

REVIEW

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# Evaluation of the association between KIR polymorphisms and systemic sclerosis: a meta-analysis

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## Abstract

**Background:** The results of investigations on the association between *killer cell immunoglobulin-like receptor (KIR)* gene polymorphisms and the risk of systemic sclerosis (SSc) are inconsistent. To comprehensively evaluate the influence of *KIR* polymorphisms on the risk of SSc, this meta-analysis was performed.

**Methods:** A systematic literature search was performed in electronic databases including Scopus and PubMed/MEDLINE to find all available studies involving *KIR* gene family polymorphisms and SSc risk prior to July 2019. Pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were measured to detect associations between *KIR* gene family polymorphisms and SSc risk.

**Results:** Five articles, comprising 571 patients and 796 healthy participants, evaluating the *KIR* gene family polymorphisms were included in the final meta-analysis according to the inclusion and exclusion criteria, and 16 *KIR* genes were assessed. None of the *KIR* genes were significantly associated with the risk of SSc.

**Conclusions:** The current meta-analysis provides evidence that *KIR* genes might not be potential risk factors for SSc risk.

**Keywords:** Killer immunoglobulin-like receptors, Systemic sclerosis, Polymorphism, Meta-analysis

## Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disorder characterized by aberrant immune system activation, vascular abnormalities, inflammatory, and excessive extracellular matrix production, which results in skin and organ fibrosis [1].

Although the pathogenesis of SSc remains obscure, it is generally accepted that the complicated interplay between environmental agents and genetic predisposing factors can lead to the initiate autoimmune responses. Dysregulation of the innate immune system has been detected in autoimmune diseases such as SSc [2]. Natural killer (NK) cells are essential components of innate immune system that contribute to the early host defense. NK cells recognize cancerous and infected host cells through killer cell immunoglobulin-like receptor (KIR)-

major histocompatibility complex (MHC) interactions and lyse them without antigen sensitization. In addition, NK cells produce various cytokines, including interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , granulocyte-macrophage colony stimulating factor, interleukin (IL)-5, IL-10, IL-13, and transforming growth factor (TGF)- $\beta$  [3, 4]. TGF- $\beta$  is defined as a profibrotic cytokine that provokes fibroblasts differentiation into myofibroblasts. Myofibroblasts are believed to be of major effector cells involved in SSc fibrosis [5, 6].

As mentioned above, genetic predisposition is associated with the onset and progression of SSc [7]. Studies have shown that the polymorphisms of genes, including *human leukocyte antigen (HLA)* [8], *signal transducer and activator of transcription 4 (STAT4)* [9], *B cell scaffold protein with ankyrin repeats 1 (BANK1)* [10], *protein tyrosine phosphatase, non-receptor type 22 (PTPN22)* [11], *TNF alpha-induced protein 3 (TNFAIP3)* [12], *methyl-CpG binding protein 2 (MECP2)* [13], *interleukin 1 receptor-associated kinase 1 (IRAK1)* [14], and *killer*

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*immunoglobulin-like receptor (KIR)* [15] increase the risk of SSc. Moreover, the first genome-wide association study (GWAS) performed in 2010 in a European ancestry population comprising 2296 SSc cases and 5171 controls disclosed the association of *CD247* gene with SSc risk [16]. As well, the French SSc GWAS on 2921 SSc patients and 6963 healthy subjects unearthed the significant association of *peroxisome proliferator-activated receptor gamma (PPARG)* with increased disease risk [17],

KIR receptors are members of the immunoglobulin superfamily, which are expressed on the surface of NK cells and subsets of T cells [18], and are encoded by genes located on human chromosome 19q13.4. Up to date, 17 highly homologous *KIR* genes have been identified in human, which are divided into three different kinds; activating (2DS1 - 2DS5, and 3DS1), inhibitory (2DL1 - 2DL4, 2DL5A, 2DL5B, 3DL1, 3DL2, and 3DL3), and pseudogenes (2DP1 and 3DP1) [19]. Previous studies have shown that *KIR* gene polymorphisms are involved in etiopathogenesis of autoimmune diseases, such as rheumatoid arthritis (RA) [20], systemic lupus erythematosus (SLE) [21, 22], multiple sclerosis (MS) [23], and etc.

