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REVIEW

The β fibrinogen gene G-455A polymorphism in Asian subjects with coronary heart disease: A meta analysis

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KEYWORDS

β-Fibrinogen gene G-455A;
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Abstract *Background:* There are many studies about the association of β fibrinogen gene G-455A polymorphism and the risk of coronary heart disease (CHD). However, the results of these studies are inconsistent.

Objective: This study aimed to investigate the association of β fibrinogen gene G-455A polymorphism with the risk of CHD using meta analysis. This study was limited to the Asian population.

Methods: Published studies from PubMed, Embase, and CNKI databases (up to December 20th, 2015) were searched for eligible publications. The following information was extracted from each study: (1) name of first author; (2) year of publication; (3) country of origin; (4) sample size of cases and controls, and (5) size of each allele. The combined odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between β fibrinogen gene G-455A polymorphism and the risk of CHD were assessed using random or fixed effect model. A comprehensive meta analysis (CMA) 2.0 was used to analyze the data.

Results: Nineteen studies (4011 cases/3673 controls) regarding the association of β fibrinogen gene G-455A polymorphism and the risk of CHD were included in this meta analysis. The results indicated that β fibrinogen gene G-455A polymorphism was associated with increased (A vs. G: OR 95% CI = 1.42 [1.19–1.70], $p < 0.001$; AA vs. GG + GA: OR 95% CI = 1.60 [1.13–2.26], $p = 0.008$; GA vs. GG + AA: OR 95% CI = 1.30 [1.07–1.58], $p = 0.008$) and decreased the risk of CHD (G vs. A: OR 95% CI = 0.70 [0.59–0.84], $p < 0.001$; GG vs. GA + AA: OR 95% CI = 0.68 [0.55–0.84], $p < 0.001$).

Conclusions: In the Asian population, the β fibrinogen gene G-455A polymorphism was associated with the risk of CHD.

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1. Introduction

Coronary heart disease (CHD), one of the main killers threatening human health [1], a common cause of death worldwide [2], resulting from atherosclerosis and thrombosis or atherothrombosis [3], is a degenerative and inflammatory process that begins within the blood vessel wall, causing it to weaken, enlarge, and eventually impair blood flow through the damaged artery [4]. CHD is the leading cause of death worldwide and has become a true pandemic without borders. World Health Organization (WHO) reported that 3.8 million men and 3.4 million women worldwide died each year caused by CHD, and more than 60% of the global burden of CHD occurred in developing countries [5]. WHO [6] estimated that 17.5 million people died due to cardiovascular disease (CVD) in 2012, representing 31% of all global deaths. Of these deaths, about 7.4 million died due to CHD. The crude mortality rate for CHD in Asia was 39.0 per 100,000 for men and 19.8 per 100,000 for women in 2011. Of these, Kazakhstan had the highest and Japan had the lowest mortality rate [7].

CHD risk factors are classified into traditional risk factors (modifiable i.e.: hypertension, diabetes, hyperlipidemia, obesity, tobacco use, and physical inactivity; and non-modifiable i.e.: age more than 45 years for men and more than 55 years for women, gender, family history of premature CHD) and selected emerging risk factors i.e.: C-reactive protein, small LDL particles, lipoprotein(a), homocysteine, lipoprotein-associated phospholipase A2, coagulation and hemostatic factors, apolipoproteins A and B, and white blood cell count [8]. Coagulation and hemostatic factors play an important role in the pathogenesis of CHD. Folsom et al. [9] studied regarding the association of hemostatic factors and the incidence of CHD. They found that elevated levels of fibrinogen were the risk factors and may play causative roles in CHD. Salomaa et al. [10] studied about the association of hemostatic factors and the risk of CHD in Finland. They showed an increase in the accumulation of fibrinogen on the subject with CHD. Zhang et al. [11] studied about fibrinogen level in Chinese population with CHD. They found that the higher fibrinogen levels were independently linked with the presence and severity of CHD.

Fibrinogen is a coagulation or inflammatory biomarker strongly associated with atherogenesis [11]. Fibrinogen is an abundant plasma protein, highly susceptible to such oxidative modifications, and is therefore a potential marker for oxidative protein damage [12]. Fibrinogen, coagulation factor I, is synthesized in the liver and the plasma concentration is 1–4.0 g/L [13]. Fibrinogen consists of three pairs of polypeptide chains (Aα/Bβ/γ) which are encoded by different genes located at q23–q32 of chromosome 4 [14]. Fibrinogen plays an essential role in the hemostatic system to cause atherosclerosis and thrombosis by bridging activated platelets and being the key substrate for thrombin to establish a consolidating fibrin network [13]. The β fibrinogen gene has been reported to confer susceptibility to thromboembolic diseases and increased plasma fibrinogen levels, and high fibrinogen levels were considered a common risk factor that exists in CHD [15]. Tybjaerg-Hansen et al. [16] showed that the A allele of the β fibrinogen G-455A gene single nucleotide polymorphism (SNP) (rs1800790) was reported to be associated with high plasma fibrinogen levels. Therefore, β fibrinogen gene G-455A polymorphism has an association with the pathogenesis of CHD through increasing levels of fibrinogen.

Several polymorphism studies investigated the association of β fibrinogen gene G-455A polymorphism with the risk of CHD, but they showed inconsistent results. Studies conducted by Ma and Chen [17], Gong et al. [18], Liu et al. [19], Ma et al. [20], Sun et al. [21], Wang et al. [22], Sun et al. [23], Wu et al.

