Genetic Variants Associated to HIV Control Are Associated With NK Cell Markers and Response to CMV

2000 HIV

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BACKGROUND

- Spontaneous HIV controllers may serve as a model for **functional cure**
- **Genetics** are known to play an important role in spontaneous HIV control
- The **functional immunological effects** of genetic variants associated to control are poorly understood
- Here, we use a **functional genomics approach** to understand via which mechanisms genetics may contribute to spontaneous HIV control

METHODS

- **1380 PLHIV of European ancestry** were included as part of the 2000HIV study (clinicaltrials.gov NTC03994835).
- **Spontaneous HIV controllers (HICs)** were defined as **viremic controllers** (VL < 10,000 cp/ml, CD4 counts > 500 cells/mm^3, in the absence of ART, for a minimum of 5 years) and **elite controllers** (VL < 75 cp/ml, CD4 counts > 500 cells/mm^3, in the absence of ART, for a minimum of 12 months).
- To find genetic variants associated to spontaneous HIV control, a **genome-wide association study** was performed, comparing 67 viremic/elite HICs to 1,195 normal progressors using a logistic regression model
- To understand the functional effects of HIV control SNPs, **QTL mapping** was performed. We associated genetic dosages with gene expression in PBMCs (eQTLs), plasma levels of 2367 proteins (pQTLs), and *ex vivo* cytokine production upon PBMC stimulation with a range of stimuli (cytQTLs) in a linear regression model