The association between *KIR* gene polymorphisms and the risk of SSc have been evaluated by several case-control studies. However, low statistical power, small sample size, clinical heterogeneity, and the extent of linkage disequilibrium between genotypes are elements which could be the cause of the inconsistent results of these studies. Meta-analysis has been proposed as an efficient method, which can integrate small studies and overcome the mentioned limitations [24]. Therefore, in this study, we perform a meta-analysis to clarify the association between *KIR* polymorphisms and susceptibility to the SSc.

## Methods

The PRISMA guidelines were exerted to prepare this article [25].

### Searches and data sources

We searched databases including PubMed/MEDLINE and Scopus to find all eligible case-control studies of *KIR* gene family polymorphisms and SSc risk up to July 2019. Moreover, we searched for non-digitally archived literature and interviewed relevant experts and research centers to identify any gray literature. The following keywords were used to search these databases: (“KIR” or “Killer cell immunoglobulin-like receptors) AND (“systemic sclerosis” OR “scleroderma”) with “OR” and “AND” and “NOT” Boolean operators in the Title/Abstract/Keywords fields. We reviewed all references to include any related studies on genotyping and polymorphisms in the *KIR* gene family. Only literature

published in English and human population studies were included in the current meta-analysis.

### Inclusion and exclusion criteria

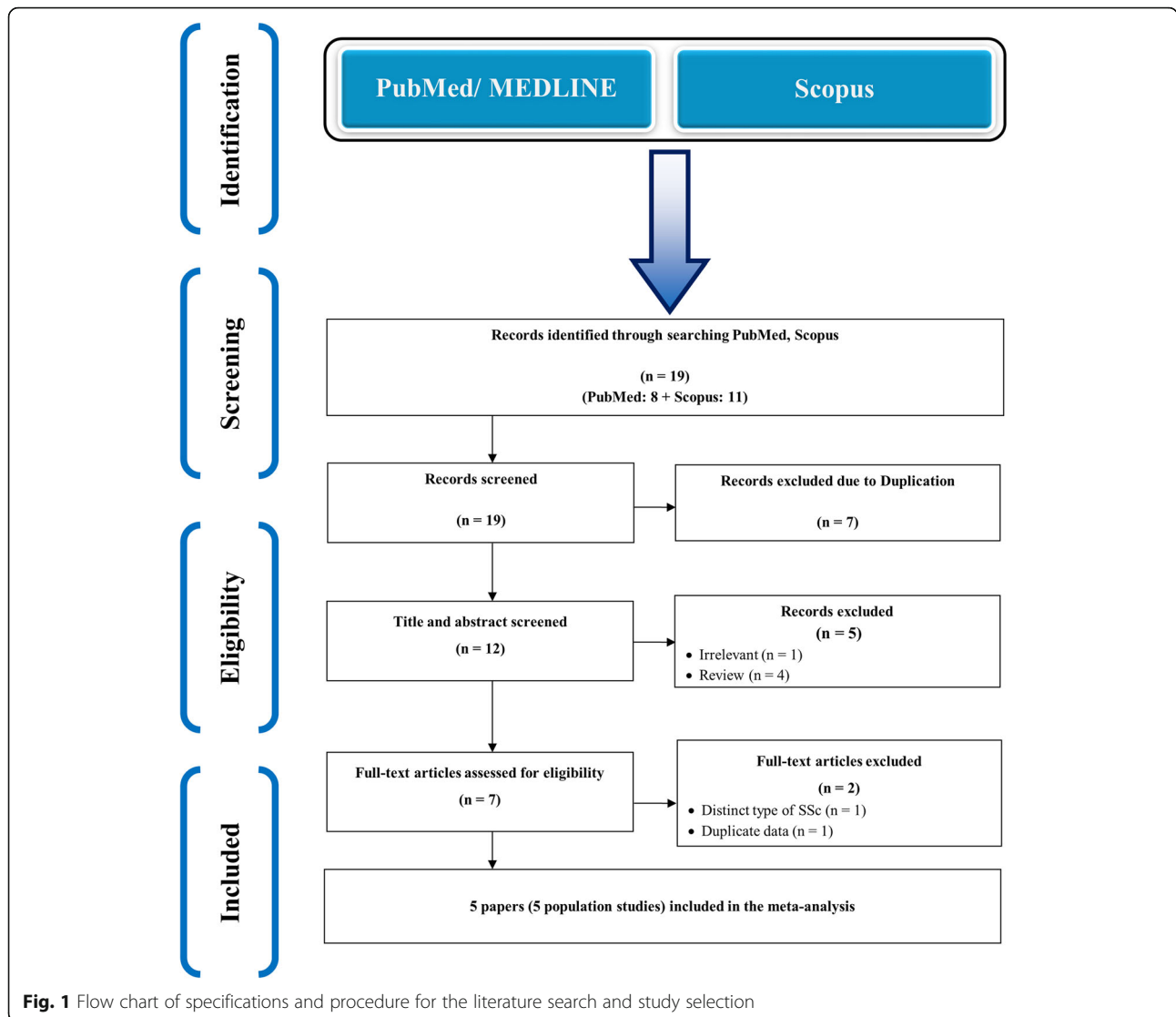
The following criteria were considered for study inclusion in this meta-analysis: (1) case-control studies that evaluated the association of *KIR* gene family polymorphisms and SSc risk; and (2) studies with available *KIR* gene polymorphism frequencies to allow for calculation of odds ratios (ORs) with 95% confidence interval (CIs). The exclusion criteria were (1) duplication or overlapping subjects in any studies; (2) publications that were letters, reviews, comments, or abstract only; and (3) studies with inadequate data with respect to *KIR* gene polymorphism frequency.

