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Research article

Association between *Killer Immunoglobulin-like receptor* genes and susceptibility to inflammatory bowel disease: An updated meta-analysis

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Background: Several studies have associated members of the *KIR* genes as susceptibility factors to inflammatory bowel diseases (IBD): ulcerative colitis (UC) and Crohn's disease (CD).
Objectives: To assess the association between the presence and absence *KIR* genes and IBD susceptibility through a meta-analysis.
Method: A systematic search was performed through the PubMed, Scopus, and Web of Science databases to obtain relevant articles published before March 2024. Associations between genes and susceptibility to IBDs were estimated by OR with 95 % CI.
Results: We found positive associations of the *KIR2DS1* and *KIR2DS3* genes with susceptibility to UC, while the *KIR2DL3* and *KIR2DS4*^{full} genes showed a negative association. In addition, the *KIR2DS1*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1* genes showed a positive association with susceptibility to CD, whereas the *KIR2DL1* gene showed a negative association.
Conclusions: Our meta-analysis indicates that individuals carrying the *KIR2DS1* and *KIR2DS3* genes exhibit increased susceptibility to UC, whereas carriers of the *KIR2DS1*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1* genes are more prone to CD. However, further studies are required to clarify the role of the *KIR* genes and their corresponding ligands in the pathology of IBD.

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1. Introduction

Inflammatory Bowel Disease (IBD) is an idiopathic chronic inflammatory process of the gastrointestinal tract that is further classified into two clinical subtypes: Ulcerative Colitis (UC) and Crohn's disease (CD) [1,2]. UC is defined as an inflammatory disease of the colon mucosa of unknown etiology. Frequently, UC is accompanied by abdominal pain, diarrhea, and hematochezia [3]. In contrast, CD patients usually suffer from inflammation of the intestinal mucosa and, therefore, any part of the gastrointestinal tract may be affected in an inconstant pattern. In addition, CD is usually associated with complications such as abscesses, fistulas, and intestinal stenosis [4].

The etiology of IBD remains unknown. However, the identified susceptibility characteristics have been classified into three categories: genetic factors, host immune system, and environmental agents including the intestinal microbiota [1,4]. A leading hypothesis for IBD suggests that dysregulation of the intestinal microbiota can trigger the immune system activation within the intestinal mucosal membrane, which is a key characteristic of its pathogenesis [1].

The Natural Killer (NK) cells are lymphocytes that play a key role in the initiation and regulation of immune responses by recognizing human leukocyte antigen (HLA) of class I through their Killer Ig-like Receptors (KIR) [5,6]. Under physiologically normal conditions, NK cells have the ability to kill their target cells unless they receive inhibitory signals [7] Consequently, several KIRs receptors enable NK cells to establish effective cell communication by recognizing HLA class I molecules [5,6]. Both KIR receptors and HLA-I molecules are encoded by highly polymorphic genes [8].

In humans, the *KIR* gene family is composed of 15 genes and two pseudogenes encoded within a region of 100–200 kb within the leukocyte receptor complex located on chromosome 19 (Ch19q13.4)[6]. The *KIR* genes may code for inhibitory receptors (KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL5A, KIR2DL5B, KIR3DL1, KIR3DL2, KIR3DL3), activation receptors (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1), or a receptor whose function depend on its location on the cell (KIR2DL4); finally, the *KIR* family includes two pseudogenes (*KIR2DP1* and *KIR3DP1*) [6]. According to the content of *KIR* genes, two distinct haplotypes can be defined: the "A" haplotype usually contains the *KIR3DL3*, *KIR2DL3*, *KIR2DP1*, *KIR2DL1*, *KIR3DP1*, *KIR2DL4*, *KIR3DL1*, *KIR2DS4*, and *KIR3DL2* genes. While "B" haplotype possesses most A haplotype genes (*KIR3DL3*, *KIR2DP1*, *KIR2DL1*, *KIR3DP1*, *KIR2DL4*, and *KIR3DL2*) plus any combination of *KIR2DS2*, *KIR2DL2*, *KIR2DL5B*, *KIR2DS3, KIR2DS5*, *KIR3DS1*, *KIR2DL5A*, and *KIR2DS1* [6]. Consequently, genotypes are named AA when the subject carries only A haplotype genes, or Bx when at least one characteristic gene of B haplotypes is included [6].

Reports have found that *KIR* genes are associated with physiological and pathological processes such as antiviral response, graft rejection, pre-eclampsia, and autoimmunity. Furthermore, a meta-analysis published by Fathollahi et al. evaluated the association of *KIR* genes with susceptibility to IBD [9], in which they highlight that the presence of *KIR2DL5* and *KIR2DS1* genes was associated with an increase in the susceptibility to UC; whereas the presence of *KIR2DS3* gene was associated with a decrease of susceptibility to CD [9]. However, new studies on the subject have been developed after their meta-analysis. Therefore, the purpose of this study was to provide an update on the association of the presence and absence of *KIR* genes with susceptibility to IBD.

