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Association between *KIR* gene polymorphisms and type 1 diabetes mellitus (T1DM) susceptibility

A PRISMA-compliant meta-analysis

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Abstract

Background: Type 1 diabetes mellitus (T1DM) is a T-cell mediated autoimmune disease with a complex genetic and immunological background. Evidence suggests that killer cell immunoglobulin-like receptor (KIR) genes are associated with T1DM, but the results are inconsistent. Here, we conducted a meta-analysis to comprehensively evaluate the effect of KIR genes on the risk of T1DM.

Methods: The PubMed, Web of Science, the Chinese Biomedical Database, and Chinese National Knowledge Infrastructure databases were systematically searched to select studies on the association between KIR polymorphisms and T1DM. The quality of each study was scoring in term of the Newcastle–Ottawa Scale. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of this association. Subgroup analysis stratified by ethnicity was also conducted. Funnel plot and Egger test were conducted to assess the publication bias.

Results: A total of 13 independent case–control studies comprising 2076 T1DM cases and 1967 controls were included in this meta-analysis. We found a negative association between the KIR2DL1 polymorphism and susceptibility to T1DM in the overall population (OR = 0.71, 95%CI = 0.51–0.98, $P = .038$), but not in ethnic-specific analysis. Additionally, a negative association between the KIR2DS1 polymorphism and susceptibility to T1DM was found in the Asians (OR = 0.76, 95%CI = 0.63–0.92, $P = .004$), but not in the Caucasians. However, the associations could not withstand Bonferroni correction. Conversely, no association between the other *KIRs* genes (*KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, and KIR3DS1*) and T1DM susceptibility was found in overall and subgroup ethnicity. No publication bias was detected in all comparisons.

Conclusions: In summary, this meta-analysis suggested that the KIR2DL1 and 2DS1 polymorphism might be a potential protective factor for T1DM in the specific ethnicity. Further subtle design studies with more sample size are still needed for a definitive conclusion.

Abbreviations: CBM = Chinese Biomedical Database, CIs = confidence intervals, CNKI = Chinese National Knowledge Infrastructure, KIR = killer cell immunoglobulin-like receptors, MHC = major histocompatibility complex, OR = odds ratios, T1DM = type 1 diabetes mellitus.

Keywords: killer cell immunoglobulin-like receptor, meta-analysis, polymorphism, type 1 diabetes mellitus

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by destruction of the pancreatic β cell by an aberrant T-cell-mediated immune response, accumulating to absolute insulin deficiency. The disease is a life-threatening condition and remains one of the leading causes of death in adolescent and young adults.[1] Until now, the aetiology and pathogenesis mechanisms of T1DM have not been elucidated, accumulating evidence suggested that genetic and environmental factors are involved in the pathogenesis of the disease.[2] Genes in the major histocompatibility complex (MHC) are closely associated with type 1 diabetes.[3,4] Approximately 89% of newly diagnosed patients possess so-called high-risk susceptibility haplotypes (HLA-DQ8 and DQ2).[5,6] The remaining patients develop the disease without the involvement of these genes, which could be explained by involvement of other genes as well as environmental factors.[7]

In humans, the killer cell immunoglobulin (Ig)-like receptors (KIRs) are members of the immunoglobulin superfamily expressed on both natural killer (NK) cells and subsets of T cells.[8] KIRs included either short (S) or long (L) cytoplasmic tails and either 3 (3D) or 2 (2D) Ig-like domains in the extracellular, which are inhibitory and activating members identified human leukocyte antigen (HLA) class I molecules.[9,10] Long-cytoplasmic tails processed 1 or 2 immunoreceptor tyrosine-based inhibitory motifs that give play to inhibit signalling pathway. Short-tailed receptors realised activating function via a lysine residue in their transmembrane domain that could pair with the adaptor proteins.[11]

The *KIR* gene cluster spans ~150 kb located within the leukocyte receptor complex on chromosome 19q13.4.[12] The KIR locus includes 2 pseudogenes (KIR2DP1 and KIR3DP1) and

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encodes 15 receptors. Six of them possess a short (S) cytoplasmic tails (KIR2DS1, 2DS2, 2DS3, 2DS4, 2DS5, and 3DS1) and participate in the activation of NK cell responses, and 7 of them have long (L) cytoplasmic tails (KIR3DL1, 3DL2, 3DL3, 2DL1, 2DL2, 2DL3, and 2DL5) which mediate inhibitory functions of the NK cells, whereas KIR2DL4 is involved in both NK cell activation and inhibition.[10]

