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Immunogenomics of killer cell Ig-like receptor (KIR) and HLA class I: Co-evolution and consequences for human health

Nicholas R. Pollock, BSc,

Genelle F. Harrison, PhD,

Paul J. Norman, PhD

Division of Biomedical Informatics and Personalized Medicine and Department of Immunology and Microbiology. Anschutz Medical Campus, University of Colorado, Aurora, CO, USA.

Abstract

Interactions of killer cell immunoglobin-like receptors (KIR) with human leukocyte antigens (HLA) class I regulate effector functions of key cytotoxic cells of innate and adaptive immunity. The extreme diversity of this interaction is genetically determined, having evolved in the ever-changing environment of pathogen exposure. Diversity of *KIR* and *HLA* genes is further facilitated by their independent segregation on separate chromosomes. That fetal implantation relies on many of the same types of immune cells as infection control, places certain constraints on the evolution of KIR interactions with HLA. Consequently, specific inherited combinations of receptors and ligands may predispose to specific immune mediated diseases, including autoimmunity. Combinatorial diversity of KIR and HLA class I can also differentiate success rates of immunotherapy directed to these diseases. Progress towards both etiopathology and predicting response to therapy is being achieved through detailed characterization of the extent and consequences of the combinatorial diversity of KIR and HLA. Achieving these goals is more tractable with the development of integrated analyses of molecular evolution, function and pathology that will establish guidelines for understanding and managing risks. Here we present what is known about the co-evolution of KIR with HLA class I and the impact of their complexity on immune function and homeostasis.

Keywords

killer cell Ig-like receptors (KIR); human leucocyte antigen (HLA); natural killer (NK) cells; innate immunity; reproduction; autoimmunity

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The ability of the immune system to distinguish healthy from unhealthy cells is critical for the effective control of pathogens and aberrant cell growth. The system must also diversify to survive in the face of emerging and evolving challenges. Killer cell immunoglobin-like receptor (KIR) interactions with their cognate ligands, human leukocyte antigen (HLA) class

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Corresponding Author: Paul J. Norman, Division of Biomedical Informatics and Personalized Medicine, Building 500, Anschutz Medical Campus, Aurora, CO 80045, USA. paul.norman@cuanschutz.edu Tel: 303-724-4481.

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I molecules, adapt to these challenges through intricate co-evolution. Unlike the molecular mediators of adaptive immunity, KIR and HLA polymorphism is genetically driven, and therefore subject to natural selection, but with consequences for immune-mediated disease. Evidence of historic and possibly ongoing co-evolution of receptors with ligands comes from their front-line roles during infection control and reproduction. That these survivalist functions lead to extreme diversity and plasticity of the genomic regions is shown through comparative studies across species and among human populations. The impact of natural selection in fostering this diversity is identified through high-resolution population genetic and molecular analyses.

KIR comprise a family of up to 13 distinct, highly polymorphic, modulators of cytotoxic cell activity[1] (Fig. 1). They are expressed on the surface of natural killer (NK) cells and some T cells and regulate immune effector functions through signal transduction[2, 3]. Unlike T or B-cell receptors, there is no somatic rearrangement of KIR, and clonal diversity is determined through expression of multiple genetically encoded receptors[4]. Most KIR interact with specific subsets of the HLA class I molecules that are expressed by healthy nucleated tissue cells. The major role of KIR interaction with HLA class I is to facilitate the recognition and destruction of unhealthy cells, whilst preventing the same from happening to healthy cells[5]. Thus, inhibitory KIR prevent cytotoxic immune cells from killing tissue cells unless their HLA class I is lost or altered by infection or mutagenesis, whereas activating KIR help identify diseased cells. Another important role of KIR-modulated cytotoxicity is to regulate antigen presenting[6] or autoantigen-specific cells[7]. In these scenarios it is easy to envision how the interaction of KIR with HLA class I is critical towards both maintaining homeostasis and preventing over-reactive immunity.

Much of the work characterizing KIR interactions with HLA class I has been centered on NK cells. NK cells fight infections and some cancers through cytotoxicity and cytokine release and also have key roles in pregnancy[8-10]. Cognate interactions of inhibitory KIR with HLA class I educates, arms, or licenses, NK cells to expect the same ligand on tissue cells[11-14]. The education process correlates with accumulation of cytotoxic and other effector abilities[15, 16]. Because they are highly variable and inherited independently, a given individual may not carry fully corresponding pairs of inhibitory KIR and HLA class I ligands[17, 18]. Accordingly, compound *KIR* and *HLA class I* genotypes predisposing to strong education of NK cells through KIR provide the greatest potential for infection control[19], whereas NK cells that lack this interaction during their development have a comparably diminished missing-self response[20]. The genetic polymorphism that determines combinatorial diversity of cognate ligand receptor pairs within a given individual is complex[21]. KIR diversity across individuals is defined by gene content variation at the *KIR* locus and enhanced by allelic variation (Fig. 2). Similarly, not every HLA class I can be a KIR ligand, and identical KIR binding sites can be present on distinct HLA class I molecules (Fig. 2). Somatic NK cell receptor diversity is also complex, with thousands of NK cell subsets observed within a given individual[22]. NK cells acquire receptor expression essentially at random during development and may express multiple KIR[20, 23]. In mature NK cells, including those that express inhibitory and activating receptors for the same ligand, the inhibitory signal dominates homeostatic function[24]. Although the focus here is NK cells, it has long been acknowledged that T cells can also acquire KIR

expression[25, 26]. This expression correlates with increased maturity both of cellular function and the individual[27]. Like NK cells, the specific KIR that are acquired appears random, but fewer are present per cell and education via HLA class I is not observed[28]. Whereas the role of activating KIR on T cells is unknown, inhibitory KIR expression likely dampens autoreactivity[27] and help strengthen and control T cell responses to virus infections[29, 30].

The importance of functional interaction of KIR with HLA is exemplified by the range and quantity of examples where it can go wrong[21]. Specific KIR and HLA allotype pairs are associated with susceptibility to infection or cancer, or poor fetal nourishment[10]. Conversely, other pairs are associated with stronger responses to specific infections, control of tumor formation, or with larger babies[10]. These extremes highlight the tenuous balance driving KIR and HLA class I co-evolution [31, 32], where further associations with immune-mediated diseases[33] may represent a form of collateral damage. Their evolution in the face of such pressures, also likely explains why the *HLA* and *KIR* genomic regions have become the most complicated and diverse of the human genome[34]. Highly polymorphic *KIR* and *HLA class I* genotypes can distinguish individuals, and there are few in common across even closely-related populations[35, 36]. Dynamic patterns of demographics and population structure add further complexity to KIR and HLA class I co-evolution[37-41]. These distinctions may manifest in differential disease susceptibility associations across human populations.

KIR Polymorphism

Gene content variation of the *KIR* locus[42] has significant consequences for cellular immunity. In addition to gene presence/absence, specific alleles are not expressed, and certain *KIR* genes may be fused or duplicated[43-45]. *KIR* gene quantity determines the number of KIR expressing cells and can correlate with effectiveness of immunity to infection[29, 46-48]. Additional to gene content variation, *KIR* sequence variation acts directly on effector functions through altering critical properties of the receptor, including ligand affinity or specificity and signal transduction ability[49-56]. The nomenclature used for *KIR* genes and alleles is given in Figure 1. Even a single nucleotide substitution can change receptor specificity from one HLA class I ligand to another or affect signal transduction. Such polymorphism can also drastically reduce the surface expression of the receptors, by affecting promoter activity, translation, or intracellular trafficking[21]. NK cell engagement with tissue cells is thus highly variable among individuals and these differences relate directly to immune function[53, 57].

HLA polymorphism

There are three HLA class I molecules that form the major ligands for KIR (HLA-A, -B, and -C). They are highly polymorphic, with over 20,000 alleles known in total[58, 59]. The nomenclature used for HLA alleles with respect to KIR ligands is given in Figure 2. The common HLA-A, -B, and -C allotypes are distinguished from each other by multiple amino acid substitutions. Like KIR, HLA class I polymorphism both within and outside the direct binding site, and genomic variants affecting the steady state expression level are all key modulators of NK cell sensitivity[31, 60-62]. The role of HLA class I is to sample

peptide fragments from intracellular protein production and present them at the cell surface for surveillance by NK or T cells. In this role, HLA class I polymorphism diversifies the specific peptide repertoires[63]. Because the binding footprint of KIR overlaps with that of the TCR, this means that KIR binding can also be dependent on variations of the presented peptide sequence[64]. This peptide specificity may increase the sensitivity for inhibitory KIR to detect infection[65], but is likely most critical for activating KIR, which may then recognize infected cells that retain HLA class I expression but carry foreign peptides[66, 67]. Differential peptide specificity also creates an opportunity for pathogen exploitation whereby a given pathogen peptide may bind more strongly to inhibitory KIR, protecting infected cells from being killed by cytotoxic cells[68-70].

Less-polymorphic HLA class I molecules -F and -G can also form ligands for KIR3DS1 and 2DL4, respectively[71, 72]. Although little is known of the implications for combinatorial diversity of these interactions, the receptors are also less polymorphic than other KIR. KIR2DL4 has two main phenotypes, defined by a single nucleotide deletion that prevents cell-surface expression of approximately 50% alleles[73]. Of the multiple KIR3DS1 allotypes (Fig. 2), only two (3DS1*013 and *014) have been observed at appreciable frequency in any population[74]. Of interest, the amino acid substitution that distinguishes 3DS1*013 from *014 occurs in the ligand-binding region and may influence its specificity for HLA/peptide complex[75]. One further mechanism of diversity is the leader peptide from some HLA-B allotypes, in addition to -A and -C allotypes, can be presented by HLA-E. Through interaction of HLA-E with the NKG2/CD94 family of receptors, NK cells are then able to monitor polymorphic HLA class I expression through a more conserved complement to the KIR/HLA system[76, 77].

KIR and HLA genotyping

Methods to genotype *HLA* to allele level are well established and adopted by clinical laboratories worldwide, providing ample material for the multitude of candidate gene association studies[34]. Because structural complexity of the locus (Fig. 2) has hindered similar attempts, gene presence/absence variation has been the method of choice[78] for most studies investigating *KIR* diversity in human health. Because gene-content variation is the major component of KIR mediated NK cell functional diversity, these studies have been highly informative and generally reproducible but can be conflicting, particularly across ancestry-distinct cohorts. A critical need then remains to refine this knowledge through considering gene dose numbers and allele diversity of the genes in question. As examples, an allele that is not expressed likely has the same phenotype as an absent gene, and the distinct expression phenotype, ligand affinity or even specificity that characterizes a given allele is not visible to gene-content only methods. For these reasons, methods have been developed to measure the *KIR* gene copy number[79], allele sequences[80], or both at once[81, 82]. Methods are also described to analyze both *KIR* and *HLA* allele diversity in a combined workflow targeted to high-throughput studies[83-85]. For much larger studies that are currently impractical to approach through DNA sequencing, imputation from whole-genome SNP data provides an alternative to analyze *KIR* gene content[86], or allele diversity[87]. As for *HLA*, the imputation methods are less accurate than direct sequencing, especially for some ethnicities or ancestry groups including Africans and South Asians[87, 88].

Combinatorial diversity of KIR and HLA class I influences infection control.

Because interactions of KIR with HLA modulate activity for some of the first cells to respond to infection, they have a critical role in ensuring survival to reproductive age, and are targets for natural selection[89, 90]. It is often difficult to test epidemiologically whether there are specific genotypes that confer resistance to a given infection[91]. Thus, although there are some recognized associations with pathogen clearance[92], it is with course or severity of chronic infection that specific KIR and HLA allotype pairs have the greatest recognized impact[30, 93-95]. The now classic example is HIV-1, where specific combinations of KIR3DL1/S1 and HLA class I allotypes can reduce viral load or prolong the time to development of AIDS[96-99]. Among other viral infections differentially controlled by KIR and HLA class I diversity, herpes viruses are the most prominent [100-102]. Of these, Epstein-Barr virus (EBV) likely has the greatest impact on human health[103], and specific combinations of KIR with HLA class I ligand allotypes can influence whether an EBV infection is controlled or leads to complication[104-107]. Importantly, specific pathogen infections can leave an imprint on NK cell clonal diversity and receptor expression, with implications for subsequent maintenance of homeostasis[108, 109].

Combinatorial diversity of KIR and HLA class I influences reproductive success

Effective fetal trophoblast invasion that occurs in the early stages of placentation is mediated by maternal uterine NK (uNK) cells. These cells are distinct from peripheral blood NK cells[110, 111], exhibiting little cytotoxicity, and interact with the fetal cells to mediate maternal spiral artery remodeling[112]. Inefficiency at this stage can lead to malnourished fetus, and preeclampsia in the latter stages of pregnancy. Of the three highly polymorphic HLA class I, only HLA-C is expressed by fetal extravillous trophoblasts. As evidenced through highly reproducible studies of life-threatening pregnancy disorders, including preeclampsia[10], KIR interaction with HLA-C is therefore a second target for natural selection acting on the combinatorial diversity of receptor and ligand allotypes. Indeed, specific alleles and combinations of *KIR* and *HLA class I* provide the most consistent genome-wide determinants of preeclampsia[113].

