Allele-level genotyping of KIR2DL4 in large European population samples reveals highly significant heterozygote excess for 9A/10A allelic variants

Gerhard Schöfl1, Jürgen Sauter2, Steffen Klasberg1, Alexander H Schmidt1,2, Vinzenz Lange1

1 DKMS Life Science Lab • Blasewitzerstr. 43 • D10307 Dresden
2 DKMS gGmbH • Kressbach 1 • 72072 Tübingen

Overview

KIR2DL4 is an evolutionarily conserved framework member of the human killer-cell immunoglobulin-like receptor (KIR) gene family. It is unique amongst KIR genes in that it may elicit both activation and inhibition signals. Moreover, KIR2DL4 alleles are polymorphic for a frameshift mutation in the transmembrane domain that leads to a truncated cytoplasmatic tail. Alleles with a 10A homopolymer in exon 7 encode receptors that are expressed on the cell surface of NK cells. In contrast, alleles with a 9A frameshift mutation have been shown to produce soluble secreted KIR2DL4 receptors. Here, we investigate allele and genotype frequencies of 9A and 10A alleles in large European population samples.

In 10/2016, DKMS Life Science Lab established an exon-based NGS workflow for KIR allele-level genotyping (Figure ??). Using samples genotyped against the IPD-KIR 2.7.0 and 2.7.1 reference databases starting 09/2017, we have performed successful allelic-resolution genotyping for KIR2DL4 for 676,158 potential bone-marrow donor samples originating from Germany (DE), Great Britain (GB), and Poland (PL). These samples were analysed for allele frequency and gene copy number variation (Figure ??, Table ??) as well as checked for presence of the 9A frameshift mutation (Figure ??).

Results

Overall, the defective 9A variant was underrepresented in Germany (AF9A = 0.469, n = 432,335) and Great Britain (AF9A = 0.437, n = 64,582) but slightly overrepresented in the Polish sample (AF9A = 0.511, n = 153,961). The fraction of homozygous individuals (10A/10A or 9A/9A) ranges from 42.9% (DE) to 44.2% (PL). Comparing expected genotype frequencies assuming Hardy-Weinberg Equilibrium (HWE) and observed genotype frequencies indicates a highly significant deviation from HWE (P < 10^-8), and a consistent heterozygote excess across all three populations (Figure ??), with inbreeding coefficients ranging from FIS = −0.144 (GB) to −0.146 (DE).

Conclusions

The high frequency of the defective 9A allelic variants in all three populations indicates no negative selection against a lack of cell surface expression of KIR2DL4. Rather, the strong signature of heterozygote excess across populations may best be explained as a result of overdominant selection (i.e., “heterozygous advantage”). This suggests that the presence of both, cell-surface-expressed KIR2DL4 receptors and soluble secreted KIR2DL4 receptors confers a selective advantage to humans.

Table 1: Estimated gene copy numbers of KIR2DL4 alleles in three European populations.

<table>
<thead>
<tr>
<th>Gene copy number</th>
<th>Sample</th>
<th>DE</th>
<th>GB</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18,058</td>
<td>2.24%</td>
<td>1.83%</td>
<td>3.34%</td>
</tr>
<tr>
<td>2</td>
<td>752,975</td>
<td>93.6%</td>
<td>94.1%</td>
<td>92.6%</td>
</tr>
<tr>
<td>3</td>
<td>32,667</td>
<td>4.06%</td>
<td>3.98%</td>
<td>3.95%</td>
</tr>
<tr>
<td>4</td>
<td>870</td>
<td>0.11%</td>
<td>0.11%</td>
<td>0.14%</td>
</tr>
</tbody>
</table>

Figure 1: Registry donors processed at DKMS Life Science Lab for HLA and KIR.

KIR_PA, KIR presence/absence level typing; KIR_AL, KIR allele-level typing.

Figure 2: 1st field allele frequencies of KIR2DL4 alleles in European populations genotyped against the IPD-KIR 2.7.0 and 2.7.1 reference databases.

Figure 3: Observed genotype frequencies vs. expected genotype frequencies assuming HWE for 9A/10A heterozygotes and 9A/9A or 10A/10A homozygotes.

DE, samples originating from Germany, n = 432,335, GB, samples originating from Great Britain, n = 64,582, PL, samples originating from Poland, n = 153,961.