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Association of Killer Cell Immunoglobulin-like Receptor (KIR) Genes and their HLA Ligands with Susceptibility to Takayasu Arteritis in the Iranian Population

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ABSTRACT

Takayasu arteritis (TA) is a chronic inflammatory disorder characterized by vascular damage and fibrosis in the intima that commonly occurs in the aorta. In many damaged sites in TA patients, natural killer (NK) cells have been shown to be hyperactivated and produce inflammatory cytokines and toxic components. Killer cell immunoglobulin-like receptors (KIRs) are found on NK cells and interact with human leukocyte antigen (HLA*)* class I ligands to activate or suppress NK cells. The present study assessed the possible role of *KIR* and their HLA ligand genes in susceptibility to TA in Iranian patients.

This case-control study included 50 TA patients and 50 healthy subjects. DNA was extracted from whole peripheral blood samples, and polymerase chain reaction with sequence-specific primers (PCR-SSP) was performed to recognize the presence or absence of polymorphism in 17 *KIR* genes and 5 HLA class I ligands in each participant.

Among the *KIR* and *HLA* genes, a significant decrease was detected in the frequency of *2DS4* (full allele) in TA patients (38%) compared with healthy controls (82%) (OR=0.13, 95%

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CI=0.05–0.34). However, none of the KIR and HLA genotypes or the interactions between these genes were associated with susceptibility to TA.

The *KIR2DS4* gene might be involved in the regulation of activation as well as the production of cytotoxic mediators of NK cells in patients with TA.

Keywords: Genetic association; Killer cell immunoglobulin-like receptor; Natural killer cell; Takayasu arteritis

INTRODUCTION

Takayasu arteritis (TA), also called TAK, is a rare systemic, large-vessel arteritis that affects mainly the aorta, its branch arteries, and rarely the pulmonary blood vessels.[1] In TA patients, inflammation and endothelial damage result in vessel wall stiffening, thrombus formation, and the development of occlusive lesions. Furthermore, the destruction of smooth muscle cells may lead to aneurysms and dilatation. Such damages and lesions usually culminate in dysfunction in the cardiovascular system, which is a sequel to ischemia.[2] The pathogenic mechanism underlying TA is granulomatous inflammation in the large arteries. The disease is also considered the third most common cause of vasculitis in children.[3]

The exact etiology of TA has not yet been completely understood; nonetheless, the role of genetic predisposition to the disease has been suggested due to the association of TA with the major histocompatibility complex (MHC) region. The strongest genetic association of TA has been observed with human leukocyte antigen (HLA)-B52 in several populations.[4] It was revealed that HLA-B52 positivity in the Japanese TA patients conferred a poor prognosis. HLA-B5 is associated with TA in Asian and Mexican populations, whereas HLA-B35, HLA-A2, and HLA-A9 are associated with the Arab population. HLA-DR4 has been shown to be associated with the disease in North American patients.[5-8] Moreover, a genome-wide association study on 449 TA patients of European-American and Turkish descent identified two independent genetic predisposing loci, namely, HLA-DQB1/HLADRB1 in the MHC class II and HLA-B/MHC-I chain-related protein A (MICA) in MHC class I regions.[9]

Among the important immune cells infiltrating the involved vascular tissues in TA patients are macrophages, γδ T cells, B lymphocytes, and natural killer (NK) cells.[10] Cell damage in the vessels and necrosis might occur due to the perforin released by cytotoxic T lymphocytes, γδ T cells, and NK cells.[11-13]

The killer cell immunoglobulin-like receptor (KIR/CD158) belongs to the immunoglobulin superfamily. It is expressed predominantly in NK cells and certain T lymphocyte subsets. These receptors bind to conserved epitopes of various HLA class I alleles;[14,15] therefore, in humans, regarding the number (2 or 3) of extracellular immunoglobulin domains and size of the intracellular tails (short vs. long), the KIR molecules are classified into 3 groups, including 1) nine inhibitory KIRs (KIR2DL1-4, 5a, 5b, and KIR3DL1-3); 2) six activating KIRs (KIR2DS1-5 and KIR3DS1); and 3) two pseudogenes (3DP1 and 2DP1).[16]

According to the studies, threre is an increased activity of NK cells in TA patients.[17] In addition, KIR molecules have an crucial role in controling the function of NK cells. Here for the first time, as far as we know, we investigated the plausible association between the *KIR* gene and the genes of their HLA ligands with susceptibility to TA in the population of Iran.

