	1.23 [0.29, 5.25]						
Subtotal (95% CI)		860		794	5.1%	1.31 [0.88, 1.96]	•					
Total events	53		45									
Heterogeneity: Chi² =	1.18, df=	4 (P =	0.88); I² :	= 0%								
Test for overall effect:	Z=1.32 ((P = 0.1	9)									
Total (95% CI)		2580		2382	100.0%	1.00 [0.93, 1.07]	•					
Total events	860		794									
Heterogeneity: Chi ² =	17.57, df	= 14 (F	= 0.23);	I ² = 20°	%							
Test for overall effect:	Z = 0.00 ((P = 1.0	CHD control									
Test for subaroup diff	erences:	Chi ^z = I	6.00. df =	2 (P =	0.05), I ^z =	: 66.6%						

Figure 4. Forest map of the relationship between TT, CT, CC genotypes of CYP4A11 gene rs1126742 and coronary heart disease.

	CHD Control		ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.1.1 AA							
LIU Junhua2012	111	168	225	297	11.4%	0.87 [0.77, 0.99]	
Svetlana Sirotina2018	477	637	526	686	35.5%	0.98 [0.92, 1.04]	
Zhenyan Fu2012a	172	276	120	180	10.2%	0.93 [0.81, 1.07]	
Zhenyan Fu2012b	51	85	94	135	5.1%	0.86 [0.70, 1.06]	
Zhenyan Fu2012c	210	277	97	132	9.2%	1.03 [0.91, 1.17]	
Zhenyan Fu2012d	35	54	36	50	2.6%	0.90 [0.69, 1.17]	
Subtotal (95% Cl)		1497		1480	74.0%	0.95 [0.91, 1.00]	•
Total events	1056		1098				
Heterogeneity: Chi ² = 5.3	35, df = 5	(P = 0.3)	87); l≥ = 7	%			
Test for overall effect: Z	= 2.15 (P :	= 0.03)					
3.1.2 AG							
LIUJunhua2012	53	168	68	297	3.4%	1 38 [1.02, 1.87]	
Svetlana Sirotina2018	160	637	158	686	10.7%	1.09 [0.90, 1.32]	
Zhenvan Eu2012a	90	276	54	180	4.6%	1 09 0 82 1 44	
Zhenvan Fu2012b	28	85	38	135	2.1%	1.17 [0.78, 1.76]	
Zhenvan Fu2012c	61	277	29	132	2.8%	1.00 [0.68, 1.48]	
Zhenvan Fu2012d	18	54	13	50	0.9%	1.28 [0.70, 2.34]	
Subtotal (95% CI)		1497		1480	24.5%	1.13 [1.00, 1.28]	◆
Total events	410		360				
Heterogeneity: Chi ² = 2.3	38, df = 5	(P = 0.7)	'9); I ² = 0	%			
Test for overall effect: Z =	= 2.01 (P :	= 0.04)					
3.1.3 GG							
LIUJunhua2012	4	168	4	297	0.2%	1.77 (0.45, 6.98)	
Svetlana Sirotina2018	n	637	n	686		Not estimable	
Zhenvan Eu2012a	14	276	6	180	0.5%	1 52 10 60 3 891	
Zhenvan Fu2012b	6	85	3	135	0.2%	3.18 [0.82, 12, 36]	
Zhenvan Eu2012c	6	277	6	132	0.6%	0.48/0.16/1.45	←
Zhenvan Fu2012d	1	54	1	50	0.1%	0.93 [0.06, 14, 41]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		1497		1480	1.5%	1.31 [0.77, 2.24]	
Total events	31		20				
Heterogeneity: Chi ² = 5.1	15, df = 4	(P = 0.2	27); I ² = 2	2%			
Test for overall effect: Z =	= 0.99 (P :	= 0.32)					
Total (95% CI)		4491		4440	100.0%	1.00 [0.96, 1.05]	
Total events	1497	-	1478				
Heterogeneity: Chi ² = 21	.54. df = 1	6 (P =	0.16); I ² =	= 26%			
Test for overall effect: 7:	= 0.06 (P :	= 0.961					0.5 0.7 1 1.5 2
1001 101 0101 dill 01001. E							

Figure 5. Forest map of the relationship between AA, AG, GG genotypes of CYP4A11 gene rs9332978 and coronary heart disease.



