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Do KIR genes impact the susceptibility to ankylosing spondylitis in Polish patients?*

Czy geny KIR są związane z rozwojem zesztywniającego zapalenia stawów kręgosłupa u polskich pacjentów?

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Summary

Aim: Ankylosing spondylitis (AS), a chronic inflammatory arthritis, is strongly associated with *HLA-B27* gene worldwide. Among immunocyte receptors reacting with HLA-B27 are killer cell immunoglobulin-like receptors (KIRs), particularly KIR3DL1 and KIR3DL2. The KIR family includes both activating and inhibitory receptors. These may be expressed on NK cells and subtypes of T cells, which via activating/inhibitory signals regulate the activity of immunocompetent cells and potentially have an impact on inflammation and autoimmunity occurrence. However, reports on the role of KIRs in AS are controversial.

Material/Methods: We examined the possible associations of *KIR* genes in 192 patients diagnosed with AS compared with 191 control individuals. *KIR* genes were typed using PCR-SSP method.

Results: No single *KIR* gene frequency was found to differ between patients and controls. Nevertheless, the genotypes containing three genes encoding activating KIRs, as well as those characterized by ratios of activating to inhibitory *KIRs* close to 1:2 (0.5–0.6) were significantly less frequent in AS than in controls. On the contrary, higher ratios (0.67–1.67) were more frequent in AS in comparison to controls.

Conclusions: Our results suggest a protective effect of the presence of 3 (but not more) genes encoding activating KIRs, and of a ratio of activating to inhibitory *KIRs* close to 1:2 (0.5–0.6) but not higher. On the other hand, higher activating to inhibitory *KIR* ratios seem to predispose to AS. This suggests a very narrow window for optimal ratio of activating to inhibitory KIRs.

Keywords: **KIR genes • ankylosing spondylitis • susceptibility • HLA-B27**

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INTRODUCTION

Ankylosing spondylitis (AS), also known as Bechterew's disease, is a chronic inflammatory arthritis that affects the spine and sacroiliac joints [18] as well as peripheral joints and extra-articular organs [12]. AS is one of the seronegative spondyloarthropathies that causes initial bone and joint erosion and subsequent ankylosis, leading to disability and decreased quality of life [21]. The prevalence of the disease is about 1% of worldwide populations, and male-to-female ratio is about 3:1 [37].

The etiology of AS is largely unknown; however, it is widely suggested that, in addition to environmental factors, genetics plays a role in both the development and clinical course of the disease. The high disease heritability is segregating with *HLA-B27* gene – more than 90% patients affected with AS are *HLA-B27* positive [37]. This association corresponds with an arthritogenic peptide hypothesis of AS, which invokes that either microbial (exogenous) or self-peptides (endogenous) uniquely bound by HLA-B27 molecule become the target for autoreactive CD8+ T cells resulting in their cytotoxicity and subsequent chronic inflammation [37]. Another hypothesis explaining the association between AS and HLA-B27 proposes the cellular stress response related to HLA-B27 misfolding as well as the influence disease susceptibility of the amount of the molecule expression [4]. It has also been postulated that HLA-B27 heavy chain dimer is a ligand which binds to the receptors on cells of innate immunity and/or on T cells, including receptors belonging to the killer cell immunoglobulin-like receptors (KIRs) [5].

KIRs are considered regulators of cytotoxic function of natural killer (NK) cells and limited subpopulation of T lymphocytes by transmitting either an activating or inhibitory signal depending on the receptor structure [2]. Thus, based on the number of extracellular domains (2 or 3) and on the feature of intracellular tail (inhibitory long, L, or activating short, S), four major groups of KIR were defined: 2DS, 3DS, 2DL and 3DL [2, 3]. KIR receptors bind to HLA class I molecules with different affinities, e.g. AS-related HLA-B27 is ligand for KIR3DL1/2 inhibitory receptors [5]; 2-domain KIRs , in turn, recognize HLA-C molecules. Interestingly, genes encoding KIR receptors are highly polymorphic in two aspects: they not only possess multiple alleles, but also are differently distributed in individual haplotypes. Only so called "framework *KIR* genes" (*KIR3DL2*, *KIR3DL3* and *KIR2DL4* genes and *KIR3DP1* pseudogene) are present in all individuals, whereas other *KIR* genes are distributed in different combinations and numbers [3, 27], and generate two groups of haplotypes, A and B. *KIR* gene cluster is in 19q13.4 chromosome region, which, in GWAS (Genome-Wide Association Study) analyses, is identified as potentially associated with AS [18, 19].

