Influence of host genetics on HIV

Exposure

HIV-

HIV+

Healthy

AIDS
HLA class I and KIR: functionally related gene clusters exhibiting extreme polymorphism

Chr. 19q13.4

Chr. 6p21.3

MHC

HLA class I and KIR: functionally related gene clusters exhibiting extreme polymorphism

Chr. 19q13.4

LRC

Haplotype A

Haplotype B

Haplotype A

Haplotype B
KIR regulate natural killer cell activity

NK cells kill targets that do not express HLA class I in the “normal” context.
HLA-B + KIR3DL1: Multiplicity of synergistic interactions

**HLA-B:** >500 alleles  
**KIR3DL1:** >20 alleles
Differential binding between KIR3DL1 and HLA-B

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Interaction</th>
<th>Class I Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>3DL1*001</td>
<td>Strong</td>
<td>B*57</td>
</tr>
<tr>
<td>3DL1*001</td>
<td>Weak</td>
<td>B*27</td>
</tr>
<tr>
<td>3DL1*001</td>
<td>None</td>
<td>B*45</td>
</tr>
</tbody>
</table>
AIDS Cohorts

• Multicenter Hemophilia Cohort Study (MHCS): Hemophilia, DCEG, NCI

• Multicenter AIDS Cohort Study (MACS): Gay men, multiple U.S. sites (NIAID)

• AIDS Linked to Intravenous Experience (ALIVE): IV drug users, Johns Hopkins

• Hemophilia Growth and Development Study (HGDS): Hemophilia, multiple U.S. sites

• San Francisco City Clinic Cohort (SFCCC): Gay men, SF Dept. of Health
Specific $\text{KIR3DL1} + \text{HLA-B}$ combinations protect against AIDS progression.
Multiple, distinct \textit{KIR3DL1} + \textit{HLA-B} compound genotypes protect against HIV (and cervical neoplasia?)

![Graph showing protection against HIV and neoplasia for different KIR3DL1 and HLA-B genotypes. The x-axis represents increasing protection, with control at the bottom and peaks at the top for HIV and neoplasia. The y-axis represents the frequency of genotypes.]

- **Ligand only**
  - B*57
  - B*27
  - Bw4 80I
  - Bw4
  - Control

- **Receptor/Ligand**
  - KIR3DL1+B*57
  - KIR3DL1+B*27
  - KIR3DL1+Bw4
  - KIR3DL1+Bw4 80I

For HIV, there is a clear increase in protection from the control to KIR3DL1+B*57, with KIR3DL1+B*27, KIR3DL1+Bw4, and KIR3DL1+Bw4 80I showing even higher protection.

For neoplasia, KIR3DL1+Bw4 shows the highest protection, followed by KIR3DL1+Bw4 80I, KIR3DL1+B*27, and B*57.
The complex, abundant epistatic effects observed for \textit{KIR3DL1} and \textit{Bw4} are unprecedented with regard to any pair of genetic loci in human disease, and underscore the primary role of KIR3DL1-Bw4 interactions in controlling HIV-1.
Collaborators on KIR3DL1 studies

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HGDS  Keith Hoots
SFCC  Susan Buchbinder
MHCS  Jim Goedert

**NCI, LGD**
Many collaborators