Rapid evolution of KIR and HLA

Structural divergence of the respective genomic regions among closely related species identifies KIR and HLA to be evolving comparatively faster than the remainder of the genome[114]. The mode of genomic expansion to contain multiple *KIR* genes is unique to primates, and among primates very few direct orthologues of a given *KIR* gene are present. For example, all but one of the KIR specific for HLA-A, -B or -C are unique to humans[115]. The impressive expansion of the *KIR* locus is captured in macaques, where almost 60 distinct *KIR* genes are known[32], with corresponding duplication of genes encoding their ligands[116]. In the context of these expansions, gene duplication leads to sequence homology that facilitates further reshuffling of gene segments to create receptors and ligands of novel functions[117]. This structural diversification of the *KIR* locus is likely ongoing in humans and frequent enough to be detected in population cohorts of relatively modest

size[118-121]. In terms of emergence, the ancestors of highly polymorphic HLA class I are ancient, tracking with jawed vertebrates, whereas KIR may be restricted to mammals, and not functional in some of them[122-124]. That different and sometimes overlapping gene families have expanded similarly in other mammals[125] indicates the critical need to retain the interaction, whilst presenting a moving target to any pathogen able to evolve evasion mechanisms. The intricacy of this co-evolution is likely best characterized by HLA-C, which evolved from a duplication of an *HLA-B* equivalent in an ancestor of hominids (humans, gorillas, chimps, orangutans)[31]. Accordingly, genomic expansion and diversification of the KIR that bind HLA-C and its orthologues is unique to hominids [126]. Although HLA-C can elicit some T cell responses, it has become specialized for interaction with KIR-expressing cells[127]. It is unknown if the specialization occurred during or since the emergence of this receptor/ligand pair. However, in modern humans, KIR interaction with HLA-C is the only KIR/HLA interaction present in every individual, with rare exceptions highly prone to virus infections[128]. Low frequency of KIR interactions with HLA-A or -B in Amerindians[129] suggest KIR interactions with HLA-C may now have a greater impact on human survival than those with HLA-A and -B.

One unique feature of human *KIR* locus expansion has been development of two functionally distinct families of *KIR* haplotypes[35] (Fig. 2). The *KIR-A* haplotype encodes every inhibitory KIR specific for polymorphic HLA class I, KIR2DL3 (C1), KIR2DL1 (C2), KIR3DL1 (Bw4) and KIR3DL2 (A3/11). The *KIR-A* haplotype encodes only one activating receptor, KIR2DS4, and this is often disabled by a 22bp deletion common to multiple alleles[119, 130]. The *KIR-A* haplotype therefore conveys maximal NK cell educating potential. By contrast, *KIR-B* haplotypes encode fewer inhibitory receptors and a greater number of activating receptors[131], in this case the inhibitory receptors often having reduced function[53]. Their functional distinctions manifest in the form of disease association, where *KIR-A* haplotypes in concert with their ligands reduce impact of virus infection and cancer[132-134], but predispose to preeclampsia[135], whereas *KIR-B* haplotypes associate with better fetal nourishment[136]. Consequently, although there is an incredible diversity of haplotype structures within and across human populations[79, 137, 138], *KIR-A* and *-B* haplotypes are represented at high frequencies in every human population[139]. That *KIR-A* and *-B* have both been carried through multiple population bottlenecks that otherwise restrict genome-wide diversity indicates they are maintained in humans through natural selection[140, 141].

Evolution of interactions between KIR and HLA Class I

The evolutionary mechanism that maintains *KIR-A* and *-B* in humans is often termed balancing selection. Balancing selection embodies frequency fluctuations of genetic variants accompanying the relative selective advantage of their respective phenotypes. In this respect *KIR-A* haplotypes have arisen to very high frequency in East Asian and Amerindian populations through positive natural selection[41, 129, 142, 143], presumably in response to specific pathogens. However Hiby *et al.* first noticed that the preeclampsia pregnancy syndrome is most prevalent in women who are homozygous for *KIR-A* and who also carry a C2-ligand fetus[135]. This disadvantage to reproductive fitness, replicated in multiple populations[136, 144-146], has produced an inverse correlation of *KIR-A* and *C2*$^{+}$*HLA-C*

frequencies across these populations[135]. The assumption is that KIR2DL1, which is carried by *KIR-A* haplotypes and interacts strongly with $C2^+$HLA-C[147], is driving the phenomenon. Indeed, the observations become more pronounced when known distinctions of ligand binding and signal transduction strength across KIR2DL1 allotypes are considered[148, 149]. Inverse correlation of allele frequencies is observed also for genetic variants impacting the relative cell surface expression levels of KIR2DL1 and $C2^+$HLA-C[150]. Finally, the haplotypes that offer protection from preeclampsia vary across populations, but all of them carry activating KIR that can bind $C2^+$HLA-C[144, 146, 151, 152]. Indicating a tenuous balance, too many activating KIR may predispose to further pregnancy complications such as acute atherosis[153]. These findings identify a unifying concept across infection and reproduction, whereby specific receptors or ligands that increase in frequency due to a selective advantage may then become a disadvantage due to the high frequency of the respective pairing. This form of co-evolution through balancing selection manifests in multiple guises across the distinct pairs of KIR and HLA class I ligands[66, 140, 154]. In populations with high pathogen exposure, natural selection acting for and against specific KIR and HLA class I allotype pairs likely remains ongoing[129, 155-157].

Diversification through admixture

Exemplifying the inverse correlation between KIR-A and $C2^+$HLA are East Asians, where the frequency of *$C2^+$HLA-C* is low and, although the preeclampsia risk remains, incidence is also low[145]. It is likely that the lack of $C2^+$HLA, whether through selection or genetic drift, has allowed interactions of HLA-A and -B with KIR to proliferate to an unusually high level in East Asia[41]. Here, there are no 'null' alleles of inhibitory KIR and the allotypes that have attenuated function are rare[158]. Accompanying this fully equipped *KIR* locus is a distinctly high ratio of *HLA class I* haplotypes carrying KIR ligands at either HLA-A or -B or both [41]. The *HLA-A* and *-B* alleles most frequent in Chinese Southern Han have ancestry distinct from their flanking genomic sequence, showing they were obtained relatively recently from admixture with neighboring populations, before rising to high frequency through natural selection[41]. Because HLA-A and -B are specialized for diversification of peptide presentation, this amplification likely serves to enhance both T cell and NK cell responses to intracellular pathogens. That adaptive introgression of *HLA* haplotypes is seen in other populations[159], suggests the phenomenon is also widespread and ongoing. Introgression from ancient humans was likely a major contributor to the current *HLA class I* allele spectrum chiefly of East Asia and Oceania[160]. Although the ancestral populations that *KIR* alleles have been obtained from are more difficult to trace, in many cases the receptors have accompanied the ligands during the admixture events[41, 160]. An example may be the recently identified open reading frame variants of *HLA-H* pseudogene, which were obtained from admixture with ancient humans[161]. These variants are expressed and functional and have a presently unidentified receptor expressed by NK cells[162].

Adaptation through diversification

As the C ligand evolved with the ancestors of modern hominids, it split into C1 and C2 forms[31]. In humans C1 and C2 are defined by a single amino acid substitution at residue 80, where C1 have asparagine and C2 have lysine. A subset of HLA-B molecules (B*46

and B*73) also carry the C1 motif, making them good at interacting with NK cells as well as presenting unique peptide repertoires to T cells[49, 163]. The motif was obtained through genomic recombination, which may have occurred in ancient humans prior to admixture with modern humans[41, 115, 160]. Subsequently, the amino acid residues that interact with KIR drive balancing selection of HLA-C that is stronger than that observed for HLA-A or -B[154, 164]. The C2-specific KIR emerged on multiple occasions[115], and are similarly defined by substitutions at a single amino acid residue, this time at position 44. The human inhibitory KIR specific for $C1^{+}$HLA-C have lysine, and those specific for $C2^{+}$HLA-C have methionine[165]. Phylogenetic based molecular diversity analyses, in conjunction with species divergence time estimates, show that residue 44 of C-ligand specific KIR evolves under positive diversifying selection[115]. Again, this mechanism of natural selection is evident in modern humans. Studies of indigenous Southern Africans identified a variant of KIR2DL1, frequent in the ≠Khomani population, that has lysine instead of methionine at residue 44[166]. The allotype (2DL1*022) is then able to bind $C1^{+}$HLA-C, instead of $C2^{+}$HLA-C that is recognized by other KIR2DL1 allotypes. In the neighboring Nama population, a different frequently-occurring substitution disables KIR2DL1 expression[148]. For reasons unknown, the frequency of $C2^{+}$HLA-C is uniquely high in southern Africa, suggesting the convergent emergence and natural selection of the two variants[148] occurred here to restore the evolutionary balance in favor of reproduction. Similar analyses of other KIR have identified examples of positively-selected single amino acid substitutions affecting interactions with their HLA class I ligands[74, 140, 167].

These simple nucleotide mutations can affect immunity to infection. It has long been known that HIV infected individuals who possess the HLA-B*57:01 allotype develop T cell immunity, but only some are protected from progression to AIDS[168]. Somewhat independently, allotype specific interactions of KIR3DL1 with $Bw4^{+}$HLA-B also affect disease progression[134]. Among KIR3DL1 allotypes, those having valine at residue 47 were recently shown to distinguish the B*57:01 non-progressors from progressors[169]. Valine 47 allotypes had no effect on carriers of HLA-B*57:03, which differs by two amino acids from B*57:01[169]. Likely explaining this difference, the two substitutions mean that HLA-B*57:01 can present the same peptides as HLA-B*57:03, but at an orientation that enhances interaction with KIR3DL1[60]. This complex scenario shows how single amino acid variations of receptor or ligand can underlie subtle functional changes that have dramatic effect on control of infection.

KIR/HLA in autoimmunity

The functional changes arising from selection-driven co-evolution of KIR with HLA class I have clear potential to drive or modulate immune-mediated disease. The often-stated adage that autoimmune disease has minimal effect on survival to reproductive age, is likely strengthened by the role of KIR and HLA interaction in reproduction itself. The majority of studies in this regard were performed before the technology to analyze KIR at high resolution became available[33, 170]. Nevertheless, these analyses are helping to unravel the incomplete penetrance observed for many autoimmune disease associations with HLA, and in some cases, revealing further complexity. A summary of associations is given in Table 1. A key example is psoriasis, where the established association with HLA-C*06:02 was

initially strengthened by including the KIR2DS1 activating receptor, which can bind to HLA-C*06:02[171, 172]. A recent study revealed further independent contributions to psoriasis susceptibility from other receptor/ligand pairs and that ligand heterozygosity increases the risk[173]. We may predict that high resolution analysis of KIR allotypes[83, 85, 87] will shed further light on these relationships. Indeed, the limited number of analyses to date have revealed, as for infection, that certain ligand and receptor combinations associate with severity rather than predisposition to disease. Here, high cell surface expressing allotypes of KIR3DL1 can protect against the severest symptoms both of Parkinson's and Behçet disease, and only in the presence of their Bw4 ligand[174, 175]. In fact, the same allotypes (KIR3DL1*015 and *002) that associate with HLA-B*57:01 HIV non-progressors [169] are implicated. One of the most recently identified examples is atopic dermatitis, where distinct compound genotypes associate respectively with susceptibility and progression of disease[176-178]. These types of relationships are likely to be recapitulated in further immune-mediated diseases such as multiple sclerosis (MS), which has established associations with KIR and HLA combinatorial diversity[176, 179]. The recent confirmation that MS is triggered by EBV infection[180, 181], places cytotoxic immune effector cells in context both of initiation and progression of the disease.

KIR/HLA in immune therapy

Based on the principle that inhibitory KIR educate NK cells to expect specific HLA class I ligands, carefully directed mismatching between donor and recipient can improve the success rate of transplantation therapy for certain leukemias. Particularly for acute myelogenous leukemia (AML), donor-derived NK cells can protect from relapse when they have been educated in the donor towards HLA class I ligands absent from the patient, likely through killing leukemic cells[182, 183]. A further advantage is that, unlike T cells, NK cells do not promote graft-vs-host disease. Multiple groups have adopted and enhanced KIR-ligand mismatching protocols[184-187] (a recent extensive review is given elsewhere[188]), which have helped pave the way towards targeted NK cell therapies for the same leukemias and other cancers[189-191]. Nevertheless, effect differences remain across transplant centers or treatment regimens[192], and further refinement of matching protocols will likely be aided through refinement of the genotyping methods[193, 194]. The above findings, together with the established links between peripheral NK cell quantity and disease course, also imply that NK cells can be harnessed to treat autoimmune and other chronic diseases, as they have for malignancies[195-198]. That presence of KIR3DS1 is significantly associated with resistance to PD-1 blockade[199] for example, and KIR3DL1 interaction with $Bw4^{+}$HLA affects monoclonal antibody therapy[200, 201] demonstrates that knowledge of the receptor and ligand genotype may also inform these therapy decisions[202]. Moreover, and resulting from the rapid and population-specific evolution, all the described allotype combinations are highly variable across populations. For example, KIR3DS1 is rare in Africa and Asia, yet highly prevalent in Oceania, indicating differential disease associations and therapy responses related to genomic ancestry are to be expected. Medical genetic and association studies have largely neglected non-European populations[203-205], an exclusion that continues despite the knowledge that inclusion of multiple ancestries increases power of such studies[206]. For all these reasons it is imperative that we can accurately characterize

combinatorial diversity of *KIR* and *HLA* at high resolution and scale[83, 85, 87], whilst encompassing all human diversity. With innovative new methods of evaluation such as KIR and HLA interaction scores[29, 148, 174] that evaluate the strength of binding and signal transduction as a proxy to infer NK cell function, it may be possible to shape the treatment or even prevent certain immune-mediated diseases based on knowledge of individual KIR and HLA compound genotypes.

