Medicine

KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS GENES IN SERONEGATIVE SPONDYLOARTHROPATHIES

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ABSTRACT

*THE SERONEGATIVE SPONDYLOARTHROPATHIES (SPA) ARE INFLAMMATORY RHEUMATIC DISEASES WITH COMMON CLINICAL FEATURES AND GENETIC SIMILARITIES NOT LIMITED ONLY TO HLA-B27. SEVERAL STUDIES SUGGESTED THAT KILLER CELL IMMUNOLOGLOBULIN-LIKE RECEPTORS (KIR) GENES ARE ONE OF THE NON-MHC GENES ASSOCIATED WITH SPA, ALONG WITH ERAP1 AND IL23R. KIR GENES ENCODE REGULATING RECEPTORS WITH ACTIVATING OR INHIBITORY FUNCTION WHICH ARE EXPRESSED BY NATURAL KILLER CELLS (NK) AND SOME OF T LYMPHOCYTES. KIR MOLECULES RECOGNIZE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) CLASS I MOLECULES, MORE PRECISELY, DISTINCT SUBSETS OF HLA-A, HLA-B, HLA-C AND HLA-G ALLOTYPES, MODULATING THE REACTIVITY OF THE NK CELL. AN IMBALANCE BETWEEN ACTIVATING AND INHIBITORY KIR ALLELES KIR3DS1 AND KIR3DL1 IN THE PRESENCE OF CERTAIN HLA-B27 ALLELES (B*2705) MAY CONTRIBUTE TO ANKYLOSING SPONDYLITIS (AS) PATHOGENESIS. THE RISK OF PSORIATIC ARTHRITIS (PSA) IS INCREASED IN SUBJECTS WITH ACTIVATING KIR2DS1 AND/OR KIR2DS2 GENES PRESENT.*

THIS ARTICLE UNDERLINES THE IMPORTANCE OF KIR GENES AND THEIR COMPLEX RELATION WITH THEIR LIGANDS, ESPECIALLY WITH HLA-B27. THIS UNIQUE ENCOUNTER MAY BE DECISIVE FOR THE IMMUNO-INFLAMMATORY RESPONSE SEEN IN AS/SPA.

KEY WORDS: KILLER CELL IMMUNOLOGLOBULIN-LIKE RECEPTORS (KIR), SPONDYLOARTHROPATHIES (SPA), HLA-B27, ANKYLOSING SPONDYLITIS (AS).

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1. INTRODUCTION

The family of inflammatory rheumatic diseases defined as seronegative spondyloarthropathies (SpA) is formed by ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), enteropathic arthropathy, acute anterior uveitis (AAU), juvenile spondyloarthritis and undifferentiated spondyloarthritis (uSpA)[6]. Although the most important clinical sign for the group is the inflammatory back pain, peripheral articular involvement (oligoarthritis, enthesitis) and extra-articular manifestations (uveitis, dactylitis, psoriasis or chronic inflammatory bowel disease) are present as well[7,8].

The association of AS with human leukocyte antigen-B27 (HLA-B27) has been documented since 1973[9,10,11]. In recent years it has become more evident that the genetic similarities shared by the SpA patients, which mirror the common clinical profile, are not limited to the major histocompatibility complex (MHC), but they may include also non-MHC genes, such as: *ERAP1*, *IL23R* and *killer cell immunoglobulin-like receptors* (*KIR*) gene complex[12,13,14,15,16].

2. NATURAL KILLER (NK) CELLS

NK cells are bone marrow-derived lymphocytes able to recognize cells with limited HLA class I expression, leading to cytotoxicity either by release of proinflammatory cytokines or directly by release of perforins or granzyme proteases[17]. Discovered around the same time as the association of HLA-B27 with AS, NK cells were able to destroy cancer cells and viral-infected cells without a preliminary MHC restricted activation, and therefore they were initially considered to be "non-specific" lymphocytes[18,19,20].

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[6]Zochling, J., and E. U. Smith. 2010. "Seronegative spondyloarthritis." Best Pract Res Clin Rheumatol no. 24 (6):747-56.

[7] Braun, J., and J. Sieper. 2010. "Spondyloarthritides." Z Rheumatol no. 69 (5):425-32.

[8] Landewe, R. B., and D. M. van der Heijde. 2011. "The recognition of patients with spondyloarthritis. New classification criteria." Ned Tijdschr Geneeskd no. 155 (30-31).

[9] Caffrey, M. F., and D. C. James. 1973. "Human lymphocyte antigen association in ankylosing spondylitis." Nature no. 242 (5393):121.

[10] Brewerton, D. A. et al. 1973. "Ankylosing spondylitis and HL-A 27." Lancet no. 1 (7809):904-7.

[11] Schlosstein, L., P. I. Terasaki, R. Bluestone, and C. M. Pearson. 1973. "High association of an HL-A antigen, W27, with ankylosing spondylitis." N Engl J Med no. 288 (14):704-6. doi: 10.1056/nejm19730405 2881403.

[12] Colbert, R. A. et al. 2010. "From HLA-B27 to spondyloarthritis: a journey through the ER." Immunol Rev no. 233 (1):181-202. doi: 10.1111/j.0105-2896.2009.00865.x..

[13] Brown, M. A. 2009. "Genetics and the pathogenesis of ankylosing spondylitis." Curr Opin Rheumatol no. 21 (4):318-23.

[14] Tsui, F. W. et al. 2014. "The genetic basis of ankylosing spondylitis: new insights into disease pathogenesis." Appl Clin Genet no. 7:105-15. doi: 10.2147/tacg.s37325.

[15] Laval, S. H., et al. 2001. "Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci." Am J Hum Genet no. 68 (4):918-26. doi: 10.1086/319509

[16] Carter, K. W. et al. 2007. "Combined analysis of three whole genome linkage scans for Ankylosing Spondylitis." Rheumatology (Oxford) no. 46 (5):763-71. doi: 10.1093/rheumatology/kel443.

[17] Thomas, G. P., and M. A. Brown. 2010. "Genetics and genomics of ankylosing spondylitis." Immunol Rev no. 233 (1):162-80. doi: 10.1111/j.0105-2896.2009.00852.x.

[18] Rosenberg, E. B. et al. 1972. "Lymphocyte cytotoxicity reactions to leukemia-associated antigens in identical twins." Int J Cancer no. 9 (3):648-58.

[19] Herberman, R. B., M. E. Nunn, and D. H. Lavrin. 1975. "Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic acid allogeneic tumors. I. Distribution of reactivity and specificity." Int J Cancer no. 16 (2):216-29.

[20] Kiessling, R., E. Klein, and H. Wigzell. 1975. ""Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype." Eur J Immunol no. 5 (2):112-7. doi: 10.1002/eji.1830050208.

This "natural", spontaneous way of killing target cells was explained by the "missing self recognition" hypothesis, which emerged before the discovery of NK cells receptors, and stated that NK cells would kill any target cells that lacked MHC class I molecules[21,22]. However, the discovery of NK cells receptors system shifted the paradigm, and now NK cells are no longer regarded as "non-specific", but rather as a group of lymphocytes with distinct specificities, determined by activating or inhibitory receptors that recognize MHC I molecules[23]. MHC class I molecules are responsible for displaying antigens of "altered" cells (tumor cells or cells infected by intracellular pathogens). To evade CD8+ T cell-mediated immunity, an evolutionary adaptation led to down-regulation of MHC I molecules on the surface these cells. NK cells adapted further, being able to recognize cells with down regulated MHC I expression[24].

NK cells belong to innate immunity, and they are the first line of defense against intracellular pathogens via interferon (IFN)-γ production, cytolysis and apoptosis. The NK cell ability to approach a target cell is restricted by the expression of the target's MHC ligands in a complex manner that is not completely understood yet[25]. Although NK cells are not a subset of T lymphocyte family (NK cells do not present the T cell receptor), they express Fas ligand on their surface, which binds the Fas receptor (CD95) present on the surface of the infected cells and induces Fas mediated apoptosis[26].

Due to their ability to interact immediately, without prior exposure to an antigen, NK cells are also essential in tumor immuno-surveillance, using alternative/non antigen-specific receptors, such as C-type lectin-like receptors (e.g., NKG2D) to mediate the lysis of tumor cells[27]. NKG2D is an activating receptor which recognizes self-proteins that are induced in tumor cells (UL16 binding proteins – ULBP, MHC class I polypeptide-related sequence A – MICA)[28]. Another form of cell cytotoxicity exerted by NK cells is called antibody-dependent cell-mediated cytotoxicity, which involves the recognition of antibody-coated target cells by the Fcγ receptor III (CD16).

NK cells are known to produce a wide variety of cytokines: proinflammatory (IFN-γ, TNF-α) and immunosuppressive (IL–10), as well as growth factors (granulocyte macrophage colony-stimulating factor or granulocyte colony-stimulating factor). NK cells also secrete a fair amount of chemokines, including CCL2 (MCP-1), CCL3 (MIP1-α), CCL4 (MIP1-β), CCL5 (RANTES),

[21] Karre, K., H. G. Ljunggren, G. Piontek, and R. Kiessling. 1986. "Selective rejection of H-2-deficient lymphoma variants suggests alternative immune defence strategy." Nature no. 319 (6055):675-8. doi: 10.1038/319675a0.
[22] Ljunggren, H. G., and K. Karre. 1990. "In search of the 'missing self': MHC molecules and NK cell recognition." Immunol Today no. 11 (7):237-44.
[23] O'Connor, Geraldine M., et al. 2006. "Putting the natural killer cell in its place." Immunology no. 117 (1):1-10. doi: 10.1111/j.1365-2567.2005.02256.x.
[24] Lodoen, M. B., and L. L. Lanier. 2005. "Viral modulation of NK cell immunity." Nat Rev Microbiol no. 3 (1):59-69. doi: 10.1038/nrmicro1066.
[25] Caligiuri, Michael A. 2008. "Human natural killer cells." Blood no. 112 (3):461-469. doi: 10.1182/blood-2007-09-077438.
[26] Ortaldo, J. R., R. T. Winkler-Pickett, S. Nagata, and C. F. Ware. 1997. "Fas involvement in human NK cell apoptosis: lack of a requirement for CD16-mediated events." J Leukoc Biol no. 61 (2):209-15.
[27] Terunuma, H., et al. 2008. "Potential role of NK cells in the induction of immune responses: implications for NK cell-based immunotherapy for cancers and viral infections." Int Rev Immunol no. 27 (3):93-110. doi: 10.1080/08830180801911743.
[28] Raulet, D. H., et al. 2013. "Regulation of ligands for the NKG2D activating receptor." Annu Rev Immunol no. 31:413-41. doi: 10.1146/annurev-immunol-032712-095951.

