Association between KIF6 rs20455 polymorphism and the risk of coronary heart disease (CHD): a pooled analysis of 50 individual studies including 40,059 cases and 64,032 controls

Yan Li 1*, Zhen Chen 2† and Hejian Song 3

Abstract

Background: The KIF6 rs20455 polymorphism has been verified as an important genetic factor of coronary heart disease (CHD), but with controversial results. The aim of this study was to explore the association between KIF6 rs20455 polymorphism and susceptibility to CHD.

Methods: All eligible studies were identified by searching Medline (mainly PubMed), EMBASE, the Web of Science, Cochrane Collaboration Database, Chinese National Knowledge Infrastructure, Wanfang Database and China Biological Medicine up to October 5, 2016. Odds ratios (ORs) with 95% confidence interval (CI) were used to explore the association between KIF6 rs20455 polymorphism and CHD risk. Begg’s and Egger’s tests were used to examine the publication bias. Subgroup analysis and sensitivity analysis were performed to test the reliability and stability of the results. All the analyses were carried out by Stata 12.0 software.

Results: A total of 28 publications including 50 individual studies were analyzed in this present work. There are no significant association found between KIF6 rs20455 polymorphism and CHD risk (Homozygote model: OR = 1.007, 95% CI = 0.952–1.066, P = 0.801; Heterozygote model: OR = 1.009, 95% CI = 0.968–1.052, P = 0.636; Dominant model: OR = 1.007, 95% CI = 0.966–1.048, P = 0.753; Recessive model: OR = 0.989, 95% CI = 0.943–1.037, P = 0.655; Allele comparison model: OR = 1.00, 95% CI = 0.971–1.030, P = 0.988). Furthermore, subgroup analyses were performed by ethnicity, source of control.

Conclusions: Our result suggests that KIF6 rs20455 polymorphism may not be associated with CHD susceptibility. However, additional very well-designed large-scale studies are warranted to confirm our results.

Keywords: Coronary heart disease, KIF6 rs20455, Polymorphism, Meta-analysis

Background

Coronary heart disease (CHD), a multifactorial heart disorder resulting from both environmental and genetic factors [1], is one of the leading causes of disability and death around the world [2]. Epidemiology studies have suggested that hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking are major risk factors for CHD [3]. In recent years, more and more studies revealed that several loci and variants are strongly associated with CHD [4, 5]. It has been estimated that approximately 50% of the variability of the major risk factors for CHD is determined by genetics [6].

The KIF6 protein is one of several molecular components that mediate intracellular transport of organelles, protein complexes, and mRNAs. A common Trp719Arg (rs20455) SNP in exon 19 of the KIF6 gene has been identified as a potential risk factor for CHD [7, 8]. The
KIF6 protein belongs to the kinesin superfamily, which is involved in the intracellular transport in a microtubule and ATP-dependent manner [9]. The rs20455 polymorphism replaces the nonpolar 'Trp' residue in codon 719 with a basic 'Arg' amino acid. This SNP lies near the putative cargo binding domain, and may alter the cargo activity of KIF6 [10]. Carriers of the 719Arg allele exhibit a 50% increased risk of events compared with non-carriers [8, 11].

Up to now, multiple large prospective and case–control studies have reported the association between KIF6 rs20455 polymorphism and the risk of CHD. However, some studies have not verified inconsistent results. Published studies have generally been restricted in terms of sample size and ethnic diversity, and individual studies may have insufficient power to achieve a comprehensive and reliable conclusion. In view of the discrepancies in the findings of previous published studies, we aimed to perform a meta-analysis of the published studies to clarify the association between KIF6 rs20455 polymorphism and CHD to get a better understanding of this relationship.

**Methods**

**Literature search**

A comprehensive search for all related studies from both electric databases, such as, Medline (mainly PubMed), Embase, Web of science, China National Knowledge Infrastructure (CNKI) et al., and hand search from references of all eligible literatures. Single or combinations of the following keywords were used: "kinesin like protein 6" or "KIF6" or "rs20455" or "719Arg", "single nucleotide polymorphism, SNP or variation, mutation", "genetic association" and "coronary heart disease" or "CHD". No language and sample size were set. When more than one studies of the same population were included in several publications, only the most recent or complete studies were included in this meta-analysis.

**Selection criteria**

Articles included should meet following criteria: an appropriate description of KIF6 rs20455 polymorphism in CHD cases and healthy controls; results expressed as odds ratio (OR); and studies with a 95% confidence interval (CI) for OR with sufficient data to calculate these numbers. While for the exclusion criteria provided as follows: studies without raw data; case-only studies, family-based studies, case reports, editorials, and review articles (including meta-analyses). In studies with overlapping cases/controls, the study with the higher quality score or the study with more information on the origin of the cases/controls was included in the meta-analysis.