In recent years, increasing attention on the role of KIR in autoimmune diseases has been received. Many case–control studies have shown that KIRs polymorphisms are associated with susceptibility to various autoimmune diseases, such as Graves' disease, systemic lupus erythematosus, multiple sclerosis, ankylosing spondylitis, and rheumatoid arthritis.[13–18] Several genetic studies also have investigated the role of *KIRs* gene in the development of T1DM, but these studies have produced diverse results.[19–30]

The evidence from meta-analysis might be powerful compared with the individual investigation. To our knowledge, no previous meta-analysis has been published about the role of *KIR* genes on the susceptibility to T1DM in different populations. Here, we carry out a systematic review and meta-analysis to investigate whether *KIR* gene contributes to the risk of T1DM in the different ethnicities.

2. Materials and methods

2.1. Literature retrieval

A comprehensive article search was conducted in the PubMed, Web of Science, the Chinese Biomedical Database (CBM), and Chinese National Knowledge Infrastructure (CNKI) databases to obtain the studies about *KIR* gene polymorphisms and the risk of T1D. Search time was range from the register to June 2017. Combinations of keywords included following: "killer cell immunoglobulin-like receptors" or "KIR" or "KIRs," "polymorphisms" or "genes" or "genotypes," "T1D" or "type 1 diabetes." In addition, we follow-up the reference lists of retrieved publications to identify additional relevant studies missed by the databases.

2.2. Inclusion and exclusion criteria

To accurately obtain the articles we need, some inclusion and exclusion criteria were drawn up in this meta-analysis. The inclusion criteria were: case–control study design; study on the association of KIR polymorphisms with susceptibility to T1DM; T1DM diagnosis and classification criteria were conform to the American Diabetes Association and revised by the World Health Organization in 1997; study provide sufficient data to calculate odds ratio (OR) with 95% confidence interval (CI).

The exclusion criteria were as follows: studies on animals; no control subjects; duplicate data; insufficient data; meeting, abstract, and case report. If repeat data were published in the different papers, the paper with relatively more sample size and higher quality was adopt.

2.3. Data extraction

Two investigators (SLL and LD) independently and carefully extracted the following information from each included study: the first author's name, year of publication, country, ethnicity of the study population, genotyping method, and the number of cases and controls. If there is inconsistent information in the extraction, we resolved by discussing with our research team.

2.4. Quality assessment

The methodological quality of the included studies was assessed by scoring according to the Newcastle–Ottawa scale (NOS). This scale contains 9 items based on 3 parts: selection of cases and controls (0–4), comparability of subjects (0–2), and ascertainment of exposure (0–3). A maximum of 9 points could be awarded according to each item, where study with NOS scores $\geq$7 points was regarded as high quality.

2.5. Statistical analysis

Crude pooled OR and its 95%CI was used to estimate the strength of association between *KIR* gene polymorphisms and the risk of T1DM. The statistical significance of OR was analyzed using Z test, and P value $<.05$ was considered as statistically significant.

The heterogeneity of results across different studies was assessed with the Q test, and I^2 statistics were used to quantify the degree of heterogeneity.[31] I^2 ranges between 0% and 100%, and I^2 values of 0% to 25%, 25% to 50%, and 50% to 75% were nominally considered low, moderate, and high estimates, respectively. A significant Q statistic ($P \leq .10$) indicated that heterogeneity existed across studies, and then the DerSimonian and Laird method in random effect model was used for meta-analysis. When the P-value of heterogeneity test was $>.1$ ($P > .10$), we used the Mante–Haenszel method in a fixed-effects model.

Sensitive analysis by omitting 1 study at a time was conducted to assess the reliability of results. The potential publication bias was examined by using the funnel plot.[32] Begg's funnel plot asymmetry was assessed by the method of Egger's linear regression test. If the P-value was $<.05$, statistically significant publication bias might exist. In association analysis, a pooled P-value of $<.05$ was considered as suggestive evidence for a genetic association. Since 14 (SNPs) associations have been examined, we applied the Bonferroni correction for multiple testing; thus, a P-value of $<.357$ was required to conclude a statistically significant association (threshold of $P=.05/14=0.00357$; P_0/N_1, $P_0=.05, N_1=14$ risk factors). All the statistical analyses were performed by Stata version 11.0 (StataCorp LP, College Station, TX).

2.6. Ethnic statement

The meta-analysis was based on previous published studies, thus no ethical approval and patient consent are required.