### Data extraction and quality assessment

All data were extracted according to the described criteria. The following information was included: first author's last name, year of publication, and frequency of *KIR* genes in SSc patients and healthy controls. The Newcastle-Ottawa Scale was used for assessing methodological quality. Studies were graded as low, moderate, or high quality according to scores of 0–3, 4–6, and 7–9, respectively. Two independent investigators without knowledge of existing scores examined the selected studies based on the criteria described above to resolve any discrepancies.

### Statistical methods

We used pooled ORs and corresponding 95% CIs for *KIR* genes to evaluate *KIR* gene family polymorphisms and SSc risk. In order to calculate the phenotypic frequency (pf %) in each group, the percentage of positive numbers between all samples was used. For calculating genotypic frequency (gf) among all participants, the formula  $gf = 1 - (1 - pf)^{1/2}$  was exerted. Cochran's Q test was used to assess heterogeneity, and the  $I^2$  method was employed for calculating the variation in the pooled estimations. For the latter test, significance was considered at  $P < 0.1$  [26]. The meta-analysis was performed with a random-effects model when heterogeneity between the individual studies was statistically significant. Otherwise, a fixed-effects model was used. Meanwhile, a sensitivity analysis was done by successively removing a particular study or group of studies (if any) that had the highest impact on the heterogeneity test. A funnel plot was established for checking the existence of publication bias. The funnel plot asymmetry was measured by Egger's linear regression test and Begg's test ( $P < 0.05$  was considered to indicate statistically significant publication bias) [27]. All statistical analyses were conducted by using data analysis and statistical software (STATA)