XCL1 (lymphotactin) and CXCL8 (IL-8)[29]. To achieve their full cytotoxic potential NK cells require activation by several cytokines, including IL-2, IL-12[30], IL-15[31] and IL-18[32].

Structurally, there are two types of NK cells receptors: immunoglobulin-like superfamily receptors: killer cell immunoglobulin-like receptors (KIR), leukocyte immunoglobulin-like receptors (LILR) or FcγR III, which identify classical HLA class I proteins, such as HLA-A, HLA-B, and HLA-C, and C-type lectin like group (CD94/NKG2), that identifies the non-polymorphic HLA-E class I protein[33]. (Table1).

The wide array of surface receptors controls NK cell reactivity, either by stimulating NK cell reactivity (activating receptors) or by depressing NK cell reactivity (inhibitory receptors)[34,35].

Table 1. NK cell surface receptors.

NK cell receptors	**C-type lectin like receptors**	**Immunoglobulin-like superfamily receptors**	
		KIR	LILR
Activating receptors	CD94/NKG2C NKR-P1C	KIR-DS family FcγR III, 2B4, NCR family	LILRA family LIR6, LIR7
Inhibitory receptors	CD94/NKG2A NKR-P1B, NKR-P1B D	KIR-DL family	LILRB family LIR1, LIR2, LIR3

There are more than 25 activating receptors which can be grouped into receptors for soluble cytokines and receptors that interact with cell surface molecules (MHC-I binding receptors and non MHC-I binding receptors). The cytokine receptors (Table 2), are involved in NK cell activation and development[36].

The activating receptors that interact with cell surface molecules (FcγR III, NCR family – NKp46, NKp44, NKp30, NKp80, NKG2D-S, CD94/NKG2C and KIR-DS) are responsible for exerting the multiple functions of NK cells [37,38,39].

[29] Walzer, T., et al. 2005. "Natural-killer cells and dendritic cells: "l'union fait la force"." Blood no. 106 (7):2252-8. doi: 10.1182/blood-2005-03-1154.
[30] Guia, S., et al. 2008. "A role for interleukin-12/23 in the maturation of human natural killer and CD56+ T cells in vivo." Blood no. 111 (10):5008-16. doi: 10.1182/blood-2007-11-122259.
[31] Lucas, M., et al. 2007. "Dendritic cells prime natural killer cells by trans-presenting interleukin 15." Immunity no. 26 (4):503-17. doi: 10.1016/j.immuni.2007.03.006
[32] Chaix, J., et al. 2008. "Cutting edge: Priming of NK cells by IL-18." J Immunol no. 181 (3):1627-31.
[33] Brown, M. A. "Genetics and the pathogenesis of ankylosing spondylitis.", 321.
[34] Vivier, E., J. A. Nunes, and F. Vely. 2004. "Natural killer cell signaling pathways." Science no. 306 (5701):1517-9. doi: 10.1126/science.1103478.
[35] Bryceson, Y. T., et al. 2006. "Activation, coactivation, and costimulation of resting human natural killer cells." Immunol Rev no. 214:73-91. doi: 10.1111/j.1600-065X.2006.00457.x.
[36] Vivier, Eric, et al. 2011. "Innate or Adaptive Immunity? The Example of Natural Killer Cells." Science (New York, N.Y.) no. 331 (6013):44-49. doi: 10.1126/science.1198687.
[37] Smith, H. R., et al. 2002. "Recognition of a virus-encoded ligand by a natural killer cell activation receptor." Proc Natl Acad Sci U S A no. 99 (13):8826-31. doi: 10.1073/pnas.092258599.
[38] Mandelboim, O., et al. 2001. "Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells." Nature no. 409 (6823):1055-60. doi: 10.1038/35059110.
[39] Walzer, T., et al. 2007. "Identification, activation, and selective in vivo ablation of mouse NK cells via NKp46." Proc Natl Acad Sci U S A no. 104 (9):3384-9. doi: 10.1073/pnas.0609692104.

Table 2. Additional NK cell receptors

Adhesion receptors	**CD2, DNAM-1, β1 integrins, β2 integrins**
Cytokine receptors	IL-1R, IL-2R, IL-12R, IL-15R, IL-18R, IL-21R, IFN-αR
Chemotactic receptors	CCR2, CCR5, CCR7, CXCR1, CXCR 3, CXCR 4, CXCR 6

The inhibitory receptors have also the two mentioned structures: the C-type lectin like group (CD94/NKG2A) and the immunoglobulin-like superfamily (KIR-L, LILRB)[40,41].

3. KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS (KIR)

KIR are essential to NK cells in identifying target cells via HLA class I molecules and provide a selective cellular cytotoxicity[42,43]. Their expression is not limited exclusively to NK cells, as KIR were also found on subsets of T cells[44,45]. Among the NK cells receptors, KIR are probably the most complex, and this is the consequence of the remarkable allelic polymorphism that *KIR* genes present. This polymorphic variation may impact on HLA selectivity and thus, alter the NK cell immunological response[46,47].

The *KIR* gene cluster is located in the leucocyte receptor complex (LRC), encoded on the long arm (q) of chromosome 19 in position 13.4[48]. To date, 15 *KIR* gene loci, including two pseudogenes that do not encode surface receptors (*KIR2DP1* and *KIR3DP*), have been identified[49]. Although some publications refer to inhibitory *KIR3DL1* and the activating *KIR3DS1* as separate genes, they are alleles of the same locus, and for that, their alleles have a non-coinciding numbering system[50]. In a similar fashion, *KIR2DL2* and *KIR2DL3* segregate as alleles of one single locus[51].

[40] Vivier, Eric, "Innate or Adaptive Immunity? The Example of Natural Killer Cells.", 45.
[41] Boyington, J. C., and P. D. Sun. 2002. "A structural perspective on MHC class I recognition by killer cell immunoglobulin-like receptors." Mol Immunol no. 38 (14):1007-21.
[42] Cauli, A., et al. 2014. "Killer-cell immunoglobulin-like receptors (KIR) and HLA-class I heavy chains in ankylosing spondylitis." Drug Dev Res no. 75 Suppl 1:S15-9. doi: 10.1002/ddr.21187.
[43] Jiao, Y. L., et al. 2008. "Polymorphisms of KIRs gene and HLA-C alleles in patients with ankylosing spondylitis: possible association with susceptibility to the disease." J Clin Immunol no. 28 (4):343-9. doi: 10.1007/s10875-008-9183-6.
[44] Lanier, L. L. 2005. "NK cell recognition." Annu Rev Immunol no. 23:225-74. doi: 10.1146/annurev.immunol.23.021704.115526.
[45] Arlettaz, L., et al. 2004. "Expression of inhibitory KIR is confined to CD8+ effector T cells and limits their proliferative capacity." Eur J Immunol no. 34 (12):3413-22. doi: 10.1002/eji.200324756.
[46] Mahfouz, R. A., et al. 2009. "Distribution of killer cell immunoglobulin-like receptor (KIR) genotypes in patients with familial Mediterranean fever." Genet Test Mol Biomarkers no. 13 (1):91-5. doi: 10.1089/gtmb.2008.0081.
[47] Middleton, D., F. Williams, and I. A. Halfpenny. 2005. "KIR genes." Transpl Immunol no. 14 (3-4):135-42. doi: 10.1016/j.trim.2005.03.002.
[48] Wende, H., M. Colonna, A. Ziegler, and A. Volz. 1999. "Organization of the leukocyte receptor cluster (LRC) on human chromosome 19q13.4." Mamm Genome no. 10 (2):154-60.
[49] Vilches, C., and P. Parham. 2002. "KIR: diverse, rapidly evolving receptors of innate and adaptive immunity." Annu Rev Immunol no. 20:217-51. doi: 10.1146/annurev.immunol.20.092501.134942.
[50] Marsh, S. G., et al. 2003a. "Killer-cell immunoglobulin-like receptor (KIR) nomenclature report, 2002." Immunogenetics no. 55 (4):220-6. doi: 10.1007/s00251-003-0571-z.
[51] Middleton, "KIR genes." 138.

KIR genes encode regulating receptors with activating or inhibitory function regarding the development, tolerance and activation of NK cells[52]. *KIR* genes variation is given by a different gene or allele content present in an individual[53], and this generates a vast haplotype diversity, which is responsible for a multitude of different genotypes observed in different populations[54].

Only four *KIR* genes (*KIR2DL4*, *KIR3DL2*, *KIR3DL3* and *KIR3DP1*) are consistently found in almost all individuals, and they are known as 'framework' genes[55]. Currently, Allele Frequency Net Database[56,57] lists 571 different KIR genotypes found in 18,583 individuals from 154 populations (http://www.allelefrequencies.net/kir6001a.asp).

The allelic variation is even greater. The most recent 2.6.0 release (January 2015) of The European Bioinformatics Institute (EMBL-EBI) Immuno Polymorphism Database[58,59] reports 753 KIR alleles (http://www.ebi.ac.uk/ipd/kir/stats.html). The institute in charge of naming the *KIR* genes is the Nomenclature Committee for Factors of the HLA System, a subcommittee of the World Health Organization[60]. The name of a *KIR* gene reflects the molecular structure of the receptor encoded by that gene. KIR molecules present an extracellular segment and an intracellular segment. The extracellular segment is formed by two or three immunoglobulin-like domains (D). Thus, the first digit following the KIR acronym represents the number of immunoglobulin-like domains in the molecule (2D or 3D).

The intracellular segment can be either short (S) or long (L). The short (S) cytoplasmic tail contains two immunoreceptor tyrosine-based activation motifs (ITAM), which, as the name suggests, are responsible for the activating action of KIR. The long (L) cytoplasmic tail may have one or two immunoreceptor tyrosine-based inhibition motifs (ITIM), giving the protein its inhibitory function[61]. (Fig. 1).