Based on the mentioned above, genes encoding KIR receptors could impact on spondyloarthropaties development; previous studies have found that several *KIR* genes are associated with the AS susceptibility [32]. In accordance with this, we evaluate whether *KIR* genes are associated with AS in Polish patients.

MATERIALS AND METHODS

AS patients and healthy controls

A total of 192 patients (161 men and 31 women) with AS were enrolled to the study. All patients fulfilled the modified New York criteria (1984) for AS diagnosis. Their average age was 55 years (range 29–84). Patients who had been diagnosed with any other autoimmune disease were excluded from the study. All patients were recruited from the inpatient and outpatient populations of the Department of Rheumatology III, Center for Rheumatology, Rehabilitation and Disability Prevention, Ustron or of the Department and Clinic of Rheumatology and Internal Medicine of the Clinical Hospital of Wroclaw Medical University. Ninety percent of the patients were HLA-B*27 positive by either serological or genetic typing (data not shown).

One hundred and ninety-one unrelated healthy volunteers (95 men and 96 women) not diagnosed with AS or with any other autoimmune disease served as the control group.

The study was approved by the Bioethics Committee of the Medical University of Wrocław. Written informed consent was obtained prior to enrolment from all subjects.

gDNA isolation and KIR genes typing

Genomic DNA was extracted from the whole blood using Invisorb Spin Blood Midi Kit (Invitek, Germany) following the manufacturer's instructions. *KIR* genes typing was performed using polymerase chain reaction with sequence-specific primers (PCR-SSP). Primer sequences were defined by Vilches et al. [33], and PCR condition was described by Niepiekło-Miniewska et al. [25]. Genotyping was focused on the presence or absence of particular *KIR* genes in the genome of the individual for analysis of the haplotypic polymorphism.

Statistical methods

Differences between controls, patients, and patient subgroups were estimated using the two-tailed Fisher's exact test and GraphPad InStat 3 software. A p value <0.05 was considered significant.

RESULTS

The goal of this study was to evaluate the impact of KIR genes on the susceptibility to ankylosing spondylitis. As shown in Table 1, there were no statistically significant differences in the frequency of *KIR* genes between AS patients and control subjects.

We also examined the differences in the number of genes encoding activating and inhibitory receptors between patients with AS and control subjects. No significant differences were found with only one exception (Table 2). The frequency of genotypes containing 3 activating genes was significantly higher in the control group than in AS patients (24.1 and 13.0, respectively; p = 0.006). Additionally, genotypes characterized by the ratio of number of activating genes to the number of inhibitory gene amounting to 0.5-0.6 were observed in 24.1% of controls and 12.5% of AS patients (p = 0.003; Table 3), whereas frequencies of lower ratio (below 0.50) genotypes were virtually identical (~45.5%) in both groups (nonsignificant), and a higher ratio (above 0.60) genotypes was more frequent in patients (41.7% vs. 30.4% in controls; p = 0.03; Table 3).

Additionally, we analyzed the frequencies of haplogroups A and Bx. Haplogroup A was considered as content of inhibitory genes (*KIR2DL1*, *KIR2DL3* and *KIR3DL1*) and only one activating gene (*KIR2DS4* mostly present as deletion variant, *KIR2DS4d*) in addition to framework genes. Haplogroups Bx contain variable gene combinations with more activating *KIRs* and are combined from either one (AB heterozygotes) or two (BB homozygotes) activating B haplotypes [23]. Nevertheless, the frequency of particular haplogroup among AS patients was identical to those observed in controls (for A and Bx haplogroups, respectively: 27.6% and 72.4% in AS group vs 27.6% and 72.4% in controls, p = 1.0).

