Review Article

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Genetic Association between ITPKC rs28493229 Polymorphism and Susceptibility to Kawasaki Disease: A Meta-Analysis

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ABSTRACT

Background: Studies investigating the association between ITPKC rs28493229 polymorphisms and Kawasaki disease (KD) risk found inconsistent data. Thus, we performed this meta-analysis to combine and analyze the available studies to get a precise estimation of the association.

Methods: Relevant studies identified in the PubMed, Web of Science, Scopus, and CNKI databases were used to perform a meta-analysis. Pooled odds ratios (OR) with a 95% confidence interval (95% CI) were calculated under fixed- and random-effects models to appraise the association.

Results: A total of eight case-control studies with 2,721 KD cases and 5,307 controls were selected. The results showed a statistically significant association between ITPKC rs28493229 polymorphism and an increased risk of KD under all five genetic models, i.e., allele (C vs. G: OR = 1.434, 95% CI 1.209-1.700, $P \leq 0.001$), homozygote (CC vs. GG: OR = 2.085, 95% CI 1.423-3.055, $P \leq 0.001$), heterozygote (CG vs. GG: OR = 1.530, 95% CI 1.359-1.722, $P \leq 0.001$), dominant (CC+CG vs. GG: OR = 1.490, 95% CI 1.229-1.806, $P \leq 0.001$), and recessive (CC vs. CG + GG: OR = 1.799, 95% CI 1.231-2.629, $P = 0.002$) in the overall population. When stratified by country, there was a significant association among Taiwanese.

Conclusion: Our meta-analysis results supported that the ITPKC rs28493229 polymorphism is strongly associated with susceptibility to KD.

Introduction

Kawasaki disease (KD; OMIM 300530) is an acute vasculitis of the medium- and small-sized arteries of childhood.[1-3] Population-based age adjusted-data showed that children under five years of age are mostly affected by KD with a male predominance. In the last decades, KD has been the Primary cause of acquired heart disease in children in East Asia, Europe, and North America.[1,4] It is noticeably more prevalent in Japan and other Asian countries (69-240 per 100.000) compared with Western countries (4-15 per 100.000) in children under the age of 5 years.[5-7] As the available data for specific diagnostic tests of KD are limited, the diagnosis is based on the presence of clinical criteria.[8,9] In 2004, American Heart Association (AHA) mounted diagnostic guidelines for the initial estimate, treatment in the acute phase, and long-term management of KD.[10] Standard treatment in acute KD consists of a single dose of high-dose intravenous immunoglobulin (IVIG) at 2 g/kg, preferably given within 10 days after the onset of fever.[11-13]

Although recent studies provide new insights into the mechanisms of immune activation in KD[14], the exact etiology of KD is still unknown. It is supposed that KD reflects an abnormal inflammatory response to one or more infectious agents or toxins in genetically predisposed people.[15] The prevalence of KD is increased in siblings with a history of KD or children with parental history of KD.[16] Inositol 1,4,5-trisphosphate (IP3) is a second messenger which transduces signals from cell surface receptors in T cells. Inositol 1,4,5-trisphosphate 3-kinase (ITPK) phosphorylates IP3 and serves as a negative regulator of the Ca^{2+} /nuclear factor of the activated T-cell signaling pathway.[17,18] Genome-wide association studies (GWAS) have emphasized the importance of functional variants in the *ITPKC* gene, which is a negative regulator of T-cell activation through the Ca2+/NFAT signaling pathway (Figure 1). Functional polymorphisms in the *ITPKC* gene may contribute to increased T cell activation, increased expression of cytokines, and immune hyper-reactivity in KD.[14,19,20]