[24], Li [25], and Lu et al. [26] showed that β fibrinogen gene G-455A polymorphism was associated with an increased risk of CHD, whereas, studies conducted by Lam et al. [27], Ma and Chen [28], Lee et al. [29], Jin et al. [30], Yamada et al. [31], Pegoraro et al. [32], Wang et al. [33], Sun et al. [34], and Onrat et al. [35] showed that β fibrinogen gene G-455A polymorphism had no significant association with an increased risk of CHD. Meta analysis study is the solution to determine the actual association of those several studies. Several meta analysis studies, i.e.: Smith et al. [36] in World populations, Gu et al. [2] in Chinese population, and Sabater-Lleal et al. [37] in European, African, and American population have reported the associations of β fibrinogen gene G-455A polymorphism with the risk of CHD, but no meta-analysis study was reported in Asian population. However, most Asian countries have higher mortality from CHD compared with western countries [7]. Therefore, meta analysis study on the association of β fibrinogen gene G-455A polymorphism with the risk of CHD in Asian population was necessary to do.

This study aimed to investigate the association of β fibrinogen gene G-455A polymorphism with the risk of CHD using meta analysis in Asian population. The results of this study are expected to be useful for the future treatment and prevention of CHD. Besides, the results of this study are also expected to be useful as the comparison to other studies regarding the β fibrinogen gene G-455A polymorphism and the risk of CHD.

2. Materials and methods

2.1. Study designs

A meta-analysis was conducted to assess the association of β fibrinogen gene G-455A polymorphism with the risk of CHD in Asian population. To achieve this goal, several studies regarding the β fibrinogen gene G-455A polymorphism with the risk of CHD were collected for calculating combined ORs 95% CI and assessed using fixed or random effect model. Articles were searched in Pubmed, Embase, and China National Knowledge Infrastructure (CNKI). The study was conducted in October 2015–February 2016.

2.2. Study procedures

The procedures of this study were (1) identify the potentially relevant studies through Pubmed, Embase, and CNKI up to December 20th, 2015; (2) determine eligibility of the study, the exclusion was done by several steps, i.e.: (a) by reading the title and abstract, (b) study designs must comply with the inclusion criteria, and (c) provide sufficient data to calculate OR 95% CI; (3) collect abstract and full text data from the studies; (4) collect the data for calculating OR 95% CI; and (5) analyze data statistically.

2.3. Eligibility criteria and data extraction

Eligibility criteria consisted of predefined inclusion and exclusion criteria. Studies were included in the analysis if they met the following inclusion criteria: (1) case–control; (2) cohort; (3) cross-sectional studies; (4) randomized-controlled trials (RCTs); (5) controlled before-and-after studies; (6) cross-over studies; (7) evaluating the associations of β fibrinogen gene G-455A polymorphism with the risk of CHD in Asian countries (Afghanistan, Armenia, Azerbaijan, Bahrain, Bangladesh, Bhutan, Brunei, Cambodia, China, Cyprus, Georgia, India, Indonesia, Iran, Iraq, Israel, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Laos, Lebanon, Malaysia, Maldives, Mongolia, Myanmar, Nepal, North Korea, Oman, Pakistan, Palestine, Philippines, Qatar, Russia, Saudi Arabia, Singapore, South Korea, Sri Lanka, Syria, Taiwan, Tajikistan, Thailand, Timor-Leste, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Vietnam, and Yemen); and (8) providing sufficient data for calculation of OR 95% CI. Some of the required data were extracted from each study for calculating OR 95% CI. The following information was extracted from each study: (1) name of first author; (2) year of publication; (3) country of origin; (4) sample size of cases and controls, (5) size of each allele.

2.4. Search strategy and literature

PubMed, Embase, and CNKI were searched with no language restrictions, using specified search terms to identify studies published up to December 20th, 2015. The search strategy involved the use of combination of the following key words: (β fibrinogen G-455A) and (variant or variation or polymorphism) and (coronary disease or coronary heart disease or coronary artery disease or myocardial infarct or ischemic heart disease or CHD or IHD or MI or cardiovascular disease or heart disease OR angina) in (Asian countries or Afghanistan, Armenia, Azerbaijan, Bahrain, Bangladesh, Bhutan, Brunei, Cambodia, China, Cyprus, Georgia, India, Indonesia, Iran, Iraq, Israel, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Laos, Lebanon, Malaysia, Maldives, Mongolia, Myanmar, Nepal, North Korea, Oman, Pakistan, Palestine, Philippines, Qatar, Russia, Saudi Arabia, Singapore, South Korea, Sri Lanka, Syria, Taiwan, Tajikistan, Thailand, Timor-Leste, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Vietnam, and Yemen). The publication languages were restricted to English. The reference lists of retrieved articles were hand-searched. If more than one article was published using the same study data, only the study with the largest sample size was included.

2.5. Study variables

2.5.1. β fibrinogen G-455A

Fibrinogen is a coagulation or inflammatory biomarker strongly associated with atherogenesis [11]. The measurement results of this variable were G and A allele. Data were obtained by the searching strategy. Nominal scale was used to assess this variable.

