

# The impact of KIR polymorphism on the risk of developing cancer: not as strong as imagined?

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*Submitted to Journal:*  
Frontiers in Genetics

*Specialty Section:*  
Cancer Genetics

*Article type:*  
Mini Review Article

*Manuscript ID:*  
168136

*Received on:*  
07 Sep 2015

*Frontiers website link:*  
[www.frontiersin.org](http://www.frontiersin.org)

### *Conflict of interest statement*

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

### *Author contribution Statement*

DGA wrote this manuscript

### *Keywords*

Killer cell immunoglobulin-like receptors, HLA genes, Cancer, Association, susceptibility

### *Abstract*

Word count: 116

The polymorphism of killer cell immunoglobulin-like receptors (KIR) has been associated with several diseases, including infection, autoimmunity and cancer. KIR molecules are superfamily of receptors expressed on the surface of natural killer cells (NK), frontline defense of innate immunity against microorganisms and neoplastic cells. Some studies have shown conflicting results concerning the role that KIR polymorphism plays in tumor susceptibility, particularly in leukemia and lymphoma. Interestingly, the presence of HLA ligands is sometimes strongly associated with several types of cancer and apparently is not related with their interaction with KIR. This manuscript briefly reviews the uncommon polymorphism of KIR and critically summarizes the recent findings with regards of the importance of KIR variation for cancer susceptibility.

# The impact of *KIR* polymorphism on the risk of developing cancer: not as strong as imagined?

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## Abstract

The polymorphism of killer cell immunoglobulin-like receptors (*KIR*) has been associated with several diseases, including infection, autoimmunity and cancer. *KIR* molecules are superfamily of receptors expressed on the surface of natural killer cells (NK), frontline defense of innate immunity against microorganisms and neoplastic cells. Some studies have shown conflicting results concerning the role that *KIR* polymorphism plays in tumor susceptibility, particularly in leukemia and lymphoma. Interestingly, the presence of HLA ligands is sometimes strongly associated with several types of cancer and apparently is not related with their interaction with *KIR*. This manuscript briefly reviews the uncommon polymorphism of *KIR* and critically summarizes the recent findings with regards of the importance of *KIR* variation for cancer susceptibility.

## 1. Introduction

Natural killer (NK) are large granular cells that constitute of approximately 5-15% of the total circulating lymphocytes in healthy individuals. These cells were initially discovered because of their ability to kill virus-induced murine leukemic cells without prior sensitization (Herberman and Ortaldo, 1981; Kiessling et al., 1975). NK are implicated in tumor surveillance and early recognition of microbial infections.

NK cells are armed with variety receptors that can either enhance or diminish the NK response against the target cell. Within the diversity of NK receptors, there are some of them that recognize soluble ligands while others interact with cell surface molecules. Included in this panel of molecules, are the killer cell immunoglobulin-like receptors (KIR), which are a family of receptors encoded by a region at chromosome 19 called leukocyte receptor complex (LRC) (Wilson et al., 2000).

As consequence of infection or malignance, cells may exhibit reduced expression of MHC molecules. NK cells are able to recognize and to attack cells with low expression of self-MHC molecules, in a model called “missing self” (Kärre, 2002; Vivier and Romagné, 2007). Nowadays, it’s known that a fine balance of activating and inhibitory signals generated by the NK receptors regulate the NK activity (Parham, 2004). Activating and inhibitory signals transduced by KIR are important to modulate NK cell response, allowing these cells to eliminate abnormal threats. *KIR* polymorphism has been associated with infection, autoimmunity and cancer (Augusto et al., 2012a; 2015b; Khakoo and Carrington, 2006; Kulkarni et al., 2008; Martin et al., 2007; van der Slik et al., 2003). The importance of KIR for reproduction is also well documented (Hiby et al., 2004; 2014; Nakimuli et al., 2015; Trowsdale and Moffett, 2008). There are strong evidences that KIR and HLA are coevolving as an integrated system (Augusto and Petzl-Erler, 2015) and that KIR-driven pressures are balancing HLA haplotypes (Augusto et al., 2015a; Capittini et al., 2012; Fasano et al., 2014; Nemat-Gorgani et al., 2014). This review will focus on the studies that have investigated the *KIR* variation and its association with the risk of developing cancer.