MATERIALS AND METHODS

Participants

For this case-control study, 50 TA patients were recruited from the outpatient clinic of Rheumatology Research Center (RRC), Shariati Hospital, Tehran, Iran, along with 50 healthy individuals with matched age, sex, and ethnic background. Patients were diagnosed with TA according to the 1990 American College of Rheumatology (ACR) Classification Criteria for TA.[18,19] Healthy individuals had a negative past medical and family history for autoimmune disorders. Written informed consent was obtained from all patients and healthy participants before inclusion in the study. The baseline and demographic characteristics of the subjects were recorded by interview at the time of blood sample collection, as well as in their hospital medical records.

About 5 mL of peripheral blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-coated tubes after venipuncture.

KIR Genotyping

Whole blood genomic DNA was extracted using the phenol/chloroform technique. The quantity and purity of the extracted DNA samples were assessed using NanoDrop (Thermo Fisher Scientific, USA) at 260-280 nm wavelengths.

To determine the presence of different alleles of the *KIR* genes, polymerase chain reaction with specific sequence primers (PCR-SSP) was accomplished by specific primers for *KIR2DS1*, *2DS2*, *2DS3*, *2DS4* (full-length allele of *2DS4*001* and variant alleles of *2DS4*003*, **004*, **006*, **007*, **009*), *2DS5*, *2DL1*, *2DL2*, *2DL3*, *2DL4*, *2DL5A*, *2DL5B*, *3DS1*, *3DL1*, *3DL2*, *3DL3*, *2DP1*, and *3DP1* (variant alleles of *3DP1*003*, **005*, **006*, and full-length alleles of *3DP1*001*, **002*, **004*). Moreover, the HLA class 1 genes, such as *HLA-A-Bw4*, *HLA-B-Bw4*^{Thr80}, *HLA-B-Bw4*^{Ile80,} *HLA-C1*^{Asn80}, and *HLA-C2*^{Lys80}, were also genotyped.

The primers (Supplementary Table 1) and PCR protocols were obtained from previous studies.[20-25] For internal control, we used *HLA-DR, G protein-coupled receptor 98 (GPR98),* and *growth hormone* (*GH1*). About 100 ng/mL DNA was added to each PCR reaction mixture. PCR reactions were conducted using the ABI/2720 PCR system (Applied Biosystems, Foster City, CA, USA). Finally, the amplified targets were determined using electrophoresis in 2% agarose gel and visualization in an ultraviolet gel imaging system (Vilber Lourmat Inc. Collégien, France).

Statistical Methods

The genotype frequencies were compared using IBM SPSS version 23 for Windows. The associations between TA risk and *KIR/HLA* genes were determined using Pearson's chi-square or Fisher's exact tests to compare the frequencies of each *KIR* gene and its HLA ligands in TA patients to the controls. Moreover, the odds ratio (OR) and 95% confidence interval (CI) were used for risk estimation. In multiple comparisons, the Benjamini-Hochberg (B-H) method was employed to control for the false discovery rate by adjusting the *p* values. A p value<0.05 was considered statistically significant. Also, the Hardy–Weinberg equilibrium was tested for controls by the chi-square test with 1 degree of freedom. Furthermore, the distribution of genotypes was determined using geometric series.

RESULTS

Frequencies of *KIR* and *HLA* Genes

The distribution of the studied genes (*KIR* and *HLA*) in TA patients and healthy subjects is shown in Table 1. There was a significant difference only in the frequency of the *2DS4* (full) gene between TA patients (38%) and healthy controls (82%). It was found that the *KIR2DS4full* gene was significantly associated with a reduced risk of TA (OR=0.13, 95% CI=0.05–0.34, p<0.001).

KIR and *HLA* Genotypes

Three genotypes were identified in the overall interaction of the *KIR* genes; none were significantly associated with the risk of TA (Table 2).

Furthermore, the evaluation of activating *KIR* genotypes led to 4 genotypes that were not significantly associated with TA susceptibility (Table 3).

Besides, the combinational analysis of inhibitory *KIR* genes revealed 5 possible genotypes with no statistically significant difference between TA patients and healthy individuals (Table 4).

Five possible combinations were identified in the full-array analysis of HLA genes; however, none had a statistically significant association with the risk of TA (Table 5).

KIR-HLA Interactions

The analysis of KIR-HLA interactions demonstrated 9 plausible combinations, in which no statistically significant association with the risk of TA was observed (Table 6).

