Genetic Regulation of Gene Expression in HIV+ T Cells and Monocytes Associated With Control of HIV

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Purpose

To investigate how human genetic variability in highly HIV affected populations modifies viral load and disease progression. From a better understanding of the HIV host-pathogen interaction, we aim to help guide the development of host-targeted HIV therapeutics.

Acknowledgements

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Conflict of Interest Disclosure: I have no conflicts of interest

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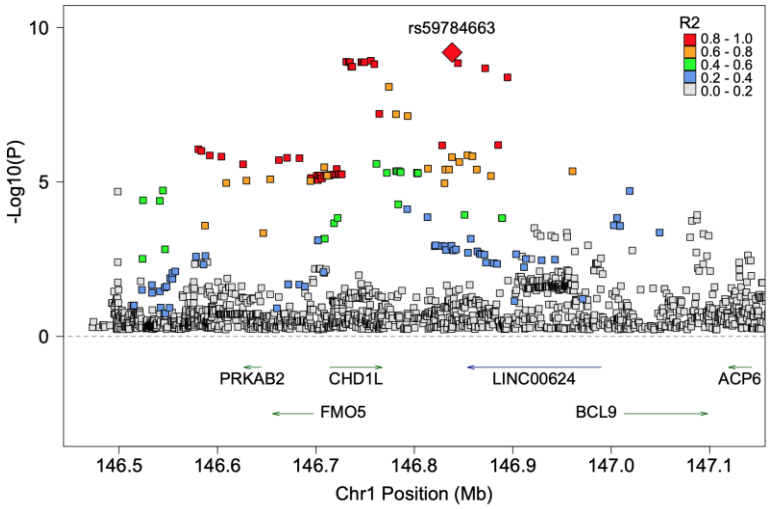
Background



A genome-wide association study with 3,879 individuals of African ancestry, conducted by our lab, identified a region of chromosome 1 significantly associated with decreased HIV set-point viral load (spVL).

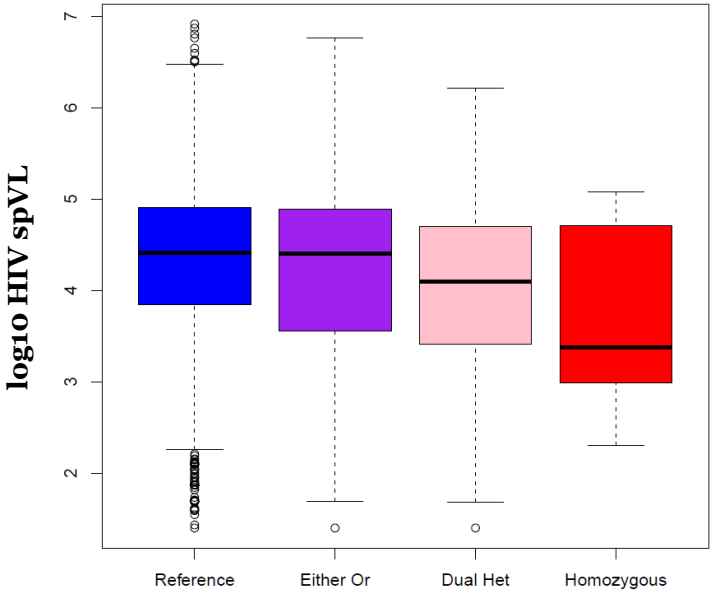
Variants in high linkage disequilibrium, shown in orange and red, to the top associated SNP (rs59784663, p < 5E-10) overlaps three coding genes: *PRKAB2, FMO5,* and *CHD1L*.

CHD1L is involved in chromatin relaxation and DNA repair[1]. *PRKAB2* is a regulatory scaffold for the AMPK complex, a master regulator kinase for low-energy states[2]. *FMO5* is part of the flavin-monooxygenase family of genes that metabolise drugs, however *FMO5* appears to lack this ability[3].

The top associated variant is only present in African populations (4-12% minor allele frequency by geographic region) and not present in European or Asian populations (minor allele frequency < 1%) . This provides support why this region has not been detected in similar studies with individuals of European or Asian ancestry.

Statistical fine-mapping of variants in linkage disequilibrium (R^2>0.6) to rs59784663 implicates rs73004025 and rs7519713 as the likely causal for driving changes to gene expression.

Allelic dosage of rs73004025 and rs7519713



Hypotheses

1. Individuals, carrying the variant rs59784663, will have differential gene and protein expression of *CHD1L, FMO5,* and/or *PRKAB2*.

2. Gene expression of *CHD1L, FMO5,* and/or *PRKAB2* will be higher in individuals carrying the alternate allele at the top associated SNP.