DISCUSSION

Etiopathogenetic factors of ankylosing spondylitis include an immune mechanism and key cell types involved in the AS-related pathological immune response are $CD8^+$ T cells, $CD4^+$ T cells and NK cells [6, 12]. NK cells and subpopulations of T lymphocytes are characterized by KIR receptors expression, and this phenomenon causes a model in which KIRs provide different levels of activation and inhibition of NK or T cells and, due to this, may lead to inflammatory and autoimmune diseases development. Due to haplotypic polymorphism of *KIR* genes, cells activation/inhibition are determined by specific *KIR* genotypes present in each individual, which potentially contribute to disease heritability [7, 11]. On the other hand, the association between *KIR* genes and AS is still controversial [10], because published results indicate a contradictory role of *KIR* genes in genetic background of AS. In this matter, some investigators suggested a predisposing role for *KIR3DS1* and protective effect of *KIR3DL1*, but others reported *KIR3DL1* to be involved in AS risk [8, 9, 15, 24, 31, 34, 38]. Nevertheless, the interaction of KIR3DL1/S1 receptors with HLA-B27 has

Table 1. *KIR* genes distribution and its influencing on AS susceptibility*

Group	KIR genes										
	2DS2	2DL3	2DL2	2DS3	2DL1	3DL1	3DS1	2DS5	2DS1	2DS4f	2DS4d
Controls (N = 191)											
Presence (N)	100	173	99	50	187	188	55	38	57	59	162
Absence (N)	91	18	92	141	4	3	136	153	134	132	29
Frequency [%]	52.4	90.6	51.8	26.2	97.9	98.4	28.9	19.9	29.8	30.9	84.8
AS patients (N = 192)											
Presence (N)	95	164	97	60	183	185	60	42	70	58	156
Absence (N)	97	28	95	132	9	7	132	150	122	134	36
Frequency [%]	49.5	85.4	50.5	31.3	95.3	96.4	31.3	21.9	36.5	30.2	81.3

*for particular *KIR* genes, no significant difference in frequency between AS patients and controls was found

Table 2. The number of inhibitory and activating *KIR* genes in analyzed groups

Groups	Number of genes encoding										
	inhibitory receptors				activating receptors						
	2	4	5	6	1	2	3*	4	5	6	7
Controls (N = 191)											
Presence (N)	0	5	107	79	39	49	46	25	20	9	3
Frequency [%]	0.0	2.6	56.0	41.4	20.4	25.7	24.1	13.1	10.5	4.7	1.6
AS patients (N = 192)											
Presence (N)	3	11	108	70	36	56	25	38	23	11	3
Frequency [%]	1.6	5.7	56.3	36.5	18.8	29.2	13.0	19.8	12.0	5.7	1.6

*AS patients vs. controls, p = 0.006, OR = 0.47 (95%CI 0.27–0.81)

been implicated in the disease pathogenesis [4]. Classical form of HLA-B27 is a ligand for KIR3DL1, and it was shown that HLA-B27 modulating NK cells cytokine secretion (e.g. downregulation of interferon γ) and adhesion functions by interacting with KIR3DL1 [1]. On the other hand, a higher surface expression of the framework gene, *KIR3DL2,* as well as a higher proportion of KIR3DL2+ NK and CD4+ cells, both resident in peripheral joints and circulated in peripheral blood, were shown in AS patients in comparison to healthy HLA-B27-negative controls [1, 30]. KIR3DS2 receptor recognizes HLA-B27 free heavy chain and this interaction may promote the expansion of T cells and other leukocytes [35]. Additionally, it cannot be excluded that such interactions lead to increased survival and expansion of activated NK cells and T cells [1, 35].

Mentioned results support the importance of NK cells and CD4+ T cells in the inflammatory pathogenesis of AS [1], but it is strongly postulated that this phenomenon could be determined by the overall balance of activating and inhibitory signals transmitting by KIRs [20, 21]. Therefore, the KIR-related AS pathogenesis studies also focused on genes for receptors recognize other HLA molecules, including HLA-C allotypes bound by two-domain KIRs. These studies found genes *KIR2DL1*, *KIR2DS1, KIR2DL3* and *KIR2DL5* to be associated with AS [16, 21, 31], and *KIR2DS5* and *KIR2DL5* to protect against AS [21, 26]. Nevertheless, no reported association has been widely replicated [10], including a study on the British [14] and Dutch population [32] and our results presented herein. Therefore, the results of worldwide analyses of potential role of three-domain *KIR* genes in AS development show differences among the populations. A possible explanation of the inter-study discrepancies are the genetic differences between examined populations. Generally, *KIR* genes are more clearly involved in AS in East Asian populations than in Caucasians. Both groups of populations are genetically fairly distant, including the frequency of *KIR* genes, which may be differentially associated with diseases in Caucasians and Asians [22]. Second, *KIR* genes contribution to AS is strongly visible in regarding on presence of KIR ligands (HLA), which were not analyzed in some studies [10, 32, 34], including our results.