2.5.2. Risk of CHD

CHD is a degenerative and inflammatory process that begins within the blood vessel wall, causing it to weaken, enlarge, and eventually impair blood flow through the damaged artery [4]. The measurement results of this variable increased or decreased the risk of CHD. The data were obtained by the

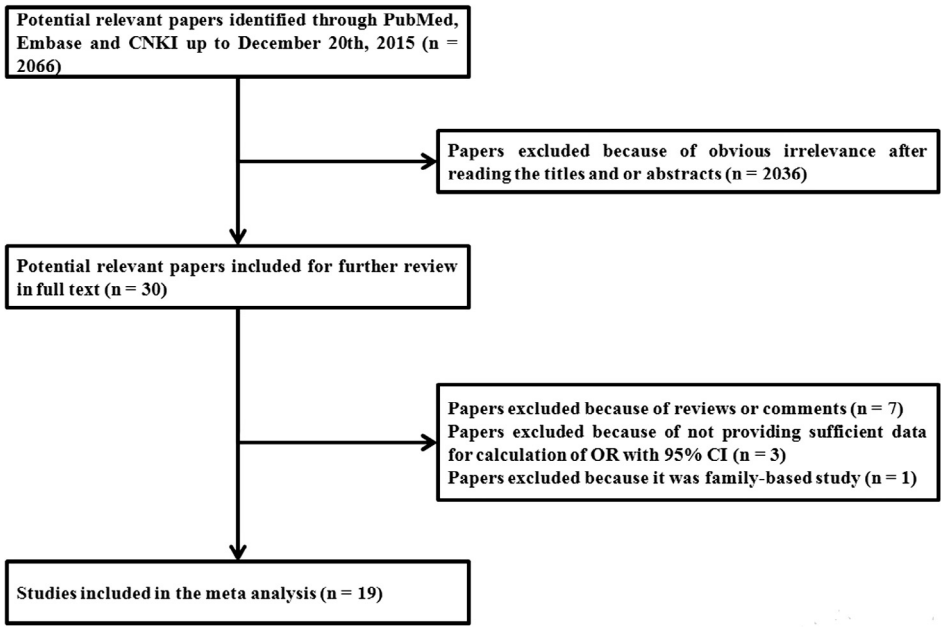

Figure 1 Selection of articles for inclusion in meta-analysis.

Table 1 Characteristics of studies included in the meta-analysis.

Author and year	Country	End point	Source of controls	Sample size	Number of samples		CHD genotype			Control genotype		
					CHD	Control	GG	GA	AA	GG	GA	AA
Ma and Chen (1999) [17]	China	CHD	HB	S	66	53	36	26	4	41	11	1
Lam et al. (1999) [27]	Hongkong	CAD	HB	S	55	209	33	13	9	111	87	11
Ma and Chen (2000) [28]	China	CHD	PB	S	94	68	58	32	4	51	16	1
Lee et al. (2001) [29]	Korea	CAD	PB	L	305	215	204	90	11	148	63	4
Gong et al. (2002) [18]	China	CHD	HB	S	148	173	74	66	8	112	54	7
Jin et al. (2002) [30]	China	CAD	PB	S	224	164	130	85	9	94	64	6
Liu et al. (2002) [19]	China	MI	HB	S	44	273	24	15	5	182	81	10
Ma et al. (2002) [20]	China	MI	HB	S	172	43	90	77	5	37	5	1
Yamada et al. (2002) [31]	Japan	MI	HB	L	445	464	346	96	3	353	104	7
Sun et al. (2004) [21]	China	CHD	PB	S	124	148	77	35	12	107	37	4
Pegoraro et al. (2005) [32]	India	MI	PB	L	195	300	150	43	2	243	57	0
Wang et al. (2005) [22]	China	MI	HB	S	40	40	21	17	2	32	7	1
Sun et al. (2007) [23]	China	CHD	HB	S	121	130	48	63	10	72	50	8
Wang et al. (2007) [33]	China	CAD	PB	S	90	115	48	34	8	74	33	8
Wu et al. (2007) [24]	China	CHD	HB	L	226	182	106	89	31	124	45	13
Li (2008) [25]	China	CHD	HB	S	86	78	44	31	11	58	18	2
Lu et al. (2008) [26]	China	MI	PB	L	508	503	358	144	6	325	162	16
Sun et al. (2009) [34]	China	CHD	PB	L	1019	466	613	372	34	297	151	18
Onrat et al. (2012) [35]	Turkey	MI	PB	S	49	49	27	15	7	25	20	4

Notes: PB, Population-based; HB, Hospital-based; CHD, coronary heart disease; CAD, coronary artery disease; MI, myocardial infarction; S = small (<400); L = large (⩾400).

searching strategy. Nominal scale was used to assess this variable.