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Table 1. Comparison between *KIR* and *HLA* gene frequencies in TA patients and control group

***KIR* alleles**	**TA (N=50) n (%)**	**Control (N=50) n (%)**	**TA *vs.* Control *p***	**Adjusted *p****	**Odds Ratio (95% CI)**
		Inhibitory			
2DL1	48 (96)	49 (98)	0.990	0.990	0.49 (0.04-5.58)
2DL2	36 (72)	30 (60)	0.205	0.41	1.71 (0.74-3.96)
2DL3	41 (82)	44 (88)	0.401	0.601	0.62 (0.21-1.90)
2DL4	50 (100)	50 (100)	-	-	-
2DL5A	25 (50)	23 (46)	0.689	0.827	1.17 (0.53-2.57)
2DL5B	36 (72)	30 (60)	0.205	0.41	1.71 (0.74-3.96)
3DL1	48 (96)	43 (86)	0.081	0.41	3.91 (0.77-19.83)
3DL2	50 (100)	50 (100)	-	-	-
3DL3	50 (100)	50 (100)	-	-	-
		Activating			
2DS1	34 (68)	32 (64)	0.673	0.801	1.19 (0.52-2.73)
2DS2	37 (74)	31 (62)	0.198	0.462	1.74 (0.74-4.08)
2DS3	23 (46)	18 (36)	0.309	0.541	1.51 (0.68-3.37)
2DS4 (full)	19 (38)	41 (82)	**<0.001**	**<0.001**	0.13 (0.05-0.34)
2DS4 (var)	21 (42)	14 (28)	0.142	0.462	1.86 (0.81-4.29)
2DS5	20 (40)	19 (38)	0.838	0.838	1.08 (0.49-2.43)
3DS1	23 (46)	21 (42)	0.687	0.801	1.17 (0.53-2.59)
		Pseudogenes			
2DP1	49 (98)	48 (96)	0.990	0.990	2.04 (0.18-23.26)
3DP1 (*full*)	20 (40)	13 (26)	0.137	0.411	1.89 (0.81-4.43)
3DP1 (*var*)	49 (98)	48 (96)	0.990	0.990	2.04 (0.18-23.26)
		***HLA* alleles**			
HLA-C1^{Asn80}	39 (78)	40 (80)	0.806	0.967	0.88 (0.34-2.32)
HLA-C2^{Lys80}	36 (72)	38 (76)	0.648	0.967	0.81 (0.33-1.98)
HLA-B-Bw4^{Thr80}	11 (22)	6 (12)	0.183	0.967	2.06 (0.70-6.11)
HLA-B-Bw4^{Ile80}	33 (66)	29 (58)	0.410	0.967	1.41 (0.62-3.16)
HLA-A-Bw4-1	16 (32)	13 (26)	0.509	0.967	1.34 (0.56-3.19)
HLA-A-Bw4-2	49 (98)	50 (100)	0.999	0.999	-

KIR, killer cell immunoglobulin-like receptor; TA, Takayasu arteritis; CI, confidence interval; HLA, human leukocyte antigen
***** FDR-adjusted *p* value for multiple testing using the Benjamini-Hochberg method; *p* values<0.05 were considered statistically significant (written in bold).

Table 2. Overall *KIR* genotypes in TA patients and healthy controls

KIR genotype	*KIR* Genes																			TA Patients n (%)	Controls n (%)	*p*	OR (95% CI)
	Inhibitory *KIR*									Activating *KIR*								Pseudogenes					
	2DL1	*2DL2*	*2DL3*	*2DL4*	*2DL5A*	*2DL5B*	*3DL1*	*3DL2*	*3DL3*	*2DS1*	*2DS2*	*2DS3*	*2DS4 (full)*	*2DS4 (var)*	*2DS5*	*3DS1*	*2DP1*	*3DP1 (full)*	*3DP1 (var)*				
1	+	+	+	+	-	+	+	+	+	-	+	-	+	+	-	-	+	+	+	3 (6)	3 (6)	-	-
2	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	-	+	3 (6)	3 (6)	-	-
3	+	-	+	+	-	-	+	+	+	-	-	-	+	+	-	-	+	-	+	3 (6)	6 (12)	0.30	0.47 (0.11-1.98)

KIR, killer cell immunoglobulin-like receptor; TA, Takayasu arteritis; OR, Odds Ratio; CI, confidence interval

Table 3. Frequency of the activating *KIR* genotypes in the TA patients and healthy controls