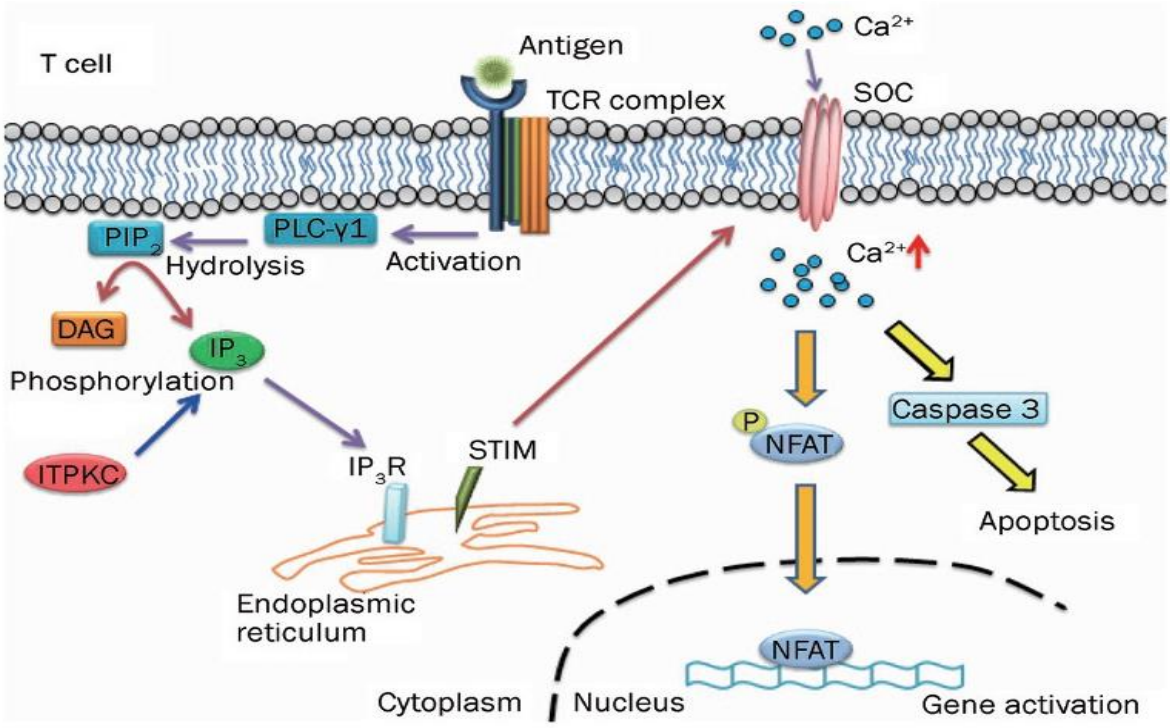

Figure 1. The ITPKC signaling pathways contribution to the susceptibility or clinical status of Kawasaki disease[20]

The C allele of the responsible SNP (rs28493229, C allele) alters the splicing efficiency of ITPKC intron 1 and then reduces the amount of mature ITPKC mRNA, which in turn results in increased signaling through the calcineurin/NFAT pathway and cell activation, and may contribute to immune hyperactivity in KD.[19]

The *ITPKC* gene, also recognized as MDR1, is located on chromosome 19q13.2. The *ITPKC* gene product is widely localized in the nucleus and cytoplasm and has both nuclear import and nuclear export activity. In 2008, Onouchi et al. provided new insights into the mechanisms of immune activation in Kawasaki disease and emphasizes the role of ITPKC rs28493229 polymorphism in the pathogenesis of KD.[14] However, some studies have shown no association between KD and polymorphism rs28493229 in ITPKC. For example, in 2018, Kim et al. reported that the ITPKC rs28493229 polymorphism has a protective effect against KD symptoms.[21] Thus, the association of the ITPKC rs28493229 polymorphism with KD risk is still ambiguous. Meta-analysis offers an opportunity to aggregate information from multiple studies, improving statistical power by increasing the sample size to exactly evaluate genetic polymorphisms outcomes on disease susceptibility. To assess the association between *ITPKC* rs28493229 polymorphism and the risk of KD, we performed a meta-analysis based on all eligible case-control studies published up to March 05, 2020.

Materials and Methods

Literate Search Strategy: Ethical approval was not required for this study, as it is a systematic review and meta-analysis. This work was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We have performed a comprehensive literature search on electronic databases including PubMed, EMBASE, Wed of Science, Elsevier, Google Scholar, Cochrane Library, SciELO, SID, WanFang, VIP, Chinese Biomedical Database (CBD), and Chinese National Knowledge Infrastructure (CNKI) to identify all relevant studies on the association between *ITPKC* rs28493229 polymorphism and Kawasaki disease risk up to March 05, 2020. Combinations of the following MeSH terms and keywords were used in the search: (“Kawasaki Disease” OR “KD” OR “Mucocutaneous Lymph Node Syndrome”) AND (‘’Inositol 1,4,5-trisphosphate 3-kinase C’’ OR ‘’ ITPKC’’ OR ‘’IP3KC’’ OR ‘’IP3-3KC’’) AND (‘’Gene’’ OR ‘’Single-Nucleotide Polymorphism” or “SNP” OR ‘’Polymorphism’’ OR ‘’Genotype’ OR ‘’Allele’’ OR ‘’Variation’’ OR ‘’Mutation’’). The search was limited to human studies published in English, Farsi, and Chinese language. We also reviewed the references list of relevant reviews and eligible publications to find other potential sources.

Inclusion Criteria: Studies meeting the following criteria were included: 1) studies with case-control or cohort design; 2) studies evaluated the association of *ITPKC* rs28493229 polymorphism and Kawasaki disease risk; 3) studies with available and sufficient data for calculating an odds ratio (OR) with 95% confidence interval (CI). The following exclusion criteria were also used: 1) animal studies or in vitro studies; 2) studies with sufficient data on genotype frequencies; 3) studies evaluated the association of other polymorphism of *ITPKC*; 4) linkage studies or family-based studies (including sibling, twins and trios-parents studies); 5) abstracts, case reports, commentaries, editorials, conference articles, reviews, proceedings and meta-analyses; and 6) duplicates or overlapping studies. If more than one study was published by the same author(s) using repeated or overlapped data, the studies with the largest sample size or the most recently published study were included in the meta-analysis.

