Preliminary Results of a large Population-based Study indicate no strong Association of KIR-/HLA-Genotype and the Risk of Developing Acute Myeloid Leukemia

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Background

Immunogenetic disease association studies may give rise to new hypotheses on the immunosurveillance of cancer. Polymorphic killer cell immunoglobulin-like receptor (KIR) genes and Acute Myeloid Leukemia (AML) have not been investigated so far in large population studies. For this purpose we typed the KIR and HLA genotype of German patients who were diagnosed with AML and compared their results to data of 51,890 German individuals who registered with DKMS. Owing to the large number of controls in this setting, even small deviations from the average distribution could be revealed. Knowledge on KIRs and their cognate HLA-ligands allowed for testing of several hypotheses of Natural Killer (NK) cell mediated leukemia surveillance.

Case Control Study

KIR- and HLA-genotype information from patients with AML was compared to data from healthy donors

Condition	AML	Healthy Donor (Lifetime Risk of AML < 1%)
Sample Size	1,454	51,890
Median Age (Range)	55 (17 – 90)	32 (19 – 59)
Population	German	German

KIR Geno-typing

HLA and KIR-typing was performed applying high-resolution amplicon-based Next Generation Sequencing (NGS). All patient and control group samples were typed by the same laboratory using the same setup and software versions.

Data Ana-lyses

All samples come from the German population, and we assume any differences in age and sex between the groups do not affect the proportions of KIR and HLA-alleles observed. We also assume the lifetime incidence of AML in the donor population is small enough to be negligible for its use as a control group. Each set of proportions were compared with individual two-sided Z-tests of differences. The overall chi-square test of differences between the two groups for all proportions is given in the figure legend. The p-values are not adjusted for multiple testing.

Results

- We did not find significant differences between the two cohorts for absence/presence of KIR2DL1, 2DL2, 2DL3, 2DP1, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1 and 3DS1 (**Fig. 1**).
- With respect to the KIR-ligands C1 and C2, patients with AML exposed C1/C1-ligands less frequently (35,9% versus 39,4%, p=0.007) compared to controls (data not shown).
- This result encouraged us to have a closer look at the inhibitory KIRs whose ligands are C1 or C2. Patients with two copies of KIR2DL1, zero copies of KIR2DL2, two copies of KIR2DL3, and with a C1/C1 KIR-ligand status were less frequent (**Fig. 2**). This effect has also been seen in an independent explorative association study, where we found that 2DL2-negative donors for stem cell transplantation reduce the risk of relapse & improve overall survival for C1/C1-patients with AML.
- A gene copy number for KIR2DL1/2DL2/2DL3 of 1/1/1 or 1/2/0 was more frequent among C1/C2 patients than healthy C1/C2 donors (**Fig. 2**).

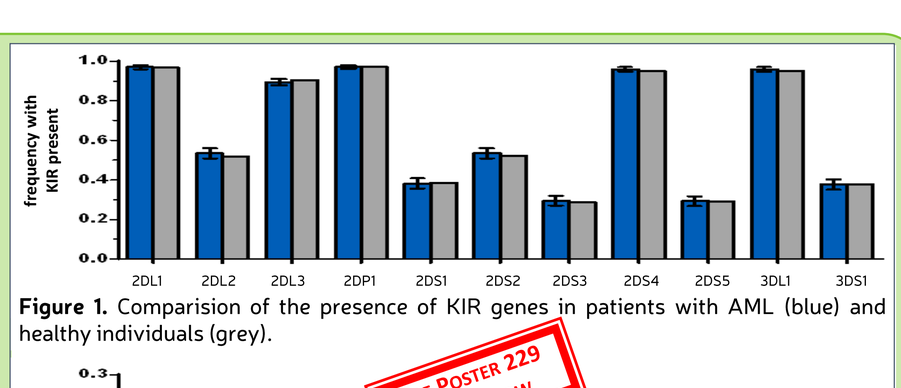

Figure 1. Comparision of the presence of KIR genes in patients with AML (blue) and healthy individuals (grey).