2.6. Statistical analysis

The correlation of β fibrinogen gene G-455A polymorphisms with risk of CHD was estimated by calculating pooled ORs and 95% CI. The significance of pooled ORs was determined by Z tests ($p < 0.05$ was considered statistically significant). A Q test was performed to evaluate whether the heterogeneity existed. Random effect model was used to calculate OR 95% CI if heterogeneity existed ($p < 0.10$). Fixed effect model was used to calculate OR 95% CI if no heterogeneity existed. Publication bias was assessed using Egger's test ($p < 0.05$ was considered statistically significant). Subgroup analyses based on cardiovascular end point (CHD = coronary heart disease,

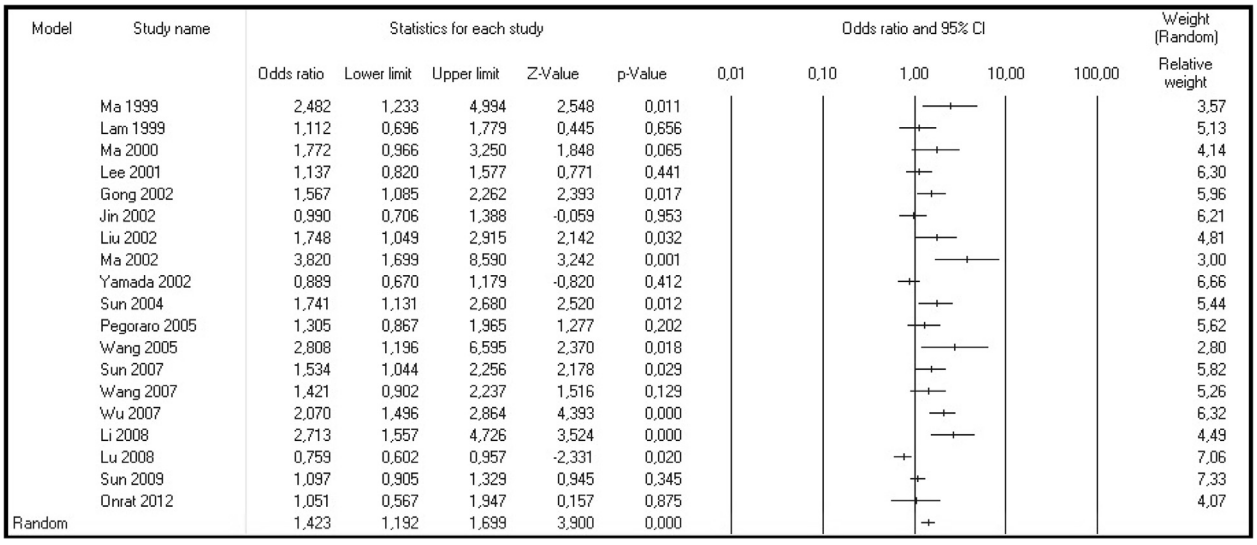

Figure 2 Meta-analysis of the association between β fibrinogen G-455A polymorphisms and CHD risk (A vs. G).

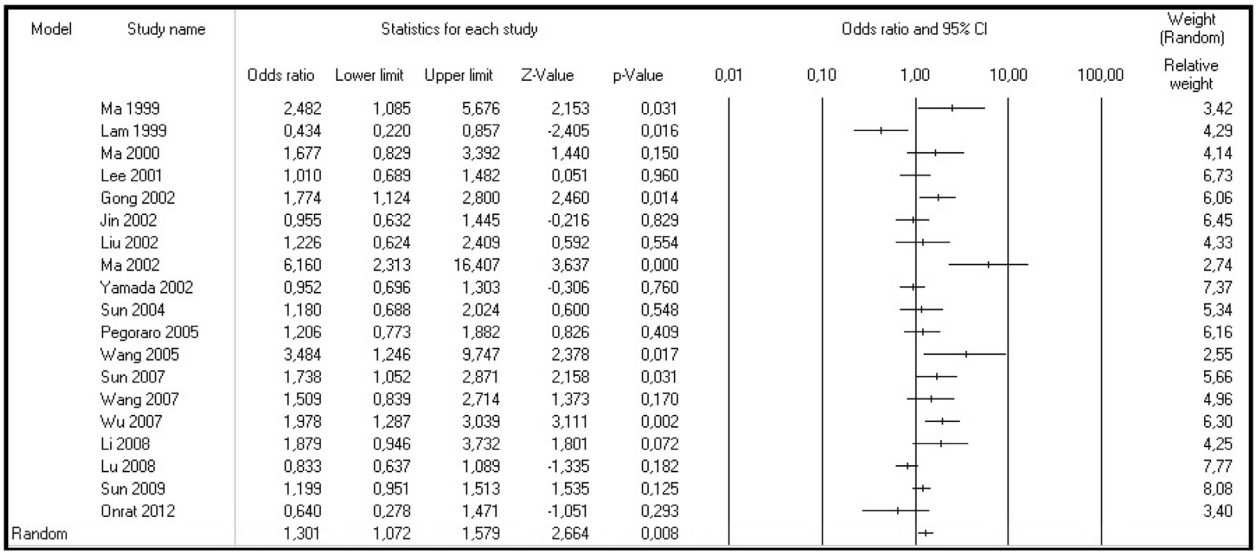

Figure 3 Meta-analysis of the association between β fibrinogen G-455A polymorphisms and CHD risk (GA vs. GG + AA).

CAD = coronary artery disease, MI = myocardial infarction), source of controls (PB = population-based, HB = hospital-based), and sample size (small <400, large $\geqslant 400$ samples) were also performed. A comprehensive meta analysis (CMA) 2.0 was used to analyze the data.

3. Results

3.1. Characteristics of the studies

A total of 2066 potentially relevant papers were identified based on the search strategy. Of these, 2036 papers were excluded because of obvious irrelevance by reading their titles and abstracts. After the full texts were read, three papers were excluded because they did not provide sufficient data for calculation of OR with 95% CI; another paper was excluded because it was a family-based study. In addition, five reviews and two comments were excluded. A flow chart demonstrating the inclusion or exclusion of studies is displayed as Fig. 1. A total of 19 studies were included in the meta analysis. Hongkong, Korea, Japan, India, and Turkey each had only one study, while 14 other studies were from China. Table 1 described the characteristics of the studies included in the meta analysis.