Figure 6. Forest map of the relationship between CC, CT, TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease.

	CHD)	Contr	ol		Risk Ratio	atio Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		<u> M-H, Fixed, 95% Cl</u>				
5.1.1 CC												
LIU Junhua2012	58	168	105	297	15.5%	0.98 [0.75, 1.27]		-				
ZHAO Ping2016	81	285	76	264	16.1%	0.99 [0.76, 1.29]						
Subtotal (95% Cl)		453		561	31.7%	0.98 [0.82, 1.18]		•				
Total events	139		181									
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); l² = 0%												
Test for overall effect: Z = 0.19 (P = 0.85)												
5.1.2 CT												
LIU Junhua2012	85	168	148	297	21.9%	1.02 [0.84, 1.23]		+				
ZHAO Ping2016	137	285	135	264	28.7%	0.94 [0.79, 1.11]		†				
Subtotal (95% CI)		453		561	50.6%	0.97 [0.86, 1.10]		•				
Total events	222		283									
Heterogeneity: Chi ² =	0.36, df=	1 (P =	0.55); l² =	= 0%								
Test for overall effect:	Z = 0.43 ((P = 0.6	6)									
5.1.3 TT												
LIU Junhua2012	25	168	44	297	6.5%	1.00 [0.64, 1.58]		-				
ZHAO Ping2016	67	285	53	264	11.3%	1.17 [0.85, 1.61]		1				
Subtotal (95% CI)		453		561	17.8%	1.11 [0.86, 1.44]		•				
Total events	92		97									
Heterogeneity: Chi ² =	0.29, df=	1 (P =	0.59); l² =	= 0%								
Test for overall effect:	Z = 0.78 ((P = 0.4)	3)									
Total (05% CI)		4250		4602	100.0%	4 00 10 04 4 401		1				
Total (95% CI)	150	1559	504	1085	100.0%	1.00 [0.91, 1.10]		T				
Total events	453	c (0)	561	~~			L					
Test for everall offer t	1.52, di =	0 (P = 10 - 4 1	0.91); F=	= 0%			0.01 0.1	i	10	100		
Test for overall effect:	∠=0.000	(F = 1.U	10) 0.00 -46	2 (7)	0.000 17	0.07		CHD control				
i est for subdroub diff	erences:	∪nr=+	U.82. dī =	Z (P =	U.00). *=	:0%						

Figure 7. Forest map of the relationship between CC, CT, TT genotypes of CYP4F2 gene rs1558139 and coronary heart disease.

3.2.2. Genetic polymorphism of CYP4F2 and risk analysis and heterogeneity analysis of coronary heart disease

Comparing the CC, CT and TT genotypes of CYP4F2 gene rs2108622 between the coronary heart disease group and the control group, the results showed that the patients with CC and TT genotypes and the wind risk patients with coronary heart disease existed in heterogeneity ($I^2=68\%$). Patients with CT genotype had a reduced risk of coronary heart disease (OR = 0.82, 95% CI: 0.74-0.92, P = 0.0006). As shown in Figure 6.

Comparing the CC, CT and TT genotypes of CYP4F2 gene rs1558139 between the coronary heart disease group and the control group, the results showed that there was no correlation between patients with CC, CT and TT genotypes and the risk of coronary heart disease (OR = 0.998,95% CI: 0.82-1.18, P = 0.85; OR = 0.97,95% CI: 0.86-1.10, P = 0.66). OR = 1.11,95% CI: 0.86-1.44, P = 0.43). As shown in Figure 7.

3.3 Subgroup analysis

The study found that there was heterogeneity between patients with CG genotype of CYP4A11 gene rs3890011 and the risk of coronary heart disease. Subgroup analysis was performed on patients with CG genotypes according to gender factors. The results showed that there was no heterogeneity between women with CG genotype and the risk of coronary heart disease ($I^2=0\%$), as shown in Figure 8. Therefore, gender may be the reason for the heterogeneity between patients with CG genotype and the risk of coronary heart disease.