KIR genotype	Activating *KIR* Gene/Allele							TA Patients n (%)	Controls n (%)	*p*	OR (95%CI)
	2DS1	*2DS2*	*2DS3*	*2DS4 (full)*	*2DS4 (var)*	*2DS5*	*3DS1*				
1	+	+	+	-	-	+	+	3 (6)	4 (8)	0.70	0.73 (0.15-3.46)
2	+	+	+	+	+	-	-	4 (8)	3 (6)	0.70	1.36 (0.28 -6.42)
3	-	+	-	+	+	-	-	4 (8)	3 (6)	0.70	1.36 (0.28 -6.42)
4	-	-	-	+	+	-	-	3 (6)	6 (12)	0.30	0.47 (0.11-1.98)

KIR, killer cell immunoglobulin-like receptor; TA, Takayasu arteritis; OR, Odds Ratio; CI, confidence interval

Table 4. Frequency of the inhibitory KIR genotypes in the TA patients and healthy controls.

KIR genotype	Inhibitory *KIR* Gene										Patients n (%)	Controls n (%)	*p*	OR (95% CI)
	2DL1	*2DL2*	*2DL3*	*2DL4*	*2DL5*	*2DL5A*	*2DL5B*	*3DL1*	*3DL2*	*3DL3*				
1	+	+	+	+	+	+	+	+	+	+	11(22)	9 (18)	0.62	1.28 (0.48-3.43)
2	+	+	-	+	+	+	+	+	+	+	4 (8)	2 (4)	0.41	2.08 (0.36-11.94)
3	+	+	+	+	-	+	+	+	+	+	16 (32)	10 (20)	0.17	1.88 (0.75-4.68)
4	+	-	+	+	+	-	+	+	+	+	0	0	-	-
5	+	-	+	+	-	-	+	+	+	+	0	0	-	-

KIR, killer cell immunoglobulin-like receptor; TA, Takayasu arteritis; OR, Odds Ratio; CI, confidence interval

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Table 5. Frequencies of HLA genotypes in TA patients and healthy controls

HLA genotype	*HLA* Gene						TA Patients n (%)	Controls n (%)	*p*	OR (95% CI)
	HLA-C1^{Asn80}	*HLA-C2^{Lys80}*	*HLA-B-Bw4^{Thr}*	*HLA-B-Bw4^{Ile80}*	*HLA-A-Bw4-1*	*HLA-A-Bw4-1*				
1	+	+	-	+	+	+	4 (8)	4 (8)	-	-
2	+	-	-	+	+	+	4 (8)	4 (8)	-	-
3	+	+	-	+	-	+	11 (22)	13 (26)	0.64	0.80 (0.32-2.01)
4	+	-	-	+	-	+	7 (14)	4 (8)	0.95	1.87 (0.51-6.84)
5	-	+	-	-	-	+	4 (8)	4 (8)	-	-

KIR, killer cell immunoglobulin-like receptor; TA, Takayasu arteritis; OR, Odds Ratio; CI, confidence interval

Table 6. Association of *KIR-HLA* gene interactions with TA risk

	KIR-HLA Interaction	TA Patients (%)	Controls (%)	*p*	OR (CI95%)
1	*KIR2DL2 − HLAC1^{Asn}*	25 (50%)	23 (46%)	0.689	1.17 (0.53-2.57)
2	*KIR2DL3 − HLAC1^{Asn}*	31 (62%)	35 (70%)	0.399	0.70 (0.30-1.60)
3	*KIR2DS2 − HLAC1^{Asn}*	27 (54%)	24 (48%)	0.548	1.27 (0.58-2.78)
4	*KIR2DL1 − HLAC2^{Lys}*	36 (72%)	38 (76%)	0.456	0.81 (0.33-1.98)
5	*KIR2DS1 − HLAC2^{Lys}*	23 (46%)	25 (50%)	0.689	0.85 (0.39-1.86)
6	*KIR3DL1 − HLABw4^{Thr}*	11 (22%)	6 (12%)	0.189	2.06 (0.70-6.11)
7	*KIR3DL1 − HLABw4^{Ile}*	31 (62%)	25 (50%)	0.228	1.63 (0.73-3.61)
8	*KIR3DS1 − HLABw4^{Thr}*	2 (4%)	3 (6%)	0.648	0.65 (0.10-4.08)
9	*KIR3DS1 − HLABw4^{Ile}*	17 (34%)	12 (24%)	0.272	1.63 (0.68-3.91)

KIR; killer cell immunoglobulin-like receptor, HLA; human leukocyte antigen, TA; Takayasu Arteritis, OR, Odds Ratio; CI; confidence interval