With the exception of *KIR2DL4* gene, which encodes both motifs[62], making KIR2DL4 the only receptor within the family with both inhibitory and activating function, a *KIR* gene encodes either a short intracellular segment (activating motifs) KIR or a long intracellular segment (inhibitory motifs) KIR. The *KIR* pseudogenes encode an intracellular tail indicated as "P" (pseudogene). The digit after S, L or P cytoplasmic tale is the number of the gene encoding a

[52] Caligiuri, Michael A. "Human natural killer cells." 461.
[53] Wilson, M. J., et al. 2000. "Plasticity in the organization and sequences of human KIR/ILT gene families." Proc Natl Acad Sci U S A no. 97 (9):4778-83. doi: 10.1073/pnas.080588597
[54] Middleton, Derek, and Faviel Gonzelez. 2010. "The extensive polymorphism of KIR genes." Immunology no. 129 (1):8-19. doi: 10.1111/j.1365-2567.2009.03208.x.
[55] Mandelboim, "Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells." 1057.
[56] Gonzalez-Galarza, F. F., S. Christmas, D. Middleton, and A. R. Jones. 2011. "Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations." Nucleic Acids Res no. 39 (Database issue):D913-9. doi: 10.1093/nar/gkq1128.
[57] Gonzalez-Galarza, F. F., et al. 2015. "Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations." Nucleic Acids Res no. 43 (Database issue):D784-8. doi: 10.1093/nar/gku1166.
[58] Robinson, J., et al. 2005. "IPD—the Immuno Polymorphism Database." Nucleic Acids Research no. 33 (suppl 1):D523-D526. doi: 10.1093/nar/gki032.
[59] Robinson, J., et al. 2013. "IPD--the Immuno Polymorphism Database." Nucleic Acids Res no. 41 (Database issue):D1234-40. doi: 10.1093/nar/gks1140/.
[60] Marsh, S. G., "Killer-cell immunoglobulin-like receptor (KIR) nomenclature report, 2002.", 221.
[61] Middleton, Derek, "The extensive polymorphism of KIR genes." 9.
[62] Rajagopalan, S., J. Fu, and E. O. Long. 2001. "Cutting edge: induction of IFN-gamma production but not cytotoxicity by the killer cell Ig-like receptor KIR2DL4 (CD158d) in resting NK cells." J Immunol no. 167 (4):1877-81.

receptor with this structure[63]. A final letter (A or B) differentiates the *KIR* genes with comparable sequences, which generate very similar protein structures (*KIR2DL5A* and *KIR2DL5B*)[64].

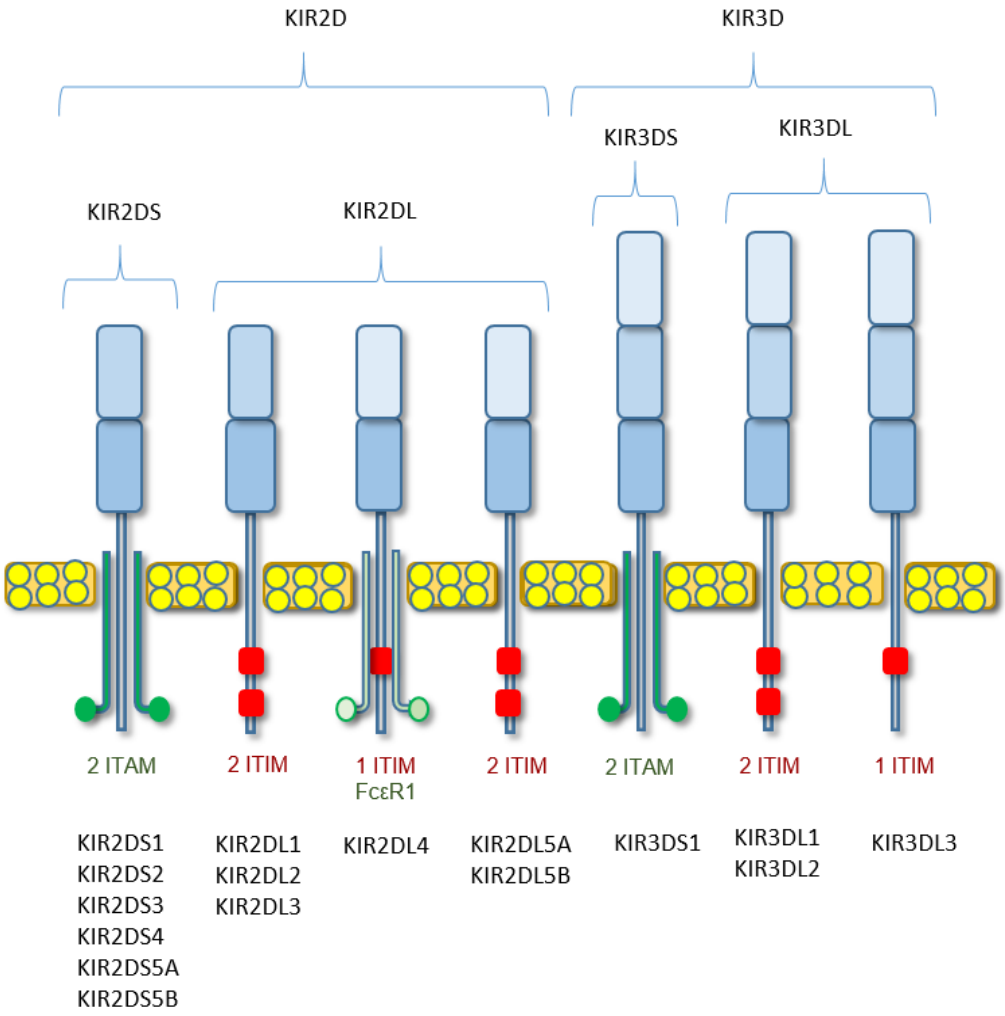

Figure 1. The structure of KIR molecules.

The numerical allelic designation is separated by the gene name with an asterisk. Similarly to the alleles of the HLA system, the first five digits indicate the alleles that differ in the exon coding sequences: the first three digits discern between alleles with non-synonymous differences, while the next two digits distinguish the alleles with synonymous differences. Finally, the last two digits distinguish alleles that only differ in a non-coding region of the sequence (e.g., intron or promoter)[65]. (Fig.2).

KIR molecules seem to identify almost exclusively HLA class I molecules present on the potentially target cell, although a relatively recent study reported the direct binding of KIR3DL2

[63] Middleton, Derek, "The extensive polymorphism of KIR genes." 11.
[64] Gomez-Lozano, N., et al. 2002. "Some human KIR haplotypes contain two KIR2DL5 genes: KIR2DL5A and KIR2DL5B." Immunogenetics no. 54 (5):314-9. doi: 10.1007/s00251-002-0476-2.
[65] Marsh, S. G., et al. 2003b. "Killer-cell immunoglobulin-like receptor (KIR) nomenclature report, 2002." Hum Immunol no. 64 (6):648-54.

to microbial CpG oligodeoxynucleotides[66], demonstrating that KIR ligands may be also non-HLA molecules. Furthermore, not all KIR molecules have a known ligand; this is the case for KIR2DL5A/B, KIR2DS5A/B and KIR3DL3.

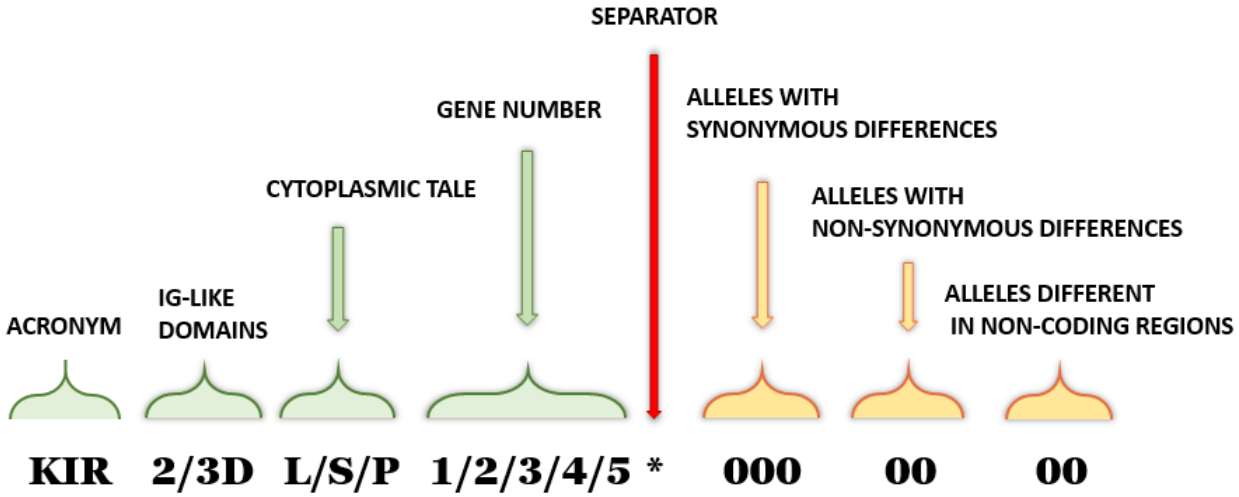

Figure 2. KIR genes and alleles nomenclature.

MHC I molecules recognized by KIR are distinct subsets of HLA-A, HLA-B, HLA-C and HLA-G allotypes[67,68,69]. KIR recognize certain peptides within HLA polypeptide structure, without distinguishing self from non-self peptides[70,71]. The specific ligands for KIR identified so far are presented in Table 3, but some further clarifications are needed.

Inhibitory KIR have a higher avidity than activating KIR for MHC I molecules[72]. KIR2DL1 recognizes HLA-C^{Lys80}, the so called HLA-C group 2 alleles (e.g., C*02, C*04, C*05, C*06)[73]. KIR2DL2 and, to a weaker extent, KIR2DL3 are receptors for HLA-C^{Asn80}, known as HLA-C group 1 (e.g., C*01, C*03, C*07, C*08), but also for some HLA-C group 2 alleles and HLA-B (B*4601, B*7301)[74]. KIR2DL4 recognizes HLA-G, but due to its unique structure (activating ITAM and inhibitory ITIM motifs present in the cytoplasmic tail), it is considered both activating and inhibitory receptor.

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[66] Sivori, S., et al. 2010. "A novel KIR-associated function: evidence that CpG DNA uptake and shuttling to early endosomes is mediated by KIR3DL2." Blood no. 116 (10):1637-47. doi: 10.1182/blood-2009-12-256586.
[67] Vilches, C. "KIR: diverse, rapidly evolving receptors of innate and adaptive immunity." 233.
[68] Moesta, A. K., et al. 2008. "Synergistic polymorphism at two positions distal to the ligand-binding site makes KIR2DL2 a stronger receptor for HLA-C than KIR2DL3." J Immunol no. 180 (6):3969-79.
[69] Sharma, D., et al. 2009. "Dimorphic motifs in D0 and D1+D2 domains of killer cell Ig-like receptor 3DL1 combine to form receptors with high, moderate, and no avidity for the complex of a peptide derived from HIV and HLA-A*2402." J Immunol no. 183 (7):4569-82. doi: 10.4049/jimmunol.0901734.
[70] Lanier, L. L. "NK cell recognition." 254.
[71] Biassoni, R., et al. 2001. "Human natural killer cell receptors and co-receptors." Immunol Rev no. 181:203-14.
[72] Stewart, C. A., et al. 2005. "Recognition of peptide-MHC class I complexes by activating killer immunoglobulin-like receptors." Proc Natl Acad Sci U S A no. 102 (37):13224-9. doi: 10.1073/pnas. 0503594102.
[73] Campbell, Kerry S., and Amanda K. Purdy. 2011. "Structure/function of human killer cell immunoglobulin-like receptors: lessons from polymorphisms, evolution, crystal structures and mutations." Immunology no. 132 (3):315-325. doi: 10.1111/j.1365-2567.2010.03398.x.
[74] Moesta, A. K., et al. 2008. "Synergistic polymorphism at two positions distal to the ligand-binding site makes KIR2DL2 a stronger receptor for HLA-C than KIR2DL3." J Immunol no. 180 (6):3969-79.