It was found that there was heterogeneity between patients with CC and TT genotypes of CYP4F2 gene rs2108622 and the risk of coronary heart disease. The patients with CC and TT genotypes from different nationalities were analyzed by subgroup analysis. The results showed that Han patients with CC genotype had an increased risk of coronary heart disease (OR=1.21,95%CI:1.08-1.37), while patients with TT genotype had a lower risk of coronary heart disease (OR=0.53,95%CI:0.35-0.81), as shown in Figure 9. Therefore, ethnic factors are the cause of heterogeneity between patients with CC and TT genotypes and the risk of coronary heart disease.

	CAD)	Control			Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl					
10.1.1 Man												
Zhenyan Fu2012a	121	276	102	180	36.0%	0.77 [0.64, 0.93]	=					
Zhenyan Fu2012b	122	277	60	132	29.1%	0.97 [0.77, 1.22]	.					
Subtotal (95% CI)		553		312	65.1%	0.86 [0.69, 1.07]	•					
Total events	243		162									
Heterogeneity: Tau ² = 0.01; Chi ² = 2.25, df = 1 (P = 0.13); I ² = 56%												
Test for overall effect:	Z = 1.38 ((P = 0.1	7)									
10.1.2 Woman												
Zhenyan Fu2012c	45	85	66	135	24.6%	1.08 [0.83, 1.41]	+					
Zhenyan Fu2012d	21	54	20	50	10.3%	0.97 [0.60, 1.57]	- <u>+</u>					
Subtotal (95% CI)		139		185	34.9%	1.06 [0.84, 1.33]	•					
Total events	66		86									
Heterogeneity: Tau ² =	0.00; Chi	² = 0.1:	5, df = 1 (P = 0.7	0); I ² = 09	6						
Test for overall effect:	Z=0.46 ((P = 0.8	65)									
Total (05% CI)		602		407	100.0%	0 02 [0 78 1 00]	•					
Total (95% CI)	200	092	240	497	100.0%	0.92 [0.76, 1.09]	•					
l otal events	309		248									
Heterogeneity: Tau ² =	0.01; Chi	*= 4.9	6, df = 3 (P = 0.1	7); I*= 39	%						
Test for overall effect: .	Z=1.00 (P = 0.3	CAD control									
Test for subgroup diffe	erences: •	Chi ² = 1	0.12 0011101									

Figure 8. Subgroup analysis of gender factors in patients with CG genotype.

3.4 Sensitivity analysis

In the study of the relationship between the CG genotype of CYP4A11 gene rs3890011 and coronary heart disease, excluding a group of data from Zhengyuan Fu, the heterogeneity of each study changed, and the results were not statistically significant (OR = 1.07,95% CI:0.96-1.19, P = 0.23). As shown in Figure 10.