2. Methods

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. Ethics committee approval was not required due to the nature of the study.

2.1. Database search

A systematic search was conducted by two researchers independently (S.S.-F., and M.E.-V.) using the Pubmed, Scopus, and Web of Science electronic databases to find the studies on the association between *KIR* genes and susceptibility to IBD. For this purpose, the following search term was used for the three databases: (KIR OR "Killer Immunoglobulin-like Receptors") AND (IBD OR "inflammatory bowel disease" OR "ulcerative colitis" OR "Crohn's disease"); and, additionally, for PubMed: "Receptors, KIR"[Mesh] AND ("Colitis, Ulcerative"[Mesh] OR "Crohn disease"[Mesh] OR "inflammatory bowel diseases"[Mesh]). The cutoff date used for the database search was March 2024.

2.2. Inclusion and exclusion criteria

Two researchers independently (S.S.-F., and M.E.-V.) applied the following inclusion criteria to include the studies in this meta-analysis: a) case-control studies that evaluated the association between *KIR* genes and IBD, UC, or CD; b) studies published in indexed journals; c) non-language restriction; d) non-geographic area restriction; e) studies published until March 31st, 2024. While, exclusion criteria were: a) insufficient data to obtain *KIR* gene frequencies; b) duplicate data. Discrepancies were resolved by consensus with a third researcher (O.G.-M.).

2.3. Data extraction

The data were extracted according to the established criteria, i.e., three researchers (G.I.P., M.A.R.-N., and C.G.-T.) independently and carefully obtained the following information: a) reference, b) studied population, c) typing method, d) typed genes, e) frequency of *KIR* genes, f) statistical power, and g) information about the used primers. The results were evaluated in consensus to avoid

discrepancies.

2.4. Quality assessment

The methodological quality assessment was carried out using the Newcastle-Ottawa Scale (NOS). The studies were classified as low quality (score 0–3), moderate (score 4–6), and high (score 7–9) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

2.5. Statistical analyses

We performed the statistical analyzes using the MedCalc version 18.2.1 program (MedCalc Software, Osten, Belgium) and the MetaEssentials workbooks [11]. Values of $p < 0.05$ were considered statistically significant.

We assessed the heterogeneity between the data of the included studies using the Cochran Q and I^2 statistical tests, considering $P < 0.10$ or $I^2 > 50$ % values, respectively, as heterogeneous. The associations between *KIR* genes and susceptibility to IBD, UC, and CD were estimated using Odds Ratio (OR) with 95 % confidence intervals (95 % CI). Heterogeneous data were evaluated using a random effect model (REM) based on the DerSimonian and Laird method; meanwhile, the other evaluations were carried out through a fixed effect model (FEM), based on the Mantel-Haenszel method. *p*-values <0.05 were considered statistically significant and adjusted with Holm-Bonferroni correction for multiple comparisons. Individual results of the included studies and the synthesis were shown through forest plots.

