Systematic Review and Meta-Analysis

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Correlations between *ISL1* rs1017 polymorphism and congenital heart disease risk

A PRISMA-compliant meta-analysis

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Abstract

Background: ISL1 promotes cardiomyocyte differentiation and plays important roles in heart development. However, whether *ISL1* rs1017 polymorphism is associated with the congenital heart disease (CHD) risk remains controversial.

Methods: Five database including PubMed, Cochrane Library, ISI Web of Science, CNKI, and Wan Fang were searched by using key words "Insulin Gene Enhancer Protein ISL1" and "Single Nucleotide Polymorphism," and "Congenital Heart Disease." Five relative articles including 6 independent studies containing 2132 cases and 3812 controls were finally recruited to our study. Meta-analyses were performed by pooling odds ratios (ORs) and 95% confidence interval (CI) from included studies using STATA 12.0 software.

Results: The associations between *ISL1* rs1017 polymorphism and the risk of CHD were statistically significant under the allele model (T vs A; OR: 1.421; 95% CI: 1.072–1.882), heterozygous model (AT vs AA; OR: 1.342; 95% CI: 1.019–1.767), and dominant model (AT+ TT vs AA; OR: 1.466; 95% CI: 1.059–2.028). Sensitivity analysis indicated that the results were not stable. Subgroup analysis demonstrated that associations were found in Caucasians under the allele model and the heterozygous model ($P < .05$), but not the dominant model ($P > .05$).

Conclusion: In summary, our meta-analysis results suggest that the T allele of *ISL1* rs1017 is a risk factor for CHD. However, further studies based on large sample size and multi-ethnic population should be conducted to further prove this correlation.

Abbreviations: CHD = congenital heart disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: congenital heart disease, ISL1, meta-analysis, single nucleotide polymorphism

1. Introduction

Congenital heart disease (CHD) is a common birth malformation defined by heart or intrathoracic great vessels structural defects that occur before birth and affect normal function of septum, valves, and the vascular drainage of the cardiac segments.[1,2] CHD is the leading non-infectious cause of infant death, with a mortality rate of >25%.[3] Chromosome abnormalities and teratogen exposure account for about 20% of CHD cases, the etiology of the remaining non-syndromic, sporadic CHD involves a complicated interaction between environmental factors and genetic factors that still remains unclear.[4]

ISL1 is a LIM homeodomain transcription factor which was first reported as a regulator of insulin expression. During embryogenesis, ISL1 is widely expressed in different cell lineages and plays an essential role in the organogenesis.[5,6] For early heart development, ISL1 serves as a marker for the cardiac progenitor cells in the second heart field, which will further differentiate to the cells of the right ventricular, right atrium, outflow tract, and pacemaker.[7–9] Previous studies have revealed that ISL1, by itself or through cooperating with a variety of transcription factors including HAND2, TBX20, GATA4, and FOXH1, regulates downstream genes transcription, such as *Mef2c*, *Myocd*, *Nkx2–5*, *SHH*, *FGF10*, and *BMP4*, which are involved in cardiac differentiation and development.[7,10–14] Moreover, *Isl1* mutation are shown to be associated with cardiac defect phenotype in the mouse and zebrafish.[12,15] Given that ISL1 plays pivotal roles in cardiac development, it is considered to be a potential genetic factor that is involved in the development of non-syndromic, sporadic CHD.

Human *ISL1* gene is located on chromosome 5q11.1. Two rare variants in the coding region of *ISL1* including a deletion

Editor: Manal Elshmaa.

ZD and WY have contributed equally to this work.

This work was supported by a grant from the Health Industry Research Project of Gansu Province (GSWSKY2016-04) and the National Natural Science Foundation of China (31670379).

The authors have declared that no competing interests exist.

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How to cite this article: Ding Z, Yang W, Yi K, Ding Y, Zhou D, Xie X, You T. Correlations between ISL1 rs1017 polymorphism and congenital heart disease risk: A PRISMA-compliant meta-analysis. Medicine 2020;99:2(e18715).