## 2. The *KIR* complex and its uncommon polymorphism

The *KIR* gene complex is located at 19q13.42 (Liu et al., 2000; Wende et al., 1999), a cluster of homologous genes that has suffered extensive expansion and contraction (Martin et al., 2003; Wende et al., 1999). As consequence, *KIR* genes exhibit an uncommon presence/absence polymorphism that result in an extensive variety of haplotypes. More than 500 *KIR* gene-content genotypes have been described among over 200 worldwide populations (Gonzalez-Galarza et al., 2015). Another level of diversity is conferred by the presence of a large number of alleles in each locus, what makes the *KIR* cluster extremely polymorphic.

The nomenclature of *KIR* genes is based on the structure of the mature protein. *KIR* genes encode two or three (2D or 3D) extracellular immunoglobulin domains that may have short (S) or long (L) cytoplasmic tails (Long et al., 1996). Except by KIR2DL4 (Kikuchi-Maki et al., 2003), all molecules that present long cytoplasmic tails are inhibitory and all KIR that present short tails are activating. *KIR* haplotypes can be

divided in two major groups: (1) haplogroup A, which classically consists of a fixed number of genes, mostly inhibitory, and (2) haplogroup B, composed by a large variation of gene-content combinations, characterized by the presence of more activating genes (Uhrberg et al., 2002). The polymorphism of *KIR* has been studied in several populations across the globe (Augusto et al., 2012b; 2013; 2015a; Hollenbach et al., 2012a; 2012b; Norman et al., 2001). Yet *KIR* allele polymorphism is poorly known.

HLA (human leukocyte antigens) class I are MHC molecules whose polymorphism has been associated with innumerable diseases. Additionally, they are known ligands for *KIR*. HLA-C2 allotypes are recognized by *KIR2DL1* (Fan et al., 1996; Wagtmann et al., 1995; Winter and Long, 1997); *KIR2DS1* also binds HLA-C2, but at lower affinity (Stewart et al., 2005). HLA-C1 and some C2 allotypes are bound by *KIR2DL2/3* (Winter et al., 1998), and predicted to be ligand for *KIR2DS2/3*. HLA function is primarily related to presentation of antigens and regulation of immune responses. During the course of evolution, HLA-A and HLA-B apparently kept their main role as T cell receptor (TCR) ligands while HLA-C seems to have had evolved as primarily *KIR* ligands (Older Aguilar et al., 2010). Still, several HLA-A and -B molecules interact with *KIR*. HLA-Bw4, that comprises about 40% of all HLA-B molecules (Müller et al., 1989) plus a subset of HLA-A (A\*23, A\*24 and A\*32)(Kostyu et al., 1980), are recognized by *KIR3DL1* (Cella et al., 1994; Stern et al., 2008). Despite the lack of direct evidence (Gillespie et al., 2007; O'Connor et al., 2007), the homology with *KIR3DL1* and the numerous disease association studies suggest that *KIR3DS1* also recognize HLA-Bw4. *KIR3DL2* recognizes HLA-A3/A11 (Döhring et al., 1996; Hansasuta et al., 2004), B27 (Hatano et al., 2015; Shaw et al., 2014) and HLA-F (Goodridge et al., 2013). Product of gene conversion with *KIR3DL2*, *KIR2DS4* also binds HLA-A11 (Graef et al., 2009) and HLA-F (Goodridge et al., 2013). HLA-A11 is also ligand for *KIR2DS2* (Liu et al., 2014).

### 3. *KIR* polymorphism in leukemia

Acute lymphoblastic leukemia (ALL) is a malignancy in the bone marrow that leads to abnormal production and consequent excess of juvenile lymphocytes. ALL comprises approximately 75% of all cases of leukemia and normally occurs in children. ALL is a heterogeneous group of cancers that typically implicates B- or T-cell precursors, therefore subdivided in B-ALL or T-ALL. Differently, chronic lymphocytic leukemia (CLL) is a slow-growing tumor of lymphoid cells and usually occurs in individuals over 55 years of age. Myeloid leukemia causes rapid growth of myeloid cells; its acute form (AML) occurs either in children or in adults and its chronic form (CML) affects primarily adults.