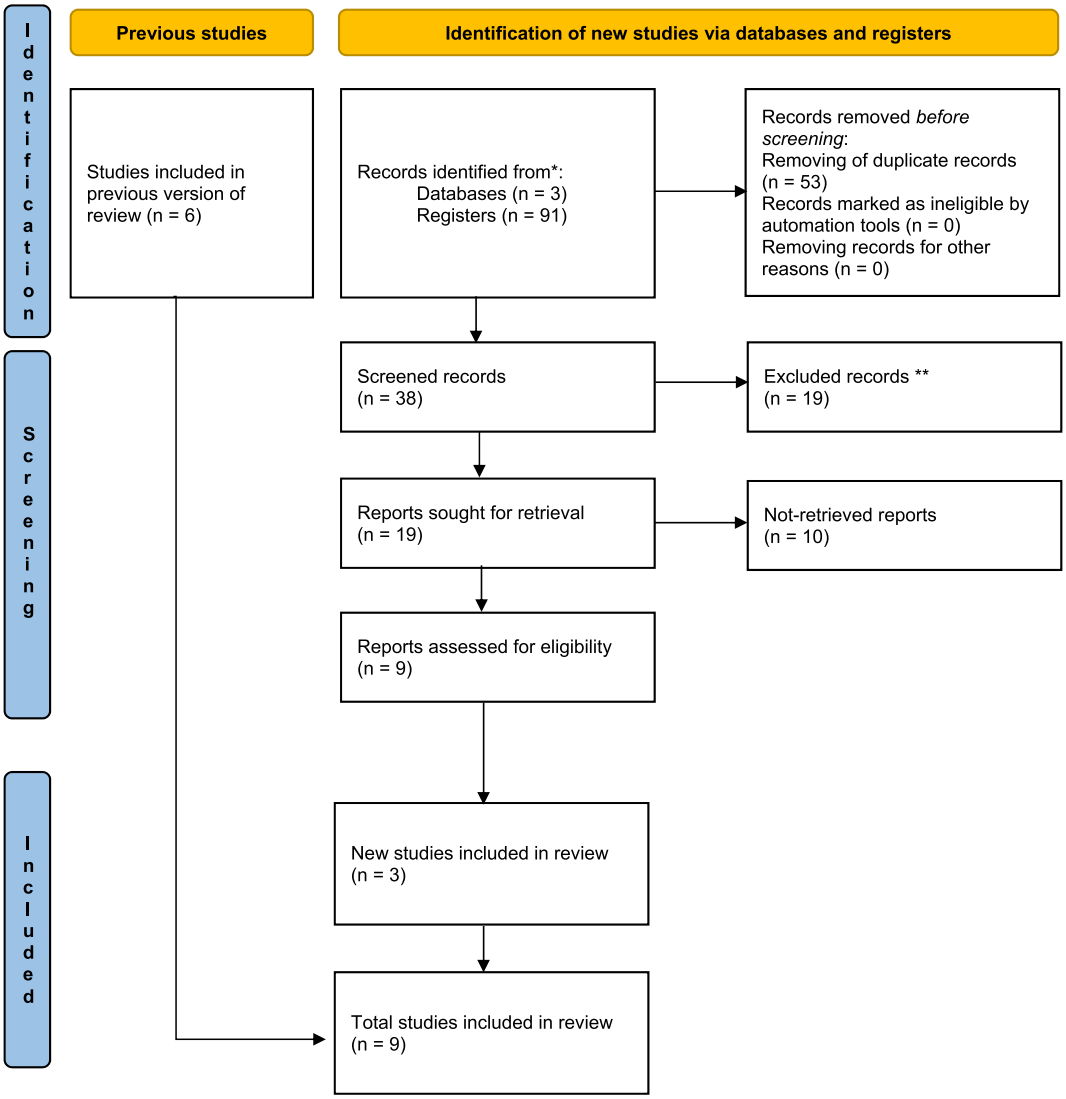

Fig. 1. Flow diagram of the search strategy for this meta-analysis.

Possible publication bias was performed using the Begg and Mazumdar tests (B & M T), as well as Egger's linear regression (E L R) when the meta-analysis included at least three studies. Additionally, we also conducted sensitivity and stability studies, which consist of excluding one article at a time from the analysis.

3. Results

3.1. Search strategy and included studies

Fig. 1 shows the process of the systematic search carried out to identify the articles included in this meta-analysis. Through the PubMed, Scopus, and Web of Science databases, 71 potential citations were identified to be included. However, we only considered 9 studies for statistical analyses after filtering based on the selection criteria [12–20].

The meta-analysis included 2867 cases (622 UC and 2245 CD) and 2686 controls, where each study evaluated a variable number of *KIR* genes. The main characteristics of included studies are shown in Table 1.

3.2. Heterogeneity

According to the Cochran Q and I^2 statistical tests, heterogeneity was observed between genic frequencies of *KIR2DL2*, *KIR2DL3*, *KIR2DL5*, *KIR2DS4,* and *KIR2DS5* in UC (Table 2); *KIR2DL2*, *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DL1* in CD (Table 3); as well as *KIR2DL2*, *KIR2DL3*, *KIR2DL5*, *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, *KIR3DL1*, and *KIR3DS1* in IBD (Table 4).

3.3. KIR genes and susceptibility to IBD

The meta-analysis revealed a positive association of the *KIR2DS1* (OR = 1.243, 95 % CI: 1.002–1.543, $p = 0.048$) and *KIR2DS3* (OR

Table 1
Main characteristics of the included studies for this meta-analysis.