**Table 1** Specifications of the included studies in this meta-analysis

Author (Ref)	Published Year	Country/ Race	Detection Technique	SSc Patients N	Controls N	KIR Polymorphisms
T. Momot [1]	2004	Germany/ Caucasian	PCR	102	100	2DL1, 2DL2, 2DL3, 2DS1, 2DS2, 2DS3, 2DS4, 3DS1, 3DL1
P. H. Salim [2]	2013	Brazilian/ Caucasian	PCR	115	115	2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1, 2DP1
JD. Tozkr [3]	2016	Turkey/ Edirne	PCR-SSP	25	40	2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DL5A, 2DL5B, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1, 2DP1, 3DP1
M. Mahmoudi [4]	2017	Iranian/ Caucasian	PCR-SSP	279	451	2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DL5A, 2DL5B, 3DL1, 3DL2, 3DL3, 2DS1, 2DS2, 2DS3, 2DS4, 2DS4 (full), 2DS4 (var), 2DS5, 3DS1, 2DP1, 3DP1, 3DP1 (full), 3DP1 (var)
AC. Machado-Sulbaran [5]	2019	Mexico	PCR-SSP	50	90	2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1, 2DP1, 3DP1

**Table 2** Meta-Analysis of the pooled association between KIR polymorphisms and SSC

KIR gene	No. of studies	SSc Positive (%) / Total	Control Positive (%) / Total	Negative (%) / Total	P-value	Pooled OR (95% CI)	Heterogeneity Test Q, I <sup>2</sup> ; P-value	Publication Bias (Begg's Test, P-value; Egger's test, P-value)	Effect Model
2DL1	5	550 (96.3%), 21 (3.7%) / 571	765 (96.1%), 31 (3.9%) / 796	31 (3.9%) / 796	0.660	1.14 (0.64–2.0)	(3.17, 0.0%; P = 0.52)	(Begg's Test, 0.99; Egger's test, 0.43)	Fixed
2DL2	5	283 (49.5%), 288 (51.5%) / 571	444 (55.8%), 352 (44.2%) / 796	352 (44.2%) / 796	0.875	0.94 (0.42–2.07)	(39.87, 89.97%; P < 0.001)	(Begg's Test, 0.99; Egger's test, 0.86)	Random
2DL3	5	498 (87.2%), 73 (12.8%) / 571	710 (89.2%), 86 (10.8%) / 796	86 (10.8%) / 796	0.306	0.84 (0.60–1.17)	(4.02, 53%; P = 0.40)	(Begg's Test, 0.70; Egger's test, 0.59)	Fixed
2DL4	4	467 (99.6%), 2 (0.4%) / 469	696 (100%), 0 (0%) / 696	0 (0%) / 696	0.335	0.42 (0.07–2.47)	(0.2, 0.0%; P = 0.97)	(Begg's Test, 0.99; Egger's test, 0.81)	Fixed
2DL5	4	180 (38.4%), 289 (61.6%) / 469	273 (39%), 423 (61%) / 696	423 (61%) / 696	0.465	0.91 (0.71–1.17)	(2.19, 0.0%; P = 0.53)	(Begg's Test, 0.39; Egger's test, 0.09)	Fixed
2DS1	5	285 (49.9%), 286 (50.1%) / 571	427 (53.6%), 369 (46.4%) / 796	369 (46.4%) / 796	0.92	0.98 (0.60–1.58)	(13.76, 70.9%; P = 0.008)	(Begg's Test, 0.99; Egger's test, 0.73)	Random
2DS2	5	322 (56.4%), 249 (43.6%) / 571	445 (55.9%), 351 (44.1%) / 796	351 (44.1%) / 796	0.923	1.01 (0.81–1.26)	(3.29, 0.0%; P = 0.51)	(Begg's Test, 0.29; Egger's test, 0.17)	Fixed
2DS3	5	193 (24.3%), 378 (75.7%) / 571	260 (32.7%), 536 (67.3%) / 796	536 (67.3%) / 796	0.582	1.07 (0.85–1.34)	(7.25, 44.89%; P = 0.122)	(Begg's Test, 0.12; Egger's test, 0.16)	Fixed
2DS4	5	321 (56.2%), 250 (43.8%) / 571	395 (49.6%), 401 (50.4%) / 796	401 (50.4%) / 796	0.838	1.03 (0.75–1.45)	(2.61, 0.0%; P = 0.62)	(Begg's Test, 0.85; Egger's test, 0.19)	Fixed
2DS5	4	164 (35%), 305 (65%) / 469	258 (37.1%), 438 (62.9%) / 696	438 (62.9%) / 696	0.444	0.81 (0.47–1.39)	(9.11, 67.10%; P = 0.02)	(Begg's Test, 0.99; Egger's test, 0.73)	Random
3DL1	5	535 (93.7%), 38 (6.3%) / 571	739 (92.8%), 57 (7.2%) / 796	57 (7.2%) / 796	0.683	1.09 (0.71–1.70)	(3.78, 0.0%; P = 0.43)	(Begg's Test, 0.99; Egger's test, 0.28)	Fixed
3DL2	4	467 (99.6%), 2 (0.4%) / 469	692 (99.4%), 4 (0.6%) / 696	4 (0.6%) / 696	0.902	1.09 (0.27–4.40)	(0.38, 0.0%; P = 0.94)	(Begg's Test, 0.90; Egger's test, 0.53)	Fixed
3DL3	4	467 (98.9%), 5 (1.1%) / 472	696 (99.6%), 3 (0.4%) / 699	3 (0.4%) / 699	0.534	0.64 (0.155–2.63)	(0.001, 0.0%; P = 0.99)	(Begg's Test, 0.99; Egger's test, 0.60)	Fixed
3DS1	5	256 (44.8%), 315 (55.2%) / 571	342 (43%), 454 (57%) / 796	454 (57%) / 796	0.377	1.10 (0.88–1.37)	(2.68, 0.0%; P = 0.61)	(Begg's Test, 0.19; Egger's test, 0.11)	Fixed
2DP1	4	460 (98.1%), 9 (1.9%) / 469	672 (96.5%), 24 (3.5%) / 696	24 (3.5%) / 696	0.182	1.672 (0.79–3.56)	(6.99, 57.13%; P = 0.07)	(Begg's Test, 0.73; Egger's test, 0.56)	Fixed
3DP1	3	150 (42.4%), 204 (57.6%) / 354	230 (39.6%), 351 (60.4%) / 581	351 (60.4%) / 581	0.152	1.28 (0.91–1.81)	(0.94, 0.0%; P = 0.62)	(Begg's Test, 0.90; Egger's test, 0.47)	Fixed