DISCUSSION

Although young or middle-aged women, especially in Asia, are predominantly affected by TA, it has been reported that all ages are susceptible to the disease, and a worldwide prevalence has been demonstrated.[26] An inflammatory process has been suggested during TA development; however, precise etiopathogenesis is not yet fully known.[27]

Remarkable progress has occurred in understanding critical pathogenic mechanisms of the disease during the past decade,[28] and several studies on biological and immunomodulatory drugs, such as tocilizumab (a humanized anti-IL-6 receptor antibody), have yielded promising outcomes in TA patients.[29,30]

The expression of KIRs on NK cells and their virtual HLA ligands have also been associated with the risk of autoimmune disorders.[31] Association of *KIR2DL3* and *KIR2DL5*, and HLA ligands, namely *HLA-C2^{Lys80}* and *HLA-B27* with ankylosing spondylitis[32] and *KIR2DS4* and *HLA-C^{w4}* with rheumatoid arthritis[33] have been reported. However, no significant association was found between the *KIR* genes and Behçet's disease susceptibility in the Iranian population. On the other hand, while *HLA-C1^{Asn80}* had a protective role against Behçet's disease risk, *HLA-B-Bw4^{Ile80}*, *HLA-C2^{Lys80}*,

HLA-B5, and *HLA-B51* were correlated with increased risk of Behçet's disease in that population.[34]

There are no reports regarding *KIR* and their *HLA* ligand polymorphisms in TA patients. For the first time, we analyzed *KIR* and *HLA* gene polymorphisms in this group of patients and found that the frequency of the *KIR2DS4* (full allele) was significantly reduced in TA patients. As an activating receptor on NK cells, it was less prevalent in the patient group. The mechanism of *KIR2DS4* (full allele) effect on the pathogenesis of TA needs further investigation.

To date, less has been revealed about the implications of genetic contribution to TA susceptibility. However, there is a consensus that HLA-B52 confers a strong genetic association with TA risk, as reported in several populations.[35-37] Studies have suggested that the high prevalence of TA in Asian countries may mirror the higher frequency of the *HLA-B52* allele in such ethnicities. For instance, the prevalence of TA has been reported to be 40 per 1 000 000 individuals in the Japanese population, where a 10% frequency has been observed for *HLA-B52*.[38] On the other hand, a low prevalence of TA has been observed in the European population, where a frequency of less than 2% of *HLA-B52* has been reported.[39] Furthermore, some studies revealed a contribution of non-HLA genes, particularly genes coding for immune and pro-inflammatory mediators, to the TA risk.[40,41]

It has been hypothesized that immune responses against antigens, probably derived from microorganisms, might be the initial step in activating immune-inflammatory and destructive events in TA. Target cells in TA (eg, endothelial cells) may contain peptides that mimick the peptides from microorganisms. This means that these peptides might be obtained by dendritic cells and presented to T cells, which in turn may further help the production of autoantibodies by B cells. NK cells have especially been implicated among immune responders in TA. A study reported that 20% of the total infiltrating cells to involved sites in TA were NK cells, ranking second most prevalent infiltrating cells after γδT cells (31%).[42] Moreover, increased perforin expression in the peripheral cytoplasmic granules of NK cells has been reported.[42] NK cells may recognize the autoantibodies against antigens on the endothelial cells, leading to cell death by antibody-dependent cellular cytotoxicity. In addition, NK cells might directly recognize target cells through NK Group 2D (NKG2D) receptors, which are activating receptors of NK cells [43] that interact with MICA, leading to the apoptosis of target cells.[17] Studies indicated an upregulation of MICA in aortic samples from TA patients,[12] proposing the role of NK cells in TA pathogenesis through NKG2D/MICA interactions.[44,45]

Considering all the results, for the first time, we tried to evaluate the association between *KIR* and *HLA* ligand genes with TA susceptibility in Iranian people. The analysis indicated that the lower occurrence of the full-length *KIR2DS4* gene in TA patients conferred a risk for the disease. Nonetheless, neither the genotypes of the *KIR* and *HLA* genes nor the interaction between the two were associated with TA predisposition. The results here should be interpreted with caution, as the number of TA patients in this study was low. Given the complicated network of receptors on the NK cells, we still have a long way to go before we reveal the exact interactions of these genes in the regulation of NK cells in TA patients.

STATEMENT OF ETHICS

This study was done based on the Declaration of Helsinki guidelines, and the Ethics Committee of the National Institute for Medical Research Development (NIMAD) approved the study protocol (Approval ID: IR.NIMAD.REC.1397.031).

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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