The importance of *KIR* polymorphism in leukemia was initially explored by Verheyden et al., who reported *KIR2DL2* and *KIR2DS2* increased in patients (Verheyden et al., 2004). Both genes are present in haplogroup B; therefore, the authors could demonstrate that haplotype A was increased in controls ( $P_c=0.01$ ). Considering that haplotype A is composed primarily by inhibitory genes, these data suggested that inhibitory *KIR* could protect against leukemia. Limitations of this study were the mixture

of all four types of leukemia listed above within the patient group and the fact that the impact of *KIR* polymorphism in each form is not necessarily the same. Despite these limitations and the difficulty to explain why inhibitory *KIR* haplotypes were protective, the association of *KIR* polymorphism and leukemia appeared substantial. However, these results could not be totally supported in a larger Chinese cohort (Zhang et al., 2010). Zhang and colleagues showed that even though *KIR2DL2* was increased in patients, it was not statically significant ( $p=0.10$ ). They demonstrated, however, that the presence of *KIR2DS4*, the most frequent short-tailed activating gene, was associated with increased susceptibility. Although this association was significant in the total patients' sample ( $OR=1.76$ ,  $p=0.008$ ), this effect seemed to be driven by CML subgroup ( $OR=3.29$ ,  $p<0.001$ ). Although Zhang's study did not analyze *KIR* haplotypes, activating *KIR* were slightly more frequent in patients (but not significant), what partially corroborates Verheyden's findings. In opposition to these previous results, Middleton et al. showed that *KIR2DL2* was protecting against leukemia (Middleton et al., 2009).

In 2011, Almalte and colleagues analyzed a Canadian-French cohort composed by 145 B-ALL patients and 30 T-ALL and compared them to 245 controls (Almalte et al., 2011). In that study, they showed strong protective associations for the presence of all six activating *KIR* analyzed. The absence of data for the *KIR* inhibitory genes in that study, however, difficulties the interpretation these results due to the impossibility of analyzing the linkage disequilibrium between loci or of verifying the *KIR* genotypes/haplotypes. Remarkably, an European cohort was further analyzed by Babor et al. and their results diverged from all former studies (Babor et al., 2012). In Babor's study, there were no significant differences of *KIR* frequencies between the Canadian-French and the previously studied European cohorts, but still, no associations were found. After that, another research group analyzed over 300 patients and performed another study (Oevermann et al., 2015). Applying careful and rigorous analyzes, Oevermann et al. corroborated Babor's results and reported absence of association of *KIR* variation and leukemia. Lack of association was once again reported in Thai patients (Vejbaesya et al., 2014).

Subsequent results brought some light to this discussion by showing the presence of homozygosity for haplotype A associated with increased risk of developing leukemia in Hispanic (de Smith et al., 2014). Because of inhibitory genes, mostly compose haplotype A, this result partially corroborated previous protective associations with the presence of activating genes from Almalte's group. In the same study, however, de Smith et al. also showed absence of association in Euro-descendants, which simultaneously corroborated other studies that had reported absence of association in Europeans (Babor et al., 2012; Oevermann et al., 2015). De Smith's results suggested the possibility of the role played by *KIR* in leukemia to vary among ethnic groups. Interestingly, three studies have shown stronger associations of leukemia with HLA: HLA-C2 (Babor et al., 2014) and specially HLA-Bw4 (Bw4/Bw4;  $OR=3.9$   $p=0.01$ ) (de Smith et al., 2014) and Bw4Ile80 ( $OR=3.32$ ,  $p=0.0005$ ). Although Bw4 and C2 are putative *KIR* ligands, due to conflicting results regarding *KIR* in leukemia, it is difficult to believe that these associations are related to *KIR* interaction but other HLA immune responses.

Together, all these studies lead us to interpret that *KIR* genes probably don't play a major role in leukemia susceptibility, and this effect may vary in different ethnic

groups. Additionally, *HLA* polymorphism has a stronger effect in leukemia susceptibility than *KIR*. This conclusion is also supported by another study, which showed only a trend of association for the presence of five or six activating *KIR* genes ( $p=0.06$ ), but a strong association for the presence of Bw4 ( $OR=0.56$ ;  $p=0.005$ ) in CLL patients (Karabon et al., 2011). Another interesting result from this same study is that, in general, the combinations *KIR3DL1/S1+Bw4* presented similar odds ratios when compared to Bw4 alone. The association of *KIR3DS1+Bw4* was only slightly stronger than Bw4 individually ( $OR=0.46$ ;  $p=0.003$ ); therefore, the effect appears to be driven mostly by Bw4. To explore *KIR-HLA* in the allelic level or expression studies like the one performed by Obama et al. (Obama et al., 2007) could be a key to bring some light to this subject.