Received: 17 May 2019 / Received in final form: 16 October 2019 / Accepted: 12 December 2019

http://dx.doi.org/10.1097/MD.0000000000018715

mutation and a nonsense mutation (p.E137X) have been reported to contribute to CHD.[16,17] Several *ISL1* polymorphisms have been reported, of which the common single nucleotide polymorphism (SNP) rs1017 in the 3′ untranslated region (3′UTR) of *ISL1* gene has been identified to be associated with the risk of CHD.[18–23] Previously, Stevens et al[18] evaluated the correlation between *ISL1* rs1017 polymorphism and CHD risk in European white population. In addition, several studies suggested that the T allele of rs1017 contribute to the risk of CHD in Chinese population.[20–22] However, Xue et al[19] were unable to identify the correlation between the *ISL1* rs1017 polymorphism and CHD risk in Chinese population. Given that the results of previous studies remain inconclusive and controversial, we conducted this meta-analysis to further evaluate the correlation between *ISL1* rs1017 polymorphism and CHD susceptibility.

2. Materials and methods

2.1. Literature search

Five databases including PubMed, Cochrane Library, ISI Web of Science, CNKI, and Wan Fang until February 20, 2019 were searched to identify relevant studies using the following search terms: (Insulin Gene Enhancer Protein ISL1 or ISL LIM Homeobox 1 or ISLET1 or ISL1 or rs1017) and ("Polymorphism, Single Nucleotide"[Mesh] or SNP or SNPs or polymorphism or mutation or variant or variation or allele or genotype), and ("Heart Defects, Congenital"[Mesh] or congenital heart disease or CHD or birth defect or heart abnormality or malformation of heart). There was no restriction on publication date and language. The references of previous articles were screened manually for potential studies.[16–22] This meta-analysis was based on previously published studies, the ethical approval and the patient consent were not necessary.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included: estimating the association between *ISL1* rs1017 polymorphism and CHD risk. Case–control studies. Genotyping data of samples are available. The distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium (HWE). The exclusion criteria were as follows: lack of control population; lack of eligible genotype frequencies; duplicated publications, and controls were not consistent with HWE.

2.3. Data extraction

Two investigators extracted data from all included publications independently according to the inclusion and exclusion criteria and the third investigator adjudicated the conflicting information until consensus was reached on every item. The following characteristics were collected from each original study: last name of the first author, year of publication, country and ethnicity of studied population, sample size of cases and controls, genotyping method, frequencies of allele or genotype in cases and controls, and *P* value for HWE test in controls.

2.4. Statistical analysis

The goodness-of-fit Chi-square test for Hardy–Weinberg equilibrium was performed in control group from each study. *P* value $>.05$ was considered as in accordance with Hardy–Weinberg equilibrium. The correlation between *ISL1* rs1017 polymorphism and CHD susceptibility was tested by odds ratios (ORs) analysis and the corresponding 95% confidence intervals (CIs) in 5 genetic models including allele model (T vs A), homozygous model (TT vs AA), heterozygous model (AT vs AA), dominant model (AT+TT vs AA), and recessive model (TT vs AT+AA). Bonferroni correction was used for homozygous model and heterozygous model. Subgroup analysis was performed based on different ethnicities. Heterogeneity among studies was assessed using the Chi-square-based Q test and I^2 test, and the heterogeneity was considered significant at $P<.10$ or $I^2>50\%$. If the *P* value for heterogeneity tests was $>.10$ ($P>.10$) or $I^2<50\%$, a fixed effects model was used to calculate the pooled OR. Otherwise, a random effects model was used. Sensitivity analysis was performed by removing one study at a time to assess the effect of each study on the combined ORs. Publication bias was explored by Begg funnel plot and Egger test, and $P<.05$ was considered as a significant publication bias. All analyses were performed by using STATA 12.0 software.

3. Results

3.1. Characteristics of the studies

The study screening process was shown in Fig. 1. Initially, a total number of 153 studies were identified from the databases or by manual search. Among of them, 144 studies were excluded as they were either duplicated studies, reviews, inadequate data, or irrelevant to the association of rs1017 polymorphism and CHD. The full text of the remaining 9 potential articles were fully examined and 3 were eliminated because of the reduplicative data. Furthermore, one study was excluded due to the inconsistency of the distribution of genotypes with HWE ($P_{HWE}<.05$).[23] Since the article of Stevens et al[18] included 2 independent studies, as a result, a total number of 5 articles including 6 independent studies were identified according to the inclusion criteria.[18–22] Finally, this meta-analysis included 2132 cases and 3812 controls and the available detailed characteristics were described in Table 1.