**Data extraction**

Two researchers extracted important information independently and carefully from all eligible studies according to the criteria listed above. Any disagreement will be resolved by the two authors through discussion or the third author. The following data were extracted from each included study: first author's surname, year of publication, country, ethnicity, genotyping method, source of control, total number of cases and controls, distributions of KIF6 rs20455 genotypes. Different ethnicity descents were categorized as Caucasian, Asian, and Mixed populations (the original studies didn't clarify the race of the subjects or mixed races).

**Statistical analysis**

We adopted pooled ORs and corresponding 95% confidence interval (CIs) to detect the association between KIF6 rs20455 polymorphism and CHD risk. Heterogeneity was explored by Q statistic [12], and the P value was <0.05 will be considered statistically significant. Heterogeneity was also assessed using the I² statistic, which takes values between 0% and 100% with higher values denoting greater degree of heterogeneity (I² = 0–25%: no heterogeneity; I² = 25–50%: moderate heterogeneity; I² = 50–75%: large heterogeneity; I² = 75–100%: extreme heterogeneity) [13]. Different statistical models will be selected according to the result of heterogeneity. Random (Der Simonian-Laird method) [14] will be used to calculate the precise results when the P value of heterogeneity was <0.05, or the I² > 50%. Otherwise, fixed effects model (Mantel-Haenszel method) will be adopted [15]. Five genetic comparison model were carried out and calculated as follows: homozygote model (GG vs. AA), heterozygote model (AG vs. AA), recessive model (GG vs. AG + AA), and dominant model (GG + AG vs. AA), and allele comparison model (G-allele vs. A-allele). Hardy-Weinberg equilibrium in the control group was tested by the chi-square test for goodness of fit, and a P value of <0.05 was considered significant. Subgroup analyses were performed by ethnicity, source of control, to confirm if our results were stable and robust [16]. Begg's funnel plots [17] and Egger's test [18] were explored to examine if potential publication bias were existed in this study. Sensitivity analysis was carried out by sequentially omitting each study and finding the influence on the overall summary estimate [19]. All the statistical analyses were finished by STATA software (version 12.0; Stata Corporation, College Station, TX). All the P values were two-sided.

**Results**

**Characteristics of all included studies**

Totally, 209 potential relevant studies were searched through several databases. Based on the including criteria listed above, only 28 articles including 50 separate studies were included finally [8, 20–46]. A flow diagram summarizing the process of study selection was present
The baseline characteristics of all included studies were listed in Table 1. Helgadottir et al. contained two individual studies [25], Samani et al. contained two individual studies [26], Assimes et al. contained 20 individual studies [31], and Wu et al. contained two separate studies [41]. Moreover, there were 37 studies from Caucasian decedent, 9 studies from Asian populations and the rest 14 studies from mixed populations. There were 20 population-based (PB) studies, 21 hospital-based (HB) studies and four family based (FB) study, three community based (CB) study, two hospital and community based (H-CB) study. Different ethnicity descents were categorized as Caucasian, Asian and Mix (the original studies didn’t clarify the race of the subjects or mixed races).

Quantitative synthesis
All the eligible data were calculated and significant heterogeneity was detected under homozygote ($I^2 = 33.9\%$; $P_{\text{heterogeneity}} = 0.012$), heterozygote ($I^2 = 35.5\%$; $P_{\text{heterogeneity}} = 0.008$), dominant ($I^2 = 39.8\%$; $P_{\text{heterogeneity}} = 0.002$), recessive ($I^2 = 26.5\%$; $P_{\text{heterogeneity}} = 0.047$) and allele comparison model ($I^2 = 44.2\%$; $P_{\text{heterogeneity}} = 0.001$) between this gene variation and the risk of CHD. So, random-effect model was used to calculate the statistical parameters. Overall, there were no significant association existed between KIF6 rs20455 polymorphism and the risk of CHD (Homozygote model: OR = 1.007, 95% CI = 0.952–1.066, $P = 0.801$, Fig. 2; Heterozygote model: OR = 1.009, 95% CI = 0.968–1.052, $P = 0.636$, Fig. 3; Dominant model: OR = 1.007, 95% CI = 0.966–1.048, $P = 0.753$, Fig. 4; Recessive model: OR = 0.989, 95% CI = 0.943–1.037, $P = 0.655$, Fig. 5; Allele comparison model: OR = 1.00, 95% CI = 0.971–1.030, $P = 0.988$, Fig. 6). Furthermore, we explored the subgroup analyses by ethnicity and source of control. All the results were listed in Table 2.