In summary, combinatorial diversity of KIR and HLA class I is driven by diversifying selection through confrontation with pathogens. The exceptional variation, both within and of interactions between them, being reinforced by population demography, including admixture events that may also be adaptive. Coexistence of functionality to support healthy pregnancies and prevent the unnecessary destruction of tissues has resulted in evolutionary patterns constrained by tradeoffs between these functions and controlling infection. For human health, this means that medical interventions and disease severity can differ across individuals and ancestries; a quandary that can be mitigated by characterizing the functional diversity of KIR and HLA class I and understanding how this diversity impacts disease and the efficacy of medical interventions.

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References

1. Moretta A, Bottino C, Vitale M, Pende D, Biassoni R, Mingari MC, et al. Receptors for HLA class-I molecules in human natural killer cells. Annu Rev Immunol 1996; 14:619–48. [PubMed: 8717527]
2. Lanier LL, Phillips JH. NK cell recognition of major histocompatibility complex class I molecules. Semin Immunol 1995; 7:75–82. [PubMed: 7579197]
3. Campbell KS, Colonna M. Human natural killer cell receptors and signal transduction. Int Rev Immunol 2001; 20:333–70. [PubMed: 11878509]
4. Valiante NM, Uhrberg M, Shilling HG, Lienert-Weidenbach K, Arnett KL, D'Andrea A, et al. Functionally and structurally distinct NK cell receptor repertoires in the peripheral blood of two human donors. Immunity 1997; 7:739–51. [PubMed: 9430220]
5. Ljunggren HG, Kärre K. In search of the 'missing self': MHC molecules and NK cell recognition. Immunol Today 1990; 11:237–44. [PubMed: 2201309]
6. Alter G, Altfeld M. Mutiny or scrutiny: NK cell modulation of DC function in HIV-1 infection. Trends Immunol 2011; 32:219–24. [PubMed: 21411368]
7. Li J, Zaslavsky M, Su Y, Guo J, Sikora MJ, van Unen V, et al. KIR(+)CD8(+) T cells suppress pathogenic T cells and are active in autoimmune diseases and COVID-19. Science 2022; 376:eabi9591. [PubMed: 35258337]
8. Barrow AD, Colonna M. Exploiting NK Cell Surveillance Pathways for Cancer Therapy. Cancers (Basel) 2019; 11.
9. Björkström NK, Strunz B, Ljunggren HG. Natural killer cells in antiviral immunity. Nat Rev Immunol 2022; 22:112–23. [PubMed: 34117484]
10. Parham P, Moffett A. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution. Nature Reviews Immunology 2013; 13:133–44.
11. Raulet DH, Vance RE. Self-tolerance of natural killer cells. Nature Reviews Immunology 2006; 6:520–31.
12. Yokoyama WM, Kim S. Licensing of natural killer cells by self-major histocompatibility complex class I. Immunol Rev 2006; 214:143–54. [PubMed: 17100882]

13. Kim S, Sunwoo JB, Yang L, Choi T, Song YJ, French AR, et al. HLA alleles determine differences in human natural killer cell responsiveness and potency. Proc Natl Acad Sci U S A 2008; 105:3053–8. [PubMed: 18287063]
14. Anfossi N, André P, Guia S, Falk CS, Roetynck S, Stewart CA, et al. Human NK cell education by inhibitory receptors for MHC class I. Immunity 2006; 25:331–42. [PubMed: 16901727]
15. Goodridge JP, Jacobs B, Saetersmoen ML, Clement D, Hammer Q, Clancy T, et al. Remodeling of secretory lysosomes during education tunes functional potential in NK cells. Nat Commun 2019; 10:514. [PubMed: 30705279]
16. Goodson-Gregg FJ, Krepel SA, Anderson SK. Tuning of human NK cells by endogenous HLA-C expression. Immunogenetics 2020; 72:205–15. [PubMed: 32219494]
17. Horton R, Wilming L, Rand V, Lovering RC, Bruford EA, Khodiyar VK, et al. Gene map of the extended human MHC. Nat Rev Genet 2004; 5:889–99. [PubMed: 15573121]
18. Wilson MJ, Torkar M, Haude A, Milne S, Jones T, Sheer D, et al. Plasticity in the organization and sequences of human KIR/ILT gene families. Proceedings of the National Academy of Sciences 2000; 97:4778–83.
19. Vieira VA, Adland E, Malone DFG, Martin MP, Groll A, Ansari MA, et al. An HLA-I signature favouring KIR-educated Natural Killer cells mediates immune control of HIV in children and contrasts with the HLA-B-restricted CD8+ T-cell-mediated immune control in adults. PLoS Pathog 2021; 17:e1010090. [PubMed: 34793581]
20. Andersson S, Fauriat C, Malmberg JA, Ljunggren HG, Malmberg KJ. KIR acquisition probabilities are independent of self-HLA class I ligands and increase with cellular KIR expression. Blood 2009; 114:95–104. [PubMed: 19304956]
21. Beziat V, Hilton HG, Norman PJ, Traherne JA. Deciphering the killer-cell immunoglobulin-like receptor system at super-resolution for natural killer and T-cell biology. Immunology 2017; 150:248–64. [PubMed: 27779741]
22. Wilk AJ, Blish CA. Diversification of human NK cells: Lessons from deep profiling. J Leukoc Biol 2018; 103:629–41. [PubMed: 29350874]
23. Béziat V, Descours B, Parizot C, Debré P, Vieillard V. NK cell terminal differentiation: correlated stepwise decrease of NKG2A and acquisition of KIRs. PLoS One 2010; 5:e11966. [PubMed: 20700504]
24. Kumar S. Natural killer cell cytotoxicity and its regulation by inhibitory receptors. Immunology 2018; 154:383–93. [PubMed: 29512837]
25. Mingari MC, Schiavetti F, Ponte M, Vitale C, Maggi E, Romagnani S, et al. Human CD8+ T lymphocyte subsets that express HLA class I-specific inhibitory receptors represent oligoclonally or monoclonally expanded cell populations. Proc Natl Acad Sci U S A 1996; 93:12433–8. [PubMed: 8901599]
26. Henel G, Singh K, Cui D, Pryshchep S, Lee WW, Weyand CM, et al. Uncoupling of T-cell effector functions by inhibitory killer immunoglobulin-like receptors. Blood 2006; 107:4449–57. [PubMed: 16469873]
27. Anfossi N, Doisne JM, Peyrat MA, Ugolini S, Bonnaud O, Bossy D, et al. Coordinated expression of Ig-like inhibitory MHC class I receptors and acquisition of cytotoxic function in human CD8+ T cells. J Immunol 2004; 173:7223–9. [PubMed: 15585844]
28. Björkström NK, Béziat V, Cichocki F, Liu LL, Levine J, Larsson S, et al. CD8 T cells express randomly selected KIRs with distinct specificities compared with NK cells. Blood 2012; 120:3455–65. [PubMed: 22968455]
29. Boelen L, Debebe B, Silveira M, Salam A, Makinde J, Roberts CH, et al. Inhibitory killer cell immunoglobulin-like receptors strengthen CD8(+) T cell-mediated control of HIV-1, HCV, and HTLV-1. Sci Immunol 2018; 3.
30. Seich Al Basatena NK, Macnamara A, Vine AM, Thio CL, Astemborski J, Usuku K, et al. KIR2DL2 enhances protective and detrimental HLA class I-mediated immunity in chronic viral infection. PLoS Pathog 2011; 7:e1002270. [PubMed: 22022261]
31. Guethlein LA, Norman PJ, Hilton HG, Parham P. Co-evolution of MHC class I and variable NK cell receptors in placental mammals. Immunological Reviews 2015; 267:259–82. [PubMed: 26284483]

32. Bruijnesteijn J, De Groot N, Van Der Wiel MKH, Otting N, De Vos-Rouweler AJM, De Groot NG, et al. Unparalleled Rapid Evolution of KIR Genes in Rhesus and Cynomolgus Macaque Populations. The Journal of Immunology 2020; 204:1770–86. [PubMed: 32111732]
33. Kulkarni S, Martin MP, Carrington M. The Yin and Yang of HLA and KIR in human disease. Semin Immunol 2008; 20:343–52. [PubMed: 18635379]
34. Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. Annu Rev Genomics Hum Genet 2013; 14:301–23. [PubMed: 23875801]
35. Parham P, Norman PJ, Abi-Rached L, Guethlein LA. Human-specific evolution of killer cell immunoglobulin-like receptor recognition of major histocompatibility complex class I molecules. Philosophical Transactions of the Royal Society B: Biological Sciences 2012; 367:800–11.
36. Solberg OD, Mack SJ, Lancaster AK, Single RM, Tsai Y, Sanchez-Mazas A, et al. Balancing selection and heterogeneity across the classical human leukocyte antigen loci: a meta-analytic review of 497 population studies. Hum Immunol 2008; 69:443–64. [PubMed: 18638659]
37. Patin E, Lopez M, Grollemund R, Verdu P, Harmant C, Quach H, et al. Dispersals and genetic adaptation of Bantu-speaking populations in Africa and North America. Science 2017; 356:543–6. [PubMed: 28473590]
38. Prugnolle F, Manica A, Charpentier M, Guegan JF, Guernier V, Balloux F. Pathogen-driven selection and worldwide HLA class I diversity. Curr Biol 2005; 15:1022–7. [PubMed: 15936272]
39. Meyer D, VR CA, Bitarello BD, DY CB, Nunes K. A genomic perspective on HLA evolution. Immunogenetics 2018; 70:5–27. [PubMed: 28687858]
40. Ebert D, Fields PD. Host-parasite co-evolution and its genomic signature. Nat Rev Genet 2020; 21:754–68. [PubMed: 32860017]
41. Deng Z, Zhen J, Harrison GF, Zhang G, Chen R, Sun G, et al. Adaptive Admixture of HLA Class I Allotypes Enhanced Genetically Determined Strength of Natural Killer Cells in East Asians. Mol Biol Evol 2021; 38:2582–96. [PubMed: 33616658]
42. Uhrberg M, Valiante NM, Shum BP, Shilling HG, Lienert-Weidenbach K, Corliss B, et al. Human diversity in killer cell inhibitory receptor genes. Immunity 1997; 7:753–63. [PubMed: 9430221]
43. Shilling HG, Lienert-Weidenbach K, Valiante NM, Uhrberg M, Parham P. Evidence for recombination as a mechanism for KIR diversification. Immunogenetics 1998; 48:413–6. [PubMed: 9799338]
44. Pyo CW, Wang R, Vu Q, Cereb N, Yang SY, Duh FM, et al. Recombinant structures expand and contract inter and intragenic diversification at the KIR locus. BMC Genomics 2013; 14:89. [PubMed: 23394822]
45. Ordóñez D, Gómez-Lozano N, Rosales L, Vilches C. Molecular characterisation of KIR2DS2*005, a fusion gene associated with a shortened KIR haplotype. Genes Immun 2011; 12:544–51. [PubMed: 21593779]
46. Norman PJ, Abi-Rached L, Gendzekhadze K, Hammond JA, Moesta AK, Sharma D, et al. Meiotic recombination generates rich diversity in NK cell receptor genes, alleles, and haplotypes. Genome Res 2009; 19:757–69. [PubMed: 19411600]
47. Chaisri S, Jayaraman J, Mongkolsapaya J, Duangchinda T, Jumniansong A, Trowsdale J, et al. KIR copy number variations in dengue-infected patients from northeastern Thailand. Hum Immunol 2022.
48. Pelak K, Need AC, Fellay J, Shianna KV, Feng S, Urban TJ, et al. Copy number variation of KIR genes influences HIV-1 control. PLoS Biol 2011; 9:e1001208. [PubMed: 22140359]
49. Moesta AK, Norman PJ, Yawata M, Yawata N, Gleimer M, Parham P. Synergistic polymorphism at two positions distal to the ligand-binding site makes KIR2DL2 a stronger receptor for HLA-C than KIR2DL3. J Immunol 2008; 180:3969–79. [PubMed: 18322206]
50. Nemat-Gorgani N, Hilton HG, Henn BM, Lin M, Gignoux CR, Myrick JW, et al. Different selected mechanisms attenuated the inhibitory interaction of KIR2DL1 with C2+ HLA-C in two indigenous human populations in Southern Africa. The Journal of Immunology 2018; 200:2640–55. [PubMed: 29549179]
51. Moradi S, Stankovic S, O'Connor GM, Pymm P, Maclachlan BJ, Faoro C, et al. Structural plasticity of KIR2DL2 and KIR2DL3 enables altered docking geometries atop HLA-C. Nature Communications 2021; 12.