Data Extraction: Two authors independently reviewed all eligible articles and extracted all necessary data according to

the inclusion criteria. For any discrepancies, a discussion was made to reach an agreement. If the two authors could not reach a consensus, then a third investigator was consulted to resolve the dispute and a final decision was made by the majority of the votes. For each eligible study, the following data were collected: first author name, year of publication, country of origin, ethnicity (Caucasian, Asian, African, Mixed populations), source of controls (hospital-based or population-based), genotyping methods, sample size, allele and genotype frequency of *ITPKC* rs28493229 polymorphism in cases and controls, Minor Allele Frequency (MAFs) and Hardy-Weinberg equilibrium (HWE) in healthy controls. In this meta-analysis different case-control groups or cohorts in one publication were considered independent studies.

Statistical Analysis: The strength of the association between *ITPKC rs28493229* polymorphism and KD risk was estimated by odds ratio (OR) with the corresponding 95% confidence intervals (CIs). The significance of pooled ORs was tested by Z-test, in which $P < 0.05$ was considered significant. The association of *ITPKC rs28493229* polymorphism was estimated under five genetic models, i.e., allele (C vs. G), homozygote (CC vs. GG), heterozygote (CG vs. GG), dominant (CC + CG vs. GG), and recessive (CC vs. CG + GG)**.** The chi-square test was used to evaluate the between-study heterogeneity. If $P < 0.10$, it was considered to have significant heterogeneity in statistics. Moreover, I^2 test to quantify the heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance ($I^2 < 25\%$, no heterogeneity; I^2 25-50%, moderate heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity).[22] When significant heterogeneity existed, we selected a random-effects model (the DerSimonian and Laird method) for statistics. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used. The Hardy-Weinberg equilibrium (HWE) of the controls was evaluated by Fisher exact test and a p-value less than 0.05 was considered significant disequilibrium (HWE-violating). Subgroup analyses by ethnicity, country, source of controls, and genotyping methods were performed to explore the potential sources of between-study heterogeneity in the meta-analysis. One-way sensitivity analysis, by which a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set for the pooled OR, was carried out to assess the stability of the results. Moreover, sensitivity analysis was done by excluding HWE-violating studies. Begg's funnel plots were generated to assess the potential influences of the publication bias on the results. An asymmetrical plot usually indicates the existence of publication bias.[23] Moreover, Egger's linear regression test which measures funnel plot asymmetry using a natural logarithm scale of OR was performed to evaluate the symmetry of the plot. All statistical tests were performed using CMA software. All P values in the meta-analysis were 2-sided, and P values less than 0.05 were considered significant.

Results

Characteristics of Selected Studies: The process of the literature search and selection is shown in figure 2. Initially, our search strategy yielded 101 possibly relevant articles. Twenty-nine studies were removed due to duplication, and 79 articles were removed because they were not case-control studies, human research, or without available data and previous meta-analyses. Finally, a total of eight case-control studies with 2,721 KD cases and 5,307 controls were included in the meta-analysis.[14,17,18,21,24-27] The characteristics of the included studies are summarized in table 1. KD cases in the studies ranged from 17 to 637 and selected studies were published between January 2008 and January 2018. In terms of ethnicity, seven studies were performed among Asians and one study was conducted among Caucasians.