Sensitivity analysis
The sensitivity analysis was performed to evaluate the influence of each individual study on the pooled OR by omitting every single study. The analysis results reflected that our results were statistically stable and reliable.

Publication bias
There was no significant publication bias found in the meta-analysis, reflected by $P$ values from Begg’s correlation (Heterozygote model: $P = 0.089$; Dominant model: $P = 0.061$; Allele comparison model: $P = 0.052$, Fig. 7)
| Author          | Year  | Country | Ethnicity | Control source | Case    | Control | $P_{HWE}$ |
|-----------------|-------|---------|-----------|----------------|---------|---------|-----------|
|                 |       |         |           |                | $AA$    | $AG$    | $GG$      | $AA$ | $AG$ | $GG$ |
| Berglund et al. | 1993  | Sweden  | Caucasian | PB             | 86      | 99      | 35        | 38   | 13   | 33   |
| Vartiainen et al.| 2000  | Finland | Caucasian | PB             | 167     | 172     | 64        | 81   | 22   | 73   |
| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
| Low et al.      | 2005  | USA     | Caucasian | HB             | 204     | 260     | 89        | 86   | 29   | 114  |
| Helgadottir et al. | 2007 | USA     | Caucasian | PB             | 875     | 497     | 370       | 399  | 106  | 174  |
| Helgadottir et al. | 2007 | USA     | Caucasian | PB             | 933     | 468     | 359       | 441  | 133  | 194  |
| Samani et al.   | 2007  | Germany | Caucasian | PB             | 1126    | 1277    | 447       | 529  | 150  | 522  |
| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
| Low et al.      | 2005  | USA     | Caucasian | HB             | 204     | 260     | 89        | 86   | 29   | 114  |
| Vartiainen et al.| 2000  | Finland | Caucasian | PB             | 167     | 172     | 64        | 81   | 22   | 73   |
| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
| Low et al.      | 2005  | USA     | Caucasian | HB             | 204     | 260     | 89        | 86   | 29   | 114  |
| Helgadottir et al. | 2007 | USA     | Caucasian | PB             | 875     | 497     | 370       | 399  | 106  | 174  |
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| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
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| Vartiainen et al.| 2000  | Finland | Caucasian | PB             | 167     | 172     | 64        | 81   | 22   | 73   |
| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
| Low et al.      | 2005  | USA     | Caucasian | HB             | 204     | 260     | 89        | 86   | 29   | 114  |
| Helgadottir et al. | 2007 | USA     | Caucasian | PB             | 875     | 497     | 370       | 399  | 106  | 174  |
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| Samani et al.   | 2007  | Germany | Caucasian | PB             | 1126    | 1277    | 447       | 529  | 150  | 522  |
| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
| Low et al.      | 2005  | USA     | Caucasian | HB             | 204     | 260     | 89        | 86   | 29   | 114  |
| Vartiainen et al.| 2000  | Finland | Caucasian | PB             | 167     | 172     | 64        | 81   | 22   | 73   |
| Senti et al.    | 2001  | Spain   | Caucasian | PB             | 312     | 317     | 134       | 139  | 39   | 141  |
| Yusuf et al.    | 2004  | Several | Asian     | PB             | 1092    | 1187    | 351       | 498  | 243  | 389  |
| Low et al.      | 2005  | USA     | Caucasian | HB             | 204     | 260     | 89        | 86   | 29   | 114  |
| Helgadottir et al. | 2007 | USA     | Caucasian | PB             | 875     | 497     | 370       | 399  | 106  | 174  |
| Helgadottir et al. | 2007 | USA     | Caucasian | PB             | 933     | 468     | 359       | 441  | 133  | 194  |
and Egger’s regression (Homozygote model: $P = 0.070$; Dominant model: $P = 0.058$; Allele comparison model: $P = 0.066$, Fig. 8). However, significant publication bias found in the meta-analysis, reflected by $P$ values from Begg’s correlation (Homozygote model: $P = 0.046$; Recessive model: $P = 0.025$) and Egger’s regression (Homozygote model: $P = 0.041$; Recessive model: $P = 0.040$). All the results are listed in Table 2.

**Discussion**

Large sample and unbiased epidemiological studies of predisposition genes polymorphisms could provide insight into the in vivo relationship between candidate genes and complex diseases. Many epidemiological studies have investigated the relationship between the KIF6 rs20455 polymorphism and the risk of CHD, but because of small sample size and the low statistical power of individual studies, results have been contradictory. In this present study, we searched all eligible studies to date and got the precise result if KIF6 rs20455 polymorphism could contribute to the risk of CHD. To the best of our knowledge, our present work was the most comprehensive one through enrolling all eligible studies.