52. Parsons MS, Zipperlen K, Gallant M, Grant M. Killer cell immunoglobulin-like receptor 3DL1 licenses CD16-mediated effector functions of natural killer cells. J Leukoc Biol 2010; 88:905–12. [PubMed: 20664023]
53. Hilton HG, Guethlein LA, Goyos A, Nemat-Gorgani N, Bushnell DA, Norman PJ, et al. Polymorphic HLA-C Receptors Balance the Functional Characteristics of KIR Haplotypes. J Immunol 2015; 195:3160–70. [PubMed: 26311903]
54. Saunders PM, Pymm P, Pietra G, Hughes VA, Hitchen C, O'Connor GM, et al. Killer cell immunoglobulin-like receptor 3DL1 polymorphism defines distinct hierarchies of HLA class I recognition. J Exp Med 2016; 213:791–807. [PubMed: 27045007]
55. Bari R, Bell T, Leung WH, Vong QP, Chan WK, Das Gupta N, et al. Significant functional heterogeneity among KIR2DL1 alleles and a pivotal role of arginine 245. Blood 2009; 114:5182–90. [PubMed: 19828694]
56. Boudreau JE, Mulrooney TJ, Le Luduec JB, Barker E, Hsu KC. KIR3DL1 and HLA-B Density and Binding Calibrate NK Education and Response to HIV. J Immunol 2016; 196:3398–410. [PubMed: 26962229]
57. Freud AG, Mundy-Bosse BL, Yu J, Caligiuri MA. The Broad Spectrum of Human Natural Killer Cell Diversity. Immunity 2017; 47:820–33. [PubMed: 29166586]
58. Maccari G, Robinson J, Hammond JA, Marsh SGE. The IPD Project: a centralised resource for the study of polymorphism in genes of the immune system. Immunogenetics 2020; 72:49–55. [PubMed: 31641782]
59. Shiina T, Hosomichi K, Inoko H, Kulski JK. The HLA genomic loci map: expression, interaction, diversity and disease. Journal of Human Genetics 2009; 54:15–39. [PubMed: 19158813]
60. Saunders PM, MacLachlan BJ, Pymm P, Illing PT, Deng Y, Wong SC, et al. The molecular basis of how buried human leukocyte antigen polymorphism modulates natural killer cell function. Proc Natl Acad Sci U S A 2020; 117:11636–47. [PubMed: 32404419]
61. Saunders PM, MacLachlan BJ, Widjaja J, Wong SC, Oates CVL, Rossjohn J, et al. The Role of the HLA Class I alpha2 Helix in Determining Ligand Hierarchy for the Killer Cell Ig-like Receptor 3DL1. J Immunol 2021; 206:849–60. [PubMed: 33441440]
62. Apps R, Qi Y, Carlson JM, Chen H, Gao X, Thomas R, et al. Influence of HLA-C expression level on HIV control. Science 2013; 340:87–91. [PubMed: 23559252]
63. Parham P, Ohta T. Population biology of antigen presentation by MHC class I molecules. Science 1996; 272:67–74. [PubMed: 8600539]
64. Peruzzi M, Parker KC, Long EO, Malnati MS. Peptide sequence requirements for the recognition of HLA-B*2705 by specific natural killer cells. J Immunol 1996; 157:3350–6. [PubMed: 8871631]
65. Sim MJ, Malaker SA, Khan A, Stowell JM, Shabanowitz J, Peterson ME, et al. Canonical and Cross-reactive Binding of NK Cell Inhibitory Receptors to HLA-C Allotypes Is Dictated by Peptides Bound to HLA-C. Front Immunol 2017; 8:193. [PubMed: 28352266]
66. Sim MJW, Rajagopalan S, Altmann DM, Boyton RJ, Sun PD, Long EO. Human NK cell receptor KIR2DS4 detects a conserved bacterial epitope presented by HLA-C. Proc Natl Acad Sci U S A 2019; 116:12964–73. [PubMed: 31138701]
67. Naiyer MM, Cassidy SA, Magri A, Cowton V, Chen K, Mansour S, et al. KIR2DS2 recognizes conserved peptides derived from viral helicases in the context of HLA-C. Sci Immunol 2017; 2.
68. Lunemann S, Martrus G, Hölzemer A, Chapel A, Ziegler M, Körner C, et al. Sequence variations in HCV core-derived epitopes alter binding of KIR2DL3 to HLA-C*03:04 and modulate NK cell function. J Hepatol 2016; 65:252–8. [PubMed: 27057987]
69. Alter G, Heckerman D, Schneidewind A, Fadda L, Kadie CM, Carlson JM, et al. HIV-1 adaptation to NK-cell-mediated immune pressure. Nature 2011; 476:96–100. [PubMed: 21814282]
70. Wauquier N, Petitdemange C, Tarantino N, Maucourant C, Coomber M, Lungay V, et al. HLA-C-restricted viral epitopes are associated with an escape mechanism from KIR2DL2 + NK cells in Lassa virus infection. EBioMedicine 2019; 40:605–13. [PubMed: 30711514]
71. Garcia-Beltran WF, Hölzemer A, Martrus G, Chung AW, Pacheco Y, Simoneau CR, et al. Open conformers of HLA-F are high-affinity ligands of the activating NK-cell receptor KIR3DS1. Nat Immunol 2016; 17:1067–74. [PubMed: 27455421]

72. Rajagopalan S, Long EO. KIR2DL4 (CD158d): An activation receptor for HLA-G. Front Immunol 2012; 3:258. [PubMed: 22934097]
73. Goodridge JP, Witt CS, Christiansen FT, Warren HS. KIR2DL4 (CD158d) genotype influences expression and function in NK cells. J Immunol 2003; 171:1768–74. [PubMed: 12902476]
74. Norman PJ, Abi-Rached L, Gendzekhadze K, Korbel D, Gleimer M, Rowley D, et al. Unusual selection on the KIR3DL1/S1 natural killer cell receptor in Africans. Nature Genetics 2007; 39:1092–9. [PubMed: 17694054]
75. O'Connor GM, Vivian JP, Gostick E, Pymm P, Lafont BA, Price DA, et al. Peptide-Dependent Recognition of HLA-B*57:01 by KIR3DS1. J Virol 2015; 89:5213–21. [PubMed: 25740999]
76. Horowitz A, Djaoud Z, Nemat-Gorgani N, Blokhuis J, Hilton HG, Beziat V, et al. Class I HLA haplotypes form two schools that educate NK cells in different ways. Sci Immunol 2016; 1.
77. Shreeve N, Depierreux D, Hawkes D, Traherne JA, Sovio U, Huhn O, et al. The CD94/NKG2A inhibitory receptor educates uterine NK cells to optimize pregnancy outcomes in humans and mice. Immunity 2021; 54:1231–44.e4. [PubMed: 33887202]
78. Yawata M, Yawata N. Practical Considerations and Workflow in Utilizing KIR Genotyping in Transplantation Medicine. Methods Mol Biol 2022; 2463:291–310. [PubMed: 35344182]
79. Jiang W, Johnson C, Jayaraman J, Simecek N, Noble J, Moffatt MF, et al. Copy number variation leads to considerable diversity for B but not A haplotypes of the human KIR genes encoding NK cell receptors. Genome Res 2012; 22:1845–54. [PubMed: 22948769]
80. Wagner I, Schefzyk D, Pruschke J, Schöfl G, Schöne B, Gruber N, et al. Allele-Level KIR Genotyping of More Than a Million Samples: Workflow, Algorithm, and Observations. Front Immunol 2018; 9:2843. [PubMed: 30564239]
81. Roe D, Vierra-Green C, Pyo CW, Eng K, Hall R, Kuang R, et al. Revealing complete complex KIR haplotypes phased by long-read sequencing technology. Genes Immun 2017; 18:127–34. [PubMed: 28569259]
82. Roe D, Williams J, Ivery K, Brouckaert J, Downey N, Locklear C, et al. Efficient Sequencing, Assembly, and Annotation of Human KIR Haplotypes. Front Immunol 2020; 11:582927. [PubMed: 33162997]
83. Norman PJ, Hollenbach JA, Nemat-Gorgani N, Marin WM, Norberg SJ, Ashouri E, et al. Defining KIR and HLA Class I Genotypes at Highest Resolution via High-Throughput Sequencing. Am J Hum Genet 2016; 99:375–91. [PubMed: 27486779]
84. Maniangou B, Legrand N, Alizadeh M, Guyet U, Willem C, David G, et al. Killer Immunoglobulin-Like Receptor Allele Determination Using Next-Generation Sequencing Technology. Front Immunol 2017; 8:547. [PubMed: 28579987]
85. Marin WM, Dandekar R, Augusto DG, Yusufali T, Heyn B, Hofmann J, et al. High-throughput Interpretation of Killer-cell Immunoglobulin-like Receptor Short-read Sequencing Data with PING. PLoS Comput Biol 2021; 17:e1008904. [PubMed: 34339413]
86. Vukcevic D, Traherne JA, Næss S, Ellinghaus E, Kamatani Y, Dilthey A, et al. Imputation of KIR Types from SNP Variation Data. Am J Hum Genet 2015; 97:593–607. [PubMed: 26430804]
87. Harrison GF, Leaton LA, Harrison EA, Kichula KM, Viken MK, Shortt J, et al. Allele imputation for the killer cell immunoglobulin-like receptor KIR3DL1/S1. PLoS Comput Biol 2022; 18:e1009059. [PubMed: 35192601]
88. Pappas DJ, Lizee A, Paunic V, Beutner KR, Motyer A, Vukcevic D, et al. Significant variation between SNP-based HLA imputations in diverse populations: the last mile is the hardest. Pharmacogenomics J 2018; 18:367–76. [PubMed: 28440342]
89. Ali A, Gyurova IE, Waggoner SN. Mutually assured destruction: the cold war between viruses and natural killer cells. Curr Opin Virol 2019; 34:130–9. [PubMed: 30877885]
90. Savoy SKA, Boudreau JE. The Evolutionary Arms Race between Virus and NK Cells: Diversity Enables Population-Level Virus Control. Viruses 2019; 11.
91. Burgner D, Jamieson SE, Blackwell JM. Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? Lancet Infect Dis 2006; 6:653–63. [PubMed: 17008174]
92. Thöns C, Senff T, Hydes TJ, Manser AR, Heinemann FM, Heinold A, et al. HLA-Bw4 80(T) and multiple HLA-Bw4 copies combined with KIR3DL1 associate with spontaneous clearance of HCV infection in people who inject drugs. J Hepatol 2017; 67:462–70. [PubMed: 28412292]