3.2. Meta-analysis

Overall, statistically significant heterogeneity ($P<.10$, $I^2>50\%$) was observed among these included studies, therefore the random effects models were used for the following analysis. Our meta-analysis demonstrated that *ISL1* rs1017 polymorphism significantly correlated with the increased risk of CHD under the allele model (T vs A; OR: 1.421; 95% CI: 1.072–1.882), heterozygous model (AT vs AA; OR: 1.342; 95% CI: 1.019–1.767), and dominant model (AT+ TT vs AA; OR: 1.466; 95% CI: 1.059–2.028). After Bonferroni correction, the results of heterozygous model and dominant model are not statistically significant, which may due to the sample size in the study pool was limited. Moreover, no statistically significant correlation was identified between the rs1017 polymorphism and the risk of CHD under the homozygous model (TT vs AA; OR: 1.656; 95% CI: 0.923–2.974) nor recessive model (TT vs AT+AA; OR: 1.393; 95% CI: 0.906–2.142).

Subgroup analysis was performed based on ethnicity. No significant correlation was observed between the rs1017 polymorphism and the CHD risk in Asians. However, statistically significant associations were found in the allele model (T vs A; OR: 1.470; 95% CI: 1.048–2.062), heterozygous model (AT

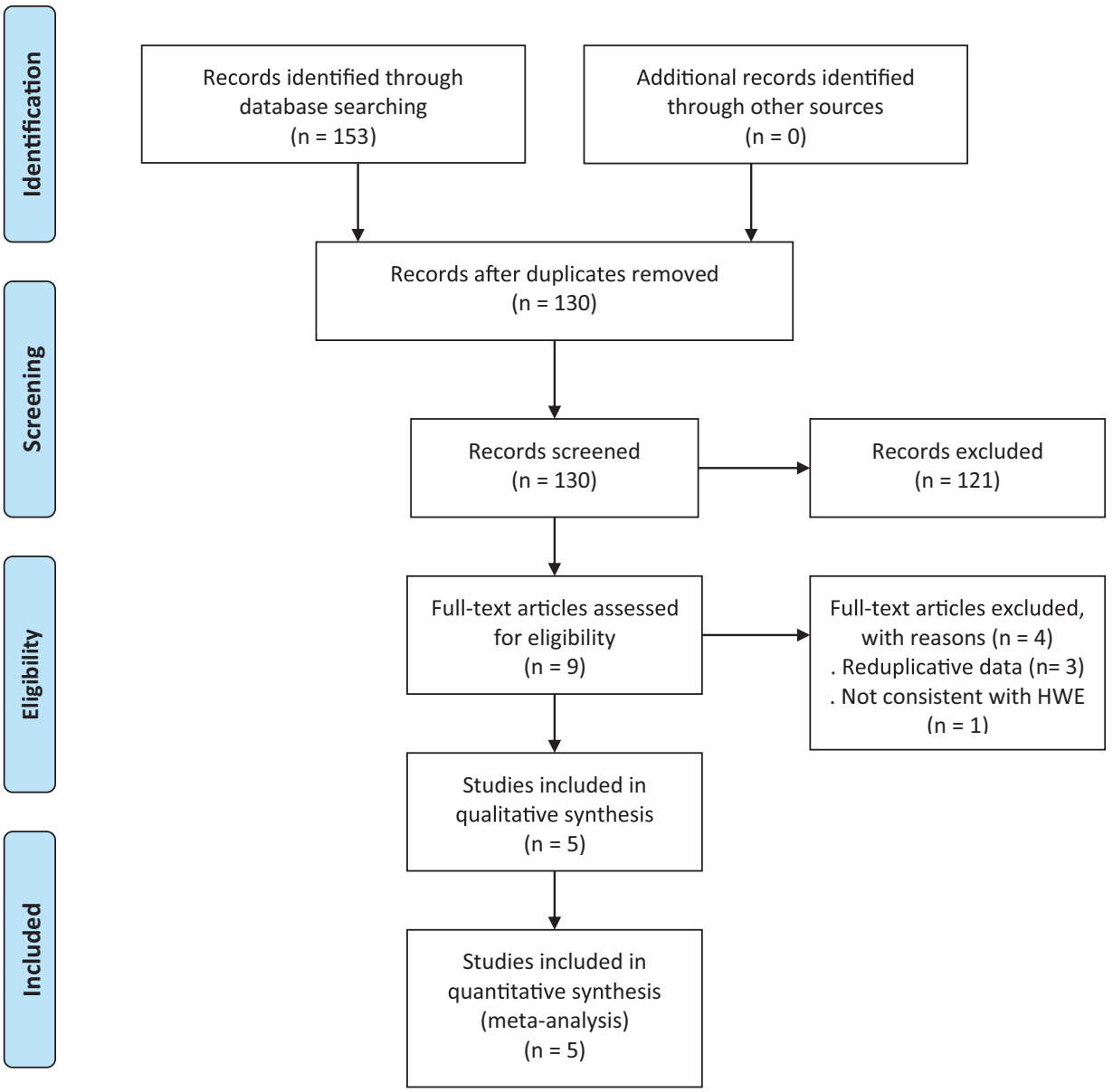

Figure 1. Flow diagram of study selection.

Table 1