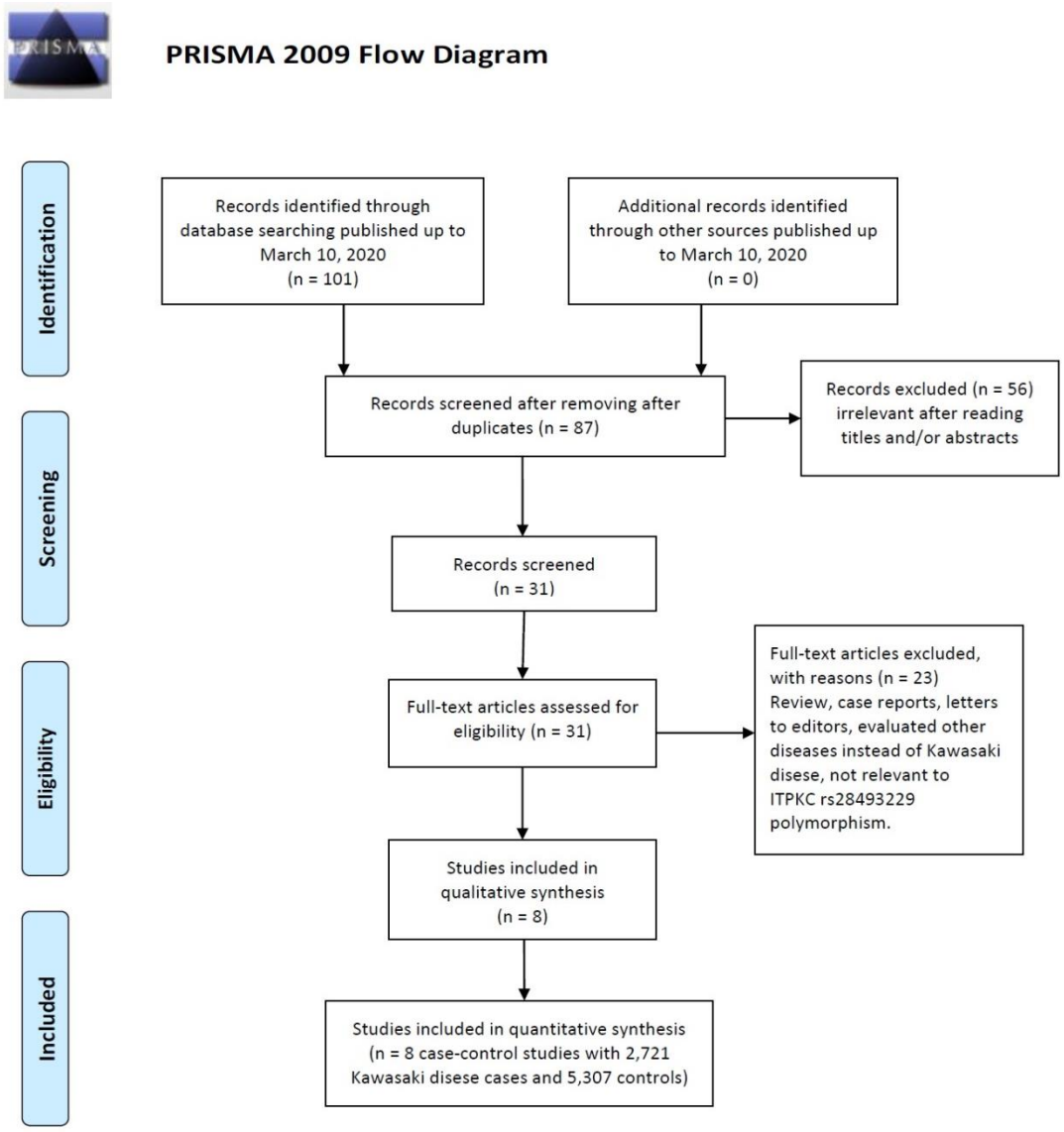

Figure 2. Flowchart of literature search and selection process

The studies have been carried out in Japan, Taiwan, China, South Korea, and Australia. As seen in table 1, three genotyping methods including TaqMan, sequencing, and RFLP-PCR were used to genotype the *ITPKC* rs28493229 polymorphism. The allele, genotype, and minor allele frequency (MAF) distributions for *ITPKC* rs28493229 polymorphism in KD cases and healthy controls were presented in table 1. Hardy-Weinberg equilibrium (HWE) was calculated for all eight publications and $P < 0.05$ was considered as a departure from HWE (Table 1).

Quantitative Data Synthesis: The summary results for the association between *ITPKC rs28493229* polymorphism and KD risk are shown in table 2. Overall, pooled data revealed a significant association between the *ITPKC rs28493229* polymorphism and an increased risk of KD under all five genetic models, i.e., allele (C vs. G: OR = 1.434, 95% CI 1.209-1.700, $P \leq 0.001$), homozygote (CC vs. GG: OR = 2.085, 95% CI 1.423-3.055, $P \leq 0.001$, Figure 2B), heterozygote (CG vs. GG: OR = 1.530, 95% CI 1.359-1.722, $P \leq 0.001$), dominant (CC+CG vs. GG: OR = 1.490, 95% CI 1.229-1.80 been carried out6, $P \leq 0.001$), and recessive (CC vs. CG+GG: OR = 1.799, 95% CI 1.231-2.629, $P = 0.002$) (Figure 3A-E).