RESULTS
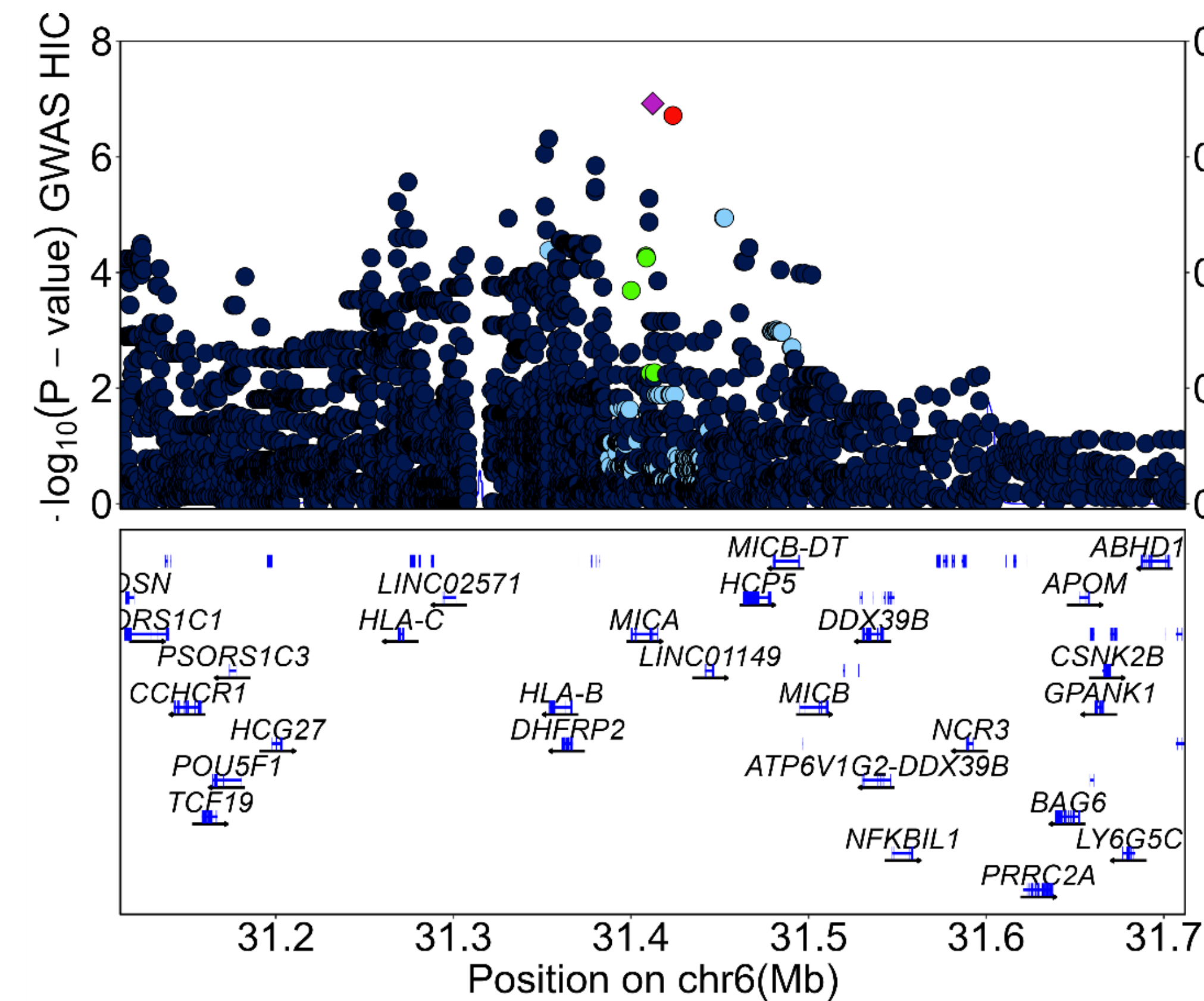
Top genetic association with HIV control found in the MHC locus
- Locus contains 3 independent (r^2 < 0.1), suggestively associated (P < 10^{-5}) SNPs
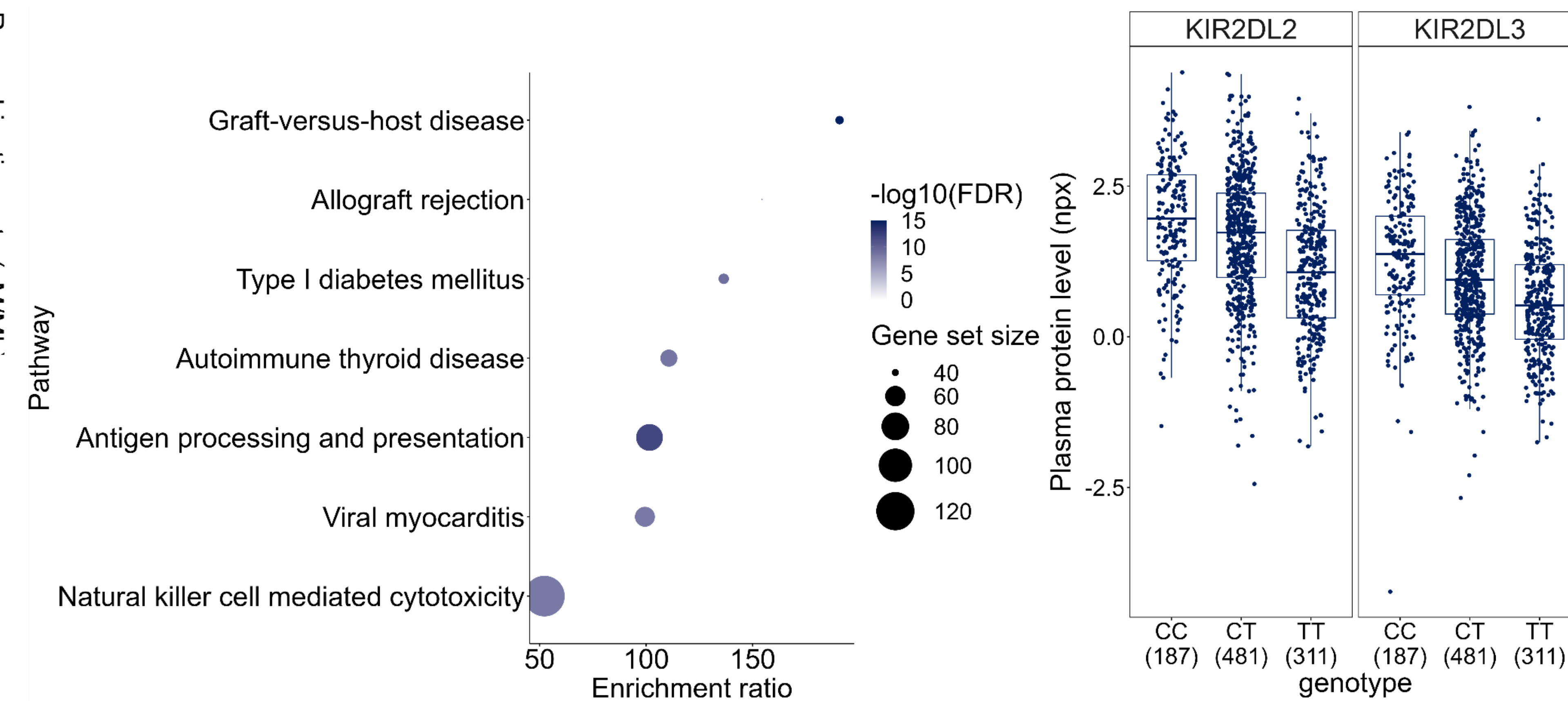
HIV control SNPs are associated to gene expression and plasma levels of NK cell receptors and NK cell receptor ligands
- Prioritization of 21 putative causal genes based on eQTLs and pQTLs (P < 5 · 10^{-8})