3. Results

3.1. Study selection and subject characteristics

The specific screening process is shown in Figure 1. The initial search of databases identified 92 potentially relevant articles. After we scan the title and abstract of all studies, 80 publications were excluded either because they were not about human subjects or the record was a review or case report without original data for calculating the OR and its 95%CI. Four publications were excluded after evaluating the remaining 16 publications due to overlapping data or duplicate publication. Finally, 12 articles that met the inclusion criteria were included in the meta-analysis. Of these 12 articles, Shastry et al[25] conducted an association study both in Latvian and Asian Indian populations, and each population was considered as a separate study. The total number of subjects enrolled in the included studies was 4043, comprising

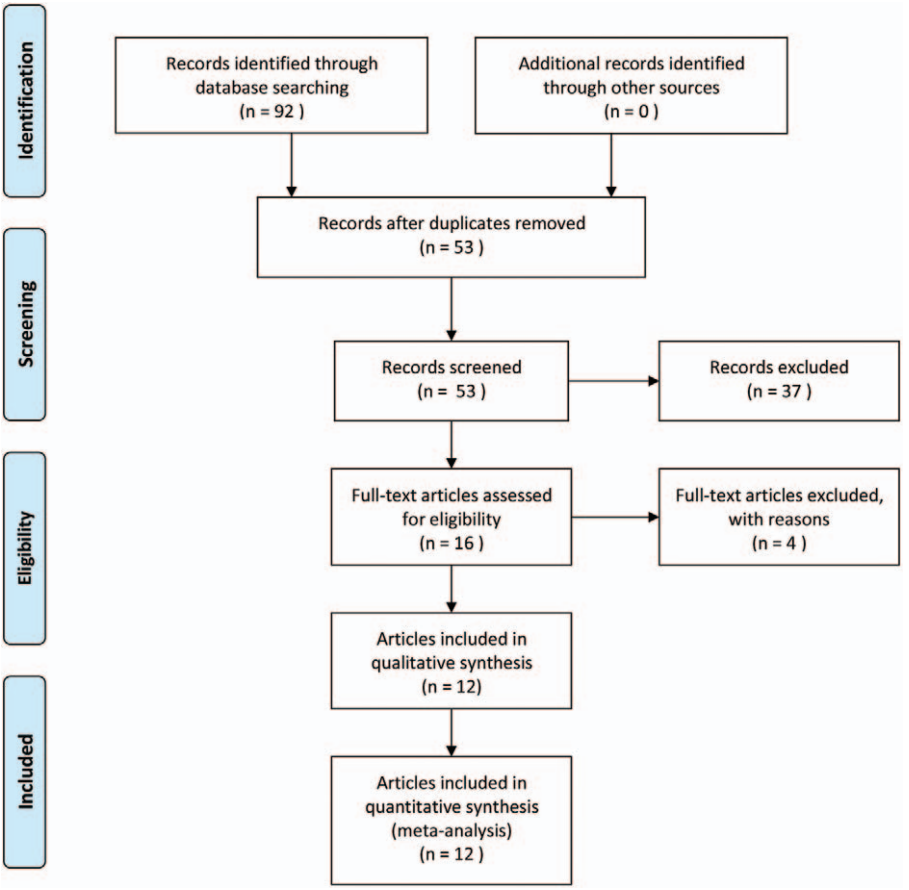

Figure 1. Flow diagram of studies included in the meta-analysis.

2076 cases and 1967 controls. Of these 13 studies, 6 were from Asians and 7 were from Caucasians. We performed ethnicity-specific meta-analysis for Asians and Caucasians. All of the studies were of high quality (NOS score >7). The main characteristics of each study included in the meta-analysis are summarized in Table 1.

3.2. Meta-analysis of KIR polymorphisms and T1DM

A summary of meta-analysis findings concerning the associations between the KIR and T1DM is shown in Table 2. The analysis revealed a significant association between the KIR2DL1 polymorphism and decreased risk of T1DM susceptibility in the overall population (OR = 0.71, 95%CI = 0.51–0.98, P = .038), but not in the ethnic-specific analysis (Fig. 2). Additionally, a negative association between the KIR2DS1 polymorphism and susceptibility to T1DM was found in the Asian population (OR = 0.76, 95% = 0.63–0.92, P = .004), but not in the Caucasians (Fig. 3). However, the P-value did not withstand the Bonferroni correction. Conversely, no association between the other *KIR* gene (*KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, and KIR3DS1*) and T1DM susceptibility was found in the overall population and subgroup ethnicity.

