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Complement factor H Y402H gene polymorphism and coronary heart disease susceptibility: a meta-analysis

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Abstract The *complement factor H* (*CFH*) Y402H (T1277C) gene polymorphism has been reported to be associated with coronary heart disease (CHD), but results were conflicting. To evaluate the role of the variant in CHD, we performed meta-analyses of all available data. Both electronic and manual searches were performed, all relevant studies were identified. ORs with 95% confidential intervals (CI) under codominant (CC versus TT, TC versus TT), dominant (CC + TC versus TT) and recessive (CC versus TT + TC) models were calculated. Publication bias was addressed. Ten studies including 11 cohorts comprising of 29,764 participants were included. No association between the *CFH* T1227C polymorphism and CHD could be found. (For overall analysis: dominant model, OR = 1.04, 95%CI: 0.97–1.11; recessive model, OR = 1.04, 95%CI: 0.97–1.11; for Caucasian subgroup: OR = 1.08 95%CI: 0.92–1.27; recessive model, OR = 1.03, 95%CI: 0.96–1.11). Two studies reported positive results in separate population (Caucasian study: recessive model, OR = 0.51, 95%CI: 0.30–0.86; Asians study: dominant model, OR = 2.37, 95%CI: 1.13–4.96). Current evidence do not support the association between the *CFH* T1277C polymorphism and CHD risk among common population. The association, which could be influenced by CHD onset age, CHD risk factors status and genetics backgrounds, might be significant in some population. More studies on different CHD onset ages and risk factor status should be encouraged.

Keywords Coronary heart disease · *Complement factor H* · Gene polymorphism · Meta-analysis

Introduction

Coronary heart disease (CHD) is one of the leading causes of mortality and mobility worldwide, especially in industrialized countries [1, 2]. Evidence of genetic susceptibility on atherosclerosis and CHD has been proposed, although the genes involved and relative risks remain largely unknown [3–5].

Atherosclerosis is a disorder with chronic inflammatory process and the complement system activation plays a role in it [6]. *Complement factor H* (*CFH*) encodes complement factor H protein which is a regulatory protein during complement activation. On one hand, it inactivates complement component C3b, preventing the formation of C3 convertase and the latter cascade reactions; on the other hand, it inhibits the activation of the alternative complement pathway and blocks the proteolytic cascade reaction that releases proinflammtory anaphylatoxins and prevents the formation of the membrane attack complex leading to cell lysis [7]. Several single nucleotide polymorphisms (SNPs) in *CFH* have been reported and the non-synonymous SNP *Y402H* (also be referred to as Tyr402His and T1277C) is of particular interest because it is located within the region of short consensus repeat domains seven binding heparin and

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C-reactive protein, which has been shown to predict the risk of coronary events [8–10]. The base transition of thymine to cytosine happens in the exon 9 of the gene and leads to a tyrosine–histidine substitution in the protein [7]. This variant has been demonstrated to be associated with age-related macular degeneration [11], which shared many common pathophysiological mechanisms with coronary artery atherosclerosis [12, 13]. All these contribute to the hypothesis that the *CFH* T1277C variant could influence complement activation, host immune status and inflammation process; thus change the development of atherosclerosis and CHD. In contrast with the strong and consistent evidence in AMD, however, previous studies have reported conflicting results on the association of the variant and CHD risk. To yield a more plausible result, we performed a meta-analysis based on available data.

Methods

Studies selection

All population-based studies reporting the association of *CFH* T1277C polymorphism and CHD risk were identified by comprehensive searches for the following databases: Medline, EMBase, BIOSIS, LILACS (http://bases.bireme.br, accessed on January, 2010), and SCOPUS (http://www.scopus.com/, accessed on January, 2010). The following terms were used for electronic searches: ("*complement factor H*", "*complement factor*" and *CFH*) AND (gene, genetic*, variant*, mutation* and polymorphism*) AND ("coronary heart disease", "coronary artery disease", angina, "myocardial infarction" and "acute coronary syndrome"). Hand searches were also performed.

Data extraction

Information was carefully extracted from all eligible publications independently by two authors. Disagreement was resolved by a discussion between the two. If a consensus could not be reached, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following information was collected: authors and date of publication, study design, ethnicity, characteristics of the controls, genotyping methods, sample size and the three genotypes frequencies. If the essential information was not presented, authors were contacted with best efforts.

Data analysis

The distributions of genotypes among controls were tested for Hardy–Weinberg Equilibrium (HWE) using exact test. The putative risk allele (C allele) in the controls was estimated by the inverse-variance method as described previously [14].