Main characteristics of the included studies.

Study	Year	Country	Ethnicity	Genotyping method	Sample size (case/control)	Genotype frequency in cases (AA/AT/TT)	Genotype frequency in controls (AA/AT/TT)	P_{HWE} of controls	MAF
Stevens*	2010	America	Caucasian	Illumina SNP array	83/425	21/43/19	182/192/51	.97	0.369
Stevens*	2010	America	Caucasian	Illumina SNP array	265/1445	91/128/46	591/672/182	.67	0.367
Xue	2012	China	Asian	TaqMan assay	1003/1012	740/244/19	771/223/18	.69	0.134
Mu	2013	China	Asian	Sequencing	35/30	20/13/2	26/4/0	.70	0.162
Lang	2013	China	Asian	Sequencing	512/612	128/240/144	134/291/187	.30	0.531
Luo	2014	China	Asian	PCR-RFLP	233/288	172/53/8	248/40/0	.21	0.105

T allele is the minor allele of rs1017.

HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, $P_{HWE} = P$ value for HWE in control group, PCR-RFLP = polymerase chain reaction–restriction fragment length polymorphism.

* In the study by Stevens, subjects from the stage 1 and the stage 2.

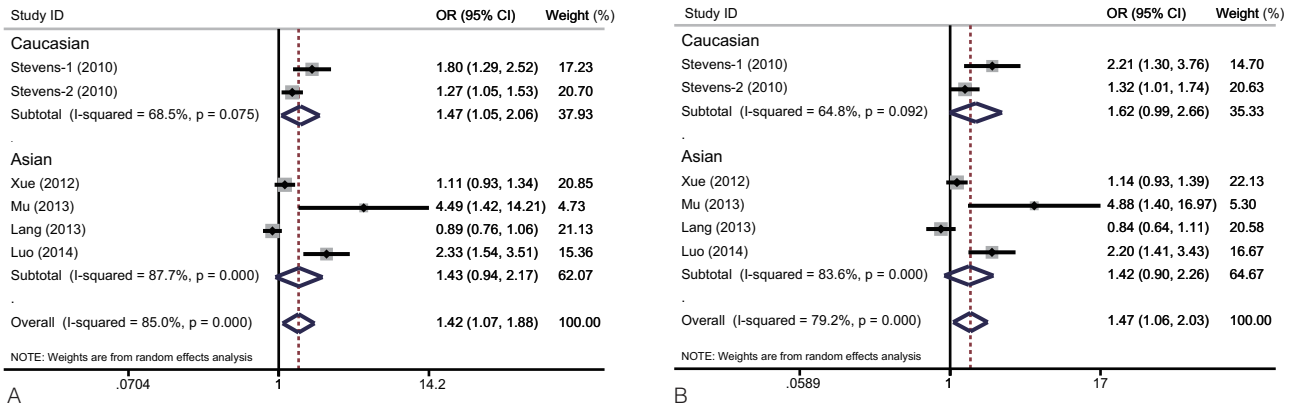

Figure 2. Forest plot for ISL1 rs1017 in allele model and dominant model. (A) Allele model (T vs A); (B) dominant model (AT+TT vs AA).

vs AA; OR: 1.365; 95% CI: 1.056–1.766), homozygous model (TT vs AA; OR: 2.161; 95% CI: 1.127–4.146), and recessive model (TT vs AT+AA; OR: 1.613; 95% CI: 1.192–2.183) in Caucasians (Fig. 2). These results were shown in Table 2.