Table 3. KIR family and MHC-I ligands

Inhibitory KIR	Ligand	Activating KIR	Ligand
KIR2DL1	HLA-C^{Lys80}	KIR2DS1	HLA-C^{Lys80}
KIR2DL2	HLA-C^{Asn80}	KIR2DS2	HLA-C^{Asn80}
KIR2DL3	HLA-C^{Asn80}	KIR2DS3	HLA-C^{Asn80}
KIR2DL4	HLA-G	KIR2DS4	HLA-C
KIR2DL5A	Unknown	KIR2DS5A	Unknown
KIR2DL5B	Unknown	KIR2DS5B	Unknown
KIR3DL1	HLA-Bw4	KIR3DS1	HLA-Bw4 (?)
KIR3DL2	HLA-A		
KIR3DL3	Unknown		

KIR3DL1 binds to Bw4 epitopes present in certain HLA-B allotypes including HLA-B*08, HLA-B*27 and HLA-B*57, but also to HLA-A*2402[75]. *KIR3DL1* gene has the most extensive polymorphisms, with 79 alleles being reported to date[76], only to match the vast diversity of the HLA-B allotypes.

KIR3DL2 recognizes certain HLA-A allotypes (A*03 and A*11)[77] and recently it was discovered that it binds even stronger to HLA-B27 free heavy chain forms (FHC), including disulfide-bonded heavy chain homodimers[78].

[75] Thananchai, H., et al. 2007. "Cutting Edge: Allele-specific and peptide-dependent interactions between KIR3DL1 and HLA-A and HLA-B." J Immunol no. 178 (1):33-7.
[76] Gonzalez-Galarza, F. F., "Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations." 784.
[77] Campbell, Kerry S. "Structure/function of human killer cell immunoglobulin-like receptors: lessons from polymorphisms, evolution, crystal structures and mutations." 321.
[78] Wong-Baeza, I., et al. 2013. "KIR3DL2 binds to HLA-B27 dimers and free H chains more strongly than other HLA class I and promotes the expansion of T cells in ankylosing spondylitis." J Immunol no. 190 (7):3216-24. doi: 10.4049/jimmunol.1202926.

The corresponding activating KIR match more or less the ligand specificity of the inhibitory receptors, although this specificity has been less characterized and their affinity is weaker[79]. Moreover, there are conflicting reports regarding the KIR3DS1 specificity for HLA-Bw4[80,81,82].

4. KIR AND SERONEGATIVE SPONDYLOARTHROPATHIES

In recent years there have been more and more association studies which link *KIR* genes with infectious diseases, cancer, autoimmune or idiopathic diseases and chronic inflammatory diseases[83]. To date, in KIR and Diseases Database[84] are a total of 1180 KIR disease-association records derived from 210 articles (http://www.allelefrequencies. net/diseases/default.asp). KIR ability to modulate and provide activation/inhibition fine tuning[85] to the immunological response of NK cells and/or T cells, based on the interaction with MHC class I molecules, may give them a key role in the pathogenesis of many diseases associated with altered innate immune system.

Thus, *KIR* genes complex has become an interesting research area in SpA, given the known association of this group of diseases with HLA-B27 (Table 4). In 2001, the first genome wide association study (GWAS) described a strong linkage between AS and non-MHC loci on chromosome 19q, where the *KIR* genes are located[86], which was later confirmed by a meta-analysis of three whole genome linkage scans for AS[87]. Given the receptor-ligand relationship between certain *KIR (KIR3DL1, -3DL2* and possible *-3DS1*) and *HLA-B* alleles, it is reasonable to assume a synergic contribution of these polymorphic loci to AS[88,89].

One of the first case-control association studies investigating *KIR* genes in AS involved two HLA-B27 positive Caucasian populations (Spanish and Azoreans - Portuguese)[90]. The inhibitory *KIR3DL1* allele was decreased in AS patients compared with the control groups in both populations, suggesting a protective effect against the development of AS, while the activating

[79] Shegarfi, Hamid, Fatemeh Naddafi, and Abbas Mirshafiey. 2012. "Natural Killer Cells and Their Role in Rheumatoid Arthritis: Friend or Foe?" The Scientific World Journal no. 2012:491974. doi: 10.1100/2012/491974.
[80] O'Connor, G. M., et al. 2007. "Functional polymorphism of the KIR3DL1/S1 receptor on human NK cells." J Immunol no. 178 (1):235-41
[81] Alter, G., et al. 2007. "Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes." J Exp Med no. 204 (12):3027-36. doi: 10.1084/jem.20070695.
[82] Carr, W. H., et al. 2007. "Cutting Edge: KIR3DS1, a gene implicated in resistance to progression to AIDS, encodes a DAP12-associated receptor expressed on NK cells that triggers NK cell activation." J Immunol no. 178 (2):647-51.
[83] Gonzalez-Galarza, F. F., "Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations." 786.
[84] Takeshita, Louise Y. C., et al. 2013. "A database for curating the associations between killer cell immunoglobulin-like receptors and diseases in worldwide populations." Database: The Journal of Biological Databases and Curation no. 2013:bat021. doi: 10.1093/database/bat021.
[85] Falco, M., et al. 2013. "KIR and KIR ligand polymorphism: a new area for clinical applications?" Tissue Antigens no. 82 (6):363-73. doi: 10.1111/tan.12262.
[86] Laval, S. H., "Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci." 922.
[87] Carter, K. W. "Combined analysis of three whole genome linkage scans for Ankylosing Spondylitis." 763.
[88] Diaz-Pena, R., M. A. Blanco-Gelaz, and C. Lopez-Larrea. 2009. "KIR genes and their role in spondyloarthropathies." Adv Exp Med Biol no. 649:286-99.
[89] Breban, M., et al. 2015. "Revisiting MHC genes in spondyloarthritis." Curr Rheumatol Rep no. 17 (6):516. doi: 10.1007/s11926-015-0516-1.
[90] Lopez-Larrea, C., et al. 2006. "Contribution of KIR3DL1/3DS1 to ankylosing spondylitis in human leukocyte antigen-B27 Caucasian populations." Arthritis Res Ther no. 8 (4):R101. doi: 10.1186/ar1988.

KIR3DS1 was increased[91]. The same group reported in 2010[92] and 2015[93] similar results in studies carried out in a larger Spanish population cohort. Díaz-Peña *et al.* showed that *KIR3DS1*013* allele has a positive susceptibility to AS, while *KIR3DL1*004* allele has a negative one[94]. Additionally, *KIR2DS1* gene frequency was significantly increased in AS patients compared with healthy controls[95]. *KIR3DL1/3DS1* gene has become the focus of several studies realized in Asian populations where it was found to be highly polymorphic, a total of 10 *KIR3DL1* alleles and 6 *KIR3DS1* alleles being identified[96]. A study that enrolled a small number of Asian patients and controls (China and Thailand) found that activating *KIR* genes are associated with AS[97]. *KIR* genotype analysis showed *3DL1/3DL1* frequency decreased in AS patients versus controls, while *3DL1/3DS1* demonstrated a significantly increased frequency in AS patients in both populations[98]. Another two association studies performed in Asian population found not only *KIR3DS1* allele to be associated with increased AS susceptibility, but also *KIR2DL5* and *KIR2DS1* in the presence of HLA-C group 2 alleles[99,100]. A more recent study which investigated *KIR3DS1/3DL1* gene contribution to AS in Chinese populations confirmed an increase frequency of the activating *KIR3DS1* allele in AS patients versus controls[101].

The importance of *KIR3DL1/3DS1* locus in AS was supported by a study involving 83 AS patients and 107 HLA-B27-positive healthy controls from the Russian population, which concluded that the presence of a functional KIR3DL1 receptor has a protective effect against AS while the activating KIR3DS1 receptor associates with AS development[102]. In the Iranian population *KIR3DL1+HLA-B (Bw4)* combination had lowers frequencies in AS patients than in controls, while, for *KIR2DS1+HLA-C2* combination, the opposite was true[103].

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[91] Lopez-Larrea, C. "Contribution of KIR3DL1/3DS1 to ankylosing spondylitis in human leukocyte antigen-B27 Caucasian populations." 101.

[92] Diaz-Pena, R., et al. 2010. "Association of the KIR3DS1*013 and KIR3DL1*004 alleles with susceptibility to ankylosing spondylitis." Arthritis Rheum no. 62 (4):1000-6. doi: 10.1002/art.27332.

[93] Diaz-Pena, R., et al. 2015. "Activating killer immunoglobulin-like receptors genes are associated with increased susceptibility to ankylosing spondylitis." Clin Exp Immunol no. 180 (2):201-6. doi: 10.1111/cei.12568.

[94] Diaz-Pena, R. "Association of the KIR3DS1*013 and KIR3DL1*004 alleles with susceptibility to ankylosing spondylitis." 1000.

[95] Diaz-Pena, R. "Activating killer immunoglobulin-like receptors genes are associated with increased susceptibility to ankylosing spondylitis." 201.

[96] Deng, Z., et al. 2015. "Allelic diversity of KIR3DL1/3DS1 in a southern Chinese population." Hum Immunol no. 76 (9):663-6. doi: 10.1016/j.humimm.2015.09.017.

[97] Diaz-Pena, R., et al. 2008. "Activating KIR genes are associated with ankylosing spondylitis in Asian populations." Hum Immunol no. 69 (7):437-42. doi: 10.1016/j.humimm.2008.04.012.

[98] Diaz-Pena, "Activating KIR genes are associated with ankylosing spondylitis in Asian populations." 437.

[99] Jiao, Y. L., "Polymorphisms of KIRs gene and HLA-C alleles in patients with ankylosing spondylitis: possible association with susceptibility to the disease." 343.

[100] Jiao, Y. L., et al. 2010. "Polymorphisms of KIR gene and HLA-C alleles: possible association with susceptibility to HLA-B27-positive patients with ankylosing spondylitis." J Clin Immunol no. 30 (6):840-4. doi: 10.1007/s10875-010-9444-z.

[101] Wang, S., et al. 2013. "Association of KIR genotype with susceptibility to HLA-B27-positive ankylosing spondylitis." Mod Rheumatol no. 23 (3):538-41. doi: 10.1007/s10165-012-0692-z.

[102] Zvyagin, I. V., et al. 2010. "Contribution of functional KIR3DL1 to ankylosing spondylitis." Cell Mol Immunol no. 7 (6):471-6. doi: 10.1038/cmi.2010.42.