93. Vollmers S, Lobermeyer A, Körner C. The New Kid on the Block: HLA-C, a Key Regulator of Natural Killer Cells in Viral Immunity. Cells 2021; 10.
94. Tukwasibwe S, Nakimuli A, Traherne J, Chazara O, Jayaraman J, Trowsdale J, et al. Variations in killer-cell immunoglobulin-like receptor and human leukocyte antigen genes and immunity to malaria. Cell Mol Immunol 2020; 17:799–806. [PubMed: 32541835]
95. Koyro TF, Kraus E, Lunemann S, Hölzemer A, Wulf S, Jung J, et al. Upregulation of HLA-F expression by BK polyomavirus infection induces immune recognition by KIR3DS1-positive natural killer cells. Kidney Int 2020.
96. Scully E, Alter G. NK Cells in HIV Disease. Curr HIV/AIDS Rep 2016; 13:85–94. [PubMed: 27002078]
97. Holzemer A, Garcia-Beltran WF, Altfeld M. Natural Killer Cell Interactions with Classical and Non-Classical Human Leukocyte Antigen Class I in HIV-1 Infection. Front Immunol 2017; 8:1496. [PubMed: 29184550]
98. Naranbhai V, Carrington M. Host genetic variation and HIV disease: from mapping to mechanism. Immunogenetics 2017; 69:489–98. [PubMed: 28695282]
99. Kiani Z, Bruneau J, Geraghty DE, Bernard NF. HLA-F on Autologous HIV-Infected Cells Activates Primary NK Cells Expressing the Activating Killer Immunoglobulin-Like Receptor KIR3DS1. J Virol 2019; 93.
100. Gao X, Tang M, Martin P, Zeng Y, Carrington M. Compound HLA/KIR genotypes influence risk of nasopharyngeal carcinoma (NPC) in a southern chinese cohort. Human Immunology 2015; 76:52-. [PubMed: 25500427]
101. Goedert JJ, Martin MP, Vitale F, Lauria C, Whitby D, Qi Y, et al. Risk of Classic Kaposi Sarcoma With Combinations of Killer Immunoglobulin-Like Receptor and Human Leukocyte Antigen Loci: A Population-Based Case-control Study. The Journal of infectious diseases 2016; 213:432–8. [PubMed: 26268853]
102. Sezgin E, An P, Winkler CA. Host genetics of cytomegalovirus (CMV) pathogenesis. Frontiers in Genetics 2019; 10:616-. [PubMed: 31396258]
103. Taylor GS, Long HM, Brooks JM, Rickinson AB, Hislop AD. The Immunology of Epstein-Barr Virus–Induced Disease. Annual Review of Immunology 2015; 33:787–821.
104. Jiang P, Nolte IM, Hepkema BG, Stulp M, van den Berg A, Diepstra A. Killer Cell Immunoglobulin-Like Receptor Haplotype B Modulates Susceptibility to EBV-Associated Classic Hodgkin Lymphoma. Front Immunol 2022; 13:829943. [PubMed: 35154153]
105. Wang X, Liu XF, Shang QN, Yu XX, Fan ZY, Cao XH, et al. Donor activating killer cell immunoglobulin-like receptors genes correlated with Epstein-Barr virus reactivation after haploidentical haematopoietic stem cell transplantation. Br J Haematol 2022; 196:1007–17. [PubMed: 34787307]
106. Tang M, Zeng Y, Poisson A, Marti D, Guan L, Zheng Y, et al. Haplotype-dependent HLA susceptibility to nasopharyngeal carcinoma in a Southern Chinese population. Genes Immun 2010; 11:334–42. [PubMed: 20072141]
107. Butsch Kovacic M, Martin M, Gao X, Fuksenko T, Chen CJ, Cheng YJ, et al. Variation of the killer cell immunoglobulin-like receptors and HLA-C genes in nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 2005; 14:2673–7. [PubMed: 16284396]
108. Sheppard S, Sun JC. Virus-specific NK cell memory. J Exp Med 2021; 218.
109. Strunz B, Hengst J, Deterding K, Manns MP, Cornberg M, Ljunggren HG, et al. Chronic hepatitis C virus infection irreversibly impacts human natural killer cell repertoire diversity. Nat Commun 2018; 9:2275. [PubMed: 29891939]
110. Vento-Tormo R, Efremova M, Botting RA, Turco MY, Vento-Tormo M, Meyer KB, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 2018; 563:347–53. [PubMed: 30429548]
111. Strunz B, Bister J, Jönsson H, Filipovic I, Crona-Guterstam Y, Kvedaraite E, et al. Continuous human uterine NK cell differentiation in response to endometrial regeneration and pregnancy. Sci Immunol 2021; 6.
112. Moffett A, Loke C. Immunology of placentation in eutherian mammals. Nature Reviews Immunology 2006; 6:584–94.

113. Yeung HY, Dendrou CA. Pregnancy Immunogenetics and Genomics: Implications for Pregnancy-Related Complications and Autoimmune Disease. Annu Rev Genomics Hum Genet 2019; 20:73–97. [PubMed: 30848957]
114. Khakoo SI, Rajalingam R, Shum BP, Weidenbach K, Flodin L, Muir DG, et al. Rapid evolution of NK cell receptor systems demonstrated by comparison of chimpanzees and humans. Immunity 2000; 12:687–98. [PubMed: 10894168]
115. Abi-Rached L, Moesta AK, Rajalingam R, Guethlein LA, Parham P. Human-specific evolution and adaptation led to major qualitative differences in the variable receptors of human and chimpanzee natural killer cells. PLoS Genet 2010; 6:e1001192. [PubMed: 21079681]
116. Daza-Vamenta R, Glusman G, Rowen L, Guthrie B, Geraghty DE. Genetic divergence of the rhesus macaque major histocompatibility complex. Genome Res 2004; 14:1501–15. [PubMed: 15289473]
117. Rajalingam R, Parham P, Abi-Rached L. Domain shuffling has been the main mechanism forming new hominoid killer cell Ig-like receptors. J Immunol 2004; 172:356–69. [PubMed: 14688344]
118. Alicata C, Ashouri E, Nemat-Gorgani N, Guethlein LA, Marin WM, Tao S, et al. KIR Variation in Iranians Combines High Haplotype and Allotype Diversity With an Abundance of Functional Inhibitory Receptors. Front Immunol 2020; 11:556. [PubMed: 32300348]
119. Amorim LM, Augusto DG, Nemat-Gorgani N, Montero-Martin G, Marin WM, Shams H, et al. High-Resolution Characterization of KIR Genes in a Large North American Cohort Reveals Novel Details of Structural and Sequence Diversity. Front Immunol 2021; 12:674778. [PubMed: 34025673]
120. Cisneros E, Moraru M, Gomez-Lozano N, Muntasell A, Lopez-Botet M, Vilches C. Haplotype-Based Analysis of KIR-Gene Profiles in a South European Population-Distribution of Standard and Variant Haplotypes, and Identification of Novel Recombinant Structures. Front Immunol 2020; 11:440. [PubMed: 32256494]
121. Tao S, Kichula KM, Harrison GF, Farias TDJ, Palmer WH, Leaton LA, et al. The combinatorial diversity of KIR and HLA class I allotypes in Peninsular Malaysia. Immunology 2021; 162:389–404. [PubMed: 33283280]
122. Bartl S, Baish MA, Flajnik MF, Ohta Y. Identification of class I genes in cartilaginous fish, the most ancient group of vertebrates displaying an adaptive immune response. J Immunol 1997; 159:6097–104. [PubMed: 9550410]
123. Kaufman J The new W family reconstructs the evolution of MHC genes. Proc Natl Acad Sci U S A 2022; 119.
124. Schwartz JC, Sanderson ND, Bickhart DM, Smith TPL, Hammond JA. The Structure, Evolution, and Gene Expression Within the Caprine Leukocyte Receptor Complex. Front Immunol 2019; 10:2302. [PubMed: 31616444]
125. Barten R, Torkar M, Haude A, Trowsdale J, Wilson MJ. Divergent and convergent evolution of NK-cell receptors. Trends Immunol 2001; 22:52–7. [PubMed: 11286693]
126. Wroblewski EE, Parham P, Guethlein LA. Two to Tango: Co-evolution of Hominid Natural Killer Cell Receptors and MHC. Front Immunol 2019; 10:177. [PubMed: 30837985]
127. Older Aguilar AM, Guethlein LA, Adams EJ, Abi-Rached L, Moesta AK, Parham P. Coevolution of Killer Cell Ig-Like Receptors with HLA-C To Become the Major Variable Regulators of Human NK Cells. The Journal of Immunology 2010; 185:4238–51. [PubMed: 20805421]
128. Mace EM, Orange JS. Emerging insights into human health and NK cell biology from the study of NK cell deficiencies. Immunol Rev 2019; 287:202–25. [PubMed: 30565241]
129. de Brito Vargas L, Beltrame MH, Ho B, Marin WM, Dandekar R, Montero-Martin G, et al. Remarkably Low KIR and HLA Diversity in Amerindians Reveals Signatures of Strong Purifying Selection Shaping the Centromeric KIR Region. Mol Biol Evol 2022; 39.
130. Maxwell LD, Wallace A, Middleton D, Curran MD. A common KIR2DS4 deletion variant in the human that predicts a soluble KIR molecule analogous to the KIR1D molecule observed in the rhesus monkey. Tissue Antigens 2002; 60:254–8. [PubMed: 12445308]
131. Pyo C-W, Guethlein LA, Vu Q, Wang R, Abi-Rached L, Norman PJ, et al. Different Patterns of Evolution in the Centromeric and Telomeric Regions of Group A and B Haplotypes of the Human Killer Cell Ig-Like Receptor Locus. PLoS ONE 2010; 5:e15115. [PubMed: 21206914]

132. Deng Z, Zhao J, Cai S, Qi Y, Yu Q, Martin MP, et al. Natural Killer Cells Offer Differential Protection From Leukemia in Chinese Southern Han. Front Immunol 2019; 10:1646. [PubMed: 31379844]
133. Khakoo SI, Thio CL, Martin MP, Brooks CR, Gao X, Astemborski J, et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science 2004; 305:872–4. [PubMed: 15297676]
134. Martin MP, Qi Y, Gao X, Yamada E, Martin JN, Pereyra F, et al. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. Nature Genetics 2007; 39:733–40. [PubMed: 17496894]
135. Hiby SE, Walker JJ, O'Shaughnessy KM, Redman CWG, Carrington M, Trowsdale J, et al. Combinations of Maternal KIR and Fetal HLA-C Genes Influence the Risk of Preeclampsia and Reproductive Success. Journal of Experimental Medicine 2004; 200:957–65. [PubMed: 15477349]
136. Hiby SE, Apps R, Chazara O, Farrell LE, Magnus P, Trogstad L, et al. Maternal KIR in Combination with Paternal HLA-C2 Regulate Human Birth Weight. The Journal of Immunology 2014; 192:5069–73. [PubMed: 24778445]
137. Norman PJ, Stephens HA, Verity DH, Chandanayingyong D, Vaughan RW. Distribution of natural killer cell immunoglobulin-like receptor sequences in three ethnic groups. Immunogenetics 2001; 52:195–205. [PubMed: 11220621]
138. Gonzalez-Galarza FF, McCabe A, Santos E, Jones J, Takeshita L, Ortega-Rivera ND, et al. Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. Nucleic Acids Res 2020; 48:D783–d8. [PubMed: 31722398]
139. Hollenbach JA, Nocedal I, Ladner MB, Single RM, Trachtenberg EA. Killer cell immunoglobulin-like receptor (KIR) gene content variation in the HGDP-CEPH populations. Immunogenetics 2012; 64:719–37. [PubMed: 22752190]
140. Gendzekhadze K, Norman PJ, Abi-Rached L, Graef T, Moesta AK, Layrisse Z, et al. Co-evolution of KIR2DL3 with HLA-C in a human population retaining minimal essential diversity of KIR and HLA class I ligands. Proc Natl Acad Sci U S A 2009; 106:18692–7. [PubMed: 19837691]
141. Penman BS, Moffett A, Chazara O, Gupta S, Parham P. Reproduction, infection and killer-cell immunoglobulin-like receptor haplotype evolution. Immunogenetics 2016; 68:755–64. [PubMed: 27517293]
142. Yawata M, Yawata N, Draghi M, Little AM, Partheniou F, Parham P. Roles for HLA and KIR polymorphisms in natural killer cell repertoire selection and modulation of effector function. J Exp Med 2006; 203:633–45. [PubMed: 16533882]
143. Augusto DG, Norman PJ, Dandekar R, Hollenbach JA. Fluctuating and Geographically Specific Selection Characterize Rapid Evolution of the Human KIR Region. Front Immunol 2019; 10:989. [PubMed: 31156615]
144. Nakimuli A, Chazara O, Hiby SE, Farrell L, Tukwasibwe S, Jayaraman J, et al. A KIR B centromeric region present in Africans but not Europeans protects pregnant women from pre-eclampsia. Proceedings of the National Academy of Sciences 2015; 112:845–50.
145. Yu H, Pan N, Shen Y, Jin S, Zhai J, Qiao D, et al. Interaction of parental KIR and fetal HLA-C genotypes with the risk of preeclampsia. Hypertension in Pregnancy 2014; 33:402–11. [PubMed: 24911933]
146. Kelemu T, Erlandsson L, Seifu D, Hansson E, Abebe M, Teklu S, et al. Polymorphism in killer cell immunoglobulin-like receptors and human leukocyte antigen-c and predisposition to preeclampsia in Ethiopian pregnant women population. J Reprod Immunol 2020; 141:103169. [PubMed: 32603992]
147. Hilton HG, Vago L, Older Aguilar AM, Moesta AK, Graef T, Abi-Rached L, et al. Mutation at positively selected positions in the binding site for HLA-C shows that KIR2DL1 is a more refined but less adaptable NK cell receptor than KIR2DL3. J Immunol 2012; 189:1418–30. [PubMed: 22772445]
148. Nemat-Gorgani N, Hilton HG, Henn BM, Lin M, Gignoux CR, Myrick JW, et al. Different Selected Mechanisms Attenuated the Inhibitory Interaction of KIR2DL1 with C2+ HLA-C in

Two Indigenous Human Populations in Southern Africa. The Journal of Immunology 2018; 200:2640–55. [PubMed: 29549179]