3.2. Quantitative data synthesis

A total of 4011 cases and 3673 controls were identified. Overall, the results showed significant association between β fibrinogen gene G-455A polymorphism with the risk of CHD. The results indicated that β fibrinogen gene G-455A polymorphisms were associated with increased (A vs. G: OR 95% CI = 1.42 [1.19–1.70], $p < 0.001$; AA vs. GG + GA: OR 95% CI = 1.60 [1.13–2.26], $p = 0.008$; GA vs. GG + AA:

Table 2 Summary ORs and 95% CIs of the association between β fibrinogen G-455A polymorphism and CHD risk.

No.	Alleles	Parameter	All	End point			Source of controls		Sample size	
				CHD	CAD	MI	HB	PB	S	L
1	A vs. G	OR	1.42	1.71	1.12	1.34	1.76	0.15	1.62	1.13
		95% CI	1.19–1.70	1.34–2.18	0.93–1.36	0.93–1.93	1.33–2.33	0.96–1.38	1.34–1.97	0.87–1.47
		P	<0.001	<0.001	0.217	0.116	<0.001	0.131	<0.001	0.369
		P_H	<0.001	0.004	0.666	<0.001	<0.001	0.016	0.025	<0.001
		P_E	0.319	0.274	<0.001	0.413	0.367	0.201	0.243	0.296
2	AA vs. GG + GA	OR	1.60	1.57	1.84	1.23	1.99	1.31	2.08	1.02
		95% CI	1.13–2.26	1.12–2.21	1.09–3.08	0.52–2.91	1.39–2.87	0.78–2.19	1.47–2.94	0.52–2.01
		P	0.008	0.009	0.021	0.639	<0.001	0.303	<0.001	0.945
		P_H	0.043	0.158	0.362	0.039	0.337	0.070	0.732	0.020
		P_E	0.453	0.370	0.137	0.822	0.217	0.501	<0.001	0.626
3	GA vs. GG + AA	OR	1.30	1.47	0.92	1.27	1.65	1.06	1.47	1.12
		95% CI	1.07–1.58	1.26–1.72	0.62–1.37	0.86–1.87	1.14–2.38	0.94–1.21	1.08–1.98	0.90–1.39
		P	0.008	<0.001	0.703	0.224	0.008	0.343	0.014	0.316
		P_H	<0.001	0.278	0.056	<0.001	<0.001	0.310	<0.001	0.024
		P_E	0.327	0.117	0.310	0.417	0.493	0.086	0.440	0.209
4	G vs. A	OR	0.70	0.58	0.88	0.75	0.57	0.87	0.62	0.89
		95% CI	0.59–0.84	0.54–0.74	0.73–1.07	0.52–1.07	0.43–0.75	0.72–1.04	0.51–0.75	0.68–1.16
		P	<0.001	<0.001	0.217	0.116	<0.001	0.131	<0.001	0.369
		P_H	<0.001	0.004	0.666	<0.001	<0.001	0.016	0.025	<0.001
		P_E	0.319	0.274	<0.001	0.413	0.367	0.201	0.243	0.296
5	GG vs. GA + AA	OR	0.68	0.53	0.94	0.72	0.52	0.88	0.58	0.86
		95% CI	0.55–0.84	0.41–0.70	0.74–1.18	0.48–1.09	0.36–0.74	0.73–1.07	0.45–0.76	0.65–1.15
		P	<0.001	<0.001	0.611	0.126	<0.001	0.196	<0.001	0.317
		P_H	<0.001	0.017	0.342	<0.001	<0.001	0.069	0.003	<0.001
		P_E	0.376	0.281	0.081	0.468	0.494	0.182	0.371	0.314

Notes: OR, odds ratio; CI, confidence interval; *P*, *P* value based on *Z* test between-study; P_H, *P* value based on *Q* test for between-study heterogeneity; P_E, *P* value based on Egger's test between-study; PB, population-based; HB, hospital-based; CHD, coronary heart disease; CAD, coronary artery disease; MI, myocardial infarction; S, small (<400); L, large (⩾400).

