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Association between the *FCGR2A* gene H131R polymorphism and risk of Kawasaki disease: a meta-analysis

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ABSTRACT. Several previous studies have investigated whether the *FCGR2A* gene H131R polymorphism confers an increased risk of Kawasaki disease (KD), but conflicting results have been reported. To further explore the association of this polymorphism with KD susceptibility, we performed an extensive search of relevant studies and conducted a meta-analysis to obtain a more precise estimate of risk. Systematic searches of the electronic databases Embase, PubMed, and Google Scholar were performed to identify relevant studies. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used for statistical analysis. Six studies were included in the meta-analysis, involving 1709 patients with KD and 3207 controls. Significant association was found between the *FCGR2A* gene H131R polymorphism and KD risk in analysis of the total population (HH *vs* RR: OR = 1.97, 95%CI = 1.55-2.50; HH *vs* HR: OR = 1.38, 95%CI = 1.21-1.57; the dominant model: OR = 0.69, 95%CI = 0.60-0.78; and the recessive model: OR = 1.65, 95%CI = 1.32-2.07). In subgroup analysis by ethnicity, significant association was found between the H131R polymorphism and KD risk

in Asians, but not in Caucasians. In addition, we found no significant association between the *FCGR2A* gene H131R polymorphism and risk of KD-associated coronary artery lesions. In conclusion, this meta-analysis suggested that the H131R polymorphism in the *FCGR2A* gene might be associated with susceptibility to KD in Asians.

Key words: H131R polymorphism; Kawasaki disease; *FCGR2A*

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited vasculitis affecting predominantly infants and young children (Rowley, 2011). The incidence of KD is 5-17 per 100,000 people in Europe and the United States, primarily in children under the age of five years. Although it was first described in 1967 by the Japanese pediatrician Tomisaku Kawasaki (Kawasaki et al., 1967), the etiology of KD is still not completely clear. The clinical characteristics of KD include prolonged fever, bilateral non-purulent conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, indurative angioedema of the hands and feet, and non-suppurative cervical lymphadenopathy (Newburger and Fulton, 2004). About 15-25% of untreated patients suffer coronary artery lesions (CAL). High-dose intravenous immunoglobulin (IVIG) therapy, given together with aspirin, has greatly reduced the prevalence of CAL when administered early in the acute phase of KD (Newburger et al., 2004).

Fcγ receptors (FcγRs) bind specifically to the γ chain of the Fc fragment of immunoglobulin G (IgG) and are located on the surface of immune cells such as monocytes, macrophages, and natural killer cells. FcγRs are directly involved in the function of these immune cells and regulate immune responses (Gerber and Mosser, 2001; Pleass and Woof, 2001). There are three highly homologous FcγR subtypes, Fcγ RI-III (Maenaka et al., 2001). Fcγ RII is a low-affinity receptor for IgG, which has two isoforms: Fcγ RIIa and b. Recent studies have shown that Fcγ RIIa is encoded by the *FCGR2A* gene (Tada et al., 2012).

Despite much investigation, the cause of KD is not yet fully understood. Twins and siblings of affected children have a risk of KD that is 10-fold higher than that of the general population (Fujita et al., 1989). This observation suggests that genetic factors may play key roles in the pathogenesis of this disease. Until now, genome-wide association studies and linkage analyses have reported a few genetic loci that have shown association with KD in subjects of Japanese, European, Korean, and Taiwanese descent (Burgner et al., 2009), including the IgG receptor gene *FCGR2A*. A point mutation (A→G) in *FCGR2A* (reference/alternative) resulting in an amino acid change at position 131, histidine (His131) to arginine (Arg131), is located in the second extracellular immunoglobulin-like domain of the FCGR2A protein (H131R); it has been suggested that this variation this variation might be related to the development of KD (Khor et al., 2011).

To date, many studies had been performed to evaluate the relationship between the H131R polymorphism in the *FCGR2A* gene and KD risk. However, the results remain controversial. Meta-analysis can be a useful tool in detecting an association that could otherwise remain masked in studies with small sample sizes, especially in those evaluating rare allele frequency polymorphisms. The aim of this study was to investigate the association between the *FCGR2A* gene H131R polymorphism and KD by conducting a meta-analysis of all eligible published case-control studies.