[103] Tajik, N., et al. 2011. "KIR3DL1+HLA-B Bw4Ile80 and KIR2DS1+HLA-C2 combinations are both associated with ankylosing spondylitis in the Iranian population." Int J Immunogenet no. 38 (5):403-9. doi: 10.1111/j.1744-313X.2011.01024.x

Table 4. Case-control association studies between KIR and SpA

Spondyloarthropathies	*KIR* gene association	Year, Population
Ankylosing spondylitis	*KIR3DL1/3DS1*	2006, Caucasians, (Spain, Portugal)[104]
	KIR3DL1/3DS1	2008, Asians (China and Thailand)[105]
	KIR3DS1, *KIR2DL5*, *KIR2DS1*	2008, Asians (China)[106]
	KIR3DL1/3DS1, *KIR3DL2*	2009, Cucasians (UK)[107]
	*KIR3DL1*004* *KIR3DS1*013*	2010, Caucasians (Spanish)[108]
	KIR3DL1/3DS1	2010, Caucasians (Russia)[109]
	KIR2DL1, *KIR2DL5*	2010, Asians (China)[110]
	KIR3DL1/3DS1 *KIR2DS1*	2011, Caucasians (Iran)[111]
	KIR3DL1/3DS1	2013, Asians (China)[112]
	KIR2DS1, *KIR3DS1*	2015, Caucasians (Spain)[113]
	KIR3DL1/3DS1	2015, Caucasians (The Netherlands)[114]
Psoriatic arthritis	*KIR2DS1*, *KIR2DS2*	2002, Caucasians (Canada)[115]
	KIR2DL2, *KIR2DS2*	2014, Caucasians (Canada)[116]

[104] Lopez-Larrea, C. "Contribution of KIR3DL1/3DS1 to ankylosing spondylitis in human leukocyte antigen-B27 Caucasian populations." 101.
[105] Diaz-Pena, R., "Activating KIR genes are associated with ankylosing spondylitis in Asian populations." 437.
[106] Jiao, Y. L., "Polymorphisms of KIRs gene and HLA-C alleles in patients with ankylosing spondylitis: possible association with susceptibility to the disease." 343.
[107] Harvey, D., et al. 2009. "Analysis of killer immunoglobulin-like receptor genes in ankylosing spondylitis." Ann Rheum Dis no. 68 (4):595-8. doi: 10.1136/ard.2008.095927
[108] Diaz-Pena, R. "Association of the KIR3DS1*013 and KIR3DL1*004 alleles with susceptibility to ankylosing spondylitis." 1000.
[109] Zvyagin, I. V., "Contribution of functional KIR3DL1 to ankylosing spondylitis." 471.
[110] Jiao, Y. L., "Polymorphisms of KIR gene and HLA-C alleles: possible association with susceptibility to HLA-B27-positive patients with ankylosing spondylitis." 840.
[111] Tajik, N., "KIR3DL1+HLA-B Bw4Ile80 and KIR2DS1+HLA-C2 combinations are both associated with ankylosing spondylitis in the Iranian population." 403.
[112] Wang, S., "Association of KIR genotype with susceptibility to HLA-B27-positive ankylosing spondylitis." 538.
[113] Diaz-Pena, R., "Activating killer immunoglobulin-like receptors genes are associated with increased susceptibility to ankylosing spondylitis." 201.
[114] Vendelbosch, S., et al. 2015. "Study on the Protective Effect of the KIR3DL1 Gene in Ankylosing Spondylitis." Arthritis Rheumatol no. 67 (11):2957-65. doi: 10.1002/art.39288.
[115] Martin, M. P., et al. 2002. "Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles." J Immunol no. 169 (6):2818-22.
[116] Chandran, V., et al. 2014. "Killer-cell immunoglobulin-like receptor gene polymorphisms and susceptibility to psoriatic arthritis." Rheumatology (Oxford) no. 53 (2):233-9. doi: 10.1093/rheumatology/ket296.

Acute anterior uveitis	*KIR3DS1, KIR2DS1, KIR2DS5, KIR3DL1 KIR2DL1*	2010, Caucasians (USA)[117]
	KIR3DL1	2013, Asians (South Korea)[118]

In contradiction with previously reported results, a UK based study which investigated *KIR3DL1, KIR3DS1* and *KIR3DL2* genes found no differences in *KIR* genotypes and *KIR3DL2* allele frequencies between the 200 AS patients and 405 controls[119]. The different inclusion criteria used in each study may partially explain the negative results[120]. Somewhat similar findings were reported by another group from The Netherlands. Genotyping the KIR locus in 303 Caucasian AS patients, 119 random controls and 50 HLA-B27+ controls no significant association of any specific *KIR* gene or haplotype with susceptibility to AS was observed, although a lower number of *KIR3DL1* allele was linked with more severe AS cases, suggesting a protective effect of *KIR3DL1* against the more severe manifestations of AS[121].

One study investigated *KIR* genes in patients with HLA-B27-associated AAU, with and without axial SpA. The results were unexpected, since lower frequencies where observed for the activating *KIR3DS1*, *KIR*2DS1, and *KIR2DS5* genes in AAU patients with axial SpA. Moreover, the inhibitory *KIR3DL1+HLA-Bw4* combination was more frequent in AAU patients than in controls ($p = 2.73 \times 10^{-28}$, $p(c) = 8.2 \times 10^{-27}$)[122]. Although these findings are diametrically opposed to the ones previously presented and the ones reported by a Korean study in UUA associated with AS[123], they may be the framework for an interesting hypothesis suggested by the authors: a low expression of activating KIR may fail to trigger an early NK cell response to clear the antigenic stimuli, and thus, their persistence may become a contributing factor to AS/SpA pathogenesis[124].

Our unpublished data showed similar results regarding the activating *KIR3DS1*013* allele. We investigated *KIR3DL1/DS1* locus in a small cohort of HLA-B27+ AS Romanian patients and HLA-B27+ matching controls. We observed a lower allele frequency for *KIR3DS1*013* in AS patients (14%) compared with controls (26%), which proved to be statistically significant ($p<0.05$).

The study of *KIR* genes in PsA is justified not only by KIR3DL1 and HLA-Bw4 (including HLA-B27) interaction, but also by the KIR2DL1, KIR2DL2, KIR2DS1, KIR2DS2 recognition of HLA-C, knowing that *HLA-Cw*0602* allele association with PsA is widely accepted[125]. The first study to investigate *KIR* genes in PsA reported that subjects with activating *KIR2DS1* and/or

[117] Levinson, R. D., et al. 2010. "Killer cell immunoglobulin-like receptors in HLA-B27-associated acute anterior uveitis, with and without axial spondyloarthropathy." Invest Ophthalmol Vis Sci no. 51 (3):1505-10. doi: 10.1167/iovs.09-4232.

[118] Moon, S. J., et al. 2013. "Diversity of killer cell immunoglobulin-like receptor genes in uveitis associated with autoimmune diseases: ankylosing spondylitis and Behcet disease." Ocul Immunol Inflamm no. 21 (2):135-43. doi: 10.3109/09273948.2012.754905.

[119] Harvey, D., "Analysis of killer immunoglobulin-like receptor genes in ankylosing spondylitis." 595.

[120] Zvyagin, I. V., "Contribution of functional KIR3DL1 to ankylosing spondylitis." 471.

[121] Vendelbosch, S., "Study on the Protective Effect of the KIR3DL1 Gene in Ankylosing Spondylitis." 2957.

[122] Levinson, R. D., "Killer cell immunoglobulin-like receptors in HLA-B27-associated acute anterior uveitis, with and without axial spondyloarthropathy." 1505.

[123] Moon, S. J., "Diversity of killer cell immunoglobulin-like receptor genes in uveitis associated with autoimmune diseases: ankylosing spondylitis and Behcet disease." 135.

[124] Levinson, R. D., "Killer cell immunoglobulin-like receptors in HLA-B27-associated acute anterior uveitis, with and without axial spondyloarthropathy." 1505.

[125] Korendowych, E., and N. McHugh. 2005. "Genetic factors in psoriatic arthritis." Curr Rheumatol Rep no. 7 (4):306-12.

KIR2DS2 genes present an increase risk to developing PsA[126]. The association of the *KIR2DS2* gene with PsA has been recently confirmed by a study which enrolled large cohorts of Canadian PsA patients (678) and controls (688). The risk of PsA is higher when *KIR2DS2* gene is present with the HLA-C ligands (C group 1), being the highest when *KIR2DS2* alleles are present in the absence of HLA-C ligands for homologous inhibitory *KIR*[127].

5. CONCLUSIONS

Although not all the results presented are concordant, several studies showed consistently increased frequencies of the activating *KIR2DS1* and *KIR3DS1* genes in SpA[128], at least in some particular populations (Spanish, Chinese).

The interaction of KIR3DL1/KIR3DS1 or KIR3DL2 with HLA-B27 may be one key element in AS pathogenesis. KIR3DL1 and possibly KIR3DS1 are able to bind the classical heterodimeric β2m/ HLA-B27 heavy chain complex which presents self, viral or bacterial peptide to CD8+ T cells, as well as homodimeric HLA-B27 heavy chain (β2m free), while KIR3DL2 binds only homodimeric HLA-B27 heavy chains complexes[129,130,131], known to be expressed on antigen presenting cells in AS[132], independent of the sequence of the presented peptides[133]. Some viral peptides were proved to inhibit KIR3DL1 recognition of HLA-B*2705[134], thus, lowering the inhibitory signals transmitted to NK cells. An imbalance between activating and inhibitory *KIR* genes/ alleles (*KIR3DL1/DS1*) in the presence of certain *HLA-B27* alleles (B*2705) may contribute to AS pathogenesis[135].

