POSTER #297

Medizinische Hochschule Hannover

# LILRA3 Deletion is a Genetic Risk Factor of HIV Infection

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## Background:

The susceptibility for HIV and the clinical course of the disease are dependent both on viral pathogenicity and genetic host factors
LILRA3 is a protein of the leukocyte immunoglobulin-like receptor family that is produced as a soluble molecule by monocytes and macrophages. A naturally occuring 6.7 kbp deletion in the gene locus of LILRA3 has been described that results in a null allele and an absence of the protein. The deletion was detected in about 3% of most ethnicities in the world. Since LILRA3 exerts various immunomodulatory functions, we studied the role of LILRA3 and its deletion in the transmission and progression of HIV-1 infection.

## Patients and Methods:

LILRA3 genotypes were determined in a cohort of 439 HIV positive individuals and 651 controls by polymerase chain reaction. Patients were categorized into 3 groups according to the progression of the HIV infection. Patients with CD4$^+$ cells >500 per µl at initial presentation that remained untreated for at least 24 months were included in the study.
Short-term progressors: loss of >50% of CD4$^+$ cells within 24 months, normal progressors: loss of CD4$^+$ cells <50% in 24 months, long-term non-progressors: patients with CD4$^+$ cells >500 per µl for 120 months. Functional studies were performed using real-time PCR, intracellular flow cytometry and ELISA.

## Results:

The prevalence of the homozygous LILRA3 deletion was significantly higher in HIV positive individuals (n= 439) than in controls (n= 651) (p= 0.02) indicating a higher susceptibility of LILRA3 deleted individuals (Figure 1A).
The progression of the disease was faster in homozygously LILRA3 deleted patients with a higher proportion of short-term progressors among homozygously deleted patients than in heterozygous (p= 0.03) and in homozygously positive (p=0.002) individuals (Figure 1B).
The relative risk for a faster progression was 4 times higher in homozygously LILRA3 negative individuals when compared to homozygously positive ones.
The decline of CD4$^+$ cells to <200/µl was faster in homozygously LILRA3 deleted patients (p= 0.018 Logrank-Test for trend). Patients with either a complete or partial deletion of LILRA3 have a significantly faster decline of CD4$^+$ cells compared to homozygously positive patients (p= 0.019) (Fig. 1C and D).
Functional analysis revealed an upregulation of the LILRA3 gene in Real-time PCR in treated HIV patients when compared to untreated patients (p= 0.007) and controls (p= 0.02) resulting in a higher LILRA3 expression in CD4$^+$ (p= 0.008) and CD14$^+$ (p= 0.02) cells of untreated patients than in controls in intracellular flow cytometry. LILRA 3 concentrations in the sera were similar between the groups, in untreated patients a correlation between viral load and LILRA3 concentration was found.