3.3. Heterogeneity test and sensitivity analysis

Heterogeneity was identified during the meta-analysis of some *KIR* gene in T1DM patients when all study subjects were considered (Table 2). However, partial heterogeneity was resolved when the data were stratified by ethnicity. Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating the statistical robustness of the results of this meta-analysis (Fig. 4).

3.4. Publication bias

Begg's funnel plots and Egger's linear regression test were performed to assess the publication bias of all the comparisons. There was no obvious evidence of asymmetry from the shapes of the funnel plots (Fig. 5). Egger's linear regression results did not demonstrate any evidence of publication bias (data not shown).

4. Discussion

Because the etiopathogenesis and progression of T1DM still have not to be elucidated, it is accept that environmental and multiple hosts' genetic factors contribute to susceptibility of T1DM. Through utilizing some genome-wide association studies (GWASs) and various candidate gene association studies, there is a considerable genetic component about the disease has been well established.[33,34] GWASs of KIR in T1DM are not yet available because this region of chromosome 19 does not have a high-coverage single-nucleotide polymorphism map.

Innate immunity has recently been found to be important in determining the fate of autoimmune responses.[35] NK cells are a critical subset of the innate effector that are not only related to

Table 1

Characteristics of individual studies included in this meta-analysis.

Author	Year	Region	NOS score	Ethnicity	Genotyping	T1DM cases	Controls	KIR polymorphisms
van der Slik et al[19]	2003	The Netherlands	7	Caucasian	PCR-SSP	149	207	KIR2DL1, KIR2DL2, **KIR2DL3 (–)**, **KIR2DL5 (–)**, KIR2DS1, KIR2DS2, **KIR2DS3 (+)**, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DS1
Nikitina-Zake et al[20]	2004	Latvia	8	Caucasian	PCR-SSP	98	100	KIR2DL1, **KIR2DL2 (+)**, KIR2DL3, KIR2DL4, **KIR2DL5 (+)**, **KIR2DS1 (+)**, **KIR2DS2 (+)**, **KIR2DS3 (+)**, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, **KIR3DS1 (+)**
Santin et al[21]	2006	Spain	7	Caucasian	PCR-SSP	76	71	KIR2DL1, **KIR2DL2**, KIR2DL3, KIR2DL5, KIR3DL1, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, **KIR2DS5**, **KIR3DS1**
Park et al[22]	2006	Korea	8	Asian	PCR-SSP	139	132	KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, **KIR2DL5**, KIR3DL1, KIR3DL2, KIR3DL3, KIR2DS1, **KIR2DS2**, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1
Middleton et al[23]	2006	UK	7	Caucasian	PCR-SSP	137	101	KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL5, KIR3DL1, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, **KIR2DS5 (+)**, KIR3DS1
Mogami et al[24]	2007	Japan	8	Asian	PCR-SSP	204	240	2DL1, 3DL1, **2DL3 (–)**, 2DS4, **2DL5 (–)**, **3DS1 (–)**, 2DS2, 2DS5, **2DL2 (–)**, 2DS1, 2DS3
Shastry et al-1[25]	2008	Latvia	7	Caucasian	PCR-SSP	45	92	**KIR2DL1 (+)**, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS1, **KIR2DS2 (+)**, KIR2DS3, **KIR2DS4 (+), KIR2DS5 (–)**, KIR3DL1, KIR3DL2, KIR3DL3, KIR3DS1
Shastry et al-2[25]	2008	India	7	Asian	PCR-SSP	86	98	KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, **KIR2DL5 (+), KIR2DS1 (–)**, KIR2DS2, KIR2DS3 (–), KIR2DS4, KIR2DS5, **KIR3DL1 (+)**, KIR3DL2, KIR3DL3, KIR3DS1
Jobim et al[26]	2010	Brazil	7	Caucasian	PCR-SSP	248	250	KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, KIR3DS1
Mehers et al[27]	2011	UK	7	Caucasian	PCR-SSP	394	168	KIR2DL1, **KIR2DL2 (+)**, KIR2DL3, KIR2DL5, KIR3DL1, KIR3DL3, **KIR2DS1 (+)**, KIR2DS2, **KIR2DS3 (+)**, KIR2DS4, KIR2DS5, KIR3DS1
Zhi et al[28]	2011	China	8	Asian	PCR-SSP	259	262	KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL5, KIR3DL1, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1
Sanjeevi et al[29]	2015	India	7	Asian	PCR-SSP	135	98	KIR2DL1, **KIR2DL2 (+)**, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, **KIR2DS4 (+)**, KIR2DS5, KIR3DS1, KIR3DL1, KIR3DL2, KIR3DL3
Osman et al[30]	2016	Saudi	8	Asian	PCR-SSP	106	148	KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, **KIR2DL5 (+), KIR2DS1 (–)**, KIR2DS2, **KIR2DS3 (–)**, KIR2DS4, KIR2DS5, **KIR3DL1 (+)**, KIR3DL2, KIR3DL3, KIR3DS1

Genes associated with susceptibility to T1DM in the study are set in bold.