Herein, we included 50 individual studies, including 40,059 cases and 64,032 controls. Overall, there was no association between KIF6 rs20455 polymorphism and CHD risk. Hamidizadeh et al. found that significant association was found between this gene polymorphism and CHD risk among Caucasian populations [43], and the result was verified in another study through enrolling 143,000 subjects [40]. However, no association was found in a meta-analysis, among South Asians, African-Americans, Hispanics, East Asians, and mixed decedent populations [39]. Furthermore, other recent studies were also found no association existed between this gene polymorphism and CHD risk [25, 26, 47–49]. When we got the subgroup analyses by ethnicity, there was also no association found among Caucasian and Asian populations. While decreased risk of this gene polymorphism and CHD risk was found among mixed populations. Of note, mixed populations means the original studies didn’t clarify the race of the subjects or mixed races.

| Author         | Year | Country | Ethnicity | Control source | Case | Control | Case | Control | $P_{\text{HWE}}$ | P | AA | AG | GG |
|----------------|------|---------|-----------|----------------|------|---------|------|---------|-----------------|----|----|----|----|
| Wu et al.      | 2012 | China   | Asian     | HB            | 356  | 568     | 104  | 164     | 88              |    | 168| 268| 132| Yes |
| Wu et al.      | 2012 | China   | Asian     | HB            | 114  | 568     | 16   | 68      | 30              |    | 168| 268| 132| Yes |
| Wu et al.      | 2014 | China   | Asian     | HB            | 288  | 346     | 74   | 141     | 73              |    | 101| 166| 79 | Yes |
| Hamidizadeh et al. | 2015 | Iran    | Asian     | HB            | 100  | 100     | 35   | 48      | 17              |    | 63 | 27 | 10 | No  |
| Vishnuprabu et al. | 2015 | India   | Caucasian | HB            | 510  | 532     | 107  | 252     | 151             |    | 121| 251| 160| Yes |
| Hubacek et al. | 2016 | Czech   | Caucasian | HB            | 1889 | 1191    | 691  | 856     | 302             |    | 440| 543| 195| Yes |
| Vatte et al.   | 2016 | Saudi Arabia | Asian   | HB            | 1002 | 984     | 277  | 513     | 212             |    | 286| 464| 234| Yes |

1–20: represents different studies in one publication; HB hospital based study, FB population based study, CB community based study, H-CB hospital and community based study, HWE Hardy-Weinberg equilibrium. Mix: the original studies didn’t clarify the race of the subjects or mixed races.
### Fig. 2
Forest plot of the association between KIF6 rs20455 gene polymorphism and CHD risk (under homozygote model)