Table 1. Characteristics of Studies Included in This Meta-Analysis

Author/Year	Country (Ethnicity)	SOC	Genotyping Methods	Case/Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
					GG	GC	CC	G	C	GG	GC	CC	G	C		
Onouchi 2008	Asians	PB	TaqMan	637/1034	376	234	27	986	288	756	249	29	1761	307	0.148	0.126
Onouchi 2011	Japan(Asian)	PB	Sequencing	546/938	330	191	25	851	241	662	261	15	1585	291	0.155	0.059
Chi 2011	Taiwan(Asian)	NS	TaqMan	385/1158	323	61	1	707	63	1008	147	3	2163	153	0.066	0.327
Lin 2011	Taiwan(Asian)	NS	Sequencing	280/492	236	43	1	515	45	454	37	1	945	39	0.040	0.787
Kuo 2011	Taiwan(Asian)	PB	TaqMan	334/1131	282	50	2	614	54	981	142	8	2104	158	0.070	0.256
Peng 2012	China(Asian)	HB	PCR-RFLP	223/318	195	27	1	417	29	274	40	4	588	48	0.075	0.078
Natividad 2013	Australia(Caucasian)	HB	Sequencing	17/26	16	1	0	33	1	22	4	0	48	4	0.077	0.670
Kim 2018	Korea(Asian)	HB	TaqMan	299/210	231	64	4	526	72	178	32	0	388	32	0.076	0.232

SOC: source of control; PB: population-based; HB: hospital-based; NS: not stated; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium

Table 2. Summary Risk Estimates for Association of ITPKC rs28493229 Polymorphism with Kawasaki Disease Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	C vs. G	Random	51.87	0.042	1.434	1.209-1.700	4.143	≤0.001	0.386	0.216
	CC vs. GG	Fixed	13.11	0.330	2.085	1.423-3.055	3.768	≤0.001	0.763	0.408
	CG vs. GG	Fixed	49.08	0.056	1.530	1.359-1.722	7.029	≤0.001	0.173	0.225
	CC+CG vs. GG	Random	54.33	0.032	1.490	1.229-1.806	4.061	≤0.001	0.173	0.193
	CC vs. CG+GG	Fixed	8.69	0.362	1.799	1.231-2.629	3.033	0.002	0.548	0.523
Taiwanese	C vs. G	Random	59.37	0.085	1.360	1.116-1.658	3.043	0.002	0.548	0.387
	CC vs. GG	Fixed	0.00	0.887	1.048	0.327-3.358	0.079	0.937	0.296	0.260
	CG vs. GG	Random	56.84	0.099	1.471	1.058-2.045	2.298	0.022	1.000	0.197
	CC+CG vs. GG	Random	58.89	0.088	1.407	1.142-1.734	3.203	0.001	1.000	0.191
	CC vs. CG+GG	Fixed	0.00	0.903	1.006	0.314-3.221	0.010	0.992	0.296	0.255
Source of Controls										
PB	C vs. G	Random	61.46	0.075	1.103	0.591-2.060	0.308	0.758	1.000	0.642
	CC vs. GG	Random	60.77	0.110	1.326	0.073-5.977	0.190	0.849	NA	NA
	CG vs. GG	Fixed	34.06	0.219	1.206	0.855-1.701	1.067	0.286	1.000	0.506
	CC+CG vs. GG	Random	51.97	0.125	1.133	0.634-2.024	0.422	0.673	1.000	0.587
	CC vs. CG+GG	Random	58.45	0.121	1.005	0.173-5.829	0.006	0.995	NA	NA
HB	C vs. G	Fixed	45.00	0.162	1.541	1.366-1.739	7.024	≤0.001	0.296	0.142
	CC vs. GG	Fixed	39.16	0.193	2.214	1.482-3.308	3.879	≤0.001	1.000	0.671
	CG vs. GG	Random	60.38	0.080	1.544	1.218-1.956	3.594	≤0.001	0.296	0.421
	CC+CG vs. GG	Random	59.82	0.083	1.578	1.256-1.982	3.913	≤0.001	0.296	0.280
	CC vs. CG+GG	Fixed	41.70	0.180	1.888	1.267-2.812	3.126	0.002	1.000	0.759

Table 2. Summary Risk Estimates for Association of ITPKC rs28493229 Polymorphism with Kawasaki Disease Risk (Continue)

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Genotyping Methods										
TaqMan	C vs. G	Fixed	42.31	0.158	1.493	1.308-1.705	5.928	≤0.001	0.734	0.441
	CC vs. GG	Fixed	0.00	0.596	1.751	1.073-2.857	2.243	0.025	0.734	0.897
	CG vs. GG	Random	50.90	0.106	1.500	1.190-1.891	3.435	0.001	0.734	0.295
	CC+CG vs. GG	Random	55.38	0.081	1.505	1.185-1.912	3.354	0.001	0.734	0.357
	CC vs. CG+GG	Fixed	0.00	0.661	1.476	0.908-2.400	1.571	0.116	0.734	0.942
Sequencing	C vs. G	Fixed	40.66	0.185	1.606	1.349-1.911	5.337	≤0.001	1.000	0.833
	CC vs. GG	Fixed	0.00	0.704	3.248	1.719-6.136	3.629	≤0.001	NA	NA
	CG vs. GG	Random	52.74	0.120	1.641	1.053-2.557	2.189	0.029	1.000	0.308
	CC+CG vs. GG	Fixed	44.85	0.163	1.656	1.357-2.021	4.967	≤0.001	1.000	0.807
	CC vs. CG+GG	Fixed	0.00	0.722	2.874	1.528-5.408	3.274	0.001	NA	NA