KIR = killer cell immunoglobulin-like receptors, NOS = Newcastle–Ottawa Scale, PCR-SSP = polymerase chain reaction-sequence specific primer, T1DM = type 1 diabetes mellitus, (+) = positive association of the gene with susceptibility to T1DM in the study, (–) = negative association of the gene with susceptibility to T1DM in the study.

Table 2

Meta-analysis of the association between KIRs polymorphisms and T1DM.

Polymorphisms	Studies	T1DM (n/N)	Control (n/N)	OR (95%CI)	*P*-value	Heterogeneity test (I^2, *P*)		Effect model
2DL1	13	1983/2076	1893/1967	**0.71 (0.51–0.98)**	**.038**	6.0	.386	F
Asians	6	876/929	943/978	0.66 (0.42–1.03)	.067	0	.990	F
Caucasians	7	1107/1147	950/989	0.77 (0.47–1.25)	.285	50.3	.060	R
2DL2	13	1018/2076	890/1967	1.30 (0.93–1.83)	.122	82.9	.000	R
Asians	6	398/929	379/978	1.18 (0.97–1.45)	.100	72.7	.003	R
Caucasians	7	620/1147	511/989	1.36 (0.78–2.38)	.278	88.4	.000	R
2DL3	13	1931/2076	1827/1967	0.99 (0.78–1.28)	.962	0.0	.796	F
Asians	6	879/929	930/978	0.88 (0.58–1.36)	.570	0.0	.581	F
Caucasians	7	1052/1147	897/989	1.06 (0.78–1.43)	.727	0.0	.716	F
2DL4	6	926/931	965/968	0.65 (0.17–2.52)	.537	0.0	.334	F
Asians	4	582/585	615/618	1.05 (0.21–5.32)	.652	–	–	–
Caucasian	2	344/346	350/350	0.20 (0.01–4.12)	.482	–	–	–
2DL5	13	1105/2076	1061/1967	0.96 (0.68–1.35)	.817	84.9	.000	R
Asians	6	477/929	546/978	0.85 (0.43–1.68)	.636	91.3	.000	R
Caucasians	7	628/1147	515/989	1.07 (0.79–1.47)	.660	65.4	.008	R
2DS1	13	892/2076	853/1967	0.92 (0.75–1.12)	.403	54.8	.009	R
Asians	6	398/929	469/978	**0.76 (0.63–0.92)**	**.004**	23.6	.257	F
Caucasians	7	494/1147	384/989	1.16 (0.97–1.38)	.107	40.0	.125	F
2DS2	13	969/2076	911/1967	1.01 (0.76–1.34)	.959	76.3	.000	R
Asians	6	369/929	428/978	0.78 (0.51–1.20)	.262	75.4	.001	R
Caucasians	7	600/1147	483/989	1.25 (0.87–1.79)	.234	73.6	.001	R
2DS3	13	571/2076	552/1967	0.98 (0.76–1.27)	.891	63.9	.001	R
Asians	6	234/929	272/978	0.78 (0.55–1.10)	.149	51.3	.068	R
Caucasians	7	337/1147	280/989	1.19 (0.86–1.65)	.297	61.7	.016	R
2DS4	13	1810/2076	1634/1967	1.16 (0.96–1.42)	.129	35.9	.100	F
Asians	6	816/929	841/978	1.22 (0.93–1.61)	.151	19.3	.310	F
Caucasians	7	994/1147	793/989	1.11 (0.84–1.46)	.479	2.5	.406	F
2DS5	13	762/2076	743/1967	0.93 (0.73–1.18)	.544	67.3	.000	R
Asians	6	373/929	385/978	1.02 (0.76–1.39)	.876	56.6	.042	R
Caucasians	7	389/1147	358/989	0.83 (0.56–1.23)	.349	75.9	.000	R
3DL1	13	1930/2076	1812/1967	1.18 (0.92–1.51)	.193	28.8	.155	F
Asians	6	843/929	898/978	1.03 (0.73–1.46)	.859	57.2	.039	R
Caucasians	7	1087/1147	914/989	1.37 (0.95–1.96)	.090	0.0	.692	F
3DL2	7	927/931	965/968	0.74 (0.16–3.35)	.695	0.0	.907	F
Asians	5	581/585	615/618	0.74 (0.16–3.35)	.695	0.0	.907	F
Caucasians	2	346/346	350/350	–	–	–	–	–
3DL3	6	1320/1325	1135/1136	0.68 (0.25–1.85)	.449	0.0	.740	F
Asians	4	974/979	785/786	1.15 (0.28–4.67)	.845	0.0	.923	F
Caucasians	2	346/346	350/350	0.36 (0.08–1.62)	.184	0.8	.315	F
3DS1	13	894/2076	817/1967	1.01 (0.89–1.15)	.837	22.1	.220	F
Asians	6	390/929	417/978	0.93 (0.77–1.12)	.455	0.0	.529	F
Caucasians	7	504/1147	400/989	1.10 (0.92–1.31)	.319	38.5	.135	F