A higher KIR3DL2 surface expression on NK and CD4+ T cells in HLA-B*2705 AS patients compared with HLA-B*2705, HLA-B*2709 and HLA-B27-negative healthy controls was reported, supporting the possible role of the KIR3DL2/HLA-B27 pair in the pathogenesis of AS[136]. A stronger interaction of KIR3DL2 with free heavy chain HLA-B27 may lead to a decreased IFN-γ production by NK cells, but also an increased proliferation and a greater survival of NK cells

[126] Martin, M. P., "Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles." 2818.
[127] Chandran, V., "Killer-cell immunoglobulin-like receptor gene polymorphisms and susceptibility to psoriatic arthritis." 233.
[128] Diaz-Pena, R., "Activating killer immunoglobulin-like receptors genes are associated with increased susceptibility to ankylosing spondylitis." 201.
[129] Cauli, A., "Killer-cell immunoglobulin-like receptors (KIR) and HLA-class I heavy chains in ankylosing spondylitis." 15.
[130] Wong-Baeza, I., "KIR3DL2 binds to HLA-B27 dimers and free H chains more strongly than other HLA class I and promotes the expansion of T cells in ankylosing spondylitis." 3216.
[131] Kollnberger, S., et al 2007. "Interaction of HLA-B27 homodimers with KIR3DL1 and KIR3DL2, unlike HLA-B27 heterotrimers, is independent of the sequence of bound peptide." Eur J Immunol no. 37 (5):1313-22. doi: 10.1002/eji.200635997.
[132] Kollnberger, S., et al. 2002. "Cell-surface expression and immune receptor recognition of HLA-B27 homodimers." Arthritis Rheum no. 46 (11):2972-82. doi: 10.1002/art.10605.
[133] Kollnberger, S., "Interaction of HLA-B27 homodimers with KIR3DL1 and KIR3DL2, unlike HLA-B27 heterotrimers, is independent of the sequence of bound peptide." 1313.
[134] Stewart-Jones, G. B., et al. 2005. "Crystal structures and KIR3DL1 recognition of three immunodominant viral peptides complexed to HLA-B*2705." Eur J Immunol no. 35 (2):341-51. doi: 10.1002/eji.200425724.
[135] Diaz-Pena, R., "KIR genes and their role in spondyloarthropathies." 286.
[136] Cauli, A., "Killer-cell immunoglobulin-like receptors (KIR) and HLA-class I heavy chains in ankylosing spondylitis." 15.

and CD4+ T cell in SpA patients[137]. Similarly, SpA patients had an increased number of NK cells expressing KIR3DL2 compared with controls. Moreover, KIR3DL2+ NK cells of SpA patients were activated, protected from apoptosis and showed a greater cytotoxicity than those from controls[138].

It was suggested that the limited production of IFN-γ by NK cells, secondary to KIR3DL2 binding to HLA-B27 free heavy chain, could promote the differentiation of proinflammatory Th17 in AS/SpA[139]. It was reported that KIR3DL2/HLA-B27 free heavy chain interaction stimulates the survival, proliferation and IL-17 production of KIR3DL2+ CD4+ T cells[140].

These results underline the importance of KIR and their complex relation with MHC class I molecules, especially with HLA-B27. This unique encounter may be the decisive, pivotal point which dictates the immuno-inflammatory response seen in AS/SpA.

[137] Wong-Baeza, I., "KIR3DL2 binds to HLA-B27 dimers and free H chains more strongly than other HLA class I and promotes the expansion of T cells in ankylosing spondylitis." 3216.

[138] Chan, A. T., et al. 2005. "Expansion and enhanced survival of natural killer cells expressing the killer immunoglobulin-like receptor KIR3DL2 in spondylarthritis." Arthritis Rheum no. 52 (11):3586-95. doi: 10.1002/art.21395.

[139] Wong-Baeza, I., "KIR3DL2 binds to HLA-B27 dimers and free H chains more strongly than other HLA class I and promotes the expansion of T cells in ankylosing spondylitis." 3216.

[140] Bowness, P., et al. 2011. "Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis." J Immunol no. 186 (4):2672-80. doi: 10.4049/jimmunol.1002653.

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REFERENCES

1. **Alter, G., M. P. Martin, N. Teigen, W. H. Carr, T. J. Suscovich, A. Schneidewind, H. Streeck, M. Waring, A. Meier, C. Brander, J. D. Lifson, T. M. Allen, M. Carrington, and M. Altfeld.** 2007. "Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes." J Exp Med no. 204 (12):3027-36. doi: 10.1084/jem.20070695.
2. **Arlettaz, L., S. Degermann, C. De Rham, E. Roosnek, and B. Huard.** 2004. "Expression of inhibitory KIR is confined to CD8+ effector T cells and limits their proliferative capacity." Eur J Immunol no. 34 (12):3413-22. doi: 10.1002/eji.200324756.
3. **Biassoni, R., C. Cantoni, D. Pende, S. Sivori, S. Parolini, M. Vitale, C. Bottino, and A. Moretta.** 2001. "Human natural killer cell receptors and co-receptors." Immunol Rev no. 181:203-14.
4. **Bowness, P., A. Ridley, J. Shaw, A. T. Chan, I. Wong-Baeza, M. Fleming, F. Cummings, A. McMichael, and S. Kollnberger.** 2011. "Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis." J Immunol no. 186 (4):2672-80. doi: 10.4049/jimmunol.1002653.
5. **Boyington, J. C., and P. D. Sun.** 2002. "A structural perspective on MHC class I recognition by killer cell immunoglobulin-like receptors." Mol Immunol no. 38 (14):1007-21.
6. **Braun, J., and J. Sieper.** 2010. "[Spondyloarthritides]." Z Rheumatol no. 69 (5):425-32.
7. **Breban, M., F. Costantino, C. Andre, G. Chiocchia, and H. J. Garchon.** 2015. "Revisiting MHC genes in spondyloarthritis." Curr Rheumatol Rep no. 17 (6):516. doi: 10.1007/s11926-015-0516-1.
8. **Brewerton, D. A., F. D. Hart, A. Nicholls, M. Caffrey, D. C. James, and R. D. Sturrock.** 1973. "Ankylosing spondylitis and HL-A 27." Lancet no. 1 (7809):904-7.
9. **Brown, M. A.** 2009. "Genetics and the pathogenesis of ankylosing spondylitis." Curr Opin Rheumatol no. 21 (4):318-23.
10. **Bryceson, Y. T., M. E. March, H. G. Ljunggren, and E. O. Long.** 2006. "Activation, coactivation, and costimulation of resting human natural killer cells." Immunol Rev no. 214:73-91. doi: 10.1111/j.1600-065X.2006.00457.x.
11. **Caffrey, M. F., and D. C. James.** 1973. "Human lymphocyte antigen association in ankylosing spondylitis." Nature no. 242 (5393):121.
12. **Caligiuri, Michael A.** 2008. "Human natural killer cells." Blood no. 112 (3):461-469. doi: 10.1182/blood-2007-09-077438.
13. **Campbell, Kerry S., and Amanda K. Purdy.** 2011. "Structure/function of human killer cell immunoglobulin-like receptors: lessons from polymorphisms, evolution, crystal structures and mutations." Immunology no. 132 (3):315-325. doi: 10.1111/j.1365-2567.2010.03398.x.
14. **Carr, W. H., D. B. Rosen, H. Arase, D. F. Nixon, J. Michaelsson, and L. L. Lanier.** 2007. "Cutting Edge: KIR3DS1, a gene implicated in resistance to progression to AIDS, encodes a DAP12-associated receptor expressed on NK cells that triggers NK cell activation." J Immunol no. 178 (2):647-51.
15. **Carter, K. W., A. Pluzhnikov, A. E. Timms, C. Miceli-Richard, C. Bourgain, B. P. Wordsworth, H. Jean-Pierre, N. J. Cox, L. J. Palmer, M. Breban, J. D. Reveille, and M. A. Brown.** 2007. "Combined analysis of three whole genome linkage scans for Ankylosing Spondylitis." Rheumatology (Oxford) no. 46 (5):763-71. doi: 10.1093/rheumatology/kel443.
16. **Cauli, A., M. Piga, G. Dessole, G. Porru, A. Floris, A. Vacca, E. Desogus, G. La Nasa, and A. Mathieu.** 2014. "Killer-cell immunoglobulin-like receptors (KIR) and HLA-class I heavy chains in ankylosing spondylitis." Drug Dev Res no. 75 Suppl 1:S15-9. doi: 10.1002/ddr.21187.
17. **Chaix, J., M. S. Tessmer, K. Hoebe, N. Fuseri, B. Ryffel, M. Dalod, L. Alexopoulou, B. Beutler, L. Brossay, E. Vivier, and T. Walzer.** 2008. "Cutting edge: Priming of NK cells by IL-18." J Immunol no. 181 (3):1627-31.
18. **Chan, A. T., S. D. Kollnberger, L. R. Wedderburn, and P. Bowness.** 2005. "Expansion and enhanced survival of natural killer cells expressing the killer immunoglobulin-like receptor KIR3DL2 in spondylarthritis." Arthritis Rheum no. 52 (11):3586-95. doi: 10.1002/art.21395.