PB: population-based; HB: hospital-based; NA: Not Applicable

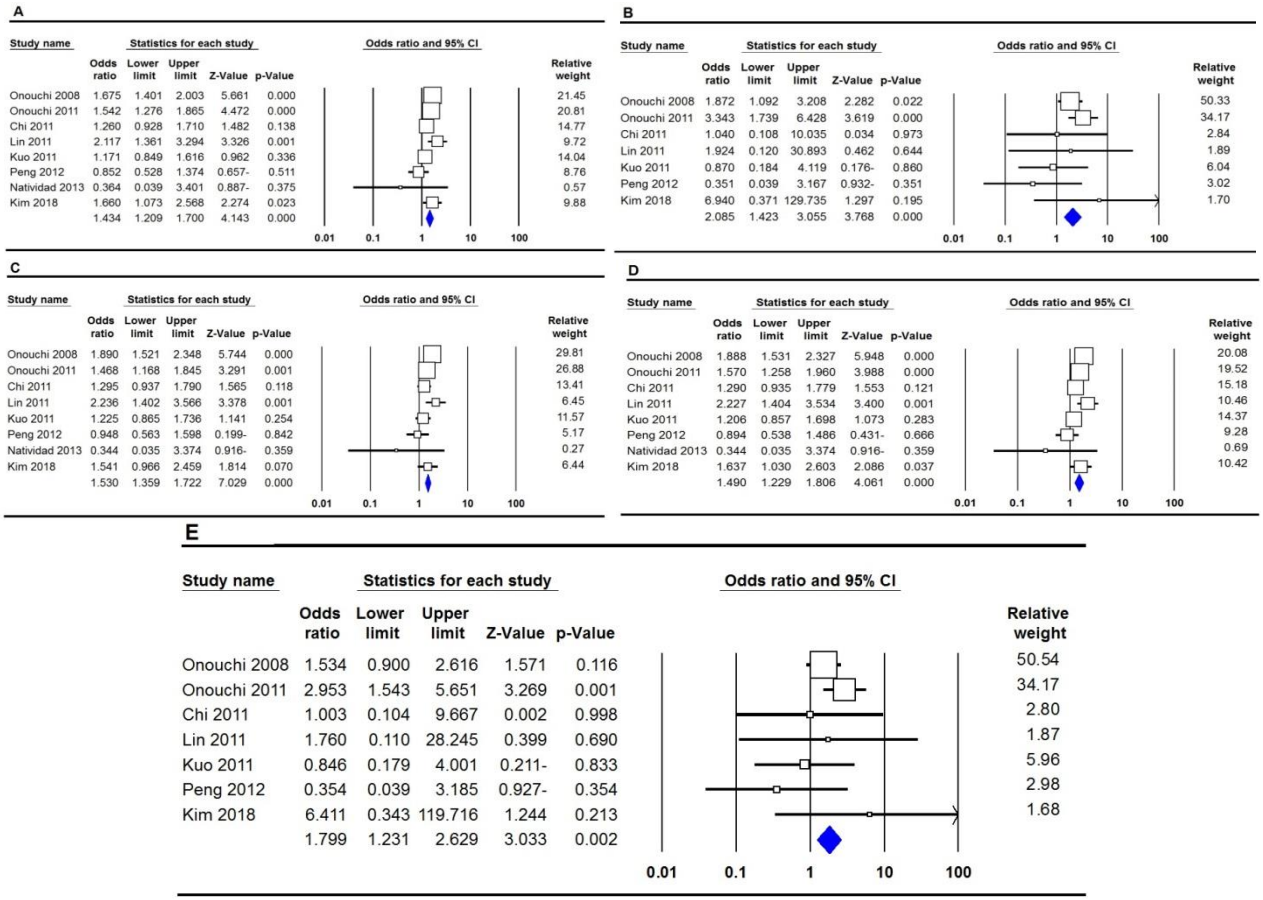

Figure 3. Forest plot for association of ITPKC rs28493229 polymorphism with risk of KD in the overall population. A: allele model (C vs. G); B: homozygote model (CC vs. GG); C: heterozygote model (CG vs. GG); D: dominant model (CC+CG vs. GG); and E: recessive model (CC vs. CG+GG)