3.3. Sensitivity analyses and publication bias

Due to the significant heterogeneity across studies, the influence of a single study on the overall meta-analysis results was evaluated by deleting one study at a time. Sensitivity analysis showed that the overall findings were not robust to potentially influential decisions by any of the included studies (Fig. 3). Moreover, the study of Lang et al[21] significantly skewed the pooled OR values for the rs1017 polymorphism in the 5 applied genetic models. After exclusion of Lang et al[21] study, the pooled OR values for the whole population were reversed for the homozygous model (TT vs AA; OR: 2.043; 95% CI: 1.139–3.663) and recessive model (TT vs AT+AA; OR: 1.636; 95% CI: 1.062–2.519), while the corresponding pooled OR values remained unchanged in any genetic models in Asian subgroup. The possible reason for greater effect of Lang et al[21] study was that it was the only study with a difference greatly from other studies in terms of minor allele frequency (MAF) (Table 1). Moreover, according to the Genome Aggregation Database, the minor T allele frequency of rs1017 is 0.157 and 0.380 in the East Asian population and the American population, respectively.

Begg funnel plot and Egger test were performed to assess the publication bias of the included studies. The Begg test showed no publication bias existed, while the Egger test suggested that publication bias was found in both the allele model (T vs A) for the whole population ($T=3.14$, $P=.035$) and the homozygous model (TT vs AA) in Asian subgroup ($T=5.05$, $P=.037$)

Table 2

Meta-analysis of published association between the ISL1 rs1017 polymorphism and CHD risk.

	Test of association			Test of heterogeneity			Egger test†		Begg test‡	
Type (No. of studies)	OR (95%CI)	Z	P	I^2, %	P#	Analysis model*	T	P	Z	P
Overall (6)										
T VS A	1.421 (1.072–1.882)	2.44	.015	85.0	<.001	Random	3.14	.035	1.88	.060
AT VS AA	1.342 (1.019–1.767)	2.10	.036	68.1	.008	Random	2.36	.077	1.13	.260
TT VS AA	1.656 (0.923–2.974)	1.69	.091	76.7	.001	Random	1.84	.139	0.75	.452
AT+TT VS AA	1.466 (1.059–2.028)	2.31	.021	79.2	<.001	Random	2.39	.075	0.75	.452
TT VS AT+AA	1.393 (0.906–2.142)	1.51	.131	66.5	.011	Random	2.10	.103	0.38	.707
Asians (4)										
T VS A	1.431 (0.944–2.171)	1.69	.091	87.7	<.001	Random	2.52	.128	1.02	.308
AT VS AA	1.322 (0.887–1.971)	1.37	.171	75.9	.006	Random	1.41	.294	0.34	.734
TT VS AA	1.284 (0.586–2.813)	0.62	.532	61.4	.051	Random	5.05	.037	1.02	.308
AT+TT VS AA	1.423 (0.896–2.260)	1.49	.135	83.6	<.001	Random	1.46	.282	0.34	.734
TT VS AT+AA	1.181 (0.620–2.251)	0.51	.613	51.1	.105	Random	3.40	.077	1.02	.308
Caucasian (2)										
T VS A	1.470 (1.048–2.062)	2.23	.026	68.5	.075	Random	-	-	0.00	1.000
AT VS AA	1.365 (1.056–1.766)	2.37	.018	49.0	.162	Fixed	-	-	0.00	1.000
TT VS AA	2.161 (1.127–4.146)	2.32	.020	63.9	.096	Random	-	-	0.00	1.000
AT+TT VS AA	1.623 (0.992–2.658)	1.93	.054	64.8	.092	Random	-	-	0.00	1.000
TT VS AT+AA	1.613 (1.192–2.183)	3.10	.002	23.6	.253	Fixed	-	-	0.00	1.000

CI = confidence interval, OR = odds ratio.