OR 95% CI = 1.30 [1.07–1.58], $p = 0.008$) and decreased the risk of CHD (G vs. A: OR 95% CI = 0.70 [0.59–0.84], $p < 0.001$; GG vs. GA + AA: OR 95% CI = 0.68 [0.55–0.84], $p < 0.001$). Forest plot regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD is described in Fig. 2 for A vs. G and Fig. 3 for the GA vs. GG + AA, while, summary ORs and 95% CIs regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD is described in Table 2. In the subgroup analysis, the β fibrinogen gene G455A polymorphism was associated with the risk of CHD in all genetic model of CHD end point subgroup (A vs. G $p < 0.001$; AA vs. GG + GA $p = 0.009$; GA vs. GG + AA $p < 0.001$; G vs. A $p < 0.001$; GG vs. GA + AA $p < 0.001$), one genetic model of CAD end point subgroup (AA vs. GG + GA $p = 0.021$), all genetic model of HB source of control subgroup (A vs. G $p < 0.001$; AA vs. GG + GA $p < 0.001$; GA vs. GG + AA $p = 0.008$; G vs. A $p < 0.001$; GG vs. GA + AA $p < 0.001$), and all genetic model of small sample size subgroup (A vs. G $p < 0.001$; AA vs. GG + GA $p < 0.001$; GA vs. GG + AA $p = 0.014$; G vs. A $p < 0.001$; GG vs. GA + AA $p < 0.001$), while, the β fibrinogen gene G455A polymorphism had no significant association with the risk of CHD in four genetic models of CAD end point subgroup (A vs. G $p = 0.217$; GA vs. GG + AA $p = 0.703$; G vs. A $p = 0.217$; GG vs. GA + AA $p = 0.611$), all genetic model of MI end point subgroup (A vs. G $p = 0.116$; AA vs. GG + GA $p = 0.639$; GA vs. GG + AA $p = 0.224$; G vs. A $p = 0.116$; GG vs. GA + AA $p = 0.126$), all genetic model of PB source of control subgroup (A vs. G $p = 0.131$; AA vs. GG + GA $p = 0.303$; GA vs. GG + AA $p = 0.343$; G vs. A $p = 0.131$; GG vs. GA + AA $p = 0.196$), and all genetic model of large sample size subgroup (A vs. G $p = 0.369$; AA vs. GG + GA $p = 0.945$; GA vs. GG + AA $p = 0.316$; G vs. A $p = 0.369$; GG vs. GA + AA $p = 0.317$).

3.3. Source of heterogeneity

Evidence for heterogeneity ($p < 0.10$) between studies was found in all multiplication (A vs. G, $p < 0.001$; AA vs. GG + GA, $p = 0.043$; GA vs. GG + AA, $p < 0.001$; G vs. A, $p < 0.001$; GG vs. GA + AA, $p < 0.001$). Therefore, the data in this study were assessed using random effects model. Summary evidence of heterogeneity regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD is described in Table 2. In the subgroup analysis, evidence for heterogeneity was found in CHD end point subgroup (A vs. G $p = 0.004$; G vs. A $p = 0.004$; GG vs. GA + AA $p = 0.017$), MI end point subgroup (A vs. G $p < 0.001$; AA vs. GG + GA $p = 0.039$; GA vs. GG + AA $p < 0.001$; G vs. A $p < 0.001$; GG vs. GA + AA $p < 0.001$), HB source of control subgroup (A vs. G $p < 0.001$; GA vs. GG + AA $p < 0.001$; G vs. A $p < 0.001$; GG vs. GA + AA $p < 0.001$), PB source of control subgroup (A vs. G $p = 0.016$; G vs. A $p = 0.016$), small sample size subgroup (A vs. G $p = 0.025$; GA vs. GG + AA $p < 0.001$; G vs. A $p = 0.025$; GG vs. GA + AA $p = 0.003$), and large sample size subgroup (A vs. G $p < 0.001$; AA vs. GG + GA

$p = 0.020$; GA vs. GG + AA $p = 0.024$; G vs. A $p < 0.001$; GG vs. GA + AA $p < 0.001$). Therefore, random effects model was used to calculate OR 95% CI in these subgroup, while, no evidence for heterogeneity was found in CHD end point subgroup (AA vs. GG + GA $p = 0.158$; GA vs. GG + AA $p = 0.278$), CAD end point subgroup (A vs. G $p = 0.666$; AA vs. GG + GA $p = 0.362$; GA vs. GG + AA $p = 0.056$; G vs. A $p = 0.666$; GG vs. GA + AA $p = 0.342$), HB source of control subgroup (AA vs. GG + GA $p = 0.337$), PB source of control subgroup (AA vs. GG + GA $p = 0.070$; GA vs. GG + AA $p = 0.310$; GG vs. GA + AA $p = 0.069$), and small sample size subgroup (AA vs. GG + GA $p = 0.732$). Therefore, fixed effect model was used to calculate OR 95% CI in these subgroup.

3.4. Potential publication bias

Using Egger's test, no publication bias could be detected (A vs. G, $p = 0.319$; AA vs. GG + GA, $p = 0.453$; GA vs. GG + AA, $p = 0.327$; G vs. A, $p = 0.319$; GG vs. GA + AA, $p = 0.376$). Summary Egger's test regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD is described in Table 2. In the subgroup analysis, no publication bias was detected in CHD end point subgroup (A vs. G $p = 0.274$; AA vs. GG + GA $p = 0.370$; GA vs. GG + AA $p = 0.117$; G vs. A $p = 0.274$; GG vs. GA + AA $p = 0.281$), CAD end point subgroup (AA vs. GG + GA $p = 0.137$; GA vs. GG + AA $p = 0.310$; GG vs. GA + AA $p = 0.081$), MI end point subgroup (A vs. G $p = 0.413$; AA vs. GG + GA $p = 0.822$; GA vs. GG + AA $p = 0.417$; G vs. A $p = 0.413$; GG vs. GA + AA $p = 0.468$), HB source of control subgroup (A vs. G $p = 0.367$; AA vs. GG + GA $p = 0.217$; GA vs. GG + AA $p = 0.493$; G vs. A $p = 0.367$; GG vs. GA + AA $p = 0.494$), PB source of control subgroup (A vs. G $p = 0.201$; AA vs. GG + GA $p = 0.501$; GA vs. GG + AA $p = 0.086$; G vs. A $p = 0.201$; GG vs. GA + AA $p = 0.182$), small sample size subgroup (A vs. G $p = 0.243$; GA vs. GG + AA $p = 0.440$; G vs. A $p = 0.243$; GG vs. GA + AA $p = 0.371$), and large sample size subgroup (A vs. G $p = 0.296$; AA vs. GG + GA $p = 0.626$; GA vs. GG + AA $p = 0.209$; G vs. A $p = 0.296$; GG vs. GA + AA $p = 0.314$), while, publication bias was detected in CAD end point subgroup (A vs. G $p < 0.001$; G vs. A $p < 0.001$) and small sample size subgroup (AA vs. GG + GA $p < 0.001$).