The Cochrane Q-test was used for heterogeneity check. A P value greater than 0.10 indicates a lack of heterogeneity among studies. ORs with 95% confidential interval (CI) were used to gauge the associations between the T1277C polymorphism and CHD risk. The pooled ORs were estimated under codominant model (CC versus TT, TC versus TT), dominant model (CC + TC versus TT) and recessive model (CC versus TC + TT), respectively. Fixed-effects model (the Mantel–Haenszel method) was used if no heterogeneity existed; otherwise, a random-effects model (the DerSimonian–Laird method) was used. Influence analysis, in which the meta-analysis estimates were computed omitting one study at a time, was performed to access the stability of the results [15]. Studies with only alleles frequencies could be obtained were included in the additive model. Egger's test was used to estimate publication bias and Begg's plot was produced [16]. All the analyses were performed using STATA version 9.2 (StataCorp. 2005. Stata Statistical Software: Release 9. College Station, TX: StataCorp LP).

Results

Studies characteristics

We finally indentified ten publications [17–26], including nine Caucasian studies [17–24, 26], one Asian study [25] and one African-American cohort [24]. Two publications reported two cohorts respectively [22, 24], and each cohort was considered separately for pooling analysis. Only allele frequencies could be obtained in Nicaud's study [21]. Hence, a total of nine studies (11 cohorts) comprising of 26,960 participants were included in codominant, dominant and recessive models and ten studies (12 cohorts) comprising of 28,746 participants were included in the additive model. The controls in two studies deviated from HWE [17, 24]. Main characteristics of included studies were listed in Table 1. The pooled C allele frequencies was 37.04% (95%CI: 36.97–38.43%), 55.88% (95%CI: 31.47–80.30%) and 37.28% (95%CI: 36.05–38.50%), respectively for Caucasians, Asians and African-Americans.

Meta-analysis results

The main results of this meta-analysis were listed in Table 2. Overall, no significant association between the *CFH* T1277C polymorphism and CHD risk could be found either in the overall analysis or subgroup analyses according to ethnicities under any assumed mode of

Table 1 Main characteristics of included studies in the meta-analysis

Study	Ethnicity	Mean age (years) (case/control)	Sample size (case/control)	Case			Control			MAF (controls)
				TT	TC	CC	TT	TC	CC	
Goverdhan et al.	Caucasian	63.29/69.10	220/228	18	99	43	86	94	48	0.21
Kardys et al.	Caucasian	NA	226/5294	81	99	46	2170	2410	714	0.13
Zee et al.	Caucasian	61.00/60.80	335/335	142	130	63	142	143	50	0.15
Meng et al.[a]	Caucasian	NA	603/883	227	270	106	341	399	143	0.16
Nicaud et al.	Caucasian	61.70/60.00	1303/483	NA	NA	NA	NA	NA	NA	0.40
Pai et al.[b]	Caucasian	65.10/65.10	788/1571	319	359	110	611	723	237	0.15
Pai et al.[c]	Caucasian	60.30/60.30	239/473	99	120	20	184	217	72	0.15
Stark et al.	Caucasian	51.40/56.90	1192/973	484	540	168	390	449	134	0.14
Volcik et al.	Caucasian	NA	1207/8217	441	562	204	3135	3809	1273	0.15
Volcik et al.	African-Am	NA	337/3010	123	175	39	1179	1418	413	0.14
Qian et al.	Asian	61.71/55.88	166/170	141	25	0	152	17	1	0.01
Pulido et al.	Caucasian	NA	264/229	96	124	44	90	113	26	0.11

[a] Data was provided by authors; *NA* genotypes frequencies could not be obtained

[b] Men cohort in the study

[c] Women cohort in the study; *African-Am* African-American, *MAF* minor allele frequency

inheritances. Subgroup analysis by study designs yielded that neither case–controls studies nor cohort studies were statistically significant (Fig. 1). Influence analysis did not alter the results and additive model showed nonsignificant results (Supplementary material). Qian et al. reported an association between CC genotype and increased early onset (mean age: <55 years for males and <65 years for females) CHD risk in Chinese population (recessive model: OR = 2.37, 95%CI: 1.13–4.96; Table 2) [25], whereas Pai's study found that the CC genotype was a protective factor for CHD in Caucasians (recessive model: OR = 0.51, 95%CI: 0.30–0.86; Table 2) [22].