- Enrichment of prioritized genes in **Natural killer cell mediated cytotoxicity pathway** (FDR = 8.1 · 10^{-9})
- In particular, HIV control SNPs are associated to **lower plasma KIR2DL2 and KIR2DL3, two inhibitory NK cell receptors**
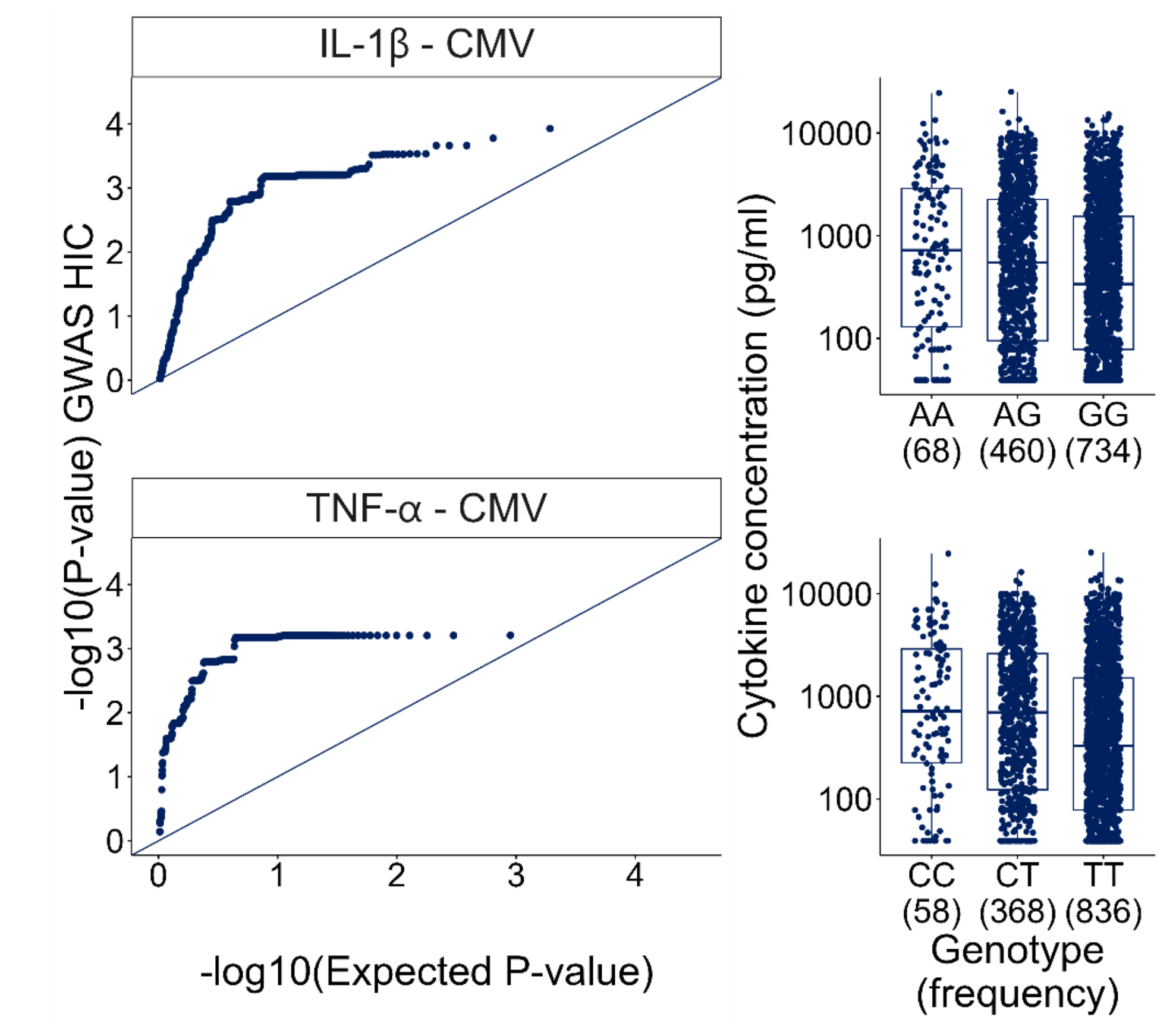
HIV control SNPs are associated with reduced IL-1β and TNF-α response upon PBMC stimulation with CMV
- Enrichment of HIV control SNPs in cytQTLs for IL-1β and TNF-α upon stimulation with CMV