	CAD		Control			Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl				
11.1.1 Han											
DAN San-Ii2009	252	420	193	412	34.7%	1.28 [1.13, 1.46]					
WANG Xiao-huan2017	306	514	104	198	31.5%	1.13 [0.98, 1.32]					
Subtotal (95% CI)		934		610	66.2%	1.21 [1.08, 1.37]					
Total events	558		297								
Heterogeneity: Tau ² = 0.0	00; Chi ² =	1.46, d	f=1(P=	0.23);	l²= 32%						
l est for overall effect: Z =	= 3.17 (P =	0.002)								
11.1.2 Mongolian											
ZHAO Ping2016	173	285	159	264	33.8%	1.01 [0.88, 1.15]	<u>+</u>				
Subtotal (95% CI)		285		264	33.8%	1.01 [0.88, 1.15]	•				
Total events	173		159								
Heterogeneity: Not appli	cable										
Test for overall effect: Z =	= 0.11 (P =	0.91)									
Total (95% CI)		1219		874	100.0%	1.14 [0.99, 1.31]					
Total events	731		456								
Heterogeneity: Tau* = 0.0	01; Chi*=	6.35, d	f= 2 (P =	0.04);	I*= 68%		0.5 0.7 1 1.5 2				
Test for overall effect: Z = 1.77 (P = 0.08) CAD control											
Test for subaroup differences: Chif = 4.03. df = 1 (P = 0.04). If = 75.2%											
A. Effect of ethnic factors on CC genotypes.											
	CAD)	Contr	ol		Risk Ratio	Risk Ratio				
Study or Subgroup	CAD Events	Total	Contr Events	ol Total	Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han	CAD Events	Total	Contr Events	ol Total	Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl				
<u>Study or Subgroup</u> 12.1.1 Han DAN San-Ii2009	CAD Events 16	<u>Total</u> 420	Contr <u>Events</u> 33	ol <u>Total</u> 412	Weight 36.5%	Risk Ratio <u>M-H, Random, 95% Cl</u> 0.48 (0.27, 0.85)	Risk Ratio M-H, Random, 95% Cl				
<u>Study or Subgroup</u> 12.1.1 Han DAN San-Ii2009 WANG Xiao-huan2017	CAD Events 16 25	Total 420 514	Contr Events 33 16	ol <u>Total</u> 412 198	Weight 36.5% 35.4%	Risk Ratio <u>M-H, Random, 95% Cl</u> 0.48 [0.27, 0.85] 0.60 [0.33, 1.10]	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% CI)	CAD Events 16 25	Total 420 514 934	Contr Events 33 16	ol <u>Total</u> 412 198 610	Weight 36.5% 35.4% 71.9%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% CI) Total events	CAD Events 16 25 41	<u>Total</u> 420 514 934	Contr Events 33 16 49	ol <u>Total</u> 412 198 610	Weight 36.5% 35.4% 71.9%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 [0.27, 0.85] 0.60 [0.33, 1.10] 0.53 [0.35, 0.81]	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0	CAD Events 16 25 41 00; Chi ² =	Total 420 514 934 0.30, d	Contr Events 33 16 49 f = 1 (P =	ol <u>Total</u> 412 198 610 0.58);	Weight 36.5% 35.4% 71.9%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 [0.27, 0.85] 0.60 [0.33, 1.10] 0.53 [0.35, 0.81]	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	CAD Events 16 25 41 20; Chi ² = : 2.94 (P =	420 514 934 0.30, d 0.003)	Contr Events 33 16 49 f = 1 (P =	rol <u>Total</u> 412 198 610 0.58);	Weight 36.5% 35.4% 71.9% I [≈] = 0%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian	CAD Events 16 25 41 20; Chi ² = : 2.94 (P =	420 514 934 0.30, d 0.003)	Contr <u>Events</u> 33 16 49 f = 1 (P =	rol <u>Total</u> 412 198 610 0.58);	Weight 36.5% 35.4% 71.9% I² = 0%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016	CAD Events 16 25 41 20; Chi ² = : 2.94 (P = 15	Total 420 514 934 0.30, d 0.003) 285	Contr Events 33 16 49 f=1 (P =	ol Total 412 198 610 0.58); 264	Weight 36.5% 35.4% 71.9% ² = 0% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81) 1.39 (0.64, 3.04)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl)	CAD Events 16 25 41 00; Chi ^z = : 2.94 (P = 15	Total 420 514 934 0.30, d 0.003) 285 285	Contr Events 33 16 49 f= 1 (P =	ol Total 412 198 610 0.58); 264 264	Weight 36.5% 35.4% 71.9% ² = 0% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81) 1.39 (0.64, 3.04) 1.39 (0.64, 3.04)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% CI) Total events	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15	Total 420 514 934 0.30, d 0.003) 285 285	Contr Events 