Evaluation of heterogeneity and publication bias

Heterogeneity was found in the following comparisons: CC versus TT, CC versus TT + TC (Table 2). When we omitted the women cohort in Pai's study [22], the results of heterogeneity tests ceased to be significant ($P_{Q\text{-test}} = 0.19$ for CC versus TT; $P_{Q\text{-test}} = 0.11$ for CC versus TT + TC). The influence analysis showed an unaffected result after an exclusion of this cohort (Supplementary material). Egger's test showed no evidence of publication bias: $P = 0.66$ for CC versus TT; $P = 0.53$ for TC versus TT; $P = 0.60$ for dominant model and $P = 0.29$ for recessive model, respectively (Fig. 2).

Discussion

Recently, studies have been carried out to test the hypothesis that *CFH* gene T1277C polymorphism might be associated with the predisposition of CHD, but results were inconsistent. The six case–control studies reported no significant association between the variant and CHD risk [17, 19, 21, 23, 25, 26] while two cohort studies found CC genotype conferred predisposition to CHD development [18, 24]. To produce a more precise result and enhance statistical power, we performed a comprehensive meta-analysis. Through a combination of all available data, this meta-analysis did not yield evidence supporting the association of the *CHF* T1277C polymorphism and CHD susceptibility in general population.

Heterogeneity, which has been found in some comparisons in the present study, might imply different true effect sizes across included studies. Further analyses of exploring heterogeneity sources revealed that heterogeneity in all comparisons could be diminished by excluding the women cohort with the mean age of 60.30 years in Pai's study [22], which showed that the C allele was a protective factor for CHD. Interestingly, Qian et al. reported that the 1277C allele conferred predisposition to early onset CHD but not to late-onset ones [25]. Additionally, Koeijvoets et al. recently reported an association of CC genotype and decreased cardiovascular disease risk in Caucasian patients (mean age: about 49.67 years) with familial hypercholesterolaemia [27]. In contrast with these evidence supporting the key role of early onset of CHD in the association [22, 25], however, Stark et al. reported negative results in Caucasian population at the mean age of 51.40 years [23] and Buraczynska et al. presented an association of the C allele and increased cardiovascular disease risk in end-stage renal disease patients [28]. Taking together, current evidence seems to support the postulation

Table 2 Main results of pooled ORs in the meta-analysis

	CC versus TT		TC versus TT		CC + TC versus TT		CC versus TT + TC	
	OR (95%CI)	$P_{Q\text{-test}}$	OR (95%CI)	$P_{Q\text{-test}}$	OR (95%CI)	$P_{Q\text{-test}}$	OR (95%CI)	$P_{Q\text{-test}}$
Total	1.07 (0.92–1.25)	0.04	1.03 (0.96–1.11)	0.88	1.04 (0.97–1.11)	0.78	1.05 (0.90–1.23)	0.01
Caucasian	1.09 (0.92–1.29)	0.02	1.01 (0.94–1.09)	0.98	1.03 (0.96–1.11)	0.78	1.08 (0.92–1.27)	0.01
Caucasian[a]	0.52 (0.30–0.90)	–	1.03 (0.74–1.43)	–	0.90 (0.66–1.24)	–	0.51 (0.30–0.86)	–
Asian	0.36 (0.01–8.89)	–	1.59 (0.82–3.06)	–	1.50 (0.78–2.86)	–	0.34 (0.01–8.39)	–
Asian[b]	1.13 (0.05–28.17)	–	2.83 (0.11–74.46)	–	0.77 (0.03–19.10)	–	2.37 (1.13–4.96)	–
African-Am	0.91 (0.62–1.32)	–	1.18 (0.93–1.51)	–	1.04 (0.97–1.11)	–	0.82 (0.58–1.17)	–

OR odd ratio, $P_{Q\text{-test}}$ *P* value of Cochrane *Q*-test of heterogeneity, – only one study was included and Cochrane *Q*-test could not be performed