#### 4. Lymphoma and multiple myeloma

The presence of large tumor cells derived from a germinal center B cell, known as Hodgkin and Reed-Sternberg, characterizes Hodgkin lymphoma (HL) (Re et al., 2005). Epstein-Barr virus (EBV) is the major environmental factor associated with HL; approximately 40% of HL patients in the Western community tested positive for EBV (Küppers, 2009). Considering the importance of *KIR* for virus elimination, it is plausible to consider them as candidate genes for HL association studies. A familial study with 90 French families and 255 first-degree siblings was the first analysis of *KIR* polymorphism in HL (Besson et al., 2007). They reported negative association for the presence of *KIR3S1*, *KIR2DL5*, *KIR2DS1* and *KIR2DS5* ( $0.42 < OR < 0.56$ ;  $0.006 < P < 0.05$ ). In that same study, they could not replicate these results in a case-control study with 68 patients. Lack of association was also reported in a Lebanese cohort, a case control study with 41 patients and 120 controls (Hoteit et al., 2015). It is important to notice that both case-control studies that reported lack of association were composed of small samples sizes, what makes difficult to exclude the relevance of *KIR* polymorphism for HL pathogenesis. Furthermore, a familial study is more powerful than a case-control study, especially in the example above, in which Besson et al. performed deep analyzes, including EBV status of each HL patient.

*KIR* variation was also studied in non-Hodgkin lymphomas and multiple myeloma. Although no associations were reported for follicular lymphoma (Khalaif et al., 2013), the sample size was too small for conclusions (20 patients and 62 controls). Similarly from what was shown for ALL, no associations were seen for individual *KIR* genes in diffuse large B-cell lymphoma (DLBCL) (Vejbaesy et al., 2014). Similar to other cancers, despite the lack of association with *KIR* variation in DLBCL, significant association was reported for the presence of HLA-Bw4 ( $OR=0.39$ ;  $p=0.003$ ). Similar odds ratio was seen for the combination *KIR3DL1+HLA-Bw4* ( $OR=0.34$ ;  $p=0.0006$ ), what suggests that *HLA* alone is driving the effect. In multiple myeloma, *KIR2DS5* and some alleles of *KIR2DS4* were associated with increased risk (Hoteit et al., 2014), but similarly to other studies analyzing lymphoma patients, the sample size was not large enough to allow more conclusive assumptions. Comprehensive studies with large and well-characterized cohorts need to be performed to verify the real impact of *KIR-HLA* in these diseases.

## 5. Breast cancer

A pilot study analyzed the presence/absence of *KIR* in breast cancer (Ozturk et al., 2012). In that study, the authors analyzed 33 patients and 77 controls and reported borderline associations: *KIR2DS1* associated with increased risk ( $p=0.03$ ) and *KIR2DL1* increased in controls ( $p=0.02$ ). In addition, the authors performed allelic typing for *KIR2DS4* and the alleles *KIR2DS4\*003/4/6/7* were overrepresented in controls ( $p=0.03$ ). Although the authors suggested that *KIR* variation might be involved in breast cancer pathogenesis, the small cohort and the borderline associations didn't provide conclusive results. These suggestions could not be corroborated by another study in a larger cohort of predominantly euro-descendants from Brazil (230 patients and 278 controls) (Jobim et al., 2013). Jobim et al. reported a strong association for the presence of *KIR2DL2* ( $OR=2.7$ ;  $p<10^{-8}$ ) and for the presence of HLA-C1 ( $OR=2.7$ ;  $p<10^{-7}$ ). The strong associations reported for breast cancer in the Brazilian cohort suggest that *KIR2DL2* combined with its ligand C1 are, in fact, altering susceptibility to breast cancer. It is important to notice that the combination *KIR2DL2+C1* in the absence of *KIR2DS2* presented odds ratio as strong as 9.9 ( $P<0.001$ ).

## 6. Colon and rectal cancers

Absence of association of *KIR* with colorectal cancer was reported in Europeans (Middleton et al., 2007); different from Koreans, in which *KIR2DS5* was increased in patients ( $OR=1.9$ ;  $p=0.0007$ ) (Kim et al., 2014). Al Omar et al. also reported lack of association of *KIR* and colon cancer (Omar et al., 2010); interestingly, they showed a strong association of the presence of HLA-Bw4 (Bw4Ile80,  $OR=3.1$ ,  $p=0.0001$ ; Bw4The80,  $OR=0.3$ ,  $p=0.0001$  in individuals *KIR3DL1+Bw4+*). HLA-Bw4Ile80 is a stronger ligand for *KIR* (Cella et al., 1994); although this association suggests that *KIR* may interfere in the susceptibility of colon cancer, it is important to note the lack of association for *KIR+HLA* combinations.