4. Discussion

Fibrinogen is a coagulation or inflammatory biomarker strongly associated with atherogenesis [11]. Fibrinogen plays an essential role in the hemostatic system by bridging activated platelets and being the key substrate for thrombin to establish a consolidating fibrin network [13]. Several prospective and cross-sectional studies have revealed that plasma fibrinogen levels had a strong predictive value for CHD. Folsom et al. [9] studied about the association of fibrinogen levels and the incidence of CHD. They found that elevated levels of fibrinogen were risk factors and may play causative roles in CHD. Salomaa et al. [10] studied about the association of fibrinogen and the risk of CHD in Finland. They showed that an elevated level of fibrinogen was associated with the risk of CHD. Zhang et al. [11] studied about the association of fibrinogen level with the risk of CHD in Chinese population. They found that a higher fibrinogen level was independently linked with the presence and severity of CHD. Eriksson et al. [38] studied about the association of plasma fibrinogen with the risk of CHD. They found that plasma fibrinogen was associated with an excess risk of CHD. Because of the effects of fibrinogen on inflammatory response, a series of studies have focused on the contribution of polymorphisms within fibrinogen cluster genes to the risk of CHD. However, results have been contradictory. This study reported the association of β fibrinogen gene G-455A polymorphism with the risk of CHD, although there were still the limited power of meta analysis due to size and heterogeneity of studies.

This results suggested that β fibrinogen gene G-455A polymorphism was associated with increased (A vs. G: OR 95% CI = 1.42 [1.19–1.70], $p < 0.001$; AA vs. GG + GA: OR 95% CI = 1.60 [1.13–2.26], $p = 0.008$; GA vs. GG + AA: OR 95% CI = 1.30 [1.07–1.58], $p = 0.008$) and decreased the risk of CHD (G vs. A: OR 95% CI = 0.70 [0.59–0.84], $p < 0.001$; GG vs. GA + AA: OR 95% CI = 0.68 [0.55–0.84], $p < 0.001$) in Asian population. Summary of ORs 95% CIs, correlation, heterogeneity, and Egger's test regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD is described in Table 2 while study characteristics are described in Table 1. Forest plot regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD is described in Fig. 2 for A vs. G and Fig. 3 for the GA vs. GG + AA. Previous meta-analysis studies have also reported the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD in different population. Smith et al. [36] studied about the association of β fibrinogen gene G-455A polymorphism with the risk of CHD in World populations. They showed a significant association between β fibrinogen gene G-455A polymorphism and the risk of CHD (OR 95% CI = 0.976 [0.916–1.040]). Gu et al. [2] studied about the association of β fibrinogen gene G-455A polymorphism with the development of CHD in Chinese population. They found that β fibrinogen gene G-455A polymorphism was associated with the development of CHD (OR 95% CI = 1.802 [1.445–2.246]). Sabater-Lleal et al. [37] studied about the correlation of 23 fibrinogen genes including β fibrinogen G-455A and the risk of CHD in European, African, and American population. They found all 23 fibrinogen-associated lead single nucleotide polymorphisms were not significant for CHD. Chen et al. [39] conducted a study on the correlation between the β fibrinogen gene -148C/T and -455G/A polymorphisms with the risk of CHD in Chinese population. They found that β fibrinogen gene G-455A polymorphism (in particular, allele A) increased susceptibility to CHD (OR 95% CI = 1.75 [1.24–2.46]). Li et al. [1] conducted a meta analysis study regarding the relationship between APO A5 -1131T/C, β fibrinogen G-455A, -148C/T, and CETP TaqIB gene polymorphisms with the risk of CHD in Chinese population. They found a significant association between β fibrinogen G-455A gene polymorphism with CHD susceptibility (OR 95% CI = 1.50 [1.25–1.81]). The results of this study had similarities with several meta-analysis studies regarding β fibrinogen gene G-455A polymorphism related to the risk of CHD, except a study by Sabater-Lleal et al. [37]. This difference was unexplainable. However, the possibilities were because of too many genes observed by Sabater-Lleal et al. [37]. Therefore, it would affect the final results. In addition,

no OR 95% CI of each allele group in Sabater-Lleal et al. [37] was provided. Therefore, the association was immeasurable. Furthermore, in the subgroup analysis, the β fibrinogen gene G455A polymorphism was associated with the risk of CHD in all genetic model of CHD end point subgroup, one genetic model of CAD end point subgroup (AA vs. GG + GA), all genetic model of HB source of control subgroup, and all genetic model of small sample size subgroup, while, the β fibrinogen gene G455A polymorphism had no significant association with the risk of CHD in four genetic models of CAD end point subgroup (A vs. G; GA vs. GG + AA; G vs. A; GG vs. GA + AA), all genetic model of MI end point subgroup, all genetic model of PB source of control subgroup, and all genetic model of large sample size subgroup. However, these results should be interpreted with caution because the relatively small sample size or multiple testing could drive false positive findings.