Study	Country	NOS	Methodology	Cases UC (n)	Cases CD (n)	Controls (n)	Genotyped genes
Beigmohammadi et al., 2020	Iran	9	PCR-SSP	100	83	274	*KIR2DS1, KIR2DS2, KIR2DS3*[d], *KIR2DS4, KIR2DS5, KIR3DS1, KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR3DL1, KIR3DL2, KIR3DL3*
Samarani et al., 2019[a]	Canada	8	PCR-SSP	0	193	245	*KIR2DS1*[d], *KIR2DS2, KIR2DS3* [d], *KIR2DS4* [d], *KIR2DS5* [d], *KIR3DS1* [d]
Samarani et al., 2019[b]	Canada	8	PCR-SSP	0	93	120	*KIR2DS1* [d], *KIR2DS2* [d], *KIR2DS3* [d], *KIR2DS4* [d], *KIR2DS5* [d], *KIR3DS1* [d]
Samarani et al., 2019[c]	Canada	7	PCR-SSP	0	164	200	*KIR2DS1, KIR2DS2* [d], *KIR2DS3* [d], *KIR2DS4* [d], *KIR2DS5* [d], *KIR3DS1* [d]
Saito et al., 2018	Japan	9	PCR-SSP	90	50	325	*KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3*[f], *KIR2DS4*[g], *KIR2DS5, KIR3DL1, KIR3DL2, KIR3DL3, KIR3DS1*
López-Hernández et al., 2016	Spain	9	PCR-SSOP	27	57	314	*KIR2DS1*[d,f], *KIR2DS2, KIR2DS3, KIR2DS5*[d,f], *KIR3DS1, KIR2DS4, KIR2DL1, KIR2DL2, KIR2DL3*[g], *KIR2DL4, KIR2DL5*[f], *KIR3DL1, KIR3DL2, KIR3DL3, KIR2DP1*
Díaz-Peña et al., 2015	Spain	9	PCR-SSOP	0	125	339	*KIR2DS1, KIR2DS2*[e], *KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1, KIR2DL1, KIR2DL2*[e], *KIR2DL3, KIR2DL4, KIR2DL5, KIR3DL1, KIR3DL2, KIR3DL3, KIR2DP1, KIR3DP1*
Wilson et al., 2009	Brazil	8	PCR-SSP	111	137	250	*KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, KIR3DS1, KIR2DS4, KIR2DL1, KIR2DL2*[g], *KIR2DL3, KIR2DL4, KIR2DL5, KIR3DL1, KIR3DL2, KIR3DL3, KIR2DP1*
Hollenbach et al., 2009	U.S.A.	8	MALDI-TOF	0	1291	299	*KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DP1*
Zhang et al., 2008	China	7	PCR-SSP	100	52	106	*KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR3DL1, KIR3DL2, KIR3DL3*
Jones et al., 2006	U.K.	9	PCR-SSP	194	0	216	*KIR2DL1, KIR2DL2*[f], *KIR2DL3, KIR2DL5, KIR2DS1, KIR2DS2*[f], *KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1, KIR3DS1*

NOS: Newcastle-Ottawa Scale; UC: Ulcerative colitis; CD: Crohn's Disease; PCR-SSP: Polymerase chain reaction - Sequence specific primers; PCR-SSOP: Polymerase chain reaction - sequence-specific oligonucleotides probes.

[a] Montreal.
[b] Ottawa.
[c] Winnipeg.
[d] positively associated with susceptibility to CD.
[e] negatively associated with susceptibility to CD.
[f] positively associated with susceptibility to UC.
[g] negatively associated with susceptibility to UC.

Table 2
Meta-analysis of the association between *KIR* genes and susceptibility to ulcerative colitis.

Gene	**Qualified studies**	**Cases (n/N)**	**Controls (n/N)**	**OR (95 % CI)**	**z- test**	***P***	p_c	**Publication bias**		**Heterogeneity**		Effect model
								E L R	**B& M T**	P_Q	I^2	
KIR2DL1	6	581/622	1453/1485	0.501 (0.302–0.832)	−2.672	0.131	1.000	0.851	0.550	0.167	38.20	FEM
KIR2DL2	6	263/622	690/1485	0.937 (0.600–1.464)	−0.285	0.776	1.000	0.851	0.866	0.002	73.28	REM
KIR2DL3	**6**	**524/622**	**1352/1485**	**0.530 (0.317 to 0.886)**	**−2.420**	**0.015**	**0.540**	**0.851**	**0.490**	**0.036**	**58.08**	REM
KIR2DL5	6	310/622	750/1485	1.101 (0.803–1.510)	0.598	0.550	1.000	0.573	0.447	0.056	53.55	REM
KIR2DS1	**5**	**246/522**	**583/1379**	**1.243 (1.002 to 1.543)**	**1.976**	**0.048**	**1.000**	**0.327**	**0.108**	**0.170**	**37.70**	FEM
KIR2DS2	5	258/522	656/1379	1.131 (0.904–1.417)	1.077	0.281	1.000	1.000	0.646	0.231	28.54	FEM
KIR2DS3	**5**	**171/522**	**397/1379**	**1.279 (1.016 to 1.610)**	**2.099**	**0.036**	**1.000**	**0.624**	**0.444**	**0.156**	**39.77**	FEM
KIR2DS4	3	364/395	746/791	0.675 (0.325–1.401)	−1.055	0.291	1.000	0.602	0.531	0.096	57.28	REM
KIR2DS4^{full}	**2**	**45/127**	**386/588**	**0.554 (0.324 to 0.947)**	**−2.161**	**0.031**	**1.000**	**-**	**-**	**0.544**	**0.00**	FEM
KIR2DS5	4	141/411	343/1129	1.313 (0.764–2.257)	0.985	0.324	1.000	0.497	0.333	0.006	75.75	REM
KIR3DL1	6	588/622	1414/1485	0.847 (0.550–1.303)	−0.758	0.449	1.000	0.573	0.371	0.657	0.00	FEM
KIR3DS1	5	236/522	577/1379	1.151 (0.931–1.422)	1.299	0.194	1.000	0.327	0.243	0.235	27.93	FEM