* Random-effects model was used when the *P* for heterogeneity test <.05, otherwise the fixed-effect model was used.

† Egger test to evaluate publication bias, $P<.05$ is considered statistically significant.

‡ Begg test to evaluate publication bias, $P<.05$ is considered statistically significant.

P value for the *Q* test.

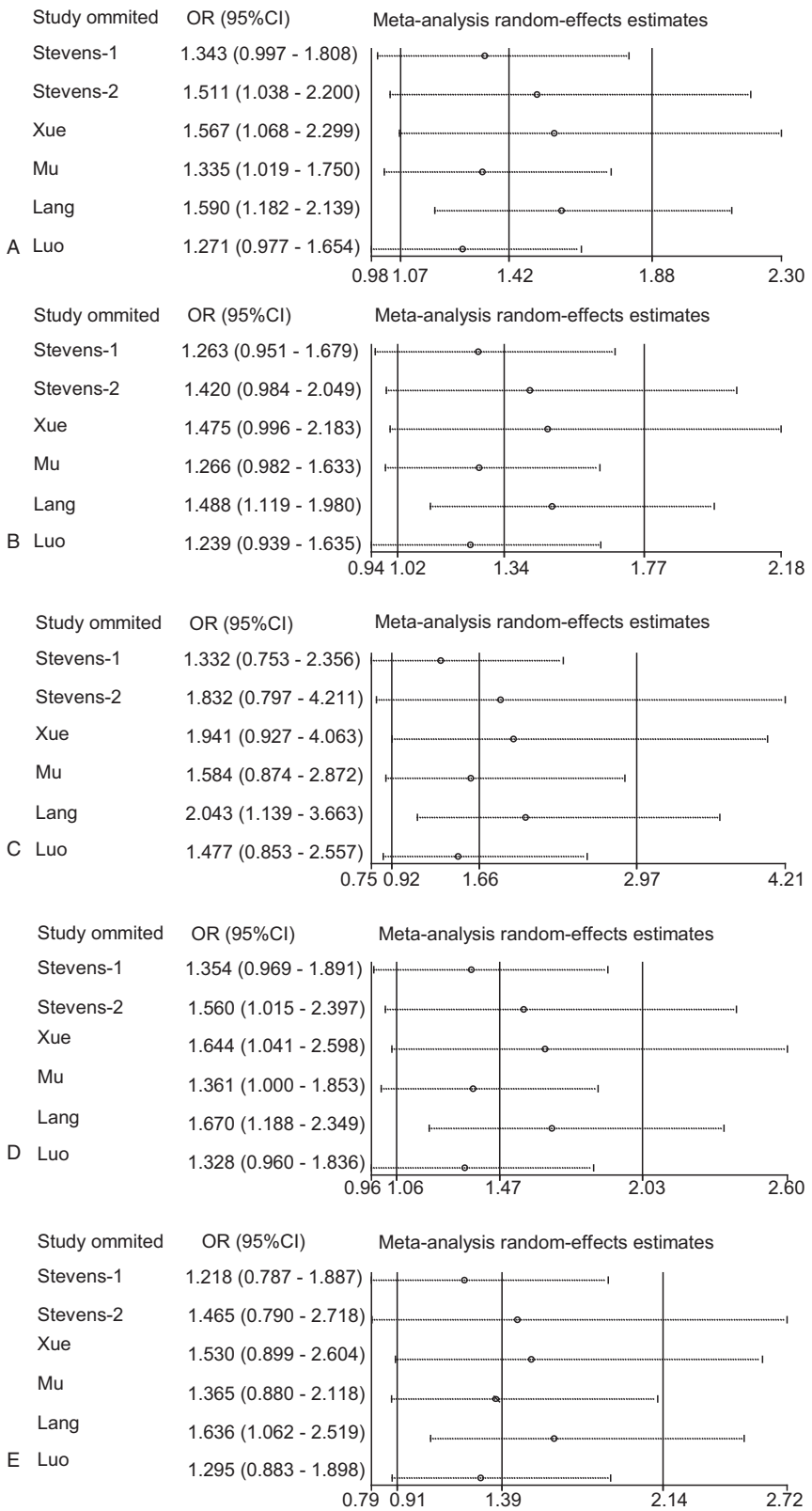

Figure 3. Sensitivity analysis results. (A) Allele model (T vs A); (B) heterozygous model (AT vs AA); (C) homozygous model (TT vs AA); (D) dominant model (AT+TT vs AA); (E) recessive model (TT vs AT+AA).

