

# **Translational Bioinformatics for Immunogenomics**

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# Welcome

A few key web sources include the [Immuno Polymorphism Database](#) and [Allele Frequency Net Database](#).

# Introduction

# 1 Human Leukocyte Antigens

## 1.1 Background

HLA is located on chromosome 6 in the Major Histocompatibility Complex (MHC).

## 1.2 HLA Class I

HLA class I molecules are expressed by healthy nucleated cells.

## 1.3 HLA Class II

HLA class II molecules are expressed by professional antigen-presenting cells (APC)—dendritic cells, macrophages, and B cells.

## 1.4 HLA Nomenclature

## 1.5 Functional Divergence

Heterozygosity of HLA class I genes is associated with better outcomes after HIV infection. This is thought to be due to a greater repertoire of HIV peptides presented and cytotoxic T cell response. However, looking at HLA class I allotype alone does not take into account differences in actual peptide repertoire. Viard and O’Uigin developed a metric to measure this difference, termed “functional divergence.” Functional divergence predicts the peptide repertoire as a continuum. They showed that greater functional divergence was associated with better HIV outcomes. Functional divergence may be relevant to other diseases where HLA heterozygosity confers advantage, such as infection, vaccination, and immunotherapy.

You can download functional divergence estimates for pairwise combinations of HLA-A, HLA-B, and HLA-C alleles from their article’s Supplementary Materials. The functional divergence measure ranges from 0 (i.e., smallest functional divergence) to 1 (i.e., greatest functional divergence).

## 1.6 HLA Imputation Programs

Name	Programming Language	Input Data	Output	Reference
<a href="#">SNP2HLA</a>	Command line in- terface	PLINK binary format	HLA class I and II alleles	<a href="#">Jia, 2013</a>
<a href="#">HIBAG</a>	R	Plink binary format	HLA class I and II alleles	<a href="#">Zheng, 2014</a>

## 2 Killer Cell Immunoglobulin-like Receptors

### 2.1 Background

KIR is located on chromosome 19 (19q13.4) in the Leukocyte Receptor Complex (LRC). KIR is expressed on the surface of Natural Killer (NK) cells and some T cells. KIR do not undergo somatic rearrangement—a key difference from T-cell receptors. KIR interacts with HLA class I—their cognate ligand—to recognize and destroy unhealthy tissue cells while preventing the same from occurring to healthy cells. Therefore, NK cells play a role in fighting infections, resisting some cancers, pregnancy, and preventing autoimmunity. For further reading and references, I highly recommend the review article by Pollock, Harrison, and Norman on the immunogenetics and co-evolution of KIR and HLA class I.

### 2.2 KIR Locus

Gene

3DL3

2DS2

2DL2/3

2DL5B

2DS3

2DL1

2DL4

3DL1

3DS1

2DL5A

2DS5

2DS4

2DS1

3DL2

Func.

Inhibit.

Activ.

Inhibit.

Inhibit.

Activ.

Inhibit.

Activ.

Inhibit.

Activ.

Inhibit.

Activ.

Activ.

Activ.

Inhibit.

Alleles

228

65

98

47

71

173

112

184

39

44

88



39

33

166

Allo-types

112

22

50

21

23

65

58

92

22

19

38

20

12

115

HLA Class I Ligand Motifs

B7H7

A\*11 C1

*B46:01 B73:01* C1 C2

PVR

?

C2

HLA-G

Bw4+ HLA-A and Bw4+ HLA-B

Bw4+ HLA-B and HLA-F

PVR

C2

A\*11 HLA-C

C2

A3 A11

## **2.3 KIR Diversity**

KIR diversity is influenced by gene content variation and sequence variation. Distinct DNA sequences of KIR genes are called “alleles.” Distinct polypeptide sequences of KIR genes are called “allotypes.” Because different DNA sequences of KIR gene can lead to the same polypeptide, there are more alleles than allotypes for a given KIR gene.

## **2.4 NK Cell Education**

## **2.5 KIR Nomenclature**

### **2.5.1 Inhibitory KIR**

The main role of inhibitory KIR is to prevent cytotoxic NK and T cells from killing tissue cells—unless their HLA class I expression is lost or altered by infection or mutagenesis.

### **2.5.2 Activating KIR**

Activating KIR help identify diseased cells for destruction by cytotoxic NK and T cells. Binding of foreign peptides by HLA class I molecules retained by infected cells may be most critical for activating KIR.

### **2.5.3 Broad KIR Haplotypes**

## **2.6 KIR Ligand Motifs**

## **2.7 KIR3DL1 and KIR3DS1**

Because of significant non-allelic recombination in the KIR region, the distinction between KIR genes and alleles can be confusing. Specifically, KIR3DL1 and KIR3DS1 are alleles of

the same gene. Of the KIR3DS1 allotypes—3DS1013 *and* 014—are observed with the greatest frequency in any population.

## **2.8 KIR Allele Imputation Programs**