KIR: Killer Immunoglobulin-like Receptor; OR: Odds Ratio; 95 % CI: 95 % Confidence Interval; FEM: Fixed-Effect Model; REM: Random-Effect Model; n/N: number of carriers a certain KIR/total; B & M T: Begg and Mazumdar test; E L R: Egger's linear regression.

Table 3
Meta-analysis of the association between *KIR* genes and susceptibility to Crohn's Disease.

Gene	**Qualified studies**	**Cases (n/N)**	**Controls (n/N)**	**OR (95 % CI)**	**z- test**	***p***	p_c	**Publication bias**		**Heterogeneity**		Effect model
								E L R	**B& M T**	P_Q	I^2	
KIR2DL1	**6**	**475/504**	**1565/1608**	**0.575 (0.350 a 0.945)**	**−2.182**	**0.029**	**1.000**	**0.658**	**0.851**	**0.292**	**19.29**	FEM
KIR2DL2	6	933/1795	960/1905	0.852 (0.609–1.192)	−0.936	0.349	1.000	0.863	0.881	0.003	69.78	REM
KIR2LD3	6	439/504	1431/1608	0.972 (0.714–1.324)	−0.178	0.859	1.000	0.155	0.099	0.167	36.03	FEM
KIR2DL5	6	269/504	830/1608	1.084 (0.876–1.341)	0.739	0.460	1.000	0.604	0.881	0.364	8.21	FEM
KIR2DS1	**8**	**515/902**	**880/2067**	**1.826 (1.246 to 2.676)**	**3.090**	**0.002**	**0.072**	**0.893**	**0.421**	**<0.001**	**79.85**	REM
KIR2DS2	8	531/902	1070/2067	1.243 (0.781–1.980)	0.917	0.359	1.000	0.522	0.621	<0.001	85.97	REM
KIR2DS3	**8**	**407/902**	**648/2067**	**1.580 (1.040 to 2.401)**	**2.144**	**0.032**	**1.000**	**0.772**	**0.621**	**<0.001**	**82.53**	REM
KIR2DS4	**7**	**678/819**	**1485/1793**	**1.862 (1.150 to 3.015)**	**2.530**	**0.011**	**0.396**	**0.006**	**0.051**	**0.021**	**62.25**	REM
$KIR2DS4^{full}$	2	75/140	386/588	0.759 (0.454–1.268)	−1.053	0.292	1.000	–	–	0.924	0.00	FEM
KIR2DS5	**7**	**419/765**	**618/1817**	**1.849 (1.201 to 2.847)**	**2.794**	**0.005**	**0.180**	**0.396**	**0.453**	**<0.001**	**80.63**	REM
KIR3DL1	6	476/504	1528/1608	0.872 (0.391–1.948)	−0.334	0.739	1.000	0.241	0.091	0.046	55.71	REM
KIR3DS1	**8**	**506/902**	**863/2067**	**1.605 (1.156 to 2.228)**	**2.827**	**0.005**	**0.180**	**0.423**	**0.621**	**<0.001**	**73.66**	REM

KIR: Killer Immunoglobulin-like Receptor; OR: Odds Ratio; 95 % CI: 95 % Confidence Interval; FEM: Fixed-Effect Model; REM: Random-Effect Model; n/N: number of carriers a certain KIR/total; B & M T: Begg and Mazumdar test; E L R: Egger's linear regression.

Table 4
Meta-analysis of the association between *KIR* genes and susceptibility to inflammatory bowel disease.