MATERIAL AND METHODS

Selection of studies

We searched the PubMed, Embase, and Google Scholar databases to retrieve papers linking the H131R polymorphism and KD risk that were available by August 2014. The search was conducted without language restrictions, using the following key words: "H131R", "Kawasaki disease", "*FCGR2A*", "single nucleotide polymorphism", and "genetic polymorphism". If more than one geographic or ethnic heterogeneous group was mentioned in a single report, information on each was extracted separately. If two or more studies completely or partially shared study populations, the one with the larger sample size was extracted.

Inclusion criteria and data extraction

Identified studies satisfied the following criteria: i) case-control studies that addressed patients with KD and healthy controls; ii) studies on the association of the H131R polymorphism and susceptibility to KD; and iii) studies that included sufficient genotype data for extraction. The exclusion criteria were as follows: i) not case-control studies that evaluated the association between the H131R polymorphism and KD risk; ii) case reports, letters, reviews, meta-analysis, or editorial articles; iii) studies that were based on incomplete raw data and those with no usable data reported; and iv) duplicate data were included in the studies.

Data extraction

Information was carefully and independently extracted from all eligible publications by two of the authors (S.Y.W. and S.B.Y.) according to the inclusion criteria listed above. Any disagreements that arose were resolved through discussion between the two authors. The following data were collected from each study: first author, year of publication, country, nationality, number of patients and controls, gene polymorphisms, and evidence of Hardy-Weinberg equilibrium (HWE).

Statistical analysis

HWE was evaluated for each study using the goodness-of-fit chi-square test. A P value of <0.05 was considered to be representative of departure from HWE (Chen et al., 2014). The strength of the associations between the H131R polymorphism in the *FCGR2A* gene and susceptibility to KD were estimated by the odds ratio (OR) and 95% confidence interval (CI) under a homozygote (HH *vs* RR) or a heterozygote comparison (HH *vs* HR), or a dominant (RR+HR *vs* HH) or a recessive model (HH+HR *vs* RR) between groups. We quantified the effect of heterogeneity using the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. When $I^2 > 50\%$ indicated heterogeneity across studies, the random-effect model was used for meta-analysis; else, the fixed-effect model was used. Sensitivity analysis was performed by removing the studies not in HWE. Begg's funnel plot analysis was conducted to estimate the potential publication bias. A P value of < 0.05 was considered to be representative of statisti-

cally significant publication bias. All the statistical tests were performed with STATA version 12.0 (StataCorp; College Station, TX, USA).

RESULTS

Study characteristics

A total of 34 potentially relevant publications up to August 2014 were systematically identified through PubMed, Embase, and Google Scholar databases. Based on our preliminary search criteria, 28 were excluded because they did not satisfy the inclusion criteria. As shown in Figure 1, a final total of 2122 patients with KD and 1565 controls were included in the meta-analysis (Taniuchi et al., 2005; Biezeveld et al., 2007; Khor et al., 2011; Ji et al., 2013; Yan et al., 2013; Chatzikyriakidou et al., 2014). The characteristics of these eight case-control studies from six articles are presented in Table 1; these contain studies of two Caucasian (Biezeveld et al., 2007; Chatzikyriakidou et al., 2014) and six Asian (Taniuchi et al., 2005; Khor et al., 2011; Ji et al., 2013; Yan et al., 2013) populations. The distribution of genotypes in the controls was consistent with HWE in all studies except for Taniuchi et al. (2005).

The patients with KD were subsequently stratified into two groups based on development of CAL after receipt of IVIG therapy. Overall, 94 patients with KD and 219 controls were included in the subgroup meta-analysis (Taniuchi et al., 2005; Biezeveld et al., 2007; Ji et al., 2013; Chatzikyriakidou et al., 2014). The characteristics of these four case-control studies are presented in Table 2.