Table 3.

Ratio of the number of genes encoding activating receptors to the number of genes encoding inhibitory receptors in analyzed groups

Groups	Ratio#		
	0.17–0.40	0.50–0.60*	0.67–1.67**
Controls (N = 191)			
Presence (N)	87	46	58
Frequency [%]	45.5	24.1	30.4
AS patients (N = 192)			
Presence (N)	88	24	80
Frequency [%]	45.8	12.5	41.7

*AS patients vs. controls, p = 0.003, OR = 0.45 (95%CI 0.26–0.77); ** AS patients vs. controls, p = 0.03, OR = 1.61 (95%CI 1.06–2.46); #ratio of the number of genes encoding activating receptors to the number of genes encoding inhibitory receptors.

KIR/HLA combinations are related with the susceptibility to autoimmune disorders [28, 29, 36], including AS [8, 20]. KIRs regulate the immune cell activities through binding to HLA class I molecules. Physiologically, NK activity is controlled by a balance between the inhibition and activation signals of KIRs, but in the autoimmune condition, the activation signals dominate and may initiate adverse immune responses [13]. This phenomenon is partially confirmed by *KIR* genes-related study: Diaz-Pena et al. found that the Hispanic AS patient group exhibits a significantly higher frequency of the activating Bx haplogroups than the controls, who are more often characterized by inhibitory A genotype [10]. The authors suggest that the combinations of B haplotypes can influence AS susceptibility because they biologically differ from A genotypes [10]. We have not observed higher representation of Bx genotypes in our patients, although, in control populations, very similar distribution of AA and Bx genotypes was observed in both studies. Nevertheless, in AS patient groups, genotypes with more than 3 activating were distributed with frequencies of 39.1%, which was higher than those observed in controls (29.9%). In accord with this, activating to inhibitory KIRs ratios above 0.6 (i.e., 0.67–1.67) were associated with a risk of AS. In contrast, at a ratio of around 1:2 (0.5–0.6), the risk of ankylosing spondylitis development was reduced, whereas lower ratios (i.e., a higher excess of inhibitory *KIRs*) had no effect on susceptibility to disease. The reason why higher num*bers of activating KIRs and higher activating to inhibi*tory *KIR* ratios were not associated with even higher protection but rather with a risk of disease is not clear. It may be speculated that only a few specific genotypes encoding about two times higher numbers of inhibitory than activating KIRs would be optimal for protection, while higher activating KIR numbers and higher activating to inhibitory KIR ratios predispose to disease. Alternatively, genes located near *KIRs* on chromosome 19 and encoding other receptors such as genes *LILRA* and *LILRB* (for leukocyte immunoglobulin-like receptors) may also play a role. For example, LILRB1 and LILRB2 inhibitory receptors, expressed on NK cells surface, react with HLA-B27-beta-2-microglobulin-peptide or free heavy chains of HLA-B27, respectively, similarly to KIR3DL1 and KIR3DL2 binding to these two forms of HLA-B27 [5, 17], and, via this interaction, may impact on NK cells, leading to either inflammation or autoimmunity. This, however, does not exclude a simultaneous *KIR* contribution.

In summary, although our study is limited by the number of subjects, the results suggest that the presence/absence polymorphism of individual *KIR* genes is not a significant factor involved in the pathogenesis of ankylosing spondylitis in Poles. However, the genetic combinations of *KIR* genes may protect against AS. The imbalance between activating and inhibitory *KIR* genes (ratio about 1:2 but not lower) as well as the presence of 3 activating genes seems to protect against AS development. On the other hand, higher activating to inhibitory *KIR* ratios seem to predispose to AS. This suggests a very narrow window for optimal ratio of activating to inhibitory *KIRs*.

In addition, there are other levels of *KIR* polymorphism, and it would be interesting to check, in a larger cohort, whether *KIR* allelic variation or combinations of KIR-HLA ligands impact the risk of AS. In addition, the possible role of *LILRA* and *LILRB* genes and molecules should also be examined.

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