



# I-120 A Genome-wide Association Study in HIV-1 Controllers

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## Hypothesis

Common variations in the human genome may be responsible for host suppression of HIV-1 replication. An adequately powered whole genome association study (WGAS) will be able to identify common DNA polymorphisms that contribute to natural viral suppression.

## Abstract

### Background

HIV-1 controllers have been characterized as individuals that are able to spontaneously control virus replication to levels below 2000 copies/ml in the absence of antiretroviral therapy. We conducted a genome-wide association study of these individuals to test the hypothesis that host genetic factors may be associated with durable suppression of virus replication.

### Methods

A multi-ethnic cohort of 464 HIV+ controllers and 747 HIV+ chronic progressors was genotyped using the Illumina 650Y platform. Genome-wide imputation up to 3 million SNPs was performed using HapMap (CEU, YRI, CHB and JPT samples from Build 35).

### Results

- 62 SNPs were genome-wide significant ( $p < 5 \times 10^{-8}$ ) in Whites, 6 in Blacks, and 0 in Hispanics.
- Two SNPs previously associated with low HIV viral load set point in Caucasians were replicated: rs9264942 in 5' region of HLA-C ( $p = 2.4 \times 10^{-15}$ ) and rs2395029, a proxy for HLA-B\*5701 ( $p = 10^{-10}$ ).
- Logistic regression identified one novel independent SNP in Whites: rs720465 ( $p = 8.8 \times 10^{-9}$ ).
- Two independent SNPs in African Americans: rs2523608 ( $p = 6.3 \times 10^{-10}$ ) and rs2853948 ( $p = 4.6 \times 10^{-9}$ ).
- Meta-analysis across populations identified 44 significant SNPs in the MHC of which five are independent.

### Conclusions

We have conducted the first genome-wide association study of a multi-ethnic cohort of HIV-1 controllers.

We have identified novel independent SNPs associated with natural control of HIV-1 infection. Meta-analysis across three ethnic groups underscores the dominant role of HLA-B\*5701 and HLA-B\*5701 in HIV-1 control.

- HIV-1 controllers (HIV+ individuals with 3 viral load measurements less than 2000 copies per ml in one year) were identified through the International HIV Controllers Study.
- Non-controllers were obtained from the AIDS Clinical Trials Group (ACTG) group 5095.

### Quality Control

- Individual samples must have high genotyping rate (> 95%) and share similar genetic background as others of same population (within 6 standard deviations along top 10 eigenvectors).
- SNPs must have high genotyping rate (> 95%), minor allele frequency > 1%, similar call rates between cases and controls, low haplotype based missingness, and be in Hardy-Weinberg equilibrium.

Genome-wide analyses (performed using PLINK and EIGENSTRAT for each ethnic group)

- Logistic regression with 10 principal components as covariates was used for association testing.
- Conditional logistic regression was used to assess independence of genome-wide associated SNPs.
- A meta-analysis is performed to identify common associations across ethnic groups.

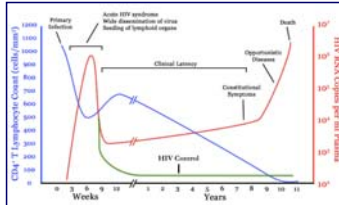


Figure 1. Stages of HIV-1 infection in chronic progressors and HIV controllers.

SNP	Locus / proxy	Univariate p-value	OR	Multivariate p-value	OR
rs2395029	HLA-B*5701	$1.0 \times 10^{-11}$	5.46	$2.9 \times 10^{-4}$	2.85
rs9264942	5' to HLA-C	$2.5 \times 10^{-11}$	3.07	$6.9 \times 10^{-11}$	2.50
rs720465	3' to TCF-19	$8.8 \times 10^{-9}$	2.27	$3.2 \times 10^{-9}$	1.59

Table 1. 3 SNPs independently associated with HIV control in Whites.