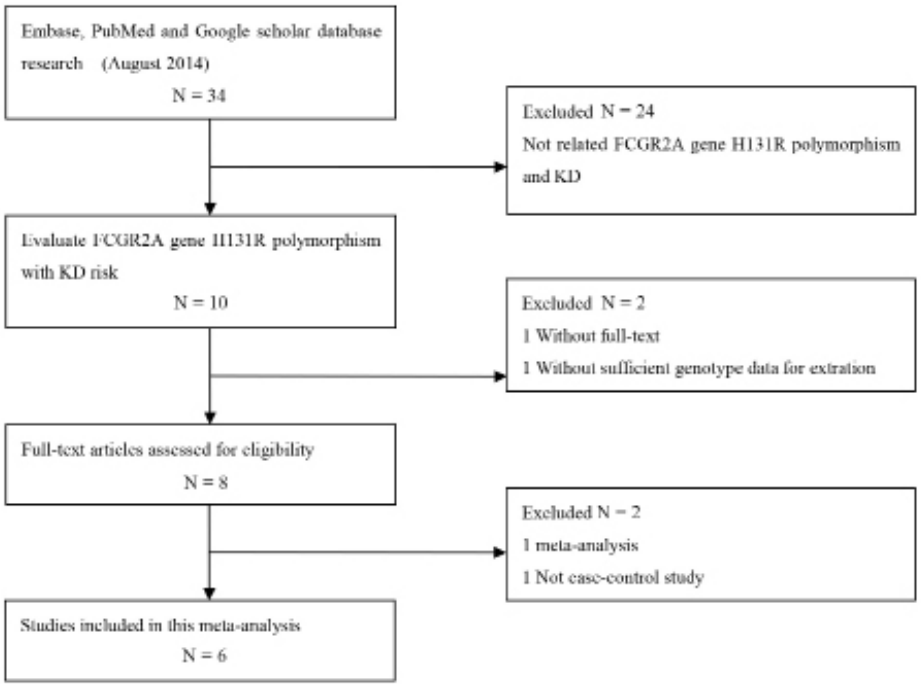

Figure 1. Flow chart showing study selection procedure.

Table 1. Studies included of the *FCGR2A* gene H131R polymorphism with KD.

Study included	Year	Area	Race	Cases/controls	Genotypes for cases			Genotypes for controls			HWE test
					HH	HR	RR	HH	HR	RR	
Taniuchi et al.	2005	Japan	Asians	65/566	45	18	2	336	213	17	0.01
Biezeveld et al.	2006	Netherlands	Caucasians	176/239	55	92	29	58	134	47	0.06
Khor et al.	2011	Taiwan	Asians	438/446	215	184	39	174	210	62	0.91
Khor et al.	2011	Hong Kong	Asians	130/568	77	47	6	233	261	74	0.95
Khor et al.	2011	Korea	Asians	460/498	285	156	18	289	179	30	0.74
Ji et al.	2013	China	Asians	35/25	23	9	3	7	12	6	0.85
Yan et al.	2013	China	Asians	358/815	192	144	22	366	374	75	0.14
Chatzikyriakidou et al.	2014	Greece	Caucasians	47/50	20	21	6	20	18	12	0.06

HWE, Hardy-Weinberg equilibrium.

Table 2. Studies included of the *FCGR2A* gene H131R polymorphism with KD-associated CAL.

Study included	Year	Area	Race	Cases/controls	Genotypes for cases			Genotypes for controls			HWE test
					HH	HR	RR	HH	HR	RR	
Taniuchi et al.	2005	Japan	Asians	18/36	9	8	1	30	5	1	0.21
Biezeveld et al.	2006	Netherlands	Caucasians	41/142	12	21	8	43	75	24	0.36
Ji et al.	2013	China	Asians	13/22	5	6	2	18	3	1	0.12
Chatzikyriakidou et al.	2014	Greece	Caucasians	22/19	10	10	2	7	9	3	0.97