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- Mahmoudi M, Fallahian F, Sobhani S, Ghoroghi S, Jamschidi A, Poursani S, et al. Analysis of killer cell immunoglobulin-like receptors (KIRs) and their HLA ligand genes polymorphisms in Iranian patients with systemic sclerosis. *Clinical rheumatology*. 2017;36 (4):853–62
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(version 11.0; Stata Corporation, College Station, TX) and MedCalc.

**Results**

**Characteristics of the eligible studies**

Figure 1 displays the inclusion/exclusion process of the potential studies with respect to the meta-analysis of *KIR* gene association with the risk of SSc. The initial search resulted in 19 related studies. Based on exclusion/inclusion criteria, 5 articles with 571 patients and 796 healthy participants were included in the final meta-analysis [15, 28–31]. All included papers were case-control studies. One paper involved the Brazilian population, and the other four studies were conducted in Europe/Germany, Turkey, Mexico, and Iran. The range of publication years was 2004 to 2019 (Table 1). Based on the Newcastle-Ottawa Scale criteria, all included studies had a total score ranging from 7 to 9. The key characteristics and the *KIR* gene frequencies of the included studies in this meta-analysis are presented in Table 1.

**Main results and sensitivity analysis**

Table 2 presents a summary of the frequency of 16 *KIR* genes, pooled ORs, and heterogeneity tests of the association between the *KIR* polymorphisms and susceptibility to SSc. The overall analysis did not show statistically significant association of *KIR* genes with SSc susceptibility. As examples, the forest plots of *KIR2DP1* (A) and *KIR3DL1* genes (B) are shown in Fig. 2.