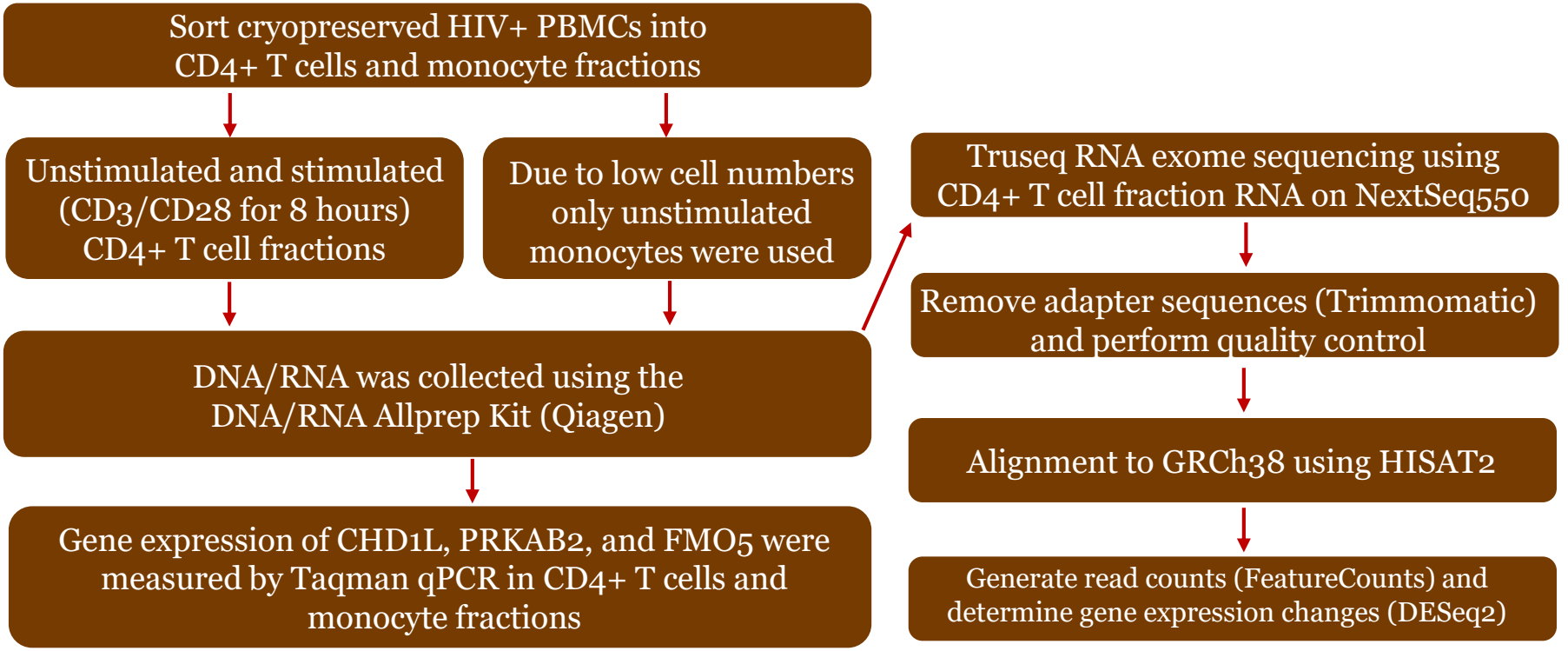
Objectives

1. Sort cryopreserved HIV+ PBMCs from individuals of African ancestry that carry the various alleles at the top associated SNP into CD4+ T cell and monocyte fractions.

2. Determine whether rs59784663 is associated with differential gene expression of *CHD1L, FMO5,* and/or *PRKAB2* in CD4+ T cells and monocytes.

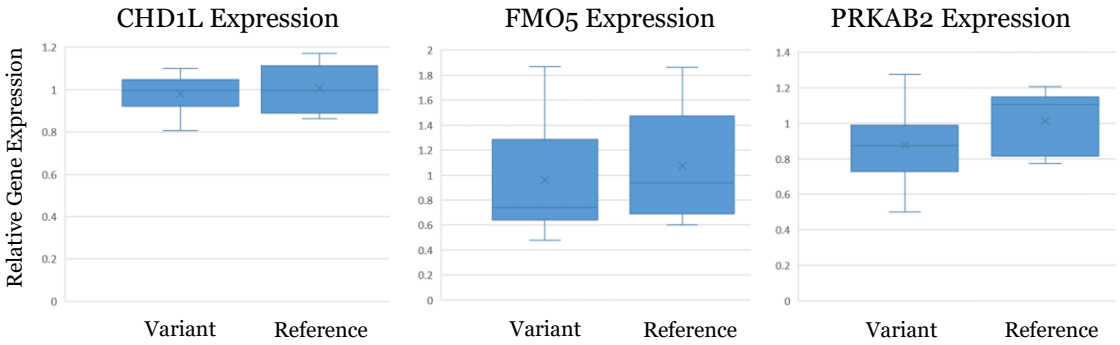
3. Determine whether gene expression pathways associated with *CHD1L, FMO5,* and/or *PRKAB2* are differentially expressed in CD4+ T cell fractions.

Methods

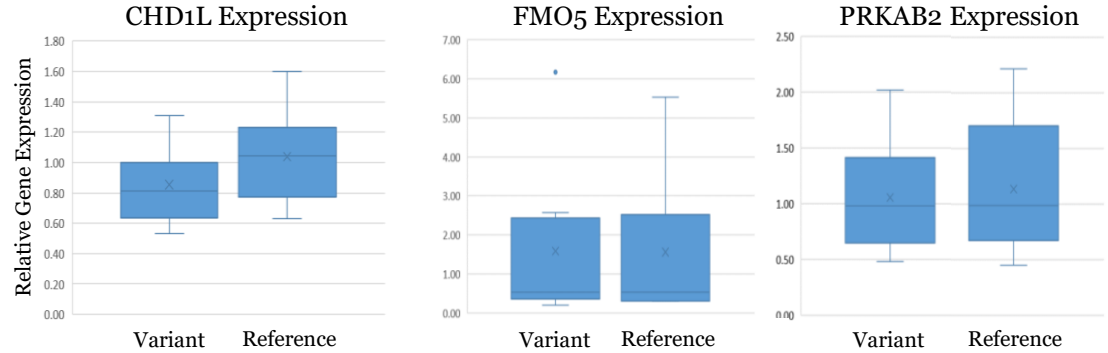


Results

Differential gene expression in <u>unstimulated CD4+ T cells</u> normalized against TBP, RPL13A, and SDHA expression