33 16 49 f=1 (P= 10 10	rol 412 198 610 0.58); 264 264	Weight 36.5% 35.4% 71.9% ² = 0% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81) 1.39 (0.64, 3.04) 1.39 (0.64, 3.04)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not appli	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15 cable	Total 420 514 934 0.30, d 0.003) 285 285	Contr Events 33 16 49 f=1 (P= 10 10	rol 412 198 610 0.58); 264 264	Weight 36.5% 35.4% 71.9% ² = 0% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81) 1.39 (0.64, 3.04) 1.39 (0.64, 3.04)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not applit Test for overall effect: Z =	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15 15 : able : 0.82 (P =	Total 420 514 934 0.30, d 0.003) 285 285 285	Contr Events 33 16 49 f=1 (P= 10 10	rol <u>Total</u> 198 610 0.58); 264 264	Weight 36.5% 35.4% 71.9% ² = 0% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81) 1.39 (0.64, 3.04) 1.39 (0.64, 3.04)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not applied Test for overall effect: Z =	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15 15 cable : 0.82 (P =	Total 420 514 934 0.30, d 0.003; 285 285 285	Contr Events 33 16 49 f= 1 (P = 10 10	rol <u>Total</u> 198 610 0.58); 264 264	Weight 36.5% 35.4% 71.9% ² = 0% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81) 1.39 (0.64, 3.04) 1.39 (0.64, 3.04)	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not applied Test for overall effect: Z = Total (95% Cl)	CAD Events 16 25 41 00; Chi ⁼ = : 2.94 (P = 15 15 15 : 0.82 (P =	Total 420 514 934 0.30, d 0.003) 285 285 285 : 0.41) 1219	Contr Events 33 16 49 f= 1 (P = 10 10	rol Total 412 198 610 0.58); 264 264 264 874	Weight 36.5% 35.4% 71.9% 1 ² = 0% 28.1% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81] 1.39 (0.64, 3.04) 1.39 (0.64, 3.04] 0.70 (0.39, 1.25]	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-li2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not applied Test for overall effect: Z = Total (95% Cl) Total events	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15 15 : 0.82 (P = 56	Total 420 514 934 0.30, d 0.003) 285 285 285 : 0.41) 1219	Contr Events 33 16 49 f=1 (P= 10 10 59	rol Total 198 610 0.58); 264 264 264 874	Weight 36.5% 35.4% 71.9% * = 0% 28.1% 28.1% 28.1%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81] 1.39 (0.64, 3.04] 1.39 (0.64, 3.04] 0.70 (0.39, 1.25]	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-Ii2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not applie Test for overall effect: Z = Total (95% Cl) Total events Heterogeneity: Tau ² = 0.1	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15 cable : 0.82 (P = 56 15; Chi ² =	Total 420 514 934 0.30, d 0.003) 285 285 285 0.41) 1219 4.79, d	Contr <u>Events</u> 33 16 49 f=1 (P= 10 10 10 59 f= 2 (P=	rol Total 412 198 610 0.58); 264 264 264 874 0.09);	Weight 36.5% 35.4% 71.9% 1 ² = 0% 28.1% 28.1% 28.1% 100.0% 1 ² = 58%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81] 1.39 (0.64, 3.04] 1.39 (0.64, 3.04] 0.70 (0.39, 1.25]	Risk Ratio M-H, Random, 95% Cl				
Study or Subgroup 12.1.1 Han DAN San-Ii2009 WANG Xiao-huan2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 12.1.2 Mongolian ZHAO Ping2016 Subtotal (95% Cl) Total events Heterogeneity: Not applie Test for overall effect: Z = Total (95% Cl) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	CAD Events 16 25 41 00; Chi ² = : 2.94 (P = 15 15 cable : 0.82 (P = 56 15; Chi ² = : 1.21 (P =	Total 420 514 934 0.30, d 0.003) 285 285 285 0.41) 1219 4.79, d 0.23)	Contr Events 33 16 49 f = 1 (P = 10 10 10 f = 2 (P =	rol Total 198 610 0.58); 264 264 264 874 0.09);	Weight 36.5% 35.4% 71.9% 1 ² = 0% 28.1% 28.1% 28.1% 100.0% 1 ² = 58%	Risk Ratio <u>M-H, Random, 95% CI</u> 0.48 (0.27, 0.85) 0.60 (0.33, 1.10) 0.53 (0.35, 0.81] 1.39 (0.64, 3.04] 1.39 (0.64, 3.04] 0.70 (0.39, 1.25]	Risk Ratio M-H, Random, 95% Cl				