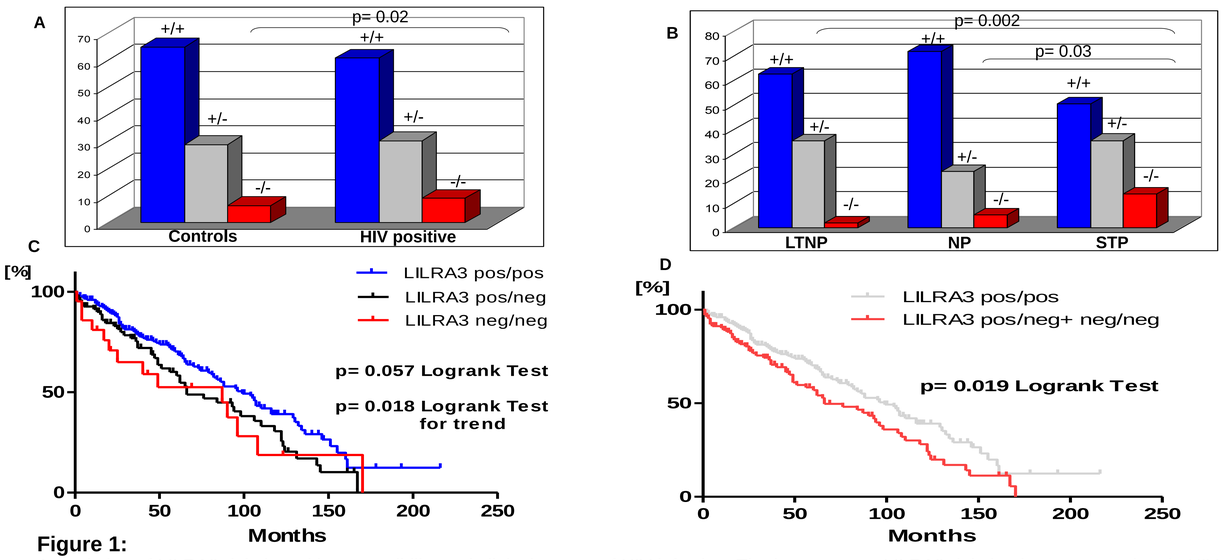



**Figure 1:**
Association of LILRA3 deletion with susceptibility and clinical course of HIV infection. The homozygous LILRA3 deletion is more prevalent in HIV patients than in controls. The progression of the disease is faster in LILRA3 deleted patients.

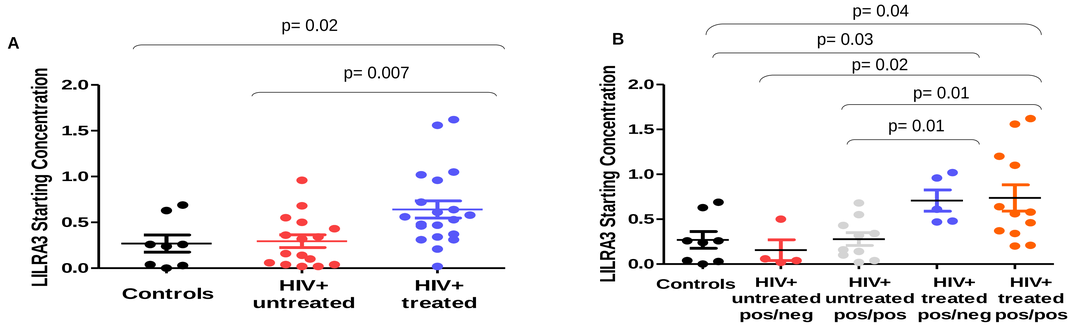



**Figure 2:**
Regulation of LILRA3 gene activity by real-time PCR. The gene expression was upregulated in treated HIV patients compared to untreated patients and controls. The upregulation was independant of the LILRA3 genotype.

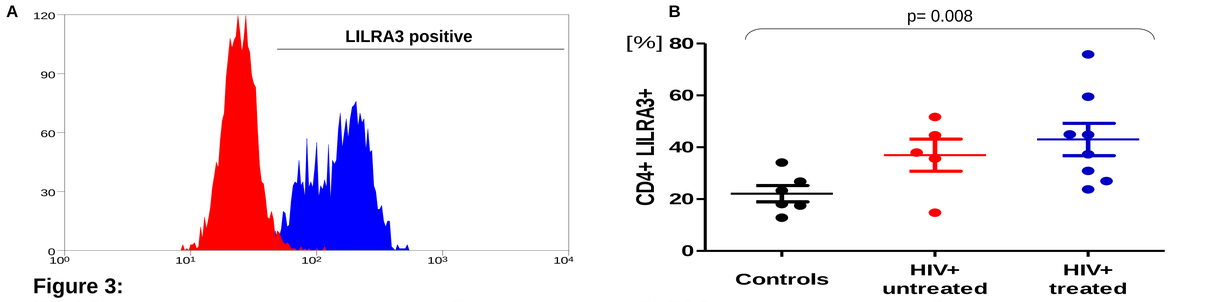



**Figure 3:**
LILRA 3 production in intracellular flow cytomtetry. The figure features the LILRA 3 expression in monocytes. Gates were set on monocytes and CD4$^+$ cells.

## Conclusions:

The homozygous LILRA3 deletion is associated with a higher susceptibility for HIV infection and with a faster disease progression.

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