Quantitative synthesis

A summary of the meta-analysis findings of the association between the H131R polymorphism in the *FCGR2A* gene and KD risk is provided in Figure 2 and Table 3. Overall, we identified a significant association of the H131R polymorphism with KD risk (HH *vs* RR: OR = 1.97, 95%CI = 1.55-2.50; HH *vs* HR: OR = 1.38, 95%CI = 1.21-1.57; dominant model: OR = 0.69, 95%CI = 0.60-0.78; recessive model: OR = 1.65, 95%CI = 1.32-2.07). In the subgroup analysis based on ethnicity, the same associations were found in Asians (HH *vs* RR: OR = 2.06, 95%CI = 1.58-2.69; HH *vs* HR: OR = 1.39, 95%CI = 1.21-1.60; dominant model: OR = 0.65, 95%CI = 0.52-0.80; recessive model: OR = 1.75, 95%CI = 1.35-2.26), but not in Caucasians (HH *vs* RR: OR = 1.62, 95%CI = 0.96-2.75; HH *vs* HR: OR = 1.25, 95%CI = 0.83-1.87; dominant model: OR = 0.75, 95%CI = 0.51-1.09; recessive model: OR = 1.38, 95%CI = 0.87-2.18). Sensitivity analysis was performed by omission of one non-HWE study (Taniuchi et al., 2005) and the result was not altered, indicating the result of meta-analysis was statistically significant (HH *vs* RR: OR = 1.99, 95%CI = 1.57-2.54; HH *vs* HR: OR = 1.36, 95%CI = 1.19-1.56; dominant model: OR = 0.69, 95%CI = 0.60-0.78; recessive model: OR = 1.67, 95%CI = 1.33-2.10).

A summary of the subgroup meta-analysis findings of association between the H131R polymorphism in the *FCGR2A* gene and KD-associated CAL risk is provided in Figure 3 and Table 4. We found no significant association between the *FCGR2A* gene H131R polymorphism and KD-associated CAL risk in any of genetic models (HH *vs* RR: OR = 0.76, 95%CI = 0.34-1.70; HH *vs* HR: OR = 0.48, 95%CI = 0.17-1.39; dominant model: OR = 2.05, 95%CI = 0.72-5.83; recessive model: OR = 0.82, 95%CI = 0.40-1.71).

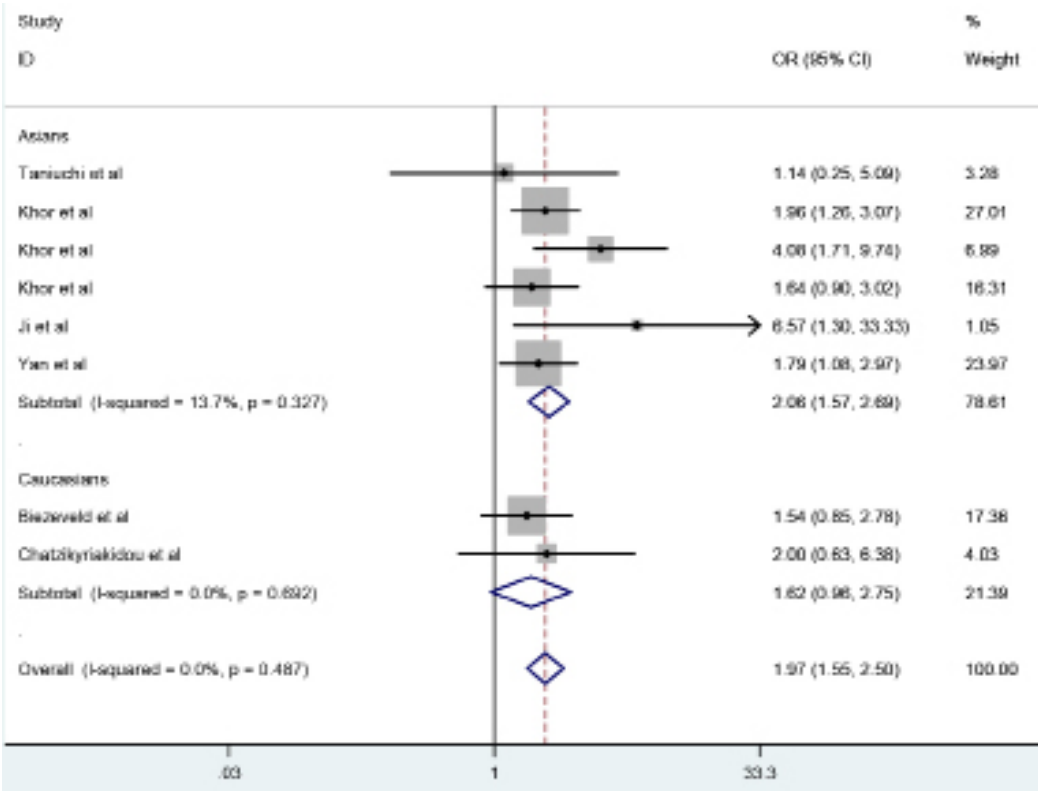

Figure 2. Forest plot of KD risk associated with the *FCGR2A* gene H131R polymorphism (HH *vs* RR).