P-value $<.05$ was highlighted with bold.

CI = confidence interval, F = fixed model, KIRs = killer cell immunoglobulin-like receptors, n/N = the number of people having a certain *KIR* gene in each group/the total number of people in each group, OR = odds ratio, R = random model, T1DM = type 1 diabetes mellitus.

antitumour and antivirus infection, but also participate in allergic reactions and autoimmune disease. Increased NK cell activity has been reported in the periphery of individuals with T1DM, but a role for these innate immune cells in the pathogenesis of T1DM has not been elucidated.[36] Inhibitory receptor on the surface could recognize and combine with the corresponding HLA class I ligands to protect their cells from attacks by NK cells. In T1DM patients, the imbalance of *KIR* gene could result in the abnormal signals of NK/T cell activation and inhibitory, thereby further damaging certain immune stability and making their cells attacked by the NK cells.[37]

In 2003, van der Slik et al[19] first showed that KIR2DS2 gene was involved in the development of T1DM. Since then, the associations between KIR genes and T1DM susceptibility in different populations have been widely reported by independent case–control studies. However, the outcomes of these studies remain to vary from study to study. The inconsistency among different studies seems to be mainly owing to the relatively small sample size of most studies and the different populations of researches, there is little statistical power to detect a slight association. Meta-analysis is an effective statistical method that could pool the results of several independent studies together to get a comprehensive result. It has been widely utilized in evaluating the relationship between candidate genes and complex diseases with a genetic predisposition. The previous meta-analysis has been conducted in the association of *KIR* gene and susceptibility to rheumatoid arthritis and systemic lupus erythematosus.[38,39] To comprehensively analyze these associations between *KIR* gene polymorphisms and patients with T1DM in different ethnic groups, a meta-analysis was performed.

The present study showed that KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, and KIR3DS1 were not associated with T1DM susceptibility in overall and subgroup

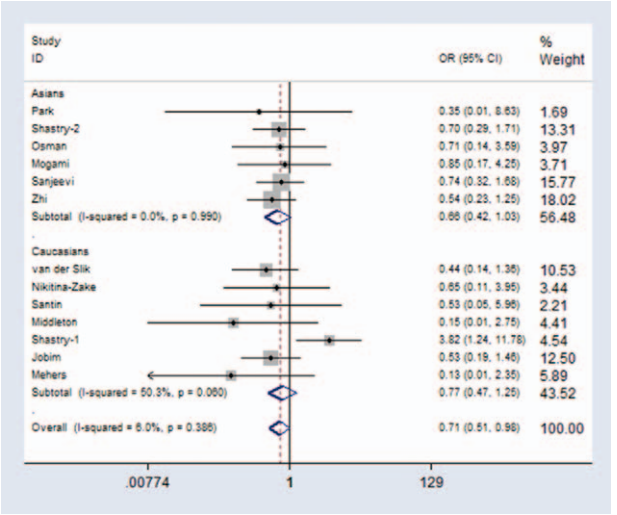

Figure 2. Forest plot for the meta-analysis of the association between KIR 2DL1 polymorphism and T1DM stratified by the ethnicity. ORs and 95%CIs for the outcome of the comparison in the overall population ($P = .038$, OR = 0.71, 95%CI = 0.51–0.98). CI = confidence interval, KIR = killer cell immunoglobulin-like receptors, OR = odds ratio, T1DM = type 1 diabetes mellitus.