**Sensitivity analysis**

A sensitivity analysis was performed by sequential omission of individual and groups of studies. The pooled ORs did not deviate with the sequential omission of any

participants or group of studies, indicating that our results were statistically robust (Fig. 3).

**Heterogeneity and publication bias**

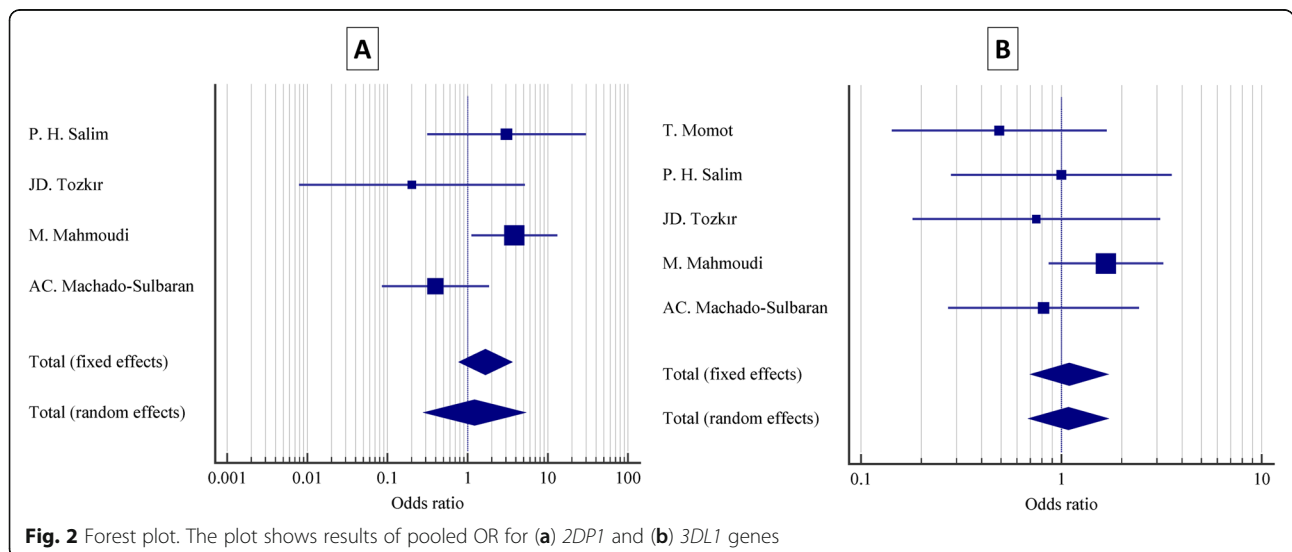
Heterogeneity between studies was observed for the *KIR2DL3* ( $I^2 = 53\%$ ;  $P = 0.40$ ) gene, while other *KIR* genes did not indicate any heterogeneity. Accordingly, the random- and fixed-effects models were applied to pool the result.