149. Huhn O, Chazara O, Ivarsson MA, Retière C, Venkatesan TC, Norman PJ, et al. High-Resolution Genetic and Phenotypic Analysis of KIR2DL1 Alleles and Their Association with Pre-Eclampsia. The Journal of Immunology 2018; 201:2593–601. [PubMed: 30249807]
150. Vargas LB, Dourado RM, Amorim LM, Ho B, Calonga-Solís V, Issler HC, et al. Single Nucleotide Polymorphism in KIR2DL1 Is Associated With HLA-C Expression in Global Populations. Front Immunol 2020; 11:1881. [PubMed: 32983108]
151. Xiong S, Sharkey AM, Kennedy PR, Gardner L, Farrell LE, Chazara O, et al. Maternal uterine NK cell-activating receptor KIR2DS1 enhances placentation. J Clin Invest 2013; 123:4264–72. [PubMed: 24091323]
152. Kennedy PR, Chazara O, Gardner L, Ivarsson MA, Farrell LE, Xiong S, et al. Activating KIR2DS4 Is Expressed by Uterine NK Cells and Contributes to Successful Pregnancy. J Immunol 2016; 197:4292–300. [PubMed: 27815424]
153. Johnsen GM, Størvold GL, Drabbels JJM, Haasnoot GW, Eikmans M, Spruyt-Gerritse MJ, et al. The combination of maternal KIR-B and fetal HLA-C2 is associated with decidua basalis acute atherosis in pregnancies with preeclampsia. Journal of Reproductive Immunology 2018; 129:23–9. [PubMed: 30055414]
154. Single RM, Martin MP, Gao X, Meyer D, Yeager M, Kidd JR, et al. Global diversity and evidence for coevolution of KIR and HLA. Nature Genetics 2007; 39:1114–9. [PubMed: 17694058]
155. Norman PJ, Hollenbach JA, Nemat-Gorgani N, Guethlein LA, Hilton HG, Pando MJ, et al. Co-evolution of human leukocyte antigen (HLA) class I ligands with killer-cell immunoglobulin-like receptors (KIR) in a genetically diverse population of sub-Saharan Africans. PLoS Genet 2013; 9:e1003938. [PubMed: 24204327]
156. Augusto DG, Petzl-Erler ML. KIR and HLA under pressure: evidences of coevolution across worldwide populations. Human Genetics 2015; 134:929–40. [PubMed: 26099314]
157. Hirayasu K, Ohashi J, Kashiwase K, Hananantachai H, Naka I, Ogawa A, et al. Significant association of KIR2DL3-HLA-C1 combination with cerebral malaria and implications for co-evolution of KIR and HLA. PLoS Pathog 2012; 8:e1002565. [PubMed: 22412373]
158. Tao S, He Y, Kichula KM, Wang J, He J, Norman PJ, et al. High-Resolution Analysis Identifies High Frequency of KIR-A Haplotypes and Inhibitory Interactions of KIR With HLA Class I in Zhejiang Han. Front Immunol 2021; 12:640334. [PubMed: 33995358]
159. Patin E, Lopez M, Grollemund R, Verdu P, Harmant C, Quach H, et al. Dispersals and genetic adaptation of Bantu-speaking populations in Africa and North America. Science 2017; 356:543–6. [PubMed: 28473590]
160. Abi-Rached L, Jobin MJ, Kulkarni S, McWhinnie A, Dalva K, Gragert L, et al. The shaping of modern human immune systems by multiregional admixture with archaic humans. Science 2011; 334:89–94. [PubMed: 21868630]
161. Paganini J, Abi-Rached L, Gouret P, Pontarotti P, Chiaroni J, Di Cristofaro J. HLAIb worldwide genetic diversity: New HLA-H alleles and haplotype structure description. Mol Immunol 2019; 112:40–50. [PubMed: 31078115]
162. Hubert L, Paganini J, Picard C, Chiaroni J, Abi-Rached L, Pontarotti P, et al. HLA-H*02:07 Is a Membrane-Bound Ligand of Denisovan Origin That Protects against Lysis by Activated Immune Effectors. J Immunol 2022; 208:49–53. [PubMed: 34872977]
163. Hilton HG, McMurtrey CP, Han AS, Djaoud Z, Guethlein LA, Blokhuis JH, et al. The Intergenic Recombinant HLA-B*46:01 Has a Distinctive Peptidome that Includes KIR2DL3 Ligands. Cell Rep 2017; 19:1394–405. [PubMed: 28514659]
164. Qutob N, Balloux F, Raj T, Liu H, Marion de Procé S, Trowsdale J, et al. Signatures of historical demography and pathogen richness on MHC class I genes. Immunogenetics 2012; 64:165–75. [PubMed: 21947542]
165. Winter CC, Long EO. A single amino acid in the p58 killer cell inhibitory receptor controls the ability of natural killer cells to discriminate between the two groups of HLA-C allotypes. J Immunol 1997; 158:4026–8. [PubMed: 9126959]

166. Hilton HG, Norman PJ, Nemat-Gorgani N, Goyos A, Hollenbach JA, Henn BM, et al. Loss and Gain of Natural Killer Cell Receptor Function in an African Hunter-Gatherer Population. PLOS Genetics 2015; 11:e1005439. [PubMed: 26292085]

167. Vivian JP, Duncan RC, Berry R, O'Connor GM, Reid HH, Beddoe T, et al. Killer cell immunoglobulin-like receptor 3DL1-mediated recognition of human leukocyte antigen B. Nature 2011; 479:401–5. [PubMed: 22020283]

168. Migueles SA, Sabbaghian MS, Shupert WL, Bettinotti MP, Marincola FM, Martino L, et al. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. Proceedings of the National Academy of Sciences 2000; 97:2709–14.

169. Martin MP, Naranbhai V, Shea PR, Qi Y, Ramsuran V, Vince N, et al. Killer cell immunoglobulin–like receptor 3DL1 variation modifies HLA-B*57 protection against HIV-1. Journal of Clinical Investigation 2018; 128:1903–12. [PubMed: 29461980]

170. Takeshita LY, Gonzalez-Galarza FF, dos Santos EJ, Maia MH, Rahman MM, Zain SM, et al. A database for curating the associations between killer cell immunoglobulin-like receptors and diseases in worldwide populations. Database (Oxford) 2013; 2013:bat021. [PubMed: 23584834]

171. Holm SJ, Sakuraba K, Mallbris L, Wolk K, Ståhle M, Sánchez FO. Distinct HLA-C/KIR Genotype Profile Associates with Guttate Psoriasis. Journal of Investigative Dermatology 2005; 125:721–30. [PubMed: 16185272]

172. Łuszczek W, Mańczak M, Cisło M, Nockowski P, Wiśniewski A, Jasek M, et al. Gene for the activating natural killer cell receptor, KIR2DS1, is associated with susceptibility to psoriasis vulgaris. Human Immunology 2004; 65:758–66. [PubMed: 15310528]

173. Ahn R, Vukcevic D, Motyer A, Nititham J, Squire DM, Hollenbach JA, et al. Large-Scale Imputation of KIR Copy Number and HLA Alleles in North American and European Psoriasis Case-Control Cohorts Reveals Association of Inhibitory KIR2DL2 With Psoriasis. Front Immunol 2021; 12:684326. [PubMed: 34177931]

174. Anderson KM, Augusto DG, Dandekar R, Shams H, Zhao C, Yusufali T, et al. Killer Cell Immunoglobulin-like Receptor Variants Are Associated with Protection from Symptoms Associated with More Severe Course in Parkinson Disease. J Immunol 2020; 205:1323–30. [PubMed: 32709660]

175. Petrushkin H, Norman PJ, Lougee E, Parham P, Wallace GR, Stanford MR, et al. KIR3DL1/S1 Allotypes Contribute Differentially to the Development of Behcet Disease. J Immunol 2019; 203:1629–35. [PubMed: 31405953]

176. Kaur G, Trowsdale J, Fugger L. Natural killer cells and their receptors in multiple sclerosis. Brain 2013; 136:2657–76. [PubMed: 22734127]

177. Margolis DJ, Mitra N, Hoffstad OJ, Kim BS, Monos DS, Phillips EJ. Association of KIR Genes and MHC Class I Ligands with Atopic Dermatitis. J Immunol 2021; 207:1522–9. [PubMed: 34408014]

178. Margolis DJ, Mitra N, Kim BS, Duke JL, Berna RA, Hoffstad OJ, et al. HLA Class I Polymorphisms Influencing Both Peptide Binding and KIR Interactions Are Associated with Remission among Children with Atopic Dermatitis: A Longitudinal Study. J Immunol 2021; 206:2038–44. [PubMed: 33863792]

179. Hollenbach JA, Pando MJ, Caillier SJ, Gourraud PA, Oksenberg JR. The killer immunoglobulin-like receptor KIR3DL1 in combination with HLA-Bw4 is protective against multiple sclerosis in African Americans. Genes Immun 2016; 17:199–202. [PubMed: 26866467]

180. Lanz TV, Brewer RC, Ho PP, Moon JS, Jude KM, Fernandez D, et al. Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM. Nature 2022.

181. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science 2022; 375:296–301. [PubMed: 35025605]

182. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 2002; 295:2097–100. [PubMed: 11896281]

183. Giebel S, Locatelli F, Lamparelli T, Velardi A, Davies S, Frumento G, et al. Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors. Blood 2003; 102:814–9. [PubMed: 12689936]

184. Cooley S, Weisdorf DJ, Guethlein LA, Klein JP, Wang T, Le CT, et al. Donor selection for natural killer cell receptor genes leads to superior survival after unrelated transplantation for acute myelogenous leukemia. Blood 2010; 116:2411–9. [PubMed: 20581313]

185. Venstrom JM, Pittari G, Gooley TA, Chewning JH, Spellman S, Haagenson M, et al. HLA-C-dependent prevention of leukemia relapse by donor activating KIR2DS1. N Engl J Med 2012; 367:805–16. [PubMed: 22931314]

186. Leung W Use of NK cell activity in cure by transplant. Br J Haematol 2011; 155:14–29. [PubMed: 21812770]

187. Malmberg KJ, Schaffer M, Ringdén O, Remberger M, Ljunggren HG. KIR-ligand mismatch in allogeneic hematopoietic stem cell transplantation. Mol Immunol 2005; 42:531–4. [PubMed: 15607809]

188. Shaffer BC, Hsu KC. Selection of allogeneic hematopoietic cell transplant donors to optimize natural killer cell alloreactivity. Semin Hematol 2020; 57:167–74. [PubMed: 33256909]

189. Myers JA, Miller JS. Exploring the NK cell platform for cancer immunotherapy. Nat Rev Clin Oncol 2021; 18:85–100. [PubMed: 32934330]

190. Tarannum M, Romee R, Shapiro RM. Innovative Strategies to Improve the Clinical Application of NK Cell-Based Immunotherapy. Front Immunol 2022; 13:859177. [PubMed: 35401529]

191. Daher M, Melo Garcia L, Li Y, Rezvani K. CAR-NK cells: the next wave of cellular therapy for cancer. Clin Transl Immunology 2021; 10:e1274. [PubMed: 33959279]

192. Schetelig J, Baldauf H, Heidenreich F, Massalski C, Frank S, Sauter J, et al. External validation of models for KIR2DS1/KIR3DL1-informed selection of hematopoietic cell donors fails. Blood 2020; 135:1386–95. [PubMed: 31932846]

193. Guethlein LA, Beyzaie N, Nemat-Gorgani N, Wang T, Ramesh V, Marin WM, et al. Following Transplantation for Acute Myelogenous Leukemia, Donor KIR Cen B02 Better Protects against Relapse than KIR Cen B01. J Immunol 2021; 206:3064–72. [PubMed: 34117109]

194. Dubreuil L, Maniangou B, Chevallier P, Quéméner A, Legrand N, Béné MC, et al. Centromeric KIR AA Individuals Harbor Particular KIR Alleles Conferring Beneficial NK Cell Features with Implications in Haplo-Identical Hematopoietic Stem Cell Transplantation. Cancers (Basel) 2020; 12.