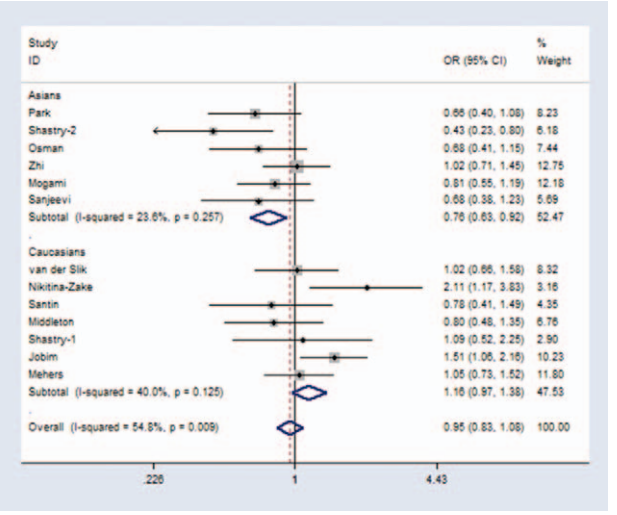

Figure 3. Forest plot for the meta-analysis of association between KIR 2DS1 polymorphism and T1DM stratified by the ethnicity. ORs and 95%CIs for the outcome of the comparison in the Asians ($P = .004$, OR = 0.76, 95%CI = 0.63–0.92). CI = confidence interval, KIR = killer cell immunoglobulin-like receptors, OR = odds ratio, T1DM = type 1 diabetes mellitus.

populations. Interestingly, our data suggested that KIR2DL1 polymorphism was associated with decreased risk of T1DM. After we did subgroup analysis by ethnicity, there was a possible negative association in the Asians ($P = .067$), but not in the Caucasians. It is possible that the reduced sample size after stratification by ethnicity thus led to a decline of statistical power in Asians. Additionally, our results showed that KIR2DS1 was negatively associated with T1DM susceptibility in the Asians, but not in the Caucasians. However, the above associations could not withstand Bonferroni correction. Therefore, current data in the literature provides only suggestive evidence to support the role of KIR2DL1 and KIR2DS1 in T1DM susceptibility. Further studies in larger cohorts are needed.

Previous studies demonstrated that functional variation of *KIR* genes on disease susceptibility is possible dependent on the combinations of KIR-HLA class I molecules present.[19,20] Some KIRs interact with specific HLA class I molecules: HLA-C group 1 (HLA-C1) molecules (asparagine at position 80) serve as the ligand for 2 inhibitory KIR (KIR2DL2 and KIR2DL3) and possibly 1 activating receptor (KIR2DS2), while the activating KIR2DS1 and inhibitory KIR2DL1 signal through HLA-C group 2 (HLA-C2) molecules (lysine at position 80), KIR3DL1 and KIR3DS1 signal through HLA-Bw4.[10] Santin et al[21] analyzed activating and inhibitory *KIR* genes in combination with aminoacid position 80 of HLA-C, and showed that individuals positive for inhibitory KIR2DL1 or activating KIR2DS1 together with group 2 (Lys^{80}) HLA-C alleles were less frequent among T1DM patients compared to control subjects, respectively. The results suggest that the effects of *KIR* genes on disease susceptibility might depend on the presence of their putative HLA ligands in an individual. The possible explanation for the discrepant association in different populations may be the geographic factors and the genetic disparity among ethnic groups. Different populations could have the difference in functional variants or different linkage disequilibrium patterns. Among eligible studies evaluating the KIR polymorphisms and