Table 3. Summary ORs and 95%CI of the *FCGR2A* gene H131R polymorphism and KD risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95%CI	z	P
Overall	HH *vs* RR	1709	3207	Fixed	0.0%	0.49	1.97	1.55-2.50	0.00	1.00
	HH *vs* HR			Fixed	21.1%	0.26	1.38	1.21-1.57	0.00	1.00
	Dominant model			Fixed	35.9%	0.14	0.69	0.60-0.78	0.00	1.00
	Recessive model			Fixed	0.0%	0.66	1.65	1.32-2.07	0.00	1.00
Asians	HH *vs* RR	1486	2918	Fixed	13.7%	0.33	2.06	1.58-2.69	0.24	0.81
	HH *vs* HR			Fixed	35.5%	0.17	1.39	1.21-1.60	0.24	0.81
	Dominant model			Random	52.2%	0.06	0.65	0.52-0.80	0.24	0.81
	Recessive model			Fixed	0.0%	0.63	1.75	1.35-2.26	0.24	0.81
Caucasians	HH *vs* RR	223	289	Fixed	0.0%	0.69	1.62	0.96-2.75	0.00	1.00
	HH *vs* HR			Fixed	21.1%	0.26	1.25	0.83-1.87	0.00	1.00
	Dominant model			Fixed	35.9%	0.14	0.75	0.51-1.09	0.00	1.00
	Recessive model			Fixed	0.0%	0.66	1.38	0.87-2.18	0.00	1.00
Consistent with HWE	HH *vs* RR	1644	2641	Fixed	0.0%	0.43	1.99	1.57-2.54	0.73	0.46
	HH *vs* HR			Fixed	30.3%	0.19	1.36	1.19-1.56	0.73	0.46
	Dominant model			Fixed	44.9%	0.09	0.69	0.60-0.78	0.73	0.46
	Recessive model			Fixed	0.0%	0.61	1.67	1.33-2.10	0.73	0.46

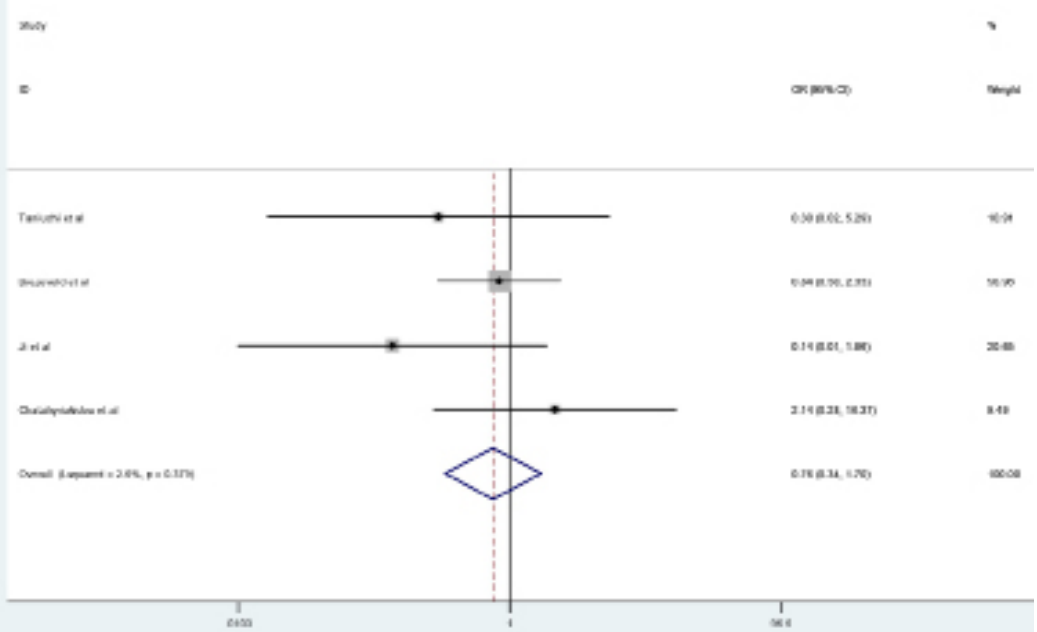

Figure 3. Forest plot of KD-associated CAL risk associated with the *FCGR2A* gene H131R polymorphism (HH *vs* RR).