[a] The data of relatively young women in Pai's study

[b] The data of early-onset cohort in Qian's study

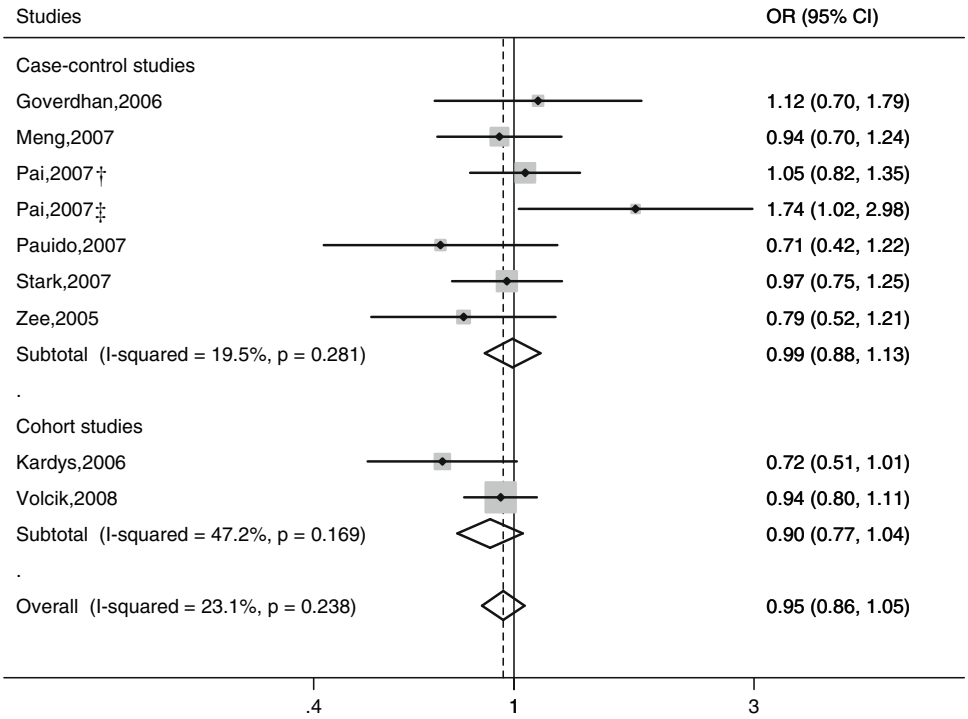

Fig. 1 Pooled OR under dominant model (CC + CT versus TT) for Caucasian subgroup. †, men cohort in the study; ‡, women cohort in the study

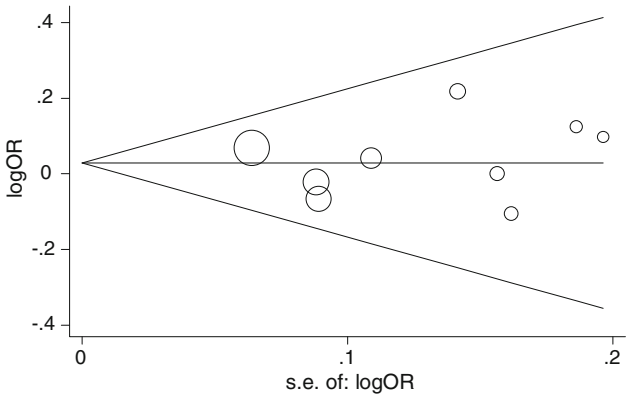

Fig. 2 Begg's plot under dominant model (CC + TC versus CC) for Caucasian subgroup

that the variant might affect CHD risk, but only in some population. The onset age of CHD may not the only factor modulating this association and CHD risk factors status and genetics background may be of potential value. The clarification of the gene effect and identification of potential influential factors require more studies.

Notably, gene effect observed in Caucasians and Asians were inverse [22, 25] and genotypes distributions in Caucasians (C allele 37.04%) were different from the one in Asians (C allele 55.88%). This indicated different genetics backgrounds in the two races but a random error due to small sample in the Asian study [22] could not be completely ruled out. Therefore, more studies are merited to give a demonstration in this population.

Some limitations should be considered in this meta-analysis. Firstly, controls were not uniformly defined. Although most of the controls were randomly selected for healthy population or screened by electrocardiogram, CHD could not be completely ruled out in these subjects. Therefore, misclassification bias may occur [29]. Secondly, sample sizes in African-American and Asian studies were small and results might be over-influenced by random-errors. Thirdly, our results were based on unadjusted estimations and lack of individual patients' data has restricted further adjustments by other CHD risk factors.

Despite limitations, this meta-analysis did not showed evidence on the association between *CFH* T1277C polymorphism and CHD risk. A need for further studies, paying more attention to onset age of CHD, studied ethnicity and different CHD risk factor status (e.g., high risk: CHD patients with diabetes mellitus, smoking, family history and hypertension; low risk: CHD patients with no established risk factor) than is now customary, there is a greater need of updated genetic epidemiology quantitative systematic reviews with proper methodology, to help minimize random error, explore heterogeneity, address publication bias and enhance statistical power [30–32]; thereby helping to better understand the association between the *CFH* T1277C polymorphism and CHD risk and interactions with other CHD risk factors.

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