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Berglund et al. | 1.02 (0.41, 2.55) | 0.36 |
| Varttinen et al. | 1.09 (0.56, 2.14) | 0.64 |
| Serfl et al. | 1.05 (0.84, 1.74) | 1.07 |
| Yusuf et al. | 1.01 (0.80, 1.28) | 3.25 |
| Low et al. | 1.00 (0.60, 1.67) | 0.67 |
| Helgadottir et al. | 0.96 (0.66, 1.40) | 1.68 |
| Helgadottir et al. | 1.18 (0.83, 1.67) | 1.88 |
| Samani et al. | 1.08 (0.84, 1.40) | 2.84 |
| Samani et al. | 1.00 (0.76, 1.31) | 2.64 |
| Meng et al. | 0.99 (0.66, 1.48) | 1.53 |
| Meiner et al. | 1.25 (0.88, 1.79) | 1.83 |
| Serre et al. | 1.20 (0.89, 1.63) | 2.29 |
| Morgan et al. | 1.12 (0.80, 1.56) | 2.00 |
| Assimes et al. | 0.57 (0.40, 0.81) | 1.84 |
| Viennemann et al. | 0.87 (0.66, 1.16) | 2.47 |
| Sutton et al. | 1.16 (0.87, 1.55) | 2.40 |
| Martineili et al. | 1.19 (0.82, 1.72) | 1.71 |
| Iakoubova et al. | 1.46 (0.91, 2.35) | 1.17 |
| Stewert et al. | 1.17 (0.93, 1.47) | 3.23 |
| Luke et al. | 0.81 (0.57, 1.15) | 1.86 |
| Bare et al. | 1.00 (0.92, 1.02) | 3.74 |
| Assimes et al. | 0.56 (0.40, 0.87) | 2.00 |
| Assimes et al. | 0.67 (0.46, 1.01) | 2.47 |
| Assimes et al. | 0.81 (0.65, 1.01) | 3.38 |
| Assimes et al. | 0.91 (0.81, 1.02) | 5.26 |
| Assimes et al. | 1.09 (0.56, 2.14) | 0.64 |
| Assimes et al. | 0.64 (0.47, 0.86) | 2.34 |
| Assimes et al. | 1.00 (0.76, 1.31) | 2.64 |
| Assimes et al. | 1.08 (0.84, 1.40) | 2.64 |
| Assimes et al. | 1.25 (0.88, 1.79) | 1.83 |
| Assimes et al. | 1.20 (0.89, 1.63) | 2.29 |
| Assimes et al. | 1.01 (0.80, 1.26) | 3.25 |
| Assimes et al. | 0.99 (0.66, 1.48) | 1.53 |
| Assimes et al. | 1.02 (0.41, 2.55) | 0.36 |
| Assimes et al. | 0.93 (0.64, 1.36) | 1.68 |
| Assimes et al. | 1.06 (0.60, 1.87) | 0.87 |
| Assimes et al. | 1.12 (0.80, 1.56) | 2.00 |
| Assimes et al. | 1.18 (0.83, 1.67) | 1.88 |
| Assimes et al. | 1.05 (0.64, 1.74) | 1.67 |
| Assimes et al. | 1.19 (0.82, 1.72) | 1.71 |
| Assimes et al. | 0.96 (0.60, 1.56) | 3.94 |
| Bhansali et al. | 0.59 (0.32, 1.07) | 0.79 |
| Peng et al. | 1.18 (0.78, 1.78) | 1.48 |
| Wu et al. | 1.08 (0.75, 1.55) | 1.78 |
| Wu et al. | 2.39 (1.25, 4.59) | 0.69 |
| Wu et al. | 1.26 (0.81, 1.95) | 1.34 |
| Hemidzadeh et al. | 3.06 (1.26, 7.40) | 0.39 |
| Vishnuprabhu et al. | 1.07 (0.67, 1.59) | 1.94 |
| Hubacek et al. | 0.99 (0.70, 1.42) | 3.40 |
| Valle et al. | 0.94 (0.73, 1.20) | 2.93 |
| Overall (I-squared = 33.9%, p = 0.012) | 1.01 (0.95, 1.07) | 100.00 |

**NOTE:** Weights are from random effects analysis.
Fig. 3 Forest plot of the association between KIF6 rs20455 gene polymorphism and CHD risk (under heterozygote model)

NOTE: Weights are from random effects analysis
Fig. 4 Forest plot of the association between KIF6 rs20455 gene polymorphism and CHD risk (under dominant model)

NOTE: Weights are from random-effects analysis
**Fig. 5** Forest plot of the association between KIF6 rs20455 gene polymorphism and CHD risk (under recessive model)