195. Yang Y, Day J, Souza-Fonseca Guimaraes F, Wicks IP, Louis C. Natural killer cells in inflammatory autoimmune diseases. Clin Transl Immunology 2021; 10:e1250. [PubMed: 33552511]

196. Guillerey C, Huntington ND, Smyth MJ. Targeting natural killer cells in cancer immunotherapy. Nat Immunol 2016; 17:1025–36. [PubMed: 27540992]

197. Pende D, Falco M, Vitale M, Cantoni C, Vitale C, Munari E, et al. Killer Ig-Like Receptors (KIRs): Their Role in NK Cell Modulation and Developments Leading to Their Clinical Exploitation. Front Immunol 2019; 10:1179. [PubMed: 31231370]

198. Zhuang X, Long EO. Inhibition-Resistant CARs for NK Cell Cancer Immunotherapy. Trends Immunol 2019; 40:1078–81. [PubMed: 31732285]

199. Trefny MP, Rothschild SI, Uhlenbrock F, Rieder D, Kasenda B, Stanczak MA, et al. A Variant of a Killer Cell Immunoglobulin-like Receptor Is Associated with Resistance to PD-1 Blockade in Lung Cancer. Clin Cancer Res 2019; 25:3026–34. [PubMed: 30765392]

200. Erbe AK, Wang W, Reville PK, Carmichael L, Kim K, Mendonca EA, et al. HLA-Bw4-I-80 Isoform Differentially Influences Clinical Outcome As Compared to HLA-Bw4-T-80 and HLA-A-Bw4 Isoforms in Rituximab or Dinutuximab-Based Cancer Immunotherapy. Front Immunol 2017; 8:675. [PubMed: 28659916]

201. Forlenza CJ, Boudreau JE, Zheng J, Le Luduec JB, Chamberlain E, Heller G, et al. KIR3DL1 Allelic Polymorphism and HLA-B Epitopes Modulate Response to Anti-GD2 Monoclonal Antibody in Patients With Neuroblastoma. J Clin Oncol 2016; 34:2443–51. [PubMed: 27069083]

202. Suppiah V, Gaudieri S, Armstrong NJ, O'Connor KS, Berg T, Weltman M, et al. IL28B, HLA-C, and KIR variants additively predict response to therapy in chronic hepatitis C virus infection in a European Cohort: a cross-sectional study. PLoS Med 2011; 8:e1001092. [PubMed: 21931540]

203. Mills MC, Rahal C. A scientometric review of genome-wide association studies. Communications biology 2019; 2:9. [PubMed: 30623105]

204. Popejoy AB, Ritter DI, Crooks K, Currey E, Fullerton SM, Hindorff LA, et al. The clinical imperative for inclusivity: race, ethnicity, and ancestry (REA) in genomics. Human mutation 2018; 39:1713–20. [PubMed: 30311373]

205. Bien SA, Wojcik GL, Hodonsky CJ, Gignoux CR, Cheng I, Matise TC, et al. The Future of Genomic Studies Must Be Globally Representative: Perspectives from PAGE. Annu Rev Genomics Hum Genet 2019; 20:181–200. [PubMed: 30978304]

206. Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, et al. Genetic analyses of diverse populations improves discovery for complex traits. Nature 2019; 570:514–8. [PubMed: 31217584]

207. Long EO, Sik Kim H, Liu D, Peterson ME, Rajagopalan S. Controlling Natural Killer Cell Responses: Integration of Signals for Activation and Inhibition. Annual Review of Immunology 2013; 31:227–58.

208. Bhatt RS, Berjis A, Konge JC, Mahoney KM, Klee AN, Freeman SS, et al. KIR3DL3 Is an Inhibitory Receptor for HHLA2 that Mediates an Alternative Immunoinhibitory Pathway to PD1. Cancer Immunol Res 2021; 9:156–69. [PubMed: 33229411]

209. Husain B, Ramani SR, Chiang E, Lehoux I, Paduchuri S, Arena TA, et al. A Platform for Extracellular Interactome Discovery Identifies Novel Functional Binding Partners for the Immune Receptors B7-H3/CD276 and PVR/CD155. Mol Cell Proteomics 2019; 18:2310–23. [PubMed: 31308249]

210. Gumperz JE, Litwin V, Phillips JH, Lanier LL, Parham P. The Bw4 public epitope of HLA-B molecules confers reactivity with natural killer cell clones that express NKB1, a putative HLA receptor. J Exp Med 1995; 181:1133–44. [PubMed: 7532677]

211. Martin MP, Gao X, Lee JH, Nelson GW, Detels R, Goedert JJ, et al. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nat Genet 2002; 31:429–34. [PubMed: 12134147]

212. Gao X, Jiao Y, Wang L, Liu X, Sun W, Cui B, et al. Inhibitory KIR and specific HLA-C gene combinations confer susceptibility to or protection against chronic hepatitis B. Clin Immunol 2010; 137:139–46. [PubMed: 20643584]

213. Di Bona D, Scafidi V, Plaia A, Colomba C, Nuzzo D, Occhino C, et al. HLA and Killer Cell Immunoglobulin-like Receptors Influence the Natural Course of CMV Infection. Journal of Infectious Diseases 2014; 210:1083–9. [PubMed: 24737799]

214. Manser AR, Scherenschlich N, Thons C, Hengel H, Timm J, Uhrberg M. KIR Polymorphism Modulates the Size of the Adaptive NK Cell Pool in Human Cytomegalovirus-Infected Individuals. J Immunol 2019; 203:2301–9. [PubMed: 31519864]

215. Townsley E, O'Connor G, Cosgrove C, Woda M, Co M, Thomas SJ, et al. Interaction of a dengue virus NS1-derived peptide with the inhibitory receptor KIR3DL1 on natural killer cells. Clin Exp Immunol 2016; 183:419–30. [PubMed: 26439909]

216. Wawina-Bokalanga T, Vanmechelen B, Lhermitte V, Marti-Carreras J, Vergote V, Koundouno FR, et al. Human Diversity of Killer Cell Immunoglobulin-Like Receptors and Human Leukocyte Antigen Class I Alleles and Ebola Virus Disease Outcomes. Emerg Infect Dis 2021; 27:76–84. [PubMed: 33350932]

217. Prakash S, Ranjan P, Ghoshal U, Agrawal S. KIR-like activating natural killer cell receptors and their association with complicated malaria in north India. Acta Trop 2018; 178:55–60. [PubMed: 29111138]

218. Digitale JC, Callaway PC, Martin M, Nelson G, Viard M, Rek J, et al. Association of Inhibitory Killer Cell Immunoglobulin-like Receptor Ligands With Higher Plasmodium falciparum Parasite Prevalence. The Journal of Infectious Diseases 2020; 224:175–83.

219. Carrington M, Wang S, Martin MP, Gao X, Schiffman M, Cheng J, et al. Hierarchy of resistance to cervical neoplasia mediated by combinations of killer immunoglobulin-like receptor and human leukocyte antigen loci. J Exp Med 2005; 201:1069–75. [PubMed: 15809352]
220. Guerini FR, Mancuso R, Agostini S, Agliardi C, Zanzottera M, Hernis A, et al. Activating KIR/HLA complexes in classic Kaposi's Sarcoma. Infect Agent Cancer 2012; 7:9. [PubMed: 22469025]
221. Hiby SE, Apps R, Sharkey AM, Farrell LE, Gardner L, Mulder A, et al. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. Journal of Clinical Investigation 2010; 120:4102–10. [PubMed: 20972337]
222. Hiby SE, Regan L, Lo W, Farrell L, Carrington M, Moffett A. Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Human Reproduction 2008; 23:972–6. [PubMed: 18263639]
223. Faridi RM, Agrawal S. Killer immunoglobulin-like receptors (KIRs) and HLA-C allorecognition patterns implicative of dominant activation of natural killer cells contribute to recurrent miscarriages. Hum Reprod 2011; 26:491–7. [PubMed: 21159685]
224. Kitawaki J, Xu B, Ishihara H, Fukui M, Hasegawa G, Nakamura N, et al. Association of killer cell immunoglobulin-like receptor genotypes with susceptibility to endometriosis. Am J Reprod Immunol 2007; 58:481–6. [PubMed: 17997746]
225. Nowak I, Ploski R, Barcz E, Dziunycz P, Kaminski P, Kostrzewa G, et al. KIR2DS5 in the presence of HLA-C C2 protects against endometriosis. Immunogenetics 2015; 67:203–9. [PubMed: 25724317]
226. Chen H, Hayashi G, Lai OY, Dilthey A, Kuebler PJ, Wong TV, et al. Psoriasis Patients Are Enriched for Genetic Variants That Protect against HIV-1 Disease. PLoS Genetics 2012; 8:e1002514. [PubMed: 22577363]
227. Nelson GW, Martin MP, Gladman D, Wade J, Trowsdale J, Carrington M. Cutting Edge: Heterozygote Advantage in Autoimmune Disease: Hierarchy of Protection/Susceptibility Conferred by HLA and Killer Ig-Like Receptor Combinations in Psoriatic Arthritis. The Journal of Immunology 2004; 173:4273–6. [PubMed: 15383555]
228. Chandran V, Bull SB, Pellett FJ, Ayearst R, Pollock RA, Gladman DD. Killer-cell immunoglobulin-like receptor gene polymorphisms and susceptibility to psoriatic arthritis. Rheumatology 2014; 53:233–9. [PubMed: 24185760]
229. Fusco C, Guerini FR, Nocera G, Ventrella G, Caputo D, Valentino MA, et al. KIRs and their HLA ligands in remitting-relapsing multiple sclerosis. J Neuroimmunol 2010; 229:232–7. [PubMed: 20826009]
230. Garcia-Leon JA, Pinto-Medel MJ, Garcia-Trujillo L, Lopez-Gomez C, Oliver-Martos B, Prat-Arrojo I, et al. Killer cell immunoglobulin-like receptor genes in Spanish multiple sclerosis patients. Mol Immunol 2011; 48:1896–902. [PubMed: 21665278]
231. Jelčić I, Hsu KC, Kakalacheva K, Breiden P, Dupont B, Uhrberg M, et al. Killer immunoglobulin-like receptor locus polymorphisms in multiple sclerosis. Multiple Sclerosis Journal 2012; 18:951–8. [PubMed: 22185807]
232. Wilson TJ, Jobim M, Jobim LF, Portela P, Salim PH, Rosito MA, et al. Study of killer immunoglobulin-like receptor genes and human leukocyte antigens class I ligands in a Caucasian Brazilian population with Crohn's disease and ulcerative colitis. Hum Immunol 2010; 71:293–7. [PubMed: 20036705]
233. Díaz-Peña R, Vidal-Castiñeira JR, Moro-García MA, Alonso-Arias R, Castro-Santos P. Significant association of the KIR2DL3/HLA-C1 genotype with susceptibility to Crohn's disease. Human Immunology 2016; 77:104–9. [PubMed: 26542067]
234. Hollenbach JA, Ladner MB, Saeteurn K, Taylor KD, Mei L, Haritunians T, et al. Susceptibility to Crohn's disease is mediated by KIR2DL2/KIR2DL3 heterozygosity and the HLA-C ligand. Immunogenetics 2009; 61:663–71. [PubMed: 19789864]
235. Saito H, Hirayama A, Umemura T, Joshita S, Mukawa K, Suga T, et al. Association between KIR-HLA combination and ulcerative colitis and Crohn's disease in a Japanese population. PLOS ONE 2018; 13:e0195778. [PubMed: 29649328]

236. Hou Y, Zhang C, Xu D, Sun H. Association of killer cell immunoglobulin-like receptor and human leucocyte antigen-Cw gene combinations with systemic lupus erythematosus. Clin Exp Immunol 2015; 180:250–4. [PubMed: 25581336]

237. Gambino CM, Di Bona D, Aiello A, Carru C, Duro G, Guggino G, et al. HLA-C1 ligands are associated with increased susceptibility to systemic lupus erythematosus. Hum Immunol 2018; 79:172–7. [PubMed: 29395276]

238. van der Slik AR, Koeleman BP, Verduijn W, Bruining GJ, Roep BO, Giphart MJ. KIR in type 1 diabetes: disparate distribution of activating and inhibitory natural killer cell receptors in patients versus HLA-matched control subjects. Diabetes 2003; 52:2639–42. [PubMed: 14514651]

239. Shastry A, Sedimbi SK, Rajalingam R, Nikitina-Zake L, Rumba I, Wigzell H, et al. Combination of KIR 2DL2 and HLA-C1 (Asn80) confers susceptibility to type 1 diabetes in Latvians. International Journal of Immunogenetics 2008; 35:439–46. [PubMed: 19046302]

240. Osman AE, Eltayeb EN, Mubasher M, Al Harthi H, Alharbi S, Hamza MA, et al. Investigation of activating and inhibitory killer cell immunoglobulin-like receptors and their putative ligands in type 1 diabetes (T1D). Hum Immunol 2016; 77:110–4. [PubMed: 26542066]

241. Jobim M, Chagastelles P, Salim PH, Portela P, Wilson TJ, Curti AG, et al. Association of killer cell immunoglobulin-like receptors and human leukocyte antigen-C genotypes in South Brazilian with type 1 diabetes. Hum Immunol 2010; 71:799–803. [PubMed: 20580654]

242. Augusto DG, Lobo-Alves SC, Melo MF, Pereira NF, Petzl-Erler ML. Activating KIR and HLA Bw4 Ligands Are Associated to Decreased Susceptibility to Pemphigus Foliaceus, an Autoimmune Blistering Skin Disease. PLoS ONE 2012; 7:e39991. [PubMed: 22768326]

243. Augusto DG, O'Connor GM, Lobo-Alves SC, Bass S, Martin MP, Carrington M, et al. Pemphigus is associated withKIR3DL2expression levels and provides evidence that KIR3DL2 may bind HLA-A3 and A11 in vivo. European Journal of Immunology 2015; 45:2052–60. [PubMed: 25867094]

244. Lopez-Larrea C, Blanco-Gelaz MA, Torre-Alonso JC, Bruges Armas J, Suarez-Alvarez B, Pruneda L, et al. Contribution of KIR3DL1/3DS1 to ankylosing spondylitis in human leukocyte antigen-B27 Caucasian populations. Arthritis Res Ther 2006; 8:R101. [PubMed: 16805919]

245. Tajik N, Shahsavar F, Poormoghim H, Radjabzadeh MF, Mousavi T, Jalali A. KIR3DL1+HLA-B Bw4Ile80 and KIR2DS1+HLA-C2 combinations are both associated with ankylosing spondylitis in the Iranian population. Int J Immunogenet 2011; 38:403–9.