19. **Chandran, V., S. B. Bull, F. J. Pellett, R. Ayearst, R. A. Pollock, and D. D. Gladman.** 2014. "Killer-cell immunoglobulin-like receptor gene polymorphisms and susceptibility to psoriatic arthritis." Rheumatology (Oxford) no. 53 (2):233-9. doi: 10.1093/rheumatology/ket296.
20. **Colbert, R. A., M. L. DeLay, E. I. Klenk, and G. Layh-Schmitt.** 2010. "From HLA-B27 to spondyloarthritis: a journey through the ER." Immunol Rev no. 233 (1):181-202. doi: 10.1111/j.0105-2896.2009.00865.x.
21. **Deng, Z., J. Zhen, B. Zhu, G. Zhang, Q. Yu, D. Wang, Y. Xu, L. He, and L. Lu.** 2015. "Allelic diversity of KIR3DL1/3DS1 in a southern Chinese population." Hum Immunol no. 76 (9):663-6. doi: 10.1016/j.humimm.2015.09.017.
22. **Diaz-Pena, R., M. A. Blanco-Gelaz, and C. Lopez-Larrea.** 2009. "KIR genes and their role in spondyloarthropathies." Adv Exp Med Biol no. 649:286-99.
23. **Diaz-Pena, R., M. A. Blanco-Gelaz, B. Suarez-Alvarez, J. Martinez-Borra, A. Lopez-Vazquez, R. Alonso-Arias, J. Bruges-Armas, J. R. Vidal-Castineira, and C. Lopez-Larrea.** 2008. "Activating KIR genes are associated with ankylosing spondylitis in Asian populations." Hum Immunol no. 69 (7):437-42. doi: 10.1016/j.humimm.2008.04.012.
24. **Diaz-Pena, R., J. R. Vidal-Castineira, R. Alonso-Arias, B. Suarez-Alvarez, J. L. Vicario, R. Solana, E. Collantes, A. Lopez-Vazquez, J. Martinez-Borra, and C. Lopez-Larrea.** 2010. "Association of the KIR3DS1*013 and KIR3DL1*004 alleles with susceptibility to ankylosing spondylitis." Arthritis Rheum no. 62 (4):1000-6. doi: 10.1002/art.27332.
25. **Diaz-Pena, R., J. R. Vidal-Castineira, J. Mulero, A. Sanchez, R. Queiro, and C. Lopez-Larrea.** 2015. "Activating killer immunoglobulin-like receptors genes are associated with increased susceptibility to ankylosing spondylitis." Clin Exp Immunol no. 180 (2):201-6. doi: 10.1111/cei.12568.
26. **Falco, M., L. Moretta, A. Moretta, and C. Bottino.** 2013. "KIR and KIR ligand polymorphism: a new area for clinical applications?" Tissue Antigens no. 82 (6):363-73. doi: 10.1111/tan.12262.
27. **Gomez-Lozano, N., C. M. Gardiner, P. Parham, and C. Vilches.** 2002. "Some human KIR haplotypes contain two KIR2DL5 genes: KIR2DL5A and KIR2DL5B." Immunogenetics no. 54 (5):314-9. doi: 10.1007/s00251-002-0476-2.
28. **Gonzalez-Galarza, F. F., S. Christmas, D. Middleton, and A. R. Jones.** 2011. "Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations." Nucleic Acids Res no. 39 (Database issue):D913-9. doi: 10.1093/nar/gkq1128.
29. **Gonzalez-Galarza, F. F., L. Y. Takeshita, E. J. Santos, F. Kempson, M. H. Maia, A. L. da Silva, A. L. Teles e Silva, G. S. Ghattaoraya, A. Alfirevic, A. R. Jones, and D. Middleton.** 2015. "Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations." Nucleic Acids Res no. 43 (Database issue):D784-8. doi: 10.1093/nar/gku1166.
30. **Guia, S., C. Cognet, L. de Beaucoudrey, M. S. Tessmer, E. Jouanguy, C. Berger, O. Filipe-Santos, J. Feinberg, Y. Camcioglu, J. Levy, S. Al Jumaah, S. Al-Hajjar, J. L. Stephan, C. Fieschi, L. Abel, L. Brossay, J. L. Casanova, and E. Vivier.** 2008. "A role for interleukin-12/23 in the maturation of human natural killer and CD56+ T cells in vivo." Blood no. 111 (10):5008-16. doi: 10.1182/blood-2007-11-122259.
31. **Harvey, D., J. J. Pointon, C. Sleator, A. Meenagh, C. Farrar, J. Y. Sun, D. Senitzer, D. Middleton, M. A. Brown, and B. P. Wordsworth.** 2009. "Analysis of killer immunoglobulin-like receptor genes in ankylosing spondylitis." Ann Rheum Dis no. 68 (4):595-8. doi: 10.1136/ard.2008.095927.
32. **Herberman, R. B., M. E. Nunn, and D. H. Lavrin.** 1975. "Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic acid allogeneic tumors. I. Distribution of reactivity and specificity." Int J Cancer no. 16 (2):216-29.
33. **Jiao, Y. L., C. Y. Ma, L. C. Wang, B. Cui, J. Zhang, L. You, Z. J. Chen, J. F. Li, and Y. R. Zhao.** 2008. "Polymorphisms of KIRs gene and HLA-C alleles in patients with ankylosing spondylitis: possible association with susceptibility to the disease." J Clin Immunol no. 28 (4):343-9. doi: 10.1007/s10875-008-9183-6.
34. **Jiao, Y. L., B. C. Zhang, L. You, J. F. Li, J. Zhang, C. Y. Ma, B. Cui, L. C. Wang, Z. J. Chen, and Y. R. Zhao.** 2010. "Polymorphisms of KIR gene and HLA-C alleles: possible association with susceptibility to HLA-B27-positive patients with ankylosing spondylitis." J Clin Immunol no. 30 (6):840-4. doi: 10.1007/s10875-010-9444-z.
35. **Karre, K., H. G. Ljunggren, G. Piontek, and R. Kiessling.** 1986. "Selective rejection of H-2-deficient lymphoma variants suggests alternative immune defence strategy." Nature no. 319 (6055):675-8. doi: 10.1038/319675a0.

36. **Kiessling, R., E. Klein, and H. Wigzell.** 1975. ""Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype." Eur J Immunol no. 5 (2):112-7. doi: 10.1002/eji.1830050208.
37. **Kollnberger, S., L. Bird, M. Y. Sun, C. Retiere, V. M. Braud, A. McMichael, and P. Bowness.** 2002. "Cell-surface expression and immune receptor recognition of HLA-B27 homodimers." Arthritis Rheum no. 46 (11):2972-82. doi: 10.1002/art.10605.
38. **Kollnberger, S., A. Chan, M. Y. Sun, L. Y. Chen, C. Wright, K. di Gleria, A. McMichael, and P. Bowness.** 2007. "Interaction of HLA-B27 homodimers with KIR3DL1 and KIR3DL2, unlike HLA-B27 heterotrimers, is independent of the sequence of bound peptide." Eur J Immunol no. 37 (5):1313-22. doi: 10.1002/eji.200635997.
39. **Korendowych, E., and N. McHugh.** 2005. "Genetic factors in psoriatic arthritis." Curr Rheumatol Rep no. 7 (4):306-12.
40. **Landewe, R. B., and D. M. van der Heijde.** 2011. "[The recognition of patients with spondyloarthritis. New classification criteria]." Ned Tijdschr Geneeskd no. 155 (30-31).
41. **Lanier, L. L.** 2005. "NK cell recognition." Annu Rev Immunol no. 23:225-74. doi: 10.1146/annurev.immunol.23.021704.115526.
42. **Laval, S. H., A. Timms, S. Edwards, L. Bradbury, S. Brophy, A. Milicic, L. Rubin, K. A. Siminovitch, D. E. Weeks, A. Calin, B. P. Wordsworth, and M. A. Brown.** 2001. "Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci." Am J Hum Genet no. 68 (4):918-26. doi: 10.1086/319509.
43. **Levinson, R. D., T. M. Martin, L. Luo, E. Ashouri, J. T. Rosenbaum, J. R. Smith, C. R. Austin, J. R. Lutt, and R. Rajalingam.** 2010. "Killer cell immunoglobulin-like receptors in HLA-B27-associated acute anterior uveitis, with and without axial spondyloarthropathy." Invest Ophthalmol Vis Sci no. 51 (3):1505-10. doi: 10.1167/iovs.09-4232.
44. **Ljunggren, H. G., and K. Karre.** 1990. "In search of the 'missing self': MHC molecules and NK cell recognition." Immunol Today no. 11 (7):237-44.
45. **Lodoen, M. B., and L. L. Lanier.** 2005. "Viral modulation of NK cell immunity." Nat Rev Microbiol no. 3 (1):59-69. doi: 10.1038/nrmicro1066.
46. **Lopez-Larrea, C., M. A. Blanco-Gelaz, J. C. Torre-Alonso, J. Bruges Armas, B. Suarez-Alvarez, L. Pruneda, A. R. Couto, S. Gonzalez, A. Lopez-Vazquez, and J. Martinez-Borra.** 2006. "Contribution of KIR3DL1/3DS1 to ankylosing spondylitis in human leukocyte antigen-B27 Caucasian populations." Arthritis Res Ther no. 8 (4):R101. doi: 10.1186/ar1988.
47. **Lucas, M., W. Schachterle, K. Oberle, P. Aichele, and A. Diefenbach.** 2007. "Dendritic cells prime natural killer cells by trans-presenting interleukin 15." Immunity no. 26 (4):503-17. doi: 10.1016/j.immuni.2007.03.006.
48. **Mahfouz, R. A., A. S. Sabbagh, W. Shamseddine, A. Bazarbachi, G. Ibrahim, T. Arayssi, N. El Hajj, R. Rayes, G. S. Zaatari, G. Khazen, and R. A. Khalaf.** 2009. "Distribution of killer cell immunoglobulin-like receptor (KIR) genotypes in patients with familial Mediterranean fever." Genet Test Mol Biomarkers no. 13 (1):91-5. doi: 10.1089/gtmb.2008.0081.
49. **Mandelboim, O., N. Lieberman, M. Lev, L. Paul, T. I. Arnon, Y. Bushkin, D. M. Davis, J. L. Strominger, J. W. Yewdell, and A. Porgador.** 2001. "Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells." Nature no. 409 (6823):1055-60. doi: 10.1038/35059110.
50. **Marsh, S. G., P. Parham, B. Dupont, D. E. Geraghty, J. Trowsdale, D. Middleton, C. Vilches, M. Carrington, C. Witt, L. A. Guethlein, H. Shilling, C. A. Garcia, K. C. Hsu, and H. Wain.** 2003a. "Killer-cell immunoglobulin-like receptor (KIR) nomenclature report, 2002." Immunogenetics no. 55 (4):220-6. doi: 10.1007/s00251-003-0571-z.
51. **Marsh, S. G., P. Parham, B. Dupont, D. E. Geraghty, J. Trowsdale, D. Middleton, C. Vilches, M. Carrington, C. Witt, L. A. Guethlein, H. Shilling, C. A. Garcia, K. C. Hsu, and H. Wain.** 2003b. "Killer-cell immunoglobulin-like receptor (KIR) nomenclature report, 2002." Hum Immunol no. 64 (6):648-54.
52. **Martin, M. P., G. Nelson, J. H. Lee, F. Pellett, X. Gao, J. Wade, M. J. Wilson, J. Trowsdale, D. Gladman, and M. Carrington.** 2002. "Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles." J Immunol no. 169 (6):2818-22.
53. **Middleton, D., F. Williams, and I. A. Halfpenny.** 2005. "KIR genes." Transpl Immunol no. 14 (3-4):135-42. doi: 10.1016/j.trim.2005.03.002.