## 7. Other cancers

Figure 1 and table 1 summarize the associations and effect seen for *KIR* and ligands in several types of cancer. Nasopharyngeal cancer (NPC) is another example of neoplasm in which *HLA* polymorphism plays a major role in its susceptibility. In Chinese, HLA-B58 and HLA-A11 have been shown to confer risk and protection, respectively, for the development of NPC (Chan et al., 1983; Hildesheim et al., 2002; Lu et al., 2003). Even though HLA-A11 is a ligand for *KIR3DL2* and *KIR2DS4* (Döhring et al., 1996; Graef et al., 2009; Hansasuta et al., 2004), these relationships have not been investigated in NPC yet. The presence of five or more activating *KIR* conferred risk to EBV positive NPC patients; HLA-Cw4 was also reduced in NPC patients (Butsch Kovacic et al., 2005). *HLA* polymorphism seems to play a strong effect also in other

cancers, such melanoma and ovarian, when comparing to a small or no effect of *KIR* for the susceptibility of those diseases (Giebel et al., 2014; Naumova et al., 2005).

The combination KIR2DL2+C1/C1 was strongly associated with protection in kidney patients ( $OR=0.08$ ;  $p=0.002$ ,  $n=40$  patients). Similarly from what was seen for breast cancer, the combination KIR-HLA showed stronger effect than either *KIR* or HLA isolated, suggesting the role of KIR-HLA combinations for the risk to develop this disease (Giebel et al., 2014; Naumova et al., 2007; Omar et al., 2010).

Activating *KIR* genes were associated with Kaposi's sarcoma (KS), a complication of KS-associated herpesvirus (KSHV) infection (Antman and Chang, 2000). Activating genes (*KIR2DS1*, *KIR3DS1*, and the combination *KIR2DS1+HLA-C2*) were significantly increased in individuals with classic KS (Guerini et al., 2012). Goedert et al. showed that KIR activation might decrease the risk of KSHV infection in an Italian cohort, while might enhance KSHV dissemination and progression to KS if infection occurs (Goedert et al., 2015).

## 8. Concluding remarks

Several studies have been performed to evaluate the importance of *KIR* for the risk of developing different cancers. Small patient and control samples analyzed in many studies limited the statistical power and the possibility of conclusive results. For other cases, such leukemia and lymphoma, different authors have reported multiple divergent results. It is interesting, however, that despite the conflicting results and sometimes lack of association with *KIR* polymorphism, the presence of HLA ligands has been consistently associated with different types of cancer. Even more interesting is the fact that, in many studies, combinations KIR-HLA don't exhibit stronger effect than HLA isolated, what suggests that the association with HLA is possibly not always related to KIR interaction. Together, all these studies suggest that KIR presence/absence polymorphism possibly don't play a major role in cancer. In other words, *HLA* might have a stronger effect than *KIR* in cancer susceptibility, possibly not related to NK modulation.

However, strong associations of *KIR* polymorphism with several tumors demonstrate that these genes play an important role in cancer, and it may vary according ethnicity or clinical forms. Analyses of KIR-HLA combinations may help to understand the tumor pathogenesis and they may contribute to comprehend the complexity of KIR-HLA as a unique system. Surprisingly, the effect of KIR-HLA interaction in cancer does not appear to be as strong as expected, considering the importance of NK cells for killing neoplastic cells. Larger cancer cohorts and different approaches, such allelic typing and functional analyzes are urged to profound the understanding of KIR-HLA combinations in cancer.

## Acknowledgements

Thanks to Maria Dias da Silva and Danielle Malheiros for kindly reading this manuscript.