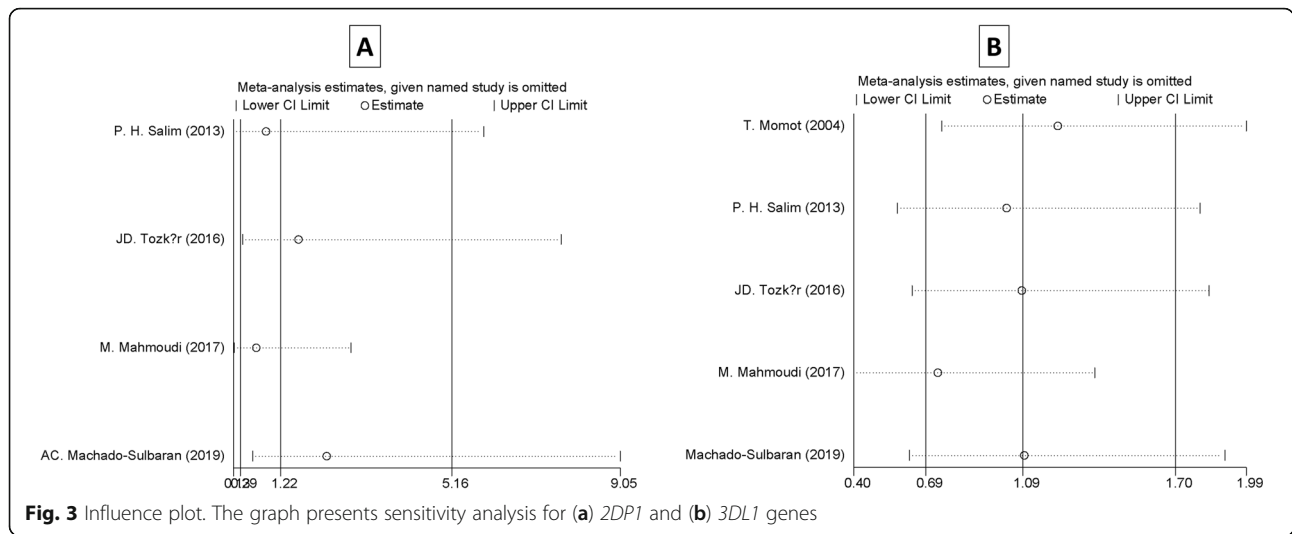
Publication bias was examined by using a funnel plot and Egger’s and Begg’s tests. No publication bias was identified (Table 2, Fig. 4).

**Discussion**

SSc is a multifactorial and systemic autoimmunity disorder that can lead to fibrosis and disturbance of regular organs function [32]. SSc has a strong dependency on both genetic and environment [33]. The multiplicity of genetic factors, environmental triggers, and their interactions involved in the development of SSc disease make its pathogenesis difficult to identify.

Up to now, several genes have been identified that may influence the risk of SSc development. *HLA* gene family is the most generally associated gene with SSc disease. An interaction between HLA molecules and *KIR* receptors on NK cells can mediate the recognition and elimination of defective and foreign cells [34]. Cytotoxic activity of NK cells and certain T cells are regulated with activating and inhibitory *KIR*s. Preceding studies revealed that the number of NK cells have been increased in the blood of SSc patients [35]. Moreover, T and NK cells phenotype and functional abnormalities were observed in SSc patients, suggesting that these cells may play a main role in the SSc pathogenesis [36–38].





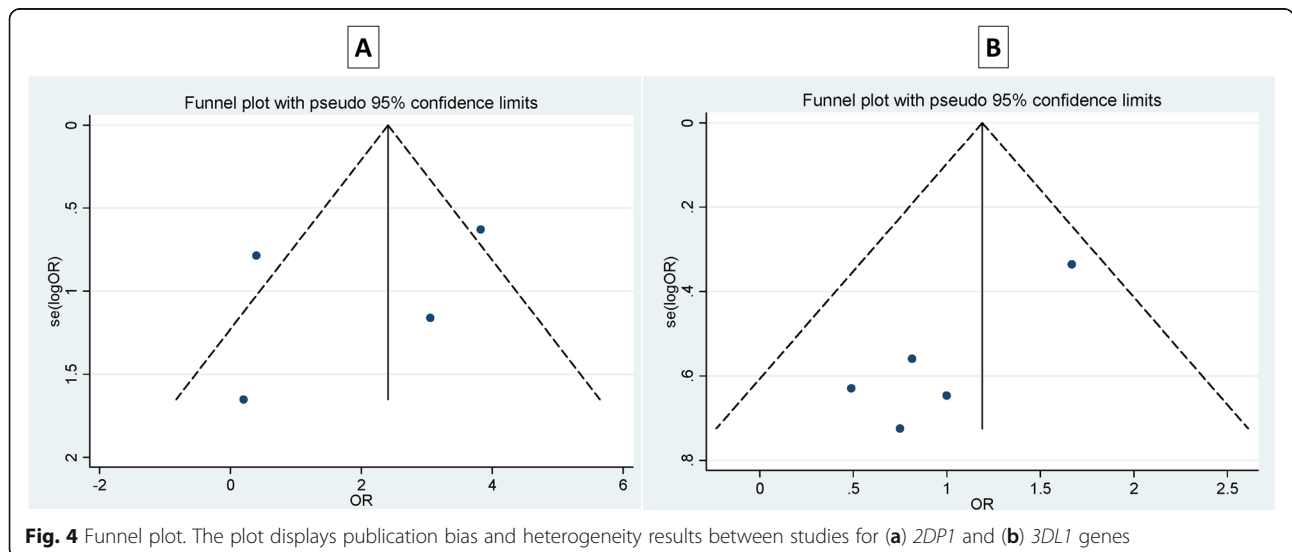
**Fig. 3** Influence plot. The graph presents sensitivity analysis for (a) *2DP1* and (b) *3DL1* genes