SNP	Locus / Proxy	Univariate p-value	OR	Multivariate p-value	OR
rs2523608	HLA-B	$6.3 \times 10^{-11}$	2.68	$5.9 \times 10^{-7}$	2.28
rs2853948	5' to HLA-C	$4.6 \times 10^{-9}$	4.07	$6.3 \times 10^{-9}$	2.91

Table 2. 2 SNPs independently associated with HIV control in African Americans.

SNP	Locus / Proxy	Univariate p-value	Multivariate p-value
rs2596473	3' to HCP5	$2.3 \times 10^{-16}$	$7.0 \times 10^{-9}$
rs12213831	MICA	$2.0 \times 10^{-8}$	$3.5 \times 10^{-9}$
rs2395029	HLA-B*5701	$4.0 \times 10^{-11}$	$3.1 \times 10^{-8}$
rs3915971	5' to HLA-C	$9.6 \times 10^{-9}$	$4.6 \times 10^{-7}$

Table 3. 4 Independent SNPs identified in meta-analysis across populations.

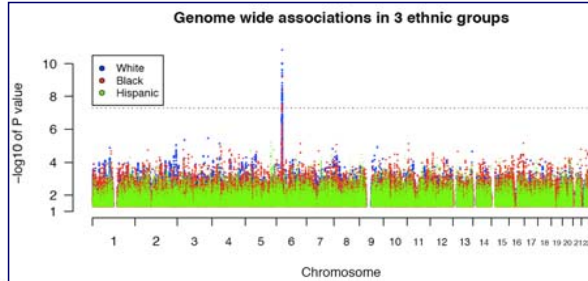


Figure 2. SNP associations to HIV controller phenotype across the genome for the White, Black, and Hispanic populations.

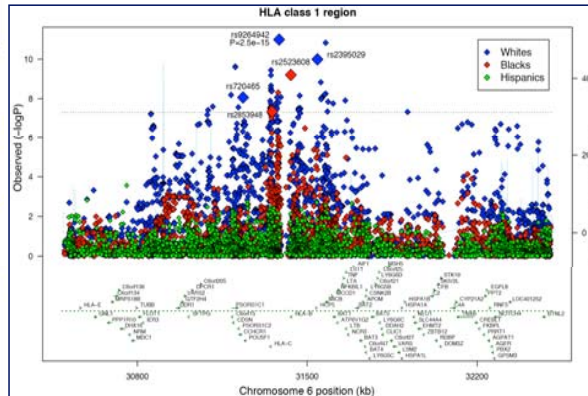


Figure 3. Enrichment of SNP associations in the major histocompatibility complex (MHC) region. Independently associated SNPs are listed with p-values.

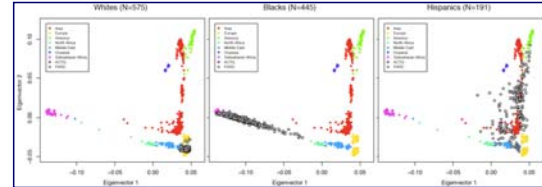


Figure 4. Genetic variability of 3 ethnic populations along 2 eigenvectors, in relation to samples from the Human Genome Diversity Project.

## Conclusions

- We have conducted the first genome-wide association study of a multi-ethnic cohort of HIV controllers and identified novel independent SNPs associated with natural control of HIV infection.
- SNP proxies for HLA-B\*5701 and HLA-C are significantly associated with host HIV control in Whites. At least one more independent association exists in the MHC.
- Two independent association signals were identified in African Americans near HLA-B and HLA-C, but additional studies are needed to determine the real causal variants.
- Conditional meta-analysis identified four independent signals across ethnic groups in the MHC, one of which was a proxy for HLA-B\*5701, and another lies in the 5' region of HLA-C.

### Limitations

- It remains difficult to identify the causal variant(s) of HIV control due to complex linkage patterns within the MHC. HLA typing is needed to understand the relationship between SNPs in the MHC and HLA alleles. Additional power is needed to detect associations in Hispanics.

## References

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