| Study ID | OR (95% CI) | Percentage | Weight |
|----------|-------------|------------|--------|
| Berglund et al. | 1.29 (0.56, 3.00) | 0.30 | 0.30 |
| Vartainen et al. | 0.98 (0.52, 1.84) | 0.53 | 0.53 |
| Serli et al. | 1.02 (0.63, 1.64) | 0.89 | 0.89 |
| Yusuf et al. | 0.99 (0.61, 1.60) | 3.43 | 3.43 |
| Low et al. | 1.07 (0.63, 1.81) | 0.73 | 0.73 |
| Helgadottir et al.1 | 1.05 (0.74, 1.48) | 1.48 | 1.48 |
| Helgadottir et al.2 | 1.11 (0.80, 1.54) | 1.69 | 1.69 |
| Samani et al.1 | 1.06 (0.83, 1.34) | 2.70 | 2.70 |
| Samani et al.2 | 1.01 (0.78, 1.30) | 2.49 | 2.49 |
| Meng et al. | 0.99 (0.68, 1.45) | 1.32 | 1.32 |
| Meier et al. | 1.24 (0.90, 1.72) | 1.69 | 1.69 |
| Sere et al. | 1.28 (0.96, 1.70) | 2.09 | 2.09 |
| Morgan et al. | 1.12 (0.82, 1.54) | 1.81 | 1.81 |
| Assimes et al. | 0.60 (0.44, 0.82) | 1.80 | 1.80 |
| Vennemann et al. | 0.88 (0.67, 1.14) | 2.32 | 2.32 |
| Sutton et al. | 1.23 (0.93, 1.62) | 2.21 | 2.21 |
| Martinei et al. | 1.28 (0.91, 1.81) | 1.53 | 1.53 |
| Iakoubova et al. | 1.13 (0.72, 1.77) | 1.00 | 1.00 |
| Stewart et al. | 0.98 (0.84, 1.13) | 4.74 | 4.74 |
| Luke et al. | 0.84 (0.67, 1.06) | 2.79 | 2.79 |
| Bane et al. | 0.94 (0.78, 1.13) | 3.77 | 3.77 |
| Assimes et al.1 | 0.60 (0.45, 0.81) | 1.96 | 1.96 |
| Assimes et al.2 | 0.88 (0.67, 1.24) | 2.32 | 2.32 |
| Assimes et al.3 | 0.89 (0.74, 1.08) | 3.59 | 3.59 |
| Assimes et al.4 | 0.95 (0.86, 1.06) | 5.79 | 5.79 |
| Assimes et al.5 | 0.98 (0.52, 1.84) | 0.63 | 0.63 |
| Assimes et al.6 | 0.62 (0.48, 0.80) | 2.50 | 2.50 |
| Assimes et al.7 | 1.01 (0.78, 1.33) | 2.49 | 2.49 |
| Assimes et al.8 | 1.06 (0.83, 1.34) | 2.70 | 2.70 |
| Assimes et al.9 | 1.24 (0.90, 1.72) | 1.69 | 1.69 |
| Assimes et al.10 | 1.28 (0.96, 1.70) | 2.09 | 2.09 |
| Assimes et al.11 | 0.99 (0.81, 1.20) | 3.43 | 3.43 |
| Assimes et al.12 | 0.99 (0.68, 1.50) | 1.32 | 1.32 |
| Assimes et al.13 | 1.29 (0.56, 3.00) | 0.30 | 0.30 |
| Assimes et al.14 | 1.02 (0.71, 1.45) | 1.47 | 1.47 |
| Assimes et al.15 | 1.07 (0.63, 1.81) | 0.73 | 0.73 |
| Assimes et al.16 | 1.12 (0.82, 1.54) | 1.81 | 1.81 |
| Assimes et al.17 | 1.11 (0.80, 1.54) | 1.69 | 1.69 |
| Assimes et al.18 | 1.02 (0.63, 1.64) | 0.89 | 0.89 |
| Assimes et al.19 | 1.28 (0.91, 1.81) | 1.53 | 1.53 |
| Assimes et al.20 | 0.92 (0.78, 1.10) | 4.00 | 4.00 |
| Bharushali et al. | 0.78 (0.47, 1.37) | 0.83 | 0.83 |
| Peng et al. | 1.08 (0.77, 1.51) | 1.61 | 1.61 |
| Wu et al.1 | 1.08 (0.80, 1.48) | 1.83 | 1.83 |
| Wu et al.2 | 1.19 (0.74, 1.91) | 0.94 | 0.94 |
| Wu et al. | 1.15 (0.80, 1.65) | 1.40 | 1.40 |
| Hamzic et al. | 1.84 (0.80, 4.25) | 0.31 | 0.31 |
| VishnuPrabhu et al. | 0.98 (0.76, 1.30) | 2.32 | 2.32 |
| Hubacek et al. | 0.98 (0.61, 1.60) | 3.44 | 3.44 |
| Yatle et al. | 0.86 (0.70, 1.06) | 3.16 | 3.16 |
| Overall (I-squared = 28.5%, p = 0.047) | 0.99 (0.94, 1.04) | 100.00 | 100.00 |