B. Effect of ethnic factors on TTgenotypes.

Figure 9. Subgroup analysis of CC and TT genotypes in patients with ethnic factors.

	CHD Contro		ol	Risk Ratio		Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-	H, Random, 95%	CI	
Svetlana Sirotina2018	244	637	236	686	56.5%	1.11 [0.97, 1.28]			—		
Zhenyan Fu2012a	121	276	102	180		Not estimable					
Zhenyan Fu2012b	45	85	66	135	16.5%	1.08 [0.83, 1.41]			+		
Zhenyan Fu2012c	122	277	60	132	21.9%	0.97 [0.77, 1.22]			+		
Zhenyan Fu2012d	21	54	20	50	5.1%	0.97 [0.60, 1.57]			+		
Total (95% CI)		1053		1003	100.0%	1.07 [0.96, 1.19]			•		
Total events	432		382								
Heterogeneity: Tau ² = 0.1	00; Chi =	1.18, 0	df = 3 (P =	: 0.76);	I²=0%		0.01	01	1	10	100
Test for overall effect: Z =	= 1.20 (P =	= 0.23)					0.01	0.1	CHD control	10	100

Figure 10. Forest Map of the relationship between CG Genotype of CYP4A11 Genotype rs3890011 and Coronary Heart Disease.

In the study of the relationship between CC and TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease, the heterogeneity of each study changed after the removal of one literature, and the results were statistically significant (OR = 1.22,95% CI: 1.10-1.34, P < 0.0001 / OR = 0.53, 95% CI: 0.35-0.80, P = 0.003). As shown in Figure 11.

0.4

	CHD Control				Dick Datia		Pick Patio					
Study of Subgroup	CHU	Tetal	Contr	Tetel	Moinbt	NISK Kallo	M H Pandom 05% Cl					
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% CI	IVI-1	1, Kandom, 95% C	<u>.</u>			
7.1.1 CC												
DAN San-li2009	252	420	193	412	35.4%	1.28 [1.13, 1.46]		-				
WANG Xiao-huan2017	306	514	104	198	34.6%	1.13 [0.98, 1.32]		- F				
ZHAO Ping2016	173	285	159	264		Not estimable						
Subtotal (95% CI)		934		610	70.0%	1.21 [1.08, 1.37]		•				
Total events	558		297									
Heterogeneity: Tau ² = 0.00; Chi ² = 1.46, df = 1 (P = 0.23); i ² = 32%												
Test for overall effect: Z =	3.17 (P =	0.002)										
7.1.2 TT												
DAN San-li2009	16	420	33	412	15.4%	0.48 [0.27, 0.85]						
WANG Xiao-huan2017	25	514	16	198	14.6%	0.60 [0.33, 1.10]						
ZHAO Ping2016	15	285	10	264		Not estimable						
Subtotal (95% CI)		934		610	30.0%	0.53 [0.35, 0.81]		◆				
Total events	41		49			- / -						
Heterogeneity: Tau ² = 0.0	0: Chi ^z =	0.30. d	f=1 (P=	0.58);	I²=0%							
Test for overall effect: Z =	2.94 (P =	0.003)										
	,											
Total (95% CI)		1868		1220	100.0%	0.94 [0.70, 1.27]		+				
Total events	599		346									
Heterogeneity: Tau ² = 0.0	6; Chi ⁼ =	16.55,	df = 3 (P :	= 0.000)9); I ² = 82	2%			+	400		
Test for overall effect: Z =	0.38 (P =	0.70)					0.01 0.1	I OLID sentest	10	100		
Test for subaroup differer	nces: Chi		CHD control									





B. CYP4F2 gene and publication bias of coronary heart disease study. Figure 12. Literature research published biased funnel chart.

 RR

For other analysis results, the results of the meta-analysis were replicated excluding in each step one of the studies included in the review. The analysis was considered robust when the results obtained were similar.

3.5 Published bias estimates

Publication bias was evaluated using Cochrane tool developed for this purpose. The funnel chart shows that the distribution of scattered spots on the left and right sides is asymmetrical and there is publication bias. As shown in Figure 12.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the association between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease. In this study, we collected data from 6 literatures and 5535 subjects. To evaluate the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease. The results showed that patients with CC genotype with CYP4A11 gene rs3890011 had a lower risk of coronary heart disease, while patients with GG genotype had an increased risk of coronary heart disease. Therefore, homozygous genotypes (CC, GG) of CYP4A11 gene rs3890011 were associated with coronary heart disease. The TT, CT and CC genotypes of CYP4A11 gene rs1126742 were not associated with coronary heart disease, the risk of coronary heart disease decreased in patients with AA genotype carrying CYP4A11 gene rs9332978, and increased in patients with AG genotype, and there was no correlation between GG genotype and the risk of coronary heart disease. Therefore, the dominant genes (AA, AG) of CYP4A11 gene rs9332978 are associated with coronary heart disease. Patients with CT genotype carrying CYP4F2 gene rs2108622 had a lower risk of coronary heart disease, while CC, CT and TT genotypes of CYP4F2 gene rs1558139 were not associated with coronary heart disease.