Moreover, we performed subgroup analysis based on country of origin and ethnicity. Because of insufficient data, we did not analyze the association between *ITPKC rs28493229* polymorphism and KD risk in Caucasians. We analyzed the association between *ITPKC rs28493229* polymorphism and KD risk in Asians, and a significant association was observed under all five genetic models. Moreover, there was a significant association among Taiwanese under three genetic models, i.e., allele (C vs. G: OR = 1.360, 95% CI 1.116-1.658, P = 0.002), heterozygote (CG vs. GG: OR = 1.471, 95% CI 1.058-2.045, P = 0.022), and dominant (CC+CG vs. GG: OR = 1.470, 95% CI 1.142-1.734, P = 0.001). In the subgroup analysis regarding the source of controls, an increased risk of KD was found in the hospital-based subgroup under all five genetic models, but not in the population-based subgroup. Furthermore, these data were further stratified by genotyping methods, a significant association between the *ITPKC rs28493229* polymorphism and KD risk was observed in TaqMan and sequencing subgroup, in agreement with the overall data.

Between-Study Heterogeneity: There was no considerable heterogeneity detected between studies included in the analysis. The I^2 value under two models, i.e., allele (C vs. G: I^2 = 51.87; P_H = 0.042) and dominant (CC + CG vs. GG: I^2 = 54.33; P_H = 0.032) was greater than 50%, indicating that the included studies show heterogeneity. Therefore, we have performed subgroup analyses by ethnicity, country, source of controls, and genotyping methods to explain the potential source of heterogeneity. As shown in

table 2, when subgroup analyses were performed, the between-study heterogeneity did not change considerably, indicating these factors might not be the major source of heterogeneity in this meta-analysis.

Sensitivity Analysis: Sensitivity analysis was performed to test the influence of individual studies on the stability of the overall ORs by omitting one study at a time. The omission of any single study did not significantly affect the pooled ORs or 95% CIs, suggesting the meta-analysis results may be reliable.

Publication Bias: Begg's and Egger's linear regression tests were used to assess the potential publication bias for the association between *ITPKC rs28493229* polymorphism and KD risk in the overall meta-analysis. Table 2 lists the publication bias assessment method with its respective P-value for each test. The shapes of the funnel plots did not show any evidence of publication bias in the overall population, as shown in figure 4. Moreover, Egger's test did not find any publication bias under all five genetic models, i.e., allele (C vs. G: P_{Beggs} = 0.386; P_{Eggers} = 0.216), homozygote (CC vs. GG: P_{Beggs} = 0.763; P_{Eggers} = 0.408), heterozygote (CG vs. GG: P_{Beggs} = 0.173; P_{Eggers} = 0.225), dominant (CC + CG vs. GG: P_{Beggs} = 0.173; P_{Eggers} = 0.193), and recessive (CC vs. CG+GG: P_{Beggs} = 0.548; P_{Eggers} = 0.523), suggesting no evidence of publication bias.

Discussion

To date, only a meta-analysis has been performed to evaluate the *ITPKC* rs28493229 polymorphism and KD risk in the global population in 2012.[28] Therefore, it is necessary to perform an updated meta-analysis to evaluate the *ITPKC* rs28493229 polymorphism and KD risk based on previous and newly published eligible case-control studies. In the current study, we systematically reviewed and meta-analyzed the relationship between *ITPKC* rs28493229 polymorphism and KD risk. The results of this meta-analysis revealed a strong association between the *ITPKC* rs28493229 polymorphism and an increased risk of KD under all five genetic models.