Gene	**Qualified studies**	**Cases (n/N)**	**Controls (n/N)**	**OR (95 % CI)**	**z- test**	***p***	p_c	**Publication bias**		**Heterogeneity**		Effect model
								E L R	**B& M T**	P_Q	I^2	
KIR2DL1	7	1056/1126	1775/1824	0.559 (0.374–0.834)	−2.847	0.099	1.000	0.751	0.881	0.118	43.08	FEM
KIR2DL2	7	1196/2417	1053/2121	0.894 (0.656–1.220)	−0.706	0.480	1.000	0.740	0.621	<0.001	77.87	REM
KIR2DL3	7	963/1126	1633/1824	0.684 (0.437–1.071)	−1.659	0.097	1.000	0.294	0.099	0.005	67.67	REM
KIR2DL5	7	579/1126	937/1824	1.079 (0.854–1.364)	0.641	0.522	1.000	0.822	0.652	0.055	51.33	REM
KIR2DS1	**9**	**761/1424**	**962/2283**	**1.670 (1.200 to 2.324)**	**3.038**	**0.002**	**0.072**	**0.026**	**0.297**	**<0.001**	**81.70**	REM
KIR2DS2	9	789/1424	1165/2283	1.226 (0.844–1.782)	1.069	0.285	1.000	0.468	0.677	<0.001	84.84	REM
KIR2DS3	**9**	**578/1424**	**705/2283**	**1.535 (1.083 to 2.175)**	**2.408**	**0.016**	**0.576**	**0.767**	**0.532**	**<0.001**	**82.33**	REM
KIR2DS4	7	985/1157	1371/1695	1.483 (0.912–2.412)	1.589	0.112	1.000	0.694	0.881	<0.001	73.95	REM
KIR2DS4^{full}	**2**	**120/267**	**386/588**	**0.649 (0.433 to 0.974)**	**−2.086**	**0.037**	**1.000**	**-**	**-**	**0.718**	**0.00**	FEM
KIR2DS5	**8**	**560/1176**	**686/2033**	**1.705 (1.126 to 2.581)**	**2.520**	**0.012**	**0.432**	**0.631**	**0.805**	**<0.001**	**85.62**	REM
KIR3DL1	7	1064/1126	1730/1824	0.895 (0.637–1.259)	−0.367	0.524	1.000	0.170	0.293	0.156	35.66	FEM
KIR3DS1	**9**	**742/1424**	**951/2283**	**1.525 (1.132 to 2.054)**	**2.770**	**0.005**	**0.180**	**0.291**	**0.404**	**<0.001**	**78.18**	REM

KIR: Killer Immunoglobulin-like Receptor; OR: Odds Ratio; 95 % CI: 95 % Confidence Interval; FEM: Fixed-Effect Model; REM: Random-Effect Model; n/N: number of carriers a certain KIR/total; B & M T: Begg and Mazumdar test; E L R: Egger's linear regression.

= 1.279, 95 % CI: 1.016–1.610, p = 0.036) genes with susceptibility to UC; conversely, the *KIR2DL3* (OR = 0.530, 95 % CI: 0.317–0.886, p = 0.015) and *KIR2DS4*^{full} (OR = 0.554, 95 % CI: 0.324–0.947, p = 0.031) genes showed a negative association (Fig. 2). The rest of the evaluated genes (*KIR2DL1*, *KIR2DL2*, *KIR2DL5*, *KIR2DS2*, *KIR2DS4*, *KIR2DS5*, *KIR3DL1,* and *KIR3DS1*) did not show significant associations with UC (Table 2). However, the associations between *KIR2DL3*, *KIR2DS1*, *KIR2DS3*, and *KIR2DS4*^{full} genes and UC susceptibility were lost after Holm–Bonferroni correction ($p_c > 0.050$).

We also analyzed the association of *KIR* genes with CD. The genes *KIR2DS1* (OR = 1.826, 95 % CI: 1.246–2.676, p = 0.002), *KIR2DS3* (OR = 1.580, 95 % CI: 1.040–2.401, p = 0.032), *KIR2DS4* (OR = 1.862, 95 % CI: 1.150–3.015, p = 0.011), *KIR2DS5* (OR = 1.849, 95 % CI: 1.201–2.847, p = 0.005), and *KIR3DS1* (OR = 1.605, 95 % CI: 1.156–2.228, p = 0.005) were positively associated with susceptibility to CD. On the other hand, the *KIR2DL1* gene (OR = 0.575, 95 % CI: 0.350–0.945, p = 0.029) was associated with a decreased susceptibility to CD (Fig. 2). The rest of the evaluated genes (*KIR2DL2*, *KIR2DL3*, *KIR2DL5*, *KIR2DS2*, *KIR2DS4*^{full}, and *KIR3DL1*) did not show significant associations with CD (Table 3). However, the associations between *KIR2DL1*, *KIR2DS1*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1* genes and CD susceptibility were lost after Holm–Bonferroni correction ($p_c > 0.050$).