NOTE: Weights are from random effects analysis.
Fig. 6 Forest plot of the association between KIF6 rs20455 gene polymorphism and CHD risk (under allele comparison model)
| Variables                          | No. | P heterogeneity | Analysis model | OR (95% CI)          | P     | P_{Begg's} | P_{Egger's} |
|-----------------------------------|-----|----------------|----------------|----------------------|-------|------------|-------------|
| **Homozygote model**              |     |                |                |                      |       |            |             |
| Total                             | 50  | 0.012          | Random model   | 1.007 (0.952–1.066)  | 0.801 | 0.106      | 0.108       |
| Ethnicity                         |     |                |                |                      |       |            |             |
| Caucasian                         | 37  | 0.45           | Fixed model    | 1.012 (0.964–1.063)  | 0.622 |            |             |
| Asian                             | 9   | 0.158          | Fixed model    | 1.038 (0.933–1.154)  | 0.494 |            |             |
| Mixed                             | 4   | 0.004          | Random model   | 0.771 (0.57–1.043)   | 0.0731|            |             |
| Source of control                 |     |                |                |                      |       |            |             |
| PB                                | 20  | 0.038          | Random model   | 0.981 (0.895–1.076)  | 0.691 |            |             |
| HB                                | 21  | 0.096          | Fixed model    | 1.027 (0.956–1.103)  | 0.891 |            |             |
| FB                                | 4   | 0.038          | Fixed model    | 0.907 (0.767–1.072)  | 0.016 |            |             |
| CB                                | 3   | 0.427          | Fixed model    | 1.019 (0.872–1.189)  | 0.816 |            |             |
| H-CB                              | 2   | 0.368          | Fixed model    | 1.073 (0.895–1.286)  | 0.446 |            |             |
| **Heterozygote model**            |     |                |                |                      |       |            |             |
| Total                             | 50  | 0.008          | Random model   | 1.009 (0.968–1.052)  | 0.636 | 0.089      | 0.070       |
| Ethnicity                         |     |                |                |                      |       |            |             |
| Caucasian                         | 37  | 0.035          | Random model   | 0.955 (0.963–1.029)  | 0.790 |            |             |
| Asian                             | 9   | 0.071          | Fixed model    | 1.089 (0.995–1.191)  | 0.065 |            |             |
| Mixed                             | 4   | 0.639          | Fixed model    | 0.893 (0.799–0.999)  | 0.047 |            |             |
| Source of control                 |     |                |                |                      |       |            |             |
| PB                                | 20  | 0.067          | Random model   | 0.979 (0.938–1.021)  | 0.316 |            |             |
| HB                                | 21  | 0.004          | Random model   | 1.040 (0.956–1.132)  | 0.356 |            |             |
| FB                                | 4   | 0.807          | Fixed model    | 0.966 (0.859–1.085)  | 0.558 |            |             |
| CB                                | 3   | 0.924          | Fixed model    | 1.064 (0.957–1.183)  | 0.254 |            |             |
| H-CB                              | 2   | 0.265          | Fixed model    | 0.967 (0.841–1.112)  | 0.637 |            |             |
| **Dominant model**                |     |                |                |                      |       |            |             |
| Total                             | 50  | 0.002          | Random model   | 1.007 (0.966–1.048)  | 0.753 | 0.061      | 0.058       |
| Ethnicity                         |     |                |                |                      |       |            |             |
| Caucasian                         | 37  | 0.034          | Random model   | 1.013 (0.970–1.057)  | 0.568 |            |             |
| Asian                             | 9   | 0.054          | Fixed model    | 1.071 (0.984–1.165)  | 0.112 |            |             |
| Mixed                             | 4   | 0.508          | Fixed model    | 0.854 (0.770–0.947)  | 0.003 |            |             |
| Source of control                 |     |                |                |                      |       |            |             |
| PB                                | 20  | 0.026          | Random model   | 0.991 (0.932–1.055)  | 0.786 |            |             |
| HB                                | 21  | 0.002          | Random model   | 1.040 (0.958–1.129)  | 0.346 |            |             |
| FB                                | 4   | 0.820          | Fixed model    | 0.948 (0.848–1.059)  | 0.342 |            |             |
| CB                                | 3   | 0.986          | Fixed model    | 1.053 (0.953–1.164)  | 0.310 |            |             |
| H-CB                              | 2   | 0.551          | Fixed model    | 0.993 (0.871–1.132)  | 0.917 |            |             |
| **Recessive model**               |     |                |                |                      |       |            |             |
| Total                             | 50  | 0.047          | Random model   | 0.989 (0.943–1.037)  | 0.655 | 0.025      | 0.040       |
| Ethnicity                         |     |                |                |                      |       |            |             |
| Caucasian                         | 37  | 0.541          | Fixed model    | 1.002 (0.959–1.048)  | 0.919 |            |             |
| Asian                             | 9   | 0.819          | Fixed model    | 0.983 (0.898–1.075)  | 0.705 |            |             |
| Mixed                             | 4   | <0.001         | Random model   | 0.811 (0.592–1.111)  | 0.191 |            |             |
| Source of control                 |     |                |                |                      |       |            |             |
### Table 2 Main results of pooled ORs with 95% CI in the meta-analysis (Continued)