Cardio-cerebrovascular disease is a common disease that seriously threatens the health of human beings, especially the middle-aged and elderly over 50 years old. it has the characteristics of high prevalence rate, high disability rate and high mortality rate. Even with the application of the most advanced and perfect treatment, more than 50% of the survivors of cerebrovascular accidents can not take care of themselves. The number of people who die from cardiovascular and cerebrovascular diseases is as high as 15 million every year, ranking first in all causes of death. Common cardiovascular and cerebrovascular diseases are hypertension, hyperlipidemia, coronary heart disease and so on. Therefore, it is particularly important to prevent the occurrence of cardiovascular and cerebrovascular diseases such as coronary heart disease. At present, many studies have shown that cytochrome P450 (CYP450) gene is associated with the pathogenesis of coronary heart disease [6-10]. Cytochrome P450 mainly includes four families of CYP1-4 and subfamilies A, B, C, D, E and F, which are involved in the biotransformation of a variety of endogenous substrates, exogenous compounds and drugs. Arachidonic acid is one of the most abundant endogenous substances in human body. CYP4A and CYP4F families are the main isoenzymes that catalyze the ω-hydroxylation of arachidonic acid to 20-HETE. [11] exogenous administration of 20-HETE can inhibit coronary vasodilation induced by vascular endothelial hyperpolarizing factor, aggravate the degree of myocardial injury caused by coronary artery ischemia, and then lead to coronary heart disease. [12]

In this paper, through sensitivity analysis, the heterogeneity of each study changed after removing a literature from the study on the relationship between CC and TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease($I^2=32\%$, $I^2=0\%$). it can be concluded that the homozygous genotypes of CYP4F2 gene rs2108622 (CC, TT) are related to the occurrence of coronary heart disease, the CC genotype is positively correlated with the occurrence of coronary heart disease, and the TT genotype is negatively correlated with the occurrence of coronary heart disease. The main difference between the deleted literature and other literature is that the research object is different. ZHAOPing's article studies the genes of Mongolian population, so we have reason to believe that ethnic factors have a great influence on the relationship between CYP4F2 gene rs2108622 and coronary heart diseas. In the study of the correlation between CG genotype of CYP4A11 gene

rs3890011 and coronary heart disease, the heterogeneity of each study changed after removing a set of data ($I^2=0\%$). The difference between the removed set of data and other data studies lies in the difference of the research objects, and the research object of removing a set of data from ZhengyuanFu is Han male. Therefore, we believe that the relationship between CG genotype of CYP4A11 gene rs3890011 and coronary heart disease is related to gender. Because of the small sample size, it is impossible to determine whether it is related to men or women.

5. Limitations

The calculated results were obtained after excluding the studies with heterogeneity, which would undoubtedly contribute to drawing some scientific conclusions in the present meta-analysis. However, the main limitation of this meta-analysis is that the sample size is small, the conclusion may not be accurate, and the pathogenesis of coronary heart disease is not clear. In the future work, we should further expand the sample size, in order to further clarify the possible pathogenesis of coronary heart disease and find genetic susceptibility genes, and then take effective intervention measures to prevent or delay the occurrence of coronary heart disease.

6. Conclusions

Based on the results of this paper, it can be concluded that the homozygous genotypes of CYP4A11 gene rs3890011 (CC, GG) are related to the occurrence of coronary heart disease in Chinese. The dominant genes of CYP4A11 gene rs9332978 (AA, AG) are related to the occurrence of coronary heart disease in Chinese. There was no correlation between TT, CT, CC genotypes of CYP4A11 gene rs1126742 and coronary heart disease in Chinese. Homozygous genotypes of CYP4F2 gene rs2108622 (CC, TT) are associated with coronary heart disease in Chinese, while CC, CT and TT genotypes of CYP4F2 gene rs1558139 are not associated with coronary heart disease in Chinese. Therefore, CYP4A11 and CYP4F2 gene polymorphisms are associated with coronary heart disease in Chinese.

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