		OR / effect	P	N	Reference
Leukemia	2DL2	<b>risk</b>	0.007	94	(Verheyden et al., 2004)
	2DS2	<b>risk</b>	0.022	94	
	A/A genotype	<b>protection</b>	0.011	94	
	2DS4	<b>1.76</b>	0.008	263	
	2DS4 in CML	<b>3.29</b>	<0.001	135	(Zhang et al., 2010)
	2DL2	<b>0.61</b>	0.029	158	(Middleton et al., 2009)
	2DL2 in CML	<b>0.39</b>	0.004	52	
	Bw4 Ile80	<b>1.72</b>	0.018	158	
	Bw4 Ile80 in AML	<b>3.32</b>	<0.001	54	
	2DL2+C1	<b>0.55</b>	0.009	158	
Lymphoma	2DL2+C1 in CML	<b>0.28</b>	<0.001	52	
	2DS2+C1	<b>0.58</b>	0.018	158	
	2DS2+C1 in CML	<b>0.33</b>	0.002	52	
	2DS1	<b>0.55</b>	0.020	100	(Almalte et al., 2011)
	2DS2	<b>0.19</b>	<0.001	100	
	2DS3	<b>0.32</b>	<0.001	100	
	2DS4	<b>0.49</b>	0.004	100	
	2DS5	<b>0.32</b>	<0.001	100	
	3DS1	<b>0.27</b>	<0.001	100	
	>4 activating KIR	<b>0.06</b>	<0.001	100	
Breast cancer	lack of association with KIR	<b>NA</b>		220	(Babor et al., 2012)
	A/A in Hipanic	<b>1.86</b>	0.03	114	(de Smith et al., 2014)
	A/A in Euro-descendants	<b>NA</b>	0.37	76	
	Bw4/Bw4 in Euro-descendants	<b>3.93</b>	0.01	76	
	Lack of association for KIR2DL1/S1 alleles	<b>NA</b>		320	(Babor et al., 2014)
	C1/C1 in ALL	<b>0.69</b>	0.005	320	
	lack of association with KIR in B-CLL	<b>NA</b>		197	(Karabon et al., 2011)
	Bw4	<b>0.56</b>	0.005	197	
	3DS1 (familial study) in HL	<b>0.44</b>	0.006	345*	(Besson et al., 2007)
	2DL5 (familial study) in HL	<b>0.56</b>	0.02	345*	
Oncology	2DS1 (familial study) in HL	<b>0.42</b>	0.01	345*	
	2DS4full (familial study) HL	<b>2.22</b>	0.03	345*	
	lack of association with KIR (case-control)	<b>NA</b>		68	
	lack of association with KIR in HL	<b>NA</b>		41	(Hoteit et al., 2015)
	lack of association with KIR in FL	<b>NA</b>		20	(Khalaf et al., 2013)
	lack of association with KIR in DLBCL	<b>NA</b>		60	(Vejbaesy et al., 2014)
	Bw4 in DLBCL	<b>0.39</b>	0.003	60	
	3DL1+Bw4 in DLBCL	<b>0.34</b>	0.001	60	

<b>Multiple myeloma</b>	2DS4*001/002	<b>risk</b>	0.04	34	(Hoteit et al., 2014)
	2DS5	<b>risk</b>	0.007	34	
<b>Nasopharyngeal</b>	>5 activating KIR	<b>3.40</b>	0.07	378	(Butsch Kovacic et al., 2005)
<b>Breast cancer</b>	2DL1	<b>risk</b>	0.03	34	(Ozturk et al., 2012)
	2DS1	<b>risk</b>	0.03	34	
	2DS4*003/4/6/7	<b>protection</b>	0.03	34	
	2DL2	<b>2.18</b>	<0.001	230	(Jobim et al., 2013)
	C1	<b>2.71</b>	<0.001	230	
	2DL2+C1 in absence of 2DS2	<b>9.95</b>	<0.001	230	
<b>Colorectal cancer</b>	lack of associations	<b>NA</b>		128	(Omar et al., 2010)
	2DS5	<b>1.9</b>	0.007	241	(Kim et al., 2014)
	lack of association with KIR	<b>NA</b>		75	(Omar et al., 2010)
	Bw4 Ile80 in 3DL1+Bw4+ individuals	<b>3.10</b>	<0.001	75	
	Bw4 Thr80 in 3DL1+Bw4+ individuals	<b>0.30</b>	<0.001	75	
	lack of associations	<b>NA</b>		90	(Middleton et al., 2007)
<b>Melanoma</b>	lack of association with KIR	<b>NA</b>		50	(Naumova et al., 2005)
	C2	<b>0.27</b>	0.017	50	
<b>Ovarian cancer</b>	lack of association with KIR	<b>NA</b>		142	(Giebel et al., 2014)
	C1	<b>3.07</b>	0.002	103	
<b>Kidney cancer</b>	2DL3+C1	<b>5.90</b>	0.009	40	(Omar et al., 2010)
	2DL2+C1-	<b>0.08</b>	0.002	40	
<b>Kaposi's sarcoma</b>	2DS1	<b>3.82</b>	0.008	32	(Guerini et al., 2012)
	3DS1	<b>4.00</b>	0.006	32	
	2DS1+C2	<b>4.24</b>	0.01	32	
	KIR3DS1+Bw4 Ile80	<b>0.60</b>	0.01	250	(Goedert et al., 2015)
<b>Lung cancer</b>	2DL3+C1/C1	<b>0.58</b>	0.007	186	(Omar et al., 2011)
<b>Prostate cancer</b>	lack of associations	<b>NA</b>		185	(Portela et al., 2012)
<b>Bladder cancer</b>	3DL1	<b>risk</b>	0.011		(Middleton et al., 2007)
	2DS4	<b>risk</b>	0.011		
<b>Laryngeal cancer</b>	lack of associations	<b>NA</b>		70	(Middleton et al., 2007)
<b>Thyroid cancer</b>		<b>1.77</b>	0.036	85	(Ashouri et al., 2012)
<b>Neuroblastoma</b>	2DL2	<b>1.57</b>	0.019	201	(Keating et al., 2015)
	2DS2	<b>1.66</b>	0.008	201	