| Variables          | No.  | \( P_{\text{heterogeneity}} \) | Analysis model | OR (95% CI)         | P    | \( P_{\text{Begg's}} \) | \( P_{\text{Egger's}} \) |
|-------------------|------|-------------------------------|----------------|----------------------|-----|-----------------|----------------|
| PB                | 20   | 0.040                         | Random model   | 0.982 (0.902–1.069)  | 0.668 |
| HB                | 21   | 0.796                         | Fixed model    | 0.989 (0.919–1.064)  | 0.715 |
| FB                | 4    | 0.004                         | Random model   | 0.924 (0.861–1.291)  | 0.643 |
| CB                | 3    | 0.287                         | Fixed model    | 1.009 (0.843–1.209)  | 0.883 |
| H-CB              | 2    | 0.142                         | Fixed model    | 1.099 (0.856–1.412)  | 0.395 |
| **Allele comparison model** | |          |                      |         |                 |      |
| **Total**         | 50   | 0.001                         | Random model   | 1.00 (0.971–1.030)   | 0.988 | 0.052 | 0.066 |
| **Ethnicity**     |      |                               |                |                      |      |                 |      |
| Caucasian         | 37   | 0.067                         | Fixed model    | 0.999 (0.977–1.022)  | 0.950 |
| Asian             | 9    | 0.186                         | Fixed model    | 1.022 (0.968–1.079)  | 0.428 |
| Mixed             | 4    | 0.009                         | Random model   | 0.855 (0.742–0.985)  | <0.001 |
| **Source of control** | |                               |                |                      |      |                 |      |
| PB                | 20   | 0.004                         | Random model   | 0.990 (0.943–1.040)  | 0.690 |
| HB                | 21   | 0.017                         | Random model   | 1.015 (0.967–1.066)  | 0.547 |
| FB                | 4    | 0.045                         | Random model   | 0.877 (0.691–1.113)  | 0.361 |
| CB                | 3    | 0.653                         | Fixed model    | 1.025 (0.953–1.102)  | 0.507 |
| H-CB              | 2    | 0.776                         | Fixed model    | 1.019 (0.931–1.115)  | 0.687 |

No. number of studies, OR odds ratio, 95% CI 95% confidence interval, HB hospital based study, PB population based study, FB family based study, CB community based study, H-CB hospital and community based study

**Fig. 7** Begg's test of the association between KIF6 rs20455 gene polymorphism and CHD risk (under allele comparison model)
the risk of CHD. We also observed no compelling evidence of an association between the KIF6 rs20455 SNP and CHD in multiple race/ethnic groups. These findings do not support the clinical utility of testing for the KIF6 rs20455 polymorphism in the primary prevention of CHD and indirectly question whether genotype information at this locus is able to identify subjects most likely to benefit from the use of statins.

Abbreviations
CHD: Coronary heart disease; CHS: Cardiovascular Health Study; CI: Confidence interval; KIF6: Kinesin-like protein 6; OR: Odds ratio; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; SNPs: Single nucleotide polymorphisms; WHS: the Women’s Health Study

Acknowledgements
We thank all our colleagues of this present work.

Funding
Not applicable.

Availability of data and materials
Please contact author for data requests.

Authors’ contributions
YL, ZC, HS participated in the design of the study. YL, ZC, HS carried out the literature search and data extraction. YL, ZC, HS participated in the analysis of eligible data. YL, ZC, HS wrote the manuscript All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Author details
1Heart Function Examination Room, the First People’s Hospital of Lianyungang, Affiliated Hospital of Xuzhou Medical University, Lianyungang, Jiangsu 222002, China. 2Department of Neurosurgery, the first People’s Hospital of Lianyungang, Lianyungang, Jiangsu 222002, China. 3Department of Cardiology, the First People’s Hospital of Lianyungang, Lianyungang, Jiangsu 222002, China.

Received: 14 February 2017 Accepted: 25 December 2017
Published online: 05 January 2018

References
1. Luo JQ, Wen JG, Zhou HH, Chen XP, Zhang W. Endothelial nitric oxide synthase gene G894T polymorphism and myocardial infarction: a meta-analysis of 34 studies involving 21,068 subjects. PLoS One. 2014;9:e87196.
2. Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality

Fig. 8 Egger’s test the association between KIF6 rs20455 gene polymorphism and CHD risk (under allele comparison model)
polymorphism in a case-control study of coronary artery disease and non-fatal myocardial infarction in the Eastern Province of Saudi Arabia. Ann Saudi Med. 2016;36(2):105–11.

47. Myocardial Infarction Genetics C, Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardlissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. 2009;41(3):334–41.

48. Wellcome Trust Case Control C. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661–78.

49. Arsenault BJ, Boekholdt SM, Hovingh GK, Hyde CL, DeMicco DA, Chatterjee A, Barter P, Deedwania P, Waters DD, LaRosa JC, Pedersen TR, Kastelein JJ. The 719Arg variant of KIF6 and cardiovascular outcomes in statin-treated, stable coronary patients of the treating to new targets and incremental decrease in end points through aggressive lipid-lowering prospective studies. Circ Cardiovasc Genet. 2012;5(1):51–7.