54. **Middleton, Derek, and Faviel Gonzelez.** 2010. "The extensive polymorphism of KIR genes." Immunology no. 129 (1):8-19. doi: 10.1111/j.1365-2567.2009.03208.x.
55. **Moesta, A. K., P. J. Norman, M. Yawata, N. Yawata, M. Gleimer, and P. Parham.** 2008. "Synergistic polymorphism at two positions distal to the ligand-binding site makes KIR2DL2 a stronger receptor for HLA-C than KIR2DL3." J Immunol no. 180 (6):3969-79.
56. **Moon, S. J., E. J. Oh, Y. Kim, K. S. Kim, S. K. Kwok, J. H. Ju, K. S. Park, H. Y. Kim, and S. H. Park.** 2013. "Diversity of killer cell immunoglobulin-like receptor genes in uveitis associated with autoimmune diseases: ankylosing spondylitis and Behcet disease." Ocul Immunol Inflamm no. 21 (2):135-43. doi: 10.3109/09273948.2012.754905.
57. **O'Connor, G. M., K. J. Guinan, R. T. Cunningham, D. Middleton, P. Parham, and C. M. Gardiner.** 2007. "Functional polymorphism of the KIR3DL1/S1 receptor on human NK cells." J Immunol no. 178 (1):235-41.
58. **O'Connor, Geraldine M., Orla M. Hart, and Clair M. Gardiner.** 2006. "Putting the natural killer cell in its place." Immunology no. 117 (1):1-10. doi: 10.1111/j.1365-2567.2005.02256.x.
59. **Ortaldo, J. R., R. T. Winkler-Pickett, S. Nagata, and C. F. Ware.** 1997. "Fas involvement in human NK cell apoptosis: lack of a requirement for CD16-mediated events." J Leukoc Biol no. 61 (2):209-15.
60. **Rajagopalan, S., J. Fu, and E. O. Long.** 2001. "Cutting edge: induction of IFN-gamma production but not cytotoxicity by the killer cell Ig-like receptor KIR2DL4 (CD158d) in resting NK cells." J Immunol no. 167 (4):1877-81.
61. **Raulet, D. H., S. Gasser, B. G. Gowen, W. Deng, and H. Jung.** 2013. "Regulation of ligands for the NKG2D activating receptor." Annu Rev Immunol no. 31:413-41. doi: 10.1146/annurev-immunol-032712-095951.
62. **Robinson, J., J. A. Halliwell, H. McWilliam, R. Lopez, and S. G. Marsh.** 2013. "IPD--the Immuno Polymorphism Database." Nucleic Acids Res no. 41 (Database issue):D1234-40. doi: 10.1093/nar/gks1140.
63. **Robinson, James, Matthew J. Waller, Peter Stoehr, and Steven G. E. Marsh.** 2005. "IPD—the Immuno Polymorphism Database." Nucleic Acids Research no. 33 (suppl 1):D523-D526. doi: 10.1093/nar/gki032.
64. **Rosenberg, E. B., R. B. Herberman, P. H. Levine, R. H. Halterman, J. L. McCoy, and J. R. Wunderlich.** 1972. "Lymphocyte cytotoxicity reactions to leukemia-associated antigens in identical twins." Int J Cancer no. 9 (3):648-58.
65. **Schlosstein, L., P. I. Terasaki, R. Bluestone, and C. M. Pearson.** 1973. "High association of an HL-A antigen, W27, with ankylosing spondylitis." N Engl J Med no. 288 (14):704-6. doi: 10.1056/nejm197304052881403.
66. **Sharma, D., K. Bastard, L. A. Guethlein, P. J. Norman, N. Yawata, M. Yawata, M. Pando, H. Thananchai, T. Dong, S. Rowland-Jones, F. M. Brodsky, and P. Parham.** 2009. "Dimorphic motifs in D0 and D1+D2 domains of killer cell Ig-like receptor 3DL1 combine to form receptors with high, moderate, and no avidity for the complex of a peptide derived from HIV and HLA-A*2402." J Immunol no. 183 (7):4569-82. doi: 10.4049/jimmunol.0901734.
67. **Shegarfi, Hamid, Fatemeh Naddafi, and Abbas Mirshafiey.** 2012. "Natural Killer Cells and Their Role in Rheumatoid Arthritis: Friend or Foe?" The Scientific World Journal no. 2012:491974. doi: 10.1100/2012/491974.
68. **Sivori, S., M. Falco, S. Carlomagno, E. Romeo, C. Soldani, A. Bensussan, A. Viola, L. Moretta, and A. Moretta.** 2010. "A novel KIR-associated function: evidence that CpG DNA uptake and shuttling to early endosomes is mediated by KIR3DL2." Blood no. 116 (10):1637-47. doi: 10.1182/blood-2009-12-256586.
69. **Smith, H. R., J. W. Heusel, I. K. Mehta, S. Kim, B. G. Dorner, O. V. Naidenko, K. Iizuka, H. Furukawa, D. L. Beckman, J. T. Pingel, A. A. Scalzo, D. H. Fremont, and W. M. Yokoyama.** 2002. "Recognition of a virus-encoded ligand by a natural killer cell activation receptor." Proc Natl Acad Sci U S A no. 99 (13):8826-31. doi: 10.1073/pnas.092258599.
70. **Stewart-Jones, G. B., K. di Gleria, S. Kollnberger, A. J. McMichael, E. Y. Jones, and P. Bowness.** 2005. "Crystal structures and KIR3DL1 recognition of three immunodominant viral peptides complexed to HLA-B*2705." Eur J Immunol no. 35 (2):341-51. doi: 10.1002/eji.200425724.
71. **Stewart, C. A., F. Laugier-Anfossi, F. Vely, X. Saulquin, J. Riedmuller, A. Tisserant, L. Gauthier, F. Romagne, G. Ferracci, F. A. Arosa, A. Moretta, P. D. Sun, S. Ugolini, and E. Vivier.** 2005. "Recognition of peptide-MHC class I complexes by activating killer immunoglobulin-like receptors." Proc Natl Acad Sci U S A no. 102 (37):13224-9. doi: 10.1073/pnas.0503594102.
72. **Tajik, N., F. Shahsavar, H. Poormoghim, M. F. Radjabzadeh, T. Mousavi, and A. Jalali.** 2011. "KIR3DL1+HLA-B Bw4Ile80 and KIR2DS1+HLA-C2 combinations are both associated with ankylosing

spondylitis in the Iranian population." Int J Immunogenet no. 38 (5):403-9. doi: 10.1111/j.1744-313X.2011.01024.x.

73. **Takeshita, Louise Y. C., Faviel F. Gonzalez-Galarza, Eduardo J. M. dos Santos, Maria Helena T. Maia, Mushome M. Rahman, Syed M. S. Zain, Derek Middleton, and Andrew R. Jones.** 2013. "A database for curating the associations between killer cell immunoglobulin-like receptors and diseases in worldwide populations." Database: The Journal of Biological Databases and Curation no. 2013:bat021. doi: 10.1093/database/bat021.
74. **Terunuma, H., X. Deng, Z. Dewan, S. Fujimoto, and N. Yamamoto.** 2008. "Potential role of NK cells in the induction of immune responses: implications for NK cell-based immunotherapy for cancers and viral infections." Int Rev Immunol no. 27 (3):93-110. doi: 10.1080/08830180801911743.
75. **Thananchai, H., G. Gillespie, M. P. Martin, A. Bashirova, N. Yawata, M. Yawata, P. Easterbrook, D. W. McVicar, K. Maenaka, P. Parham, M. Carrington, T. Dong, and S. Rowland-Jones.** 2007. "Cutting Edge: Allele-specific and peptide-dependent interactions between KIR3DL1 and HLA-A and HLA-B." J Immunol no. 178 (1):33-7.
76. **Thomas, G. P., and M. A. Brown.** 2010. "Genetics and genomics of ankylosing spondylitis." Immunol Rev no. 233 (1):162-80. doi: 10.1111/j.0105-2896.2009.00852.x.
77. **Tsui, F. W., H. W. Tsui, A. Akram, N. Haroon, and R. D. Inman.** 2014. "The genetic basis of ankylosing spondylitis: new insights into disease pathogenesis." Appl Clin Genet no. 7:105-15. doi: 10.2147/tacg.s37325.
78. **Vendelbosch, S., S. C. Heslinga, M. John, K. van Leeuwen, J. Geissler, M. de Boer, M. W. Tanck, T. K. van den Berg, J. B. Crusius, I. E. van der Horst-Bruinsma, and T. W. Kuijpers.** 2015. "Study on the Protective Effect of the KIR3DL1 Gene in Ankylosing Spondylitis." Arthritis Rheumatol no. 67 (11):2957-65. doi: 10.1002/art.39288.
79. **Vilches, C., and P. Parham.** 2002. "KIR: diverse, rapidly evolving receptors of innate and adaptive immunity." Annu Rev Immunol no. 20:217-51. doi: 10.1146/annurev.immunol.20.092501.134942.
80. **Vivier, E., J. A. Nunes, and F. Vely.** 2004. "Natural killer cell signaling pathways." Science no. 306 (5701):1517-9. doi: 10.1126/science.1103478.
81. **Vivier, Eric, David H. Raulet, Alessandro Moretta, Michael A. Caligiuri, Laurence Zitvogel, Lewis L. Lanier, Wayne M. Yokoyama, and Sophie Ugolini.** 2011. "Innate or Adaptive Immunity? The Example of Natural Killer Cells." Science (New York, N.Y.) no. 331 (6013):44-49. doi: 10.1126/science.1198687.
82. **Walzer, T., M. Blery, J. Chaix, N. Fuseri, L. Chasson, S. H. Robbins, S. Jaeger, P. Andre, L. Gauthier, L. Daniel, K. Chemin, Y. Morel, M. Dalod, J. Imbert, M. Pierres, A. Moretta, F. Romagne, and E. Vivier.** 2007. "Identification, activation, and selective in vivo ablation of mouse NK cells via NKp46." Proc Natl Acad Sci U S A no. 104 (9):3384-9. doi: 10.1073/pnas.0609692104.
83. **Walzer, T., M. Dalod, S. H. Robbins, L. Zitvogel, and E. Vivier.** 2005. "Natural-killer cells and dendritic cells: "l'union fait la force"." Blood no. 106 (7):2252-8. doi: 10.1182/blood-2005-03-1154.
84. **Wang, S., G. Li, R. Ge, Z. Duan, Z. Zeng, T. Zhang, J. Gao, T. Yang, S. Liu, S. Wu, D. Fan, S. Xu, J. Xu, L. Zhang, Z. Shuai, D. Ye, Y. Zou, and F. Pan.** 2013. "Association of KIR genotype with susceptibility to HLA-B27-positive ankylosing spondylitis." Mod Rheumatol no. 23 (3):538-41. doi: 10.1007/s10165-012-0692-z.
85. **Wende, H., M. Colonna, A. Ziegler, and A. Volz.** 1999. "Organization of the leukocyte receptor cluster (LRC) on human chromosome 19q13.4." Mamm Genome no. 10 (2):154-60.
86. **Wilson, M. J., M. Torkar, A. Haude, S. Milne, T. Jones, D. Sheer, S. Beck, and J. Trowsdale.** 2000. "Plasticity in the organization and sequences of human KIR/ILT gene families." Proc Natl Acad Sci U S A no. 97 (9):4778-83. doi: 10.1073/pnas.080588597.
87. **Wong-Baeza, I., A. Ridley, J. Shaw, H. Hatano, O. Rysnik, K. McHugh, C. Piper, S. Brackenbridge, R. Fernandes, A. Chan, P. Bowness, and S. Kollnberger.** 2013. "KIR3DL2 binds to HLA-B27 dimers and free H chains more strongly than other HLA class I and promotes the expansion of T cells in ankylosing spondylitis." J Immunol no. 190 (7):3216-24. doi: 10.4049/jimmunol.1202926.
88. **Zochling, J., and E. U. Smith.** 2010. "Seronegative spondyloarthritis." Best Pract Res Clin Rheumatol no. 24 (6):747-56.
89. **Zvyagin, I. V., I. Z. Mamedov, O. V. Britanova, D. B. Staroverov, E. L. Nasonov, A. G. Bochkova, A. V. Chkalina, A. A. Kotlobay, D. O. Korostin, D. V. Rebrikov, S. Lukyanov, Y. B. Lebedev, and D. M. Chudakov.** 2010. "Contribution of functional KIR3DL1 to ankylosing spondylitis." Cell Mol Immunol no. 7 (6):471-6. doi: 10.1038/cmi.2010.42.