**Table 1 – List of the main association studies that analyzed KIR polymorphism in cancer.**

OR=odds ratio; P=p-value; N=patient sample size; A/A=homozygote genotype for haplogroup A; CML=chronic myeloid leukemia; AML=acute myeloid leukemia; HL=Hodgkin's lymphoma; FL=follicular lymphoma; DLBCL=diffuse large B-cell lymphoma. Red=risk (OR>1); blue=protection (OR<1); green=not associated (NA); \*this is a familial study composed with 345 individuals in total. Not all families were informative for all analyzes.

## **Figure and legend**

### **Figure 1 – Summary of the cancers for which *KIR* polymorphism have been analyzed**

Blue boxes=statistically significant association of cancer with KIR and/or HLA ligand;  
yellow boxes=borderline associations, lack of association or studies with reduced sample size.

In review

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In review

Figure 1.TIF

### Leukemia

Conflicting results: activating genes strongly protective *versus* lack of association. *KIR* genes seem not to play major role in leukemia susceptibility, and the effect may vary across ethnic groups. Presence of HLA-C2 and Bw4 is strongly associated with differential susceptibility and it may not be necessary related to *KIR*

### Lymphoma

Hodgkin's: presence of activating genes was statistically associated in a familial study, but this result was not replicate in two case-control studies.

Non-Hodgkin: HLA-Bw4 was decreased in diffuse large B-cell lymphoma patients.

### Lung cancer

No associations for individual *KIR* or *HLA* genes individually. Borderline associations for some *KIR+HLA* combinations. Only a single case-control study with small sample size.

### Ovarian cancer

Borderline association (risk) with presence of KIR2DS4-full. HLA-C1 strongly associated with risk, probably not related to its interaction with *KIR*.

### Colorectal cancer

Lack of association with *KIR* genes in multiple studies. Strong association with HLA-Bw4, probably not related to *KIR* function

### Breast cancer

*KIR2DL2* and HLA-C1 confers risk.

### Prostate cancer

Lack of associations reported by a single study.

### Laryngeal cancer

Lack of associations reported by a single study.

### Bladder cancer

*KIR3DL1* and *KIR2DS4* decreased in patients. Single study with limited sample size

### Multiple myeloma

*KIR2DS5* increased in patients. in a study with limited sample size

### Melanoma

Presence of HLA-C1 decreased in controls in a limited sample size. No associations with *KIR*.

### Kaposi's sarcoma

*KIR2DS1*, *KIR3DS1* and *KIR2DS1+HLA-C2* confer risk. *KIR* activation protects against infection but enhances progression

### Kidney cancer

No association for individual *KIR* genes. HLA-C1/C1 and Bw4Ile80 decreased in controls. Stronger effect for *KIR2DL2+C1/C1*

### Nasopharingeal

Five or more activating *KIR* slightly increased in EBV positive patients.

### Neuroblastoma

2DL2 and 2DS2 confer increased risk.

### Thyroid cancer

Borderline association (risk) with presence of *KIR2DS5*