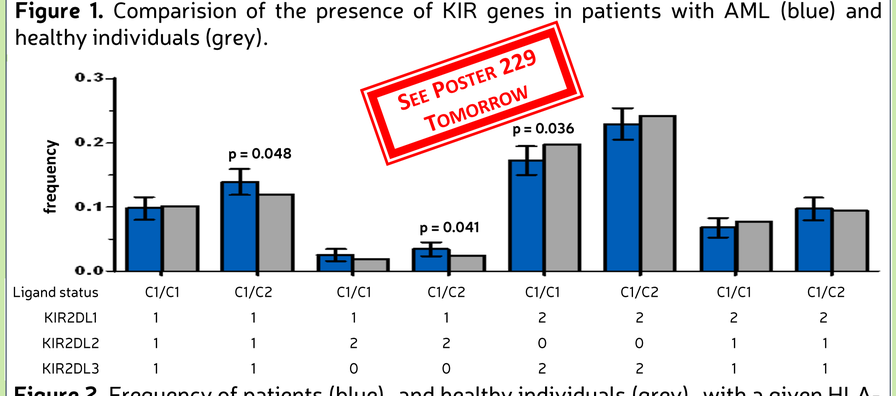

Figure 2. Frequency of patients (blue) and healthy individuals (grey) with a given HLA-C-KIR-ligand status and gene copy number of KIR2DL1/2/3 (displayed below the graph). Overall chi-square test p-value = 0.048.

- We tested the receptor ligand model by Venstrom et al. (NEJM, 2012). *KIR2DS1*-positive individuals whose 2DS1-positive NK-cells had been educated by C1/C1 or C1/C2 ligands, were equally distributed among patients and controls (data not shown).
- No significant differences were found with respect to HLA-Bw4-80I/80T, the cognate ligand for KIR3DL1. When grouped into strong-inhibiting, weak-inhibiting and non-inhibiting KIR3DL1 and cognate ligand combinations, no differences were found and the three groups were equally represented among patients and controls (data not shown).
- Testing the model combining KIR3DL1 and KIR2DS1, and their respective cognate ligands by Boudreau et al. (JCO, 2017) did also not reveal significant differences of the frequency of healthy donors or patients with AML **(Fig. 3).**
- When grouped by telomeric or centromeric gene content (assignment according to Cooley et al., Blood, 2010) the major haplotypes A/A, A/B, and B/B were almost equally distributed among patients and controls **(Fig. 4)**.

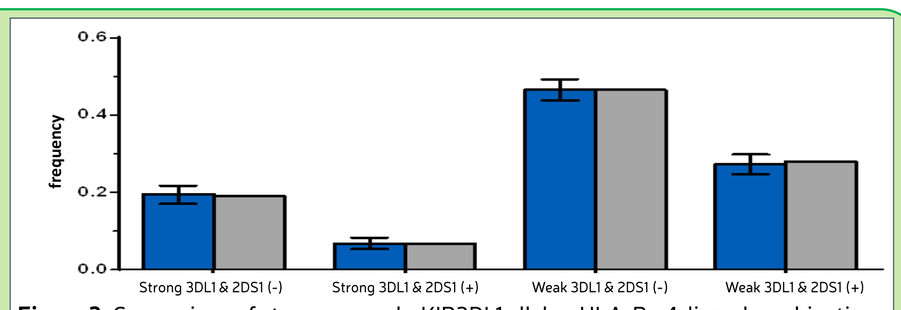

Figure 3. Comparison of strong or weak KIR3DL1 allele - HLA-Bw4-ligand combinations with (+) or without (-) C1/C1 or C1/C2 educated KIR2DS1-positive patients with AML (blue) and healthy individuals (grey). Overall chi-square test p-value = 0.97.

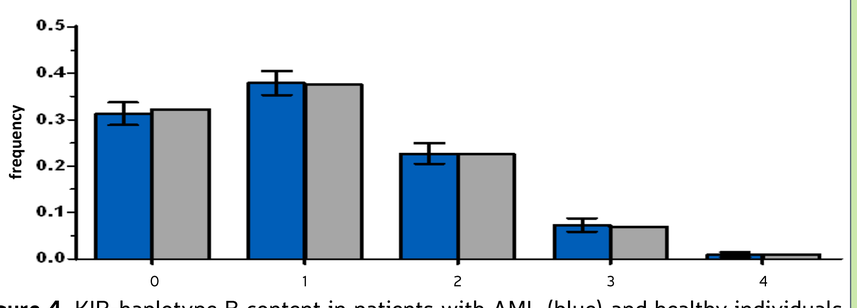

Figure 4. KIR-haplotype B content in patients with AML (blue) and healthy individuals (grey). Given a B-content score of 4 describes a cenB/B - telB/B diplotype. Overall chi-square test p-value = 0.90.

Conclusions & Outlook

The current results suggest that there could be a weak association of KIR-genotype and HLA-C-KIR-ligand status combinations with the risk of developing AML.

Next Steps

- ⇨ To test other models and for allelic distribution of other KIR genes
- ⇨ To test for the distribution of other NK receptor – ligand combinations in future case-control studies

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