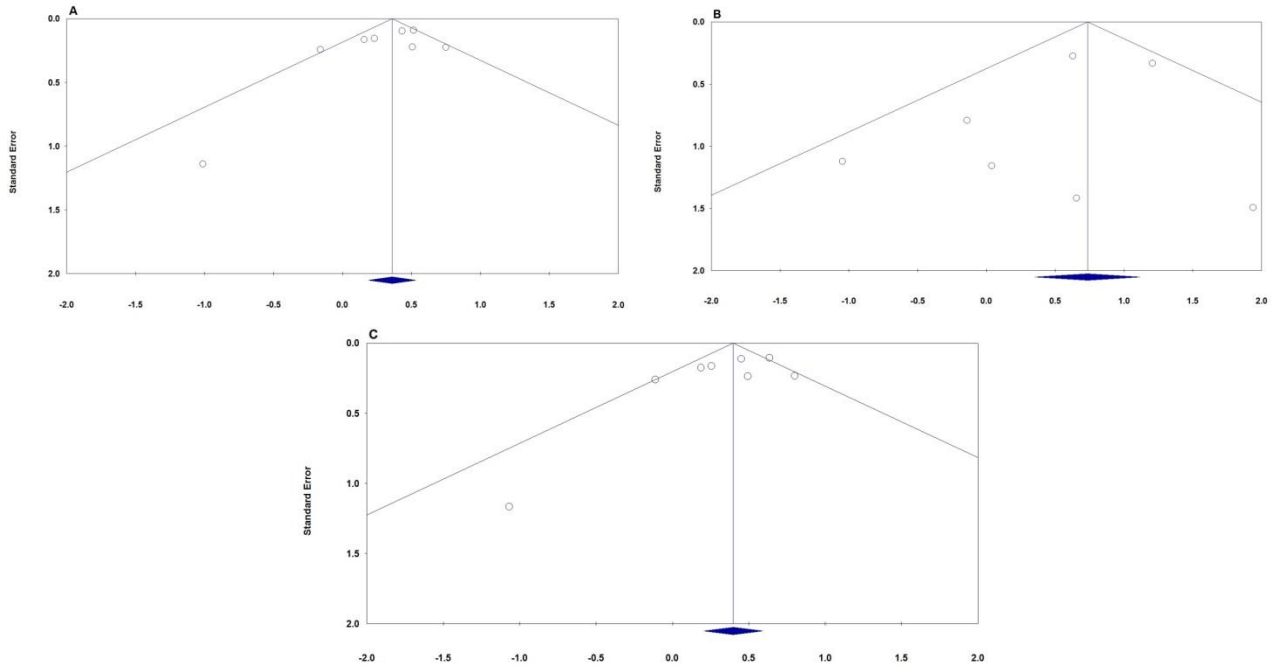

Figure 4. The funnel plots of publication bias for association of the ITPKC rs28493229 polymorphism with risk of KD in the overall population. A: allele model (C vs. G); B: homozygote model (CC vs. GG); and C: dominant model (CC+CG vs. GG)

Our pooled data strongly support the *ITPKC* rs28493229 polymorphism role in the development of pediatric KD. In 2008, Onouchi et al., found that the *ITPKC* rs28493229 polymorphism was significantly associated with increased susceptibility to KD and an increased risk of coronary artery lesions in US and Japanese children.[14] Two years later, another case-control study performed by Chi et al. evaluated the association among 385 unrelated Taiwanese pediatric patients with KD (222 male and 163 female). The results of this study did not reveal a significant association between *ITPKC* rs28493229 polymorphism and KD risk KD or CALs in Taiwanese children.[17] Khor et al., in a large case-control GWAS in 2,173 KD patients and 9,383 healthy controls evaluated the association of this locus with KD risk. Their results confirmed the previous findings of a genetic association in the region of the *ITPKC* gene.[29] In 2018, Kim et al. in the most recently published study revealed a significant association between the *ITPKC* rs28493229 polymorphism and an increased risk of KD in Korean children.[21] In 2012, Lou et al., in a meta-analysis based on seven case-control studies with 3,821 cases, and 12,802 controls evaluated the relationship of *ITPKC* rs28493229 polymorphism with KD risk under the allele genetic model. Their results showed a significant association between the C allele of rs28493229 polymorphism and an increased risk of KD (OR = 1.53, 95% CI = 1.34-1.74, P < 0.001).[28] However, their polled data remains an open field, because their data reliability and the number of included studies were smaller than that needed to receive a reliable conclusion. Moreover, they evaluated the association only under the allele genetic model, and subgroup analyses were also not conducted.

Between-study heterogeneity is to be expected in a meta-analysis. The clinical variation, study design, ethnicity, sample size, source of controls, genotyping method, and HWE are among the major causes of heterogeneity.[30-34] In the current meta-analysis, we perceived that significant heterogeneity was found in two 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.

Similar to other meta-analyses, there were several limitations in the current study. First of all, we only searched the literature issued in English and Chinese. Thus, potentially relevant papers published in other languages may not be identified, which might introduce potential selection bias. Second, the majority of the included studies in this meta-analysis were conducted on Asians which may introduce ethnicity bias, and further studies should perform on Caucasians and Africans. Third, because of the limited study number in subgroup analysis, the power used to detect the association between *ITPKC rs28493229* polymorphism and KD risk may not be strong enough. Fourth, there was a significant heterogeneity under the allele and dominant genetic models in the overall population, which could be because the analysis included few studies in the analysis or due to insufficient data that limited further subgroup analysis. So, more relevant case-control studies are required to be performed and then included in the meta-analysis to get more reliable and scientific data. Finally, this meta-analysis exclusively concentrated on the association between *ITPKC rs28493229* polymorphism and KD risk without considering gene-gene or gene-environment interactions. Therefore, to comprehensively demonstrate the etiology of KD, it is extremely required to study the combined interaction of the related genes.

Conclusion

In summary, our pooled data revealed that the *ITPKC rs28493229* was significantly

associated with susceptibility to childhood KD. The results of this meta-analysis may improve our understanding of the role of *ITPKC rs28493229* polymorphism in the etiology of KD, and aid in the diagnosis of high-risk patients with KD. Because of the limitations mentioned above in the meta-analysis, larger and well-designed studies in different ethnicities are needed to confirm our data.

Conflict of Interest

The authors have no conflict of interest.

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