HIV control SNPs in the MHC locus are associated with

↓KIR2DL2/3
NK cell

CMV → ↓IL-1β
↓TNF-α
PBMCs
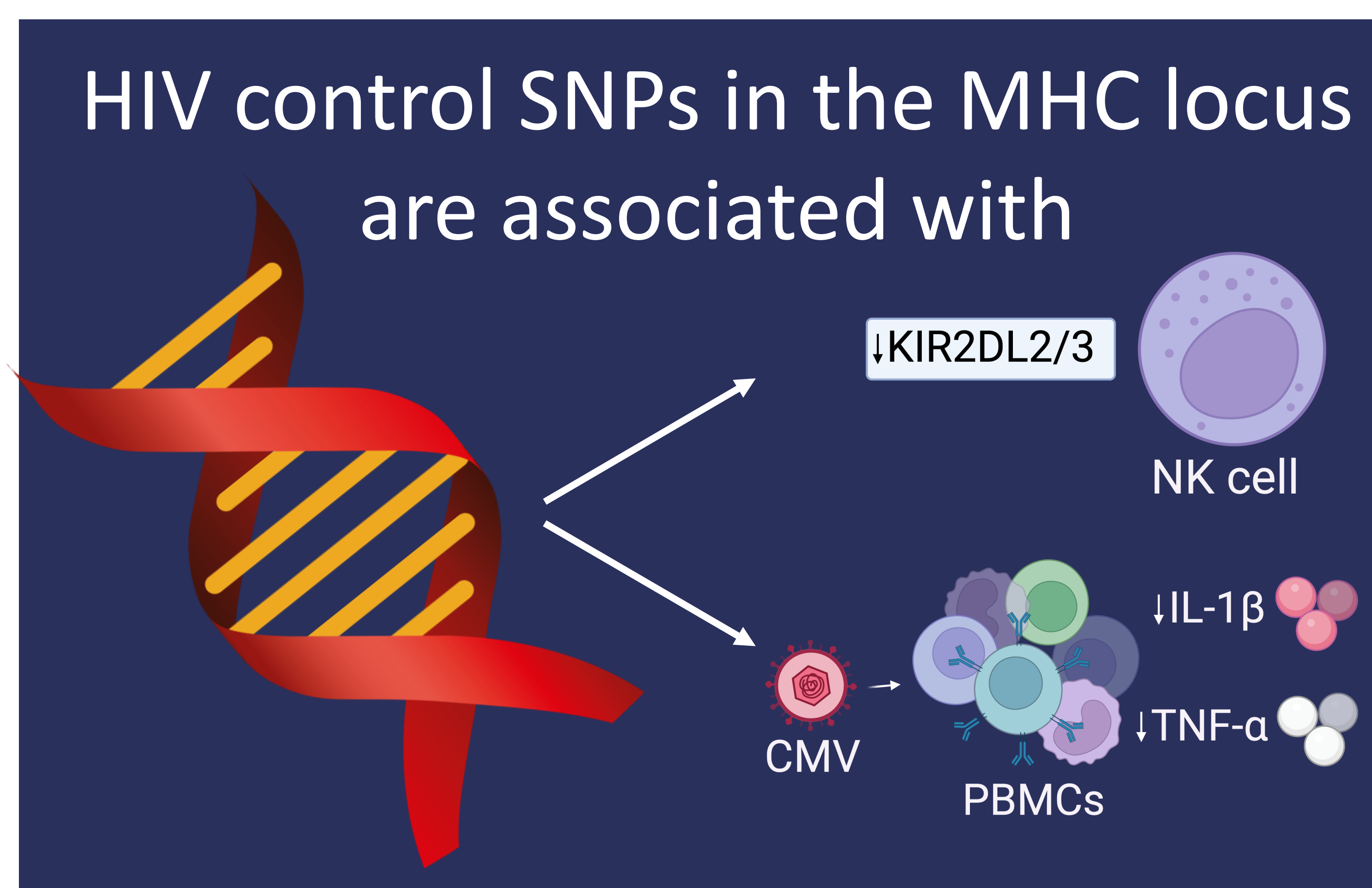
CONCLUSIONS

- The strongest genetic association to spontaneous HIV control was observed in the **MHC locus**
- HIV control SNPs regulate **plasma levels of inhibitory NK cell receptors KIR2DL2/DL3** and NK cell receptor ligands
- HIV control SNPs are associated with **reduced pro-inflammatory responses to CMV**

CONTACT INFORMATION

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