Finally, we found positive associations through the global analysis between *KIR2DS1* (OR = 1.670, 95 % CI: 1.200–2.324, p = 0.002), *KIR2DS3* (OR = 1.535, 95 % CI: 1.083–2.175, p = 0.016), *KIR2DS5* (OR = 1.705, 95 % CI: 1.126–2.581, p = 0.012), and *KIR3DS1* (OR = 1.525, 95 % CI: 1.132–2.054, p = 0.005) genes and IBD susceptibility. Meanwhile, *KIR2DS4*^{full} gene (OR = 0.649, 95 % CI: 0.433–0.974, p = 0.037) was associated with a decrease in IBD susceptibility (Table 4). However, after Holm–Bonferroni correction, the associations between *KIR2DS1*, *KIR2DS3*, *KIR2DS4*^{full}, *KIR2DS5* and *KIR3DS1* genes and IBD were lost after Holm–Bonferroni correction ($p_c > 0.050$).

3.4. Publication bias

According to Egger's linear regression, publication bias was observed in studies of the *KIR2DS4* gene associated with CD susceptibility (Table 3). No potential publication bias was identified in the other analyses (Tables 2–4).

3.5. Sensitivity and stability studies

The significant associations between *KIR2DL3*, *KIR2DS1*, *KIR2DS3,* and *KIR2DS4*^{full} genes and susceptibility to UC showed poor stability when a study was excluded from the pool. Similarly, the associations of the *KIR2DS3*, *KIR2DS4,* and *KIR2DL1* genes with susceptibility to CD showed low stability when some studies from the pool were excluded. However, the associations between the *KIR2DS1*, *KIR2DS5,* and *KIR3DS1* genes and susceptibility to CD maintained significance after sensitivity and stability studies (Supplementary Tables).

4. Discussion

The education and effector function of NK cells is based on the interaction of a repertoire of activating and inhibitory receptors that recognize HLA-I molecules expressed by the target cells of individuals [8]. This complex and sophisticated system of receptors is generated through events of chromosomal recombinations, point mutations, alternative splicing and stochastic expression [8]. This genetic variability has been associated with different diseases, especially processes of loss of immunological tolerance, viral infections and cancer [21,22].

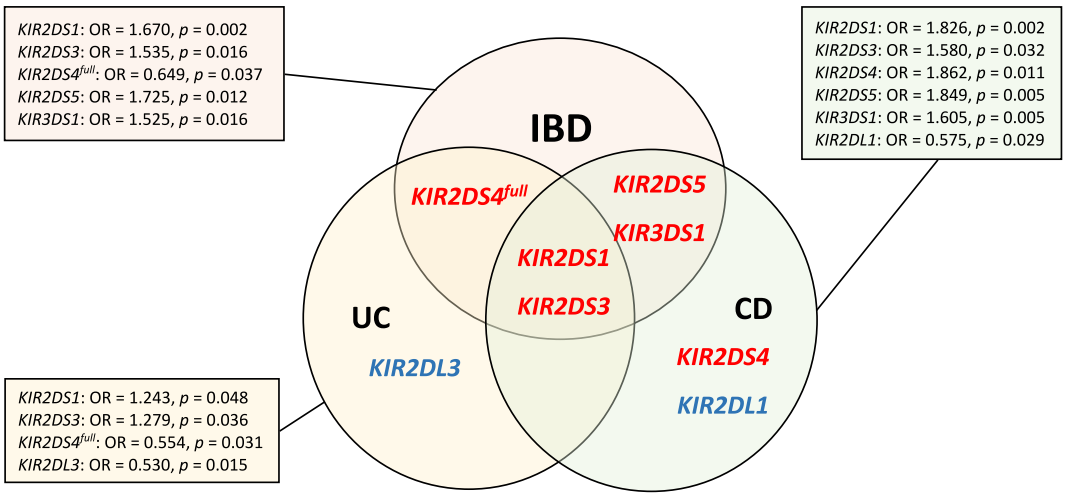

Fig. 2. Diagram with the associations identified through this meta-analysis. Positive associations with susceptibility are shown in red, while negative associations are shown in blue. IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease.

IBD is a complex disease whose pathogenesis involves different environmental, immunological, and genetic factors [1]. Notably, genes of the *KIR* family have been regarded as key players due to their association with variable susceptibility to the disease [9]. In this meta-analysis, we performed a comprehensive evaluation of the association of *KIR* genes with susceptibility to IBD through relevant studies on the topic.

Our meta-analysis update included 9 studies with a total of 2867 cases (UC = 622; CD = 2245) and 2688 controls that evaluated a variable number of *KIR* genes. Previously, in 2018, Fathollahi et al. published a meta-analysis that evaluated the association of the *KIR* genes with susceptibility to IBD that included 6 studies with a total of 2109 cases (UC = 432, CD = 1677) and 1524 controls [9]. Compared to the previous study, our search was performed on an additional platform (Web of Science) and it increased the sample size by over 50 %.