These results also indicated that the A allele of β fibrinogen gene G-455A was correlated with susceptibility to the risk of CHD, while the G allele was correlated with reduced risk of CHD. See Table 2 for detail about summary of ORs 95% CIs regarding the correlation of β fibrinogen gene G-455A polymorphism with the risk of CHD. Theoretically, these results were unexplainable clearly. However, several studies had supported these results. Theodoraki et al. [40] conducted a study regarding the effect of fibrinogen A (FGA), fibrinogen B (FGB), and fibrinogen G (FGG) genes SNPs and haplotypes on susceptibility to CAD in a homogeneous Greek population. They showed that rs1800789 or G allele of β fibrinogen G-455A seem to confer protection to CHD. Rallidis et al. [41] conducted a study regarding the association of β fibrinogen gene G-455A with development of myocardial infarction. They found that the presence of the G allele of β fibrinogen G-455A had a protective effect against the development of non-fatal myocardial infarction ⩽35 years of age in Greek population. Other studies showed that A allele of β fibrinogen G-455A was associated with an increased risk of CHD. Smith et al. [36] conducted a meta analysis regarding the relationship between β fibrinogen G-455A with CHD risk in World populations. They showed a significant association between A allele of β fibrinogen G-455A and an increased risk of CHD (OR 95% CI = 0.976 [0.916–1.040]). Chen et al. [39] conducted a meta analysis regarding correlation of β fibrinogen gene -148C/T and -455G/A polymorphisms and susceptibility to CHD in Chinese population. They showed that A allele of β fibrinogen G-455A increased susceptibility to CHD (OR 95% CI = 1.75 [1.24–2.46]). A study by Folsom et al. [42] analyzed regarding the relationship between β fibrinogen G-455A with CHD risk. They found that plasma fibrinogen was higher significantly in A allele of β fibrinogen G-455A. Papageorgiou et al. [43] conducted a study on the effects of the G455A and the G58A fibrinogen genetic polymorphisms on prothrombotic profile, endothelial function and the risk of CHD in a Caucasian population. They found that A allele of β fibrinogen G-455A was associated with increased fibrinogen levels, although no significant effect was observed. Therefore, the results of this study that showed A allele of β fibrinogen G-455A correlated with the susceptibility of CHD was possible because A allele of β fibrinogen G-455A had an association with increased levels of plasma fibrinogen. In the previous discussion we explained that the increased level of plasma fibrinogen had a close correlation with the risk of CHD as reported by Folsom et al. [9], Salomaa et al. [10], Zhang et al. [11], and Eriksson et al. [38].

Atherosclerosis plays an important role in the occurrence of CHD [3]. The role of fibrinogen in the atherosclerosis process is complex. The role of fibrinogen to cause atherosclerosis includes: (1) fibrinogen is bound to platelet GpIIb/IIIa membrane receptors and forms a web that provides stability to the newly-formed thrombus, (2) fibrinogen promotes the adhesion of platelets and white blood cells to the endothelial surface [40], (3) fibrinogen is involved in the earliest stages of plaque formation to encourage smooth muscle cell (SMC) migration and proliferation, and contribute to the growth of plaques [44], (4) fibrin influences accumulation of the lipid core in fibrous plaques which appears to bind the lipoprotein Lp(a) with high affinity, thereby immobilizing its lipid moiety within the lesion [45], (5) fibrinogen regulates or controls the expression of P-selectin during the formation and or development of atherosclerosis and thus facilitates atherosclerotic lesion development and promotes plaque formation [46]. These mechanisms are thought to underlie the results of this study that showed a correlation between β fibrinogen gene G-455A polymorphism with the risk of CHD.

There were several limitations in the meta-analysis. First, this analysis was primarily based on unadjusted effect estimates. Therefore, the potential covariates including age, gender, and environmental factors such as smoking and levels of HDL cholesterol, which might influence the effect estimates, were not controlled for. Second, the possibility of a false negative remains due to the small size of the studies even when combined. Thus, further studies with a larger sample size are required to investigate the associations. Third, this study could not be generalized to the all Asian population because most samples of this study were Chinese population, while the population of other Asian countries was very limited.

5. Conclusions and suggestions

In summary, this meta analyses suggested that β fibrinogen gene G-455A polymorphism was associated with decreased and increased the risk of CHD in Asian population. Further studies considering gene–environment interactions should be conducted to investigate the associations between β fibrinogen gene G-455A polymorphisms and the risk of CHD. It is necessary to study the correlation of β fibrinogen gene G-455A polymorphisms with the risk of CHD in Kazakhstan, a country with the highest mortality rate of CHD in Asia, because none of the studies reported the correlation of β fibrinogen gene G-455A polymorphisms with the risk of CHD in Kazakhstan.

Note

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Author contributions

Conceived and designed the experiments, Jonny Karunia Fajar (JKF). Performed the experiments, JKF. Analyzed the data,

JKF. Contributed reagents/material/analysis tools, JKF. Wrote the manuscript, JKF. Reference collection and data management, JKF. Statistical analyses and paper writing, JKF. Study design, JKF.

Conflicts of interest

The authors declared that there is no conflict of interest regarding the publication of this paper.

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