There is a balance between inhibitory and activating *KIR* in healthy individuals. The imbalance between activating and inhibitory *KIR* genes might influence the pathogenesis of SSc through upregulation of activation or downregulation of inhibition, or a combination of both [15].

Some investigations have been performed with regard to the *KIR* genes polymorphisms and SSc disease in populations. For instance, Momot et al. reported that the combination of *KIR2DS2<sup>+</sup>/KIR2DL2<sup>-</sup>* was associated with the risk of SSc disease [28]. The results of a study by Salim and colleagues also demonstrated the same results. In addition, they suggested that *KIR2DL2<sup>+</sup>* might be a potential protective factor for SSc [39]. Likewise, an investigation showed that the frequency of *KIR2DS3* gene polymorphism in SSc patients was more than healthy controls [30]. In another

study, Mahmoudi et al. demonstrated that none of the single *KIR* genes affected the risk of SSc. Moreover, they reported that the combination of *KIR3DL1* with *HLA* ligands can be a powerful marker for diagnosing of SSc [15].

As mentioned above, findings of the studies evaluating the association between *KIR* gene polymorphisms and the risk of SSc disease in populations are controversial. Consequently, the present meta-analysis was accomplished to quantitatively assess the relevance of *KIR* polymorphisms with susceptibility to SSc. In this meta-analysis, the results of five case-control studies with a total of 571 SSc cases and 796 healthy controls were integrated and evaluated. Contrary to what has been observed in previous association studies, no significant association was observed between *KIR* genes and the risk of SSc.



**Fig. 4** Funnel plot. The plot displays publication bias and heterogeneity results between studies for (a) *2DP1* and (b) *3DL1* genes



There are a number of limitations in the present meta-analysis. First, we could not perform further subgroup analysis with respect to ethnicity because of insufficient studies. Third, the meta-analysis was performed based on the data of a limited 5 studies. Therefore, this meta-analysis may have publication bias. In spite of mentioned limitations, this is the first meta-analysis focusing on the correlation between *KIR* genes polymorphisms and susceptibility to SSc.

## Conclusion

In conclusion, this was the first meta-analysis of *KIR* genes in association with SSc. It was detected that *KIR* genes are not involved in conferring a susceptibility risk to SSc development.

## Abbreviations

CI: Confidence interval; IFN: Interferon; IL: Interleukin; KIR: Killer cell immunoglobulin-like receptor; MHC: Major histocompatibility complex; MS: Multiple sclerosis; NK: Natural killer; OR: Odds ratios; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; TGF: Transforming growth factor; TNF: Tumor necrosis factor

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Not applicable.

## Authors' contributions

EK; Performed literature search and prepared the draft of the paper. SM; Participated in manuscript preparation and draw the figures. SA; Participated in manuscript preparation and designed the Table. FG; Developed the main idea and read the manuscript critically. RMX; Read the manuscript critically. PHS; Read the manuscript critically. HK; Participated in manuscript preparation and designed the work. EF; Developed the main idea, designed the work, and read the manuscript critically. MM; Developed the main idea, designed the work, and read the manuscript critically. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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