(Table 2). Publication bias of the Egger test might be due to the small number of studies we included.

4. Discussion

As a member of the LIM homeodomain transcription factor, ISL1 is a marker molecule for cardiac progenitor cells and is highly expressed in fetal heart.[6–8] Studies have shown that ISL1 plays an important role in cardiomyocyte differentiation and heart development.[11–13] The abnormal expression *ISL1* may be one of the factors causing non-syndromic, sporadic CHD. Two loss-of-function mutations of *ISL1* have been reported to contribute to the high risk of CHD.[16,17] In recent years, a number of studies have been carried out to explore the relationship between *ISL1* rs1017 polymorphism and the CHD risk. Unfortunately, previous findings of *ISL1* rs1017 polymorphism on CHD susceptibility were controversial and inconclusive.

To our knowledge, the present study was the first meta-analysis aimed to investigate the association between *ISL1* rs1017 polymorphism and the CHD risk. Our study evaluated the available data including a total of 2132 cases and 3812 controls. The results showed that T allele of the rs1017 was associated with an increased risk of CHD in overall population. However, stratified analysis by ethnicity showed that the rs1017 polymorphism was associated with CHD risk in Caucasians population but not in Asians. The different results between Caucasians and Asians may be caused by the different genetic and environmental background in different races. Moreover, only 2 groups of Caucasians study data were included, further studies are needed to verify the results for Caucasians in current study.

In addition, we noticed that significant heterogeneity was found in all genetic models. After subgroup analyses by ethnicity, the heterogeneity still existed with a slight reduction. Meanwhile, other available variables including publication year, sample size, and genotyping method could not be considered as the source of the heterogeneity, suggesting the existence of other unknown factors influencing the heterogeneity among included studies. When considering the subtypes of CHD as a subgroup variable, 3 of included studies contain the variable data.[19,21,22] Unfortunately, only one study described accurate phenotype–genotype information for CHD subtypes,[21] and one set of available data may not be suitable for meta-analysis of CHD subtypes. Besides, the variables of patient's background and disease history were not described in the included original studies. Next, sensitivity analysis by deleting one study at a time indicated that the pooled OR values were not robust. Among all the included studies, the study by Lang et al[21] had the greatest effect on the pooled OR values under the homozygous model and recessive model. The heterogeneity became stable with a slight reduction after deleting the study. The study by Lang et al[21] was recognized as one of the sources for heterogenicity. It was the only study with the differences greatly from other studies and databases in terms of minor allele frequency (MAF). No publication bias was identified by Begg test, while the Egger test result suggested the publication bias in the allele model in overall population and in the homozygous model in Asian subgroup. Given the small number of the included studies, the reliability of these 2 methods were limited. More evidence based on large sample size and multi-ethnicities are needed to support the conclusion.

The present meta-analysis reviewed the currently available data to investigate the correlation between *ISL1* rs1017 polymorphism and the CHD risk, the results were more reliable than individual studies. However, some limitations in our study should still be pointed out. Firstly, the number of studies we have included was limited, from which the majority of the subjects were for Asian population. The available variables in those studies were also very limited. Secondly, sensitivity analysis revealed that the pooled OR values were not robust, the study by Lang et al had a significant effect on the pooled OR values. Significant heterogenicity and publication bias among studies were observed. The limited available variables hampered to further examine the source of heterogenicity. Thirdly, the current study only studies 1 polymorphism of *ISL1*, rs1017, the results might lack stability on the overall relationship, especially for non-syndromic, sporadic CHD caused by multiple factors.

In conclusion, this meta-analysis provided evidence that *ISL1* rs1017 polymorphism might affect the susceptibility to CHD. Specifically, the T allele of rs1017 polymorphism might be a risk factor for CHD in the Caucasian population. Further multi-ethnic studies with lager sample size are required to clarify this relationship.

Author contributions

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Writing – original draft: Zhaohong Ding, Wenke Yang.

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