In this meta-analysis, we found positive associations between susceptibility to IBD and the genes that code for activation receptors. Our analysis showed that the genes involved in UC susceptibility are *KIR2DS1* and *KIR2DS3*; while in CD the participating genes are *KIR2DS1*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1*. Other works have studied the association with diseases of *KIR* haplotypes, rather than individual *KIR* genes. Interestingly, all these positively associated *KIR* genes are located in the telomeric region. This fact could be explained by the complete segregation of the region that extends from the *KIR2DL4* gene to the *KIR3DL2* gene; however, only a few articles include a table with the genotypes identified among the participants, thus there is a need for this data to test this hypothesis.

The *KIR2DS1, KIR2DS3, KIR2DS4, KIR2DS5,* and *KIR3DS1* genes are notable for their role coding for activation receptors. In this context, it has been observed that individuals carrying a higher number of *KIR* genes that code for activation receptors have a stronger immune response against pathogens, but are more susceptible to developing autoimmune diseases [6]. Indeed, the *KIR2DS1*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1* genes may facilitate the activation of NK cell functions, e.g., granule-mediated cytotoxicity and production of the proinflammatory cytokines IFN-γ and TNF-α, through the signaling of the KIR receptors by recognizing their corresponding ligands. In particular, *KIR2DS1* is the member of the *KIR* gene family with the highest number of positive associations towards susceptibility to autoimmune diseases, including psoriatic arthritis [23], psoriasis vulgaris [24], and ankylosing spondylitis [25]. Also, the *KIR2DS3* gene has been positively associated with susceptibility to psoriatic arthritis [23]. Furthermore, *KIR2DS5* and *KIR3DS1* genes have been associated with an increased risk of developing ankylosing spondylitis [25].

Regarding viral infections, the presence of *KIR2DS1* and *KIR2DS3* was associated with Epstein Barr reactivation [26]. In contrast, in another study, the presence of *KIR2DS1* was associated with a lower risk of cytomegalovirus infection after kidney transplantation [27]. These contrasting data could be the result of the varying expression and activation mechanisms of this gene family depending on each cell.

Our results indicate that being a carrier of the *KIR2DL1* and *KIR2DL3* genes, which code for inhibitory receptors, decreases the risk of developing CD and UC, respectively. Likewise, in type 1 diabetes, carriers of the *KIR2DL1* gene displayed decreased susceptibility [28]. Therefore, the expression of KIR2DL1 or KIR2DL3 receptors could mediate inhibitory events through the recruitment of protein tyrosine phosphatases that remove the phosphate groups of key intermediary molecules required for signaling of the activation receptor [6]. In this sense, it has been reported that the KIR2DL1 and KIR2DL3 receptors participate in the education of NK cells. In addition to genetic variability, it has been reported that differences in ligand affinity and expression levels of *KIR/HLA* alleles influence the response of NK cells, that is, both *KIR2DL1* and *KIR2DL3* alleles exhibit different affinity depending of the *HLA-C* alleles that they recognize as ligands [29]. Therefore, carrier individuals who express these receptors could have competent NK cells able to recognize HLA class I molecules and successfully regulate the effector response [30,31].

The conclusions of our study must also consider the main limitations that we encountered: a) Despite the fact that the number of studies has increased, there are still ethnic groups in which the association of *KIR* genes with susceptibility to IBD has not been studied or has been studied only to a limited extent, making it difficult to perform sub-analyses; b) The methods for typing some *KIR* genes typing do not allow for differentiation between *KIR* alleles and allele groups; c) Typing of *HLA class I* alleles is not performed in all studies, which does not allow for a full analysis of receptor/ligand genotype; d) The meta-analysis was performed without a protocol prepared or a registration in PROSPERO.

5. Conclusion

In conclusion, our meta-analysis suggests the participation of activating KIR receptors in the susceptibility to IBD. The carriers of the *KIR2DS1* and *KIR2DS3* genes seem to be more susceptible to UC, while the carriers of the *KIR2DS1*, *KIR2DS3*, *KIR2DS4*, *KIR2DS5*, and *KIR3DS1* genes are more susceptible to CD. In contrast, *KIR2DL3* and *KIR2DL1* seem to confer protection against UC and CD, respectively. However, more studies are required to clarify the role of the *KIR* genes and their corresponding ligands in the pathology of IBD.

Data availability statement

Data included in article/supplementary material/referenced in article.

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CRediT authorship contribution statement

Giovanna Isabel Ponce: Formal analysis, Data curation. **Miguel Ángel Recendiz-Nuñez:** Formal analysis, Data curation. **César García-Torreros:** Formal analysis, Data curation. **Sonia Sifuentes-Franco:** Writing – review & editing, Supervision, Methodology. **Moisés Enciso-Vargas:** Writing – original draft, Validation, Conceptualization. **Irám Pablo Rodríguez-Sánchez:** Writing – original draft, Validation. **Selene Guadalupe Huerta-Olvera:** Writing – review & editing, Methodology. **Omar Graciano-Machuca:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33903.

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