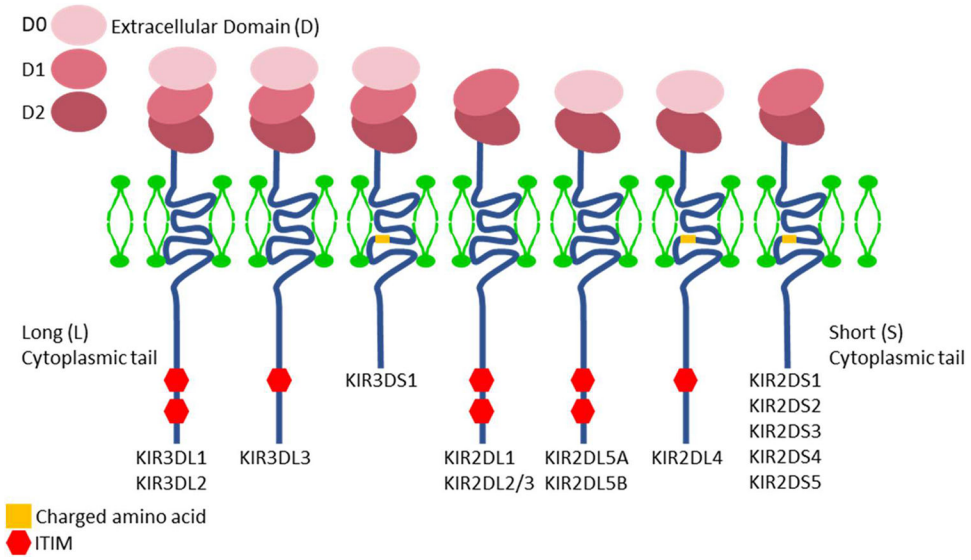

Figure 1. KIR Nomenclature and Function

KIR nomenclature incorporates both structure and function. KIR can have either two (2D) or three (3D) extracellular immunoglobulin domains accompanied by either a long (L) or short (S) cytoplasmic tail; KIR2DL1 or KIR3DS1 for example. Inhibitory KIR have long cytoplasmic tails containing immune tyrosine-based inhibitory motifs (ITIMs), whereas the KIR with short cytoplasmic tails are activating receptors that associate with the DAP12 signaling molecule via a positively charged lysine residue in their transmembrane domain. DAP12 carries immunoreceptor tyrosine-based activation motifs (ITAMs). KIR2DL4 is an exception, having an ITIM domain but also an arginine residue in the transmembrane domain that associates with the activating molecule FcεRI-γ[207]. The alleles of each *KIR* are named in order of discovery, with the first three digits distinguishing each unique protein coding sequence, the fourth and fifth digits depicting synonymous differences in the coding sequence, and the sixth and seventh digits depicting differences in the surrounding introns[58]. 'Allele' refers to each distinct DNA sequence of a given KIR (or HLA) gene, and when this encodes a distinct polypeptide sequence then this is termed an 'allotype'.

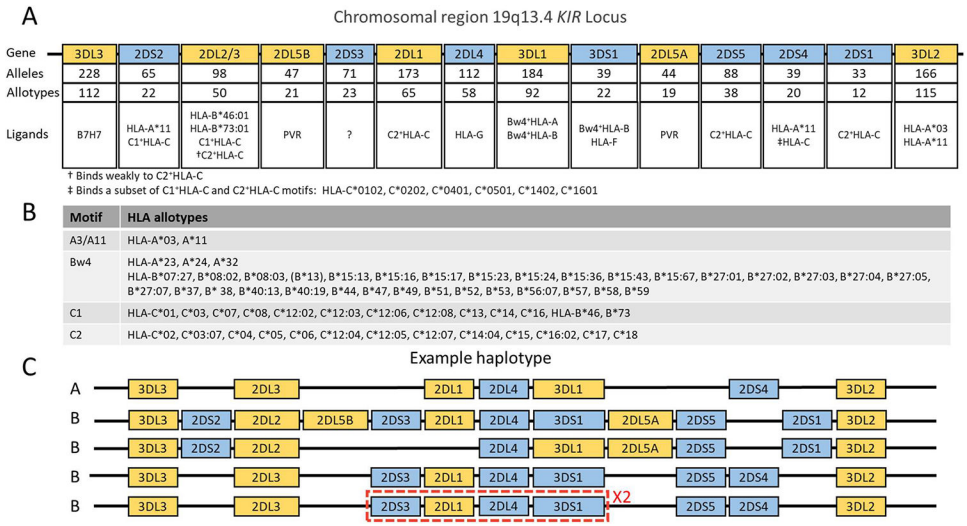

Figure 2. Genomic Arrangement of KIR and List of Cognate Ligands

A: The *KIR* genomic region contains up to 13 distinct genes, encoding inhibitory KIR (yellow), or activating KIR (blue). Below each gene is shown the number of alleles (distinct DNA sequence) and allotypes (distinct polypeptide sequence) of each KIR (as of February 2022)[58]. The known KIR ligands are shown underneath. KIR3DL3 and KIR2DL5A/B do not have known HLA ligands; B7H7[208] is a member of the B7 family and PVR[209] is the polio virus receptor. The ligand for KIR2DS3 remains unknown. *KIR2DL2* and *KIR2DL3* where originally described as distinct genes but are now known to be alleles of the same locus, annotated as *KIR2DL2/3*. The same is true for *KIR3DL1* and *KIR3DS1* (*KIR3DL1/S1*). Here KIR3DL1 and KIR3DS1 are shown separately to differentiate between their known ligands.

B: Lists the HLA class I allotypes that carry specific amino acid motifs enabling their function as KIR ligands. The Bw4 motif is characterized by residues 77-83 (N, L, R, I/T, A, L, R) in the external-facing α1-helix[210] of the listed HLA-A or -B allotypes. Residues 77-80 characterize the C1 (S, L, R, N) and C2 (N, L, R, K) motifs of HLA-C and some HLA-B allotypes. The specific A3/11 motif is unknown. (B*13 may not bind to KIR3DL1 due to specific polymorphism outside of the Bw4 motif[61]). *HLA* alleles are named by colon-separated field; the first field denotes serology type, second field polypeptide sequence (allotype), and subsequent fields depict synonymous and intron variants respectively.

C. Shown is a representation of the *KIR* genomic region, with five examples of haplotypes distinguished by their gene content. Here, haplotype refers to the configuration of genes and/or alleles inherited from one parent. The *KIR-A* haplotype encodes the maximum number of inhibitory KIR specific for HLA class I (KIR2DL1, 2DL3, 3DL1 and 3DL2). The *KIR-B* haplotype is more diverse in gene content and encodes a greater number of activating receptors. The red dashed box spanning *KIR2DS3* to *KIR3DS1* on the lower haplotype is to highlight a known segmental duplication that can occur on the *KIR-B* haplotype[44].

Table 1:
KIR/HLA associations with infection diseases, reproductive health and autoimmunity

Shown are associations of specific KIR and HLA allotype combinations with infection, reproductive health, or autoimmunity. The alleles found to have the greatest effect on the association are given where reported (most studies to date have analyzed KIR gene content only). Associations were included if they represent known receptor ligand combinations, the p values were corrected for multiple testing, and if there was no reported and/or observed inaccuracies in the statistical analysis or methods. Additional individual KIR and HLA associations are collated in the KIR and Diseases Database[170].

Condition	KIR	HLA	Allele(s) of greatest effect	Risk/ Protective	Study population	Reference
Infectious diseases						
HIV-1	3DL1	Bw4^{+}HLA	High expressing 3DL1 (e.g.*015)	Protective	USA mixed ancestry	131, 149
	3DS1	Bw4^{+}HLA		Protective	USA mixed ancestry	211
Hepatitis C virus	2DL3	C1^{+}HLA-C		Protective	USA mixed ancestry	133
	2DS2	HLA-C*01:02		Protective	UK	67
Hepatitis B virus	2DL3	C1^{+}HLA-C		Protective	Han Chinese	212
Human cytomegalovirus	*KIR-A* haplotype	Bw4^{+}HLA		Risk	Italy	213
	2DL1	C2^{+}HLA-C		Protective	Germany	214
Human T-cell leukemia virus -I	2DL2	HLA-C*08		Protective	Japan	30
Dengue virus	2DS2	HLA-C*01:02		Protective	UK	67
	3DL1	HLA-B*57		Risk	Thailand	215
Ebola	3DL1	Bw4^{+}HLA	Low-affinity Bw4^{Thr80}	Risk	Guinea	216
	3DL1	Bw4^{+}HLA	High-affinity Bw4^{Ile80}	Protective	Guinea	216
Malaria	2DL3	C1^{+}HLA-C		Risk	Thailand, North India	157, 217
	2DL1	C1^{+}HLA-C		Protective	Uganda	218
Human papilloma virus (Causing cervical cancer)	3DS1^{neg}	Bw4^{+}HLA, C2^{+}HLA-C		Protective	USA mixed, Puerto Rico	219
Kaposi's sarcoma	2DS1	C2^{+}HLA-C		Risk	Italy	220
Epstein-Barr virus associated Hodgkin lymphoma	2DL2, 2DS2	C1^{+}HLA-C		Protective	Netherlands	104
Bacterial infection (RecA+)	2DS4	HLA-C*05:01		Protective	n/a (functional study)	66
Reproductive health						
Pre-eclampsia	2DS1	C2^{+}HLA-C (fetal)		Protective	UK	221
	KIR-A haplotype	C2^{+}HLA-C (fetal)		Risk	UK, Uganda	135,144
	2DS5	C2^{+}HLA-C (fetal)	2DS5*006	Protective	Uganda	144

Condition	KIR	HLA	Allele(s) of greatest effect	Risk/ Protective	Study population	Reference
Infectious diseases						
	2DL1	C2$^+$HLA-C (fetal)	*KIR-A* haplotype 2DL1 (*001, *002, *003)	Risk	UK	149
Recurrent miscarriage	2DS1	C2$^+$HLA-C		Protective	UK	222
	2DL1	C2$^+$HLA-C		Protective	India	223
	2DS2	C1$^+$HLA-C		Risk	India	223
Low birth weight	2DS1	C2$^+$HLA-C (fetal)		Protective	UK, Norway	136
Endometriosis	3DL1	Bw4$^+$HLA		Risk	Japan	224
	2DS5	C2$^+$HLA-C		Protective	Poland	225
Autoimmunity						
Psoriasis	2DS1	HLA-C*06		Risk	Poland	172
	3DS1	Bw4$^+$HLA		Risk	European	226
Psoriatic arthritis	2DS1, 2DS2	HLA-C		Risk	Canada	227
	2DS2	C1$^+$HLA-C		Risk	Canada	228
Multiple sclerosis	2DS1	C2$^+$HLA-C		Protective	Italy	229
	2DL1	C2$^+$HLA-C		Risk	Spain	230
	3DL1	Bw4$^+$HLA		Protective	Spain, African American	230, 179
	2DL3	C1$^+$HLA-C		Protective	Germany	231
Crohn's disease	2DL2	C1$^+$HLA-C		Protective	Brazil	232
	2DL3	C1$^+$HLA-C		Risk	Spanish	233
	2DL2/3	C1+HLA-C		Risk	USA European/ Jewish	234
	2DL2/3	C2+HLA-C		Protective	USA European/ Jewish	234
	3DL1	Bw4$^+$HLA		Risk	Japan	235
Ulcerative colitis	2DL2	C1$^+$HLA-C		Protective	Brazil	232
	3DL1	Bw4$^+$HLA		Risk	Japan	235
	2DL1	C2$^+$HLA-C		Protective	Japan	235
Systemic lupus erythematosus	2DS1	C2$^+$HLA-C		Risk	Han Chinese	236
	2DS2	C1$^+$HLA-C		Risk	Italy	237
Type 1 diabetes	2DS2	C1$^+$HLA-C		Risk	Netherlands, Latvia	238, 239
	2DL2/L3	C1$^+$HLA-C		Risk	Latvia	239
	2DL1	C2$^+$HLA-C		Protective	Saudi, Brazil	240,241
Pemphigus Foliaceus	3DS1	Bw4$^+$HLA		Protective	Brazil	242
	3DL2	HLA-A*03/*11	3DL2*001	Risk	Brazil	243
Ankylosing spondylitis	3DS1	Bw4$^+$HLA		Risk	Spain, Portugal	244
	3DL1	Bw4$^+$HLA		Protective	Spain, Portugal, Iran	244, 245
	2DS1	C2$^+$HLA-C		Risk	Iran	245

Condition	KIR	HLA	Allele(s) of greatest effect	Risk/ Protective	Study population	Reference
Infectious diseases						
Atopic dermatitis	2DS5, 2DS1	$C2^{+}$HLA-C		Risk	USA mixed	[177]