Table 4. Summary ORs and 95%CI of the *FCGR2A* gene H131R polymorphism and KD-associated CAL risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95%CI	z	P
Overall	HH *vs* RR	94	219	Fixed	2.6%	0.38	0.76	0.34-1.70	0.00	1.00
	HH *vs* HR			Fixed	64.8%	0.04	0.48	0.17-1.39	0.00	1.00
	Dominant model			Fixed	68.4%	0.02	2.05	0.72-5.83	0.00	1.00
	Recessive model			Fixed	0.0%	0.65	0.82	0.40-1.71	0.00	1.00

Publication bias

The funnel plot and the Begg test were used to assess the publication bias. There was no evidence of publication bias in our study (Tables 3 and 4) (all $P > 0.05$).

DISCUSSION

KD is an acute, self-limited vasculitis that primarily affects children younger than five years of age. Although the incidence is highest in Asians, it is one of the leading causes of acquired heart disease in all ethnicities across the world (Yanagawa et al., 1995). Possible causes proposed for the disease have included infection, autoimmune diseases, and genetic susceptibility. However, the exact causative agent is still unknown (Lin and Hwang, 1987; Fildes et al., 1992; Stuber et al., 1996). Many studies have evaluated the *FCGR2A* gene H131R polymorphism with the risk for human immune system diseases, including erythematosus, arthritis, and ulcerative colitis (Nimmerjahn, 2006; Harley et al., 2008; Asano et al., 2009).

Recently, a variety of studies have focused on the association between the *FCGR2A* gene H131R polymorphism and KD. However, the results have been inconsistent. The most likely reason for the inconsistencies among these studies is that they are case-control studies with small sample sizes. To help resolve these conflicting results, we conducted this meta-analysis to combine similar kinds of studies to increase the sample size and statistical power, and thereby obtain a more authentic result.

This is the first systematic study of the association between the *FCGR2A* gene H131R polymorphism and KD risk using meta-analysis. The results suggested that there was significant association between the *FCGR2A* gene H131R polymorphism and KD risk in the overall population. Considering that the result might be affected by ethnicity, we performed a race-related subgroup analysis, and found significant association in Asians, but not in Caucasians. The results suggest a possible role for ethnic differences in genetic backgrounds and living environment in the etiology of KD. Further subgroup meta-analysis revealed that the H131R polymorphism is not associated with any alteration in the risk of KD-associated CAL. Furthermore, the sensitivity analysis confirmed the significant association between the *FCGR2A* gene H131R polymorphism and KD risk. Finally, we found no evidence of publication bias in this meta-analysis ($P > 0.05$).

The mechanism of how the *FCGR2A* gene H131R polymorphism relates to KD risk is still unclear. Fcγ RIIa is commonly expressed on immune responsive cells like macrophages, neutrophils, monocytes, and dendritic cells (Pleass and Woof, 2011). The H allele of the H131R polymorphism results in a point mutation leading to a substitution from arginine to histidine, leading to increased immune responses, as H131 binds human IgG2, whereas R131 does not (Pleass and Woof, 2011). In addition, a previous study demonstrated that H131R and another variant, HLA gene rs2857151, synergistically increased KD risk (Onouchi et al., 2012). Further studies with larger sample sizes should be taken into consideration to investigate the possible relationships between these and other variants.

The present study has some limitations. First, our meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs, or when they did, the ORs were not adjusted by the same potential confounders such as age, gender, ethnicity, and exposures. Missing information for data analysis might cause a serious confounding bias. Second, the effect of potential gene-gene and gene-environment interactions could not be addressed in this meta-analysis. Third, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Nevertheless, caution should be exercised when considering this conclusion.

In conclusion, our study indicated that the H131R polymorphism in the *FCGR2A* gene might be associated with KD risk in Asians. Further studies with the consideration of gene-gene and gene-environment interactions should be performed to further evaluate this association.

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