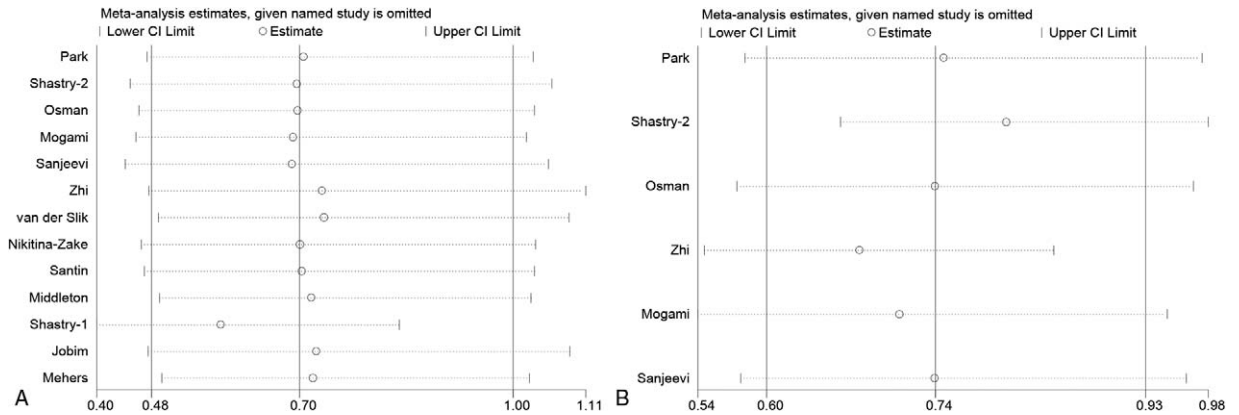

Figure 4. (A) Sensitive analysis of KIR 2DL1 polymorphism and T1DM risk in the overall population. (B) Sensitive analysis of KIR 2DS1 polymorphism and T1DM risk in the Asians. KIR = killer cell immunoglobulin-like receptors, T1DM = type 1 diabetes mellitus.

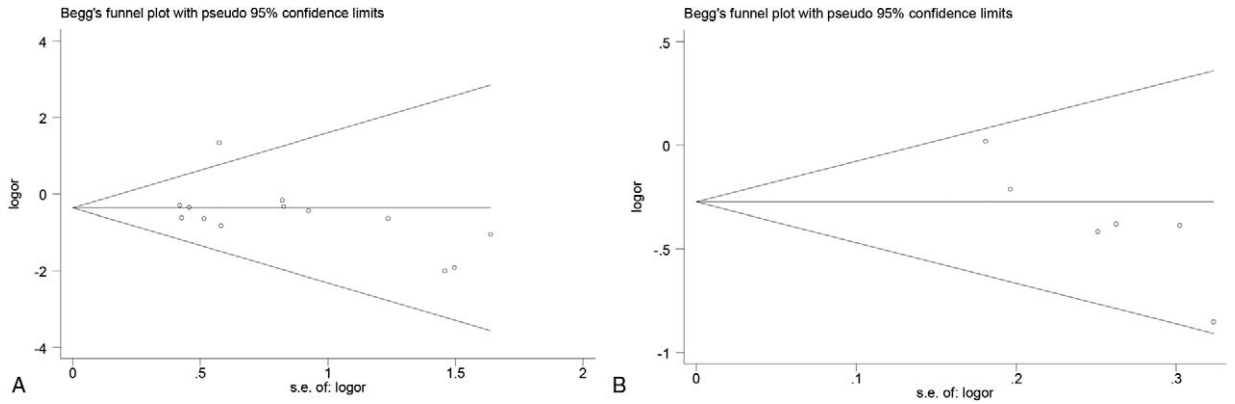

Figure 5. (A) Begger's funnel asymmetry plot of KIR 2DL1 polymorphism and T1DM risk in all study subjects. (B) Begger's funnel asymmetry plot of KIR 2DS1 polymorphism and T1DM risk in the Asians. KIR = killer cell immunoglobulin-like receptors, T1DM = type 1 diabetes mellitus.

T1DM, the results of sensitivity analysis by excluding 1 study at a time further strengthened the reliability and validity of the results.

To our knowledge, this is the first comprehensive meta-analysis investigating the association between KIR polymorphisms and T1DM. The strength of this study is that a large number of subjects and various ethnicities were included. Nevertheless, there are several limitations in the present meta-analysis that should be taken into consideration. First, although the overall sample size is relatively large, the sample size of each study and the number of studies in different race groups are scanty, and this might cause insufficient statistical power to detect slight association in the specific ethnicity. Second, significant heterogeneity across studies was found in some comparisons, although the sensitive analysis was performed and did not find any significant change of results when 1 study was excluded at a time. Third, the studies for ethnicity were mainly from the population of Asian and Caucasian origin. Thus, the findings apply to only these populations, and further studies in other ethnic populations were required. Furthermore, the present meta-analysis was based on uncorrected estimates. A more precise analysis could be performed if the potential confounding factors including sex, age, environmental factors, and other lifestyle factors were available.

In summary, this meta-analysis demonstrated that the KIR2DL1 polymorphism decreased the risk of T1DM susceptibility in the overall population and KIR2DS1 decreased the risk of T1DM susceptibility in the Asian population. Further well-designed studies will be needed to unravel KIR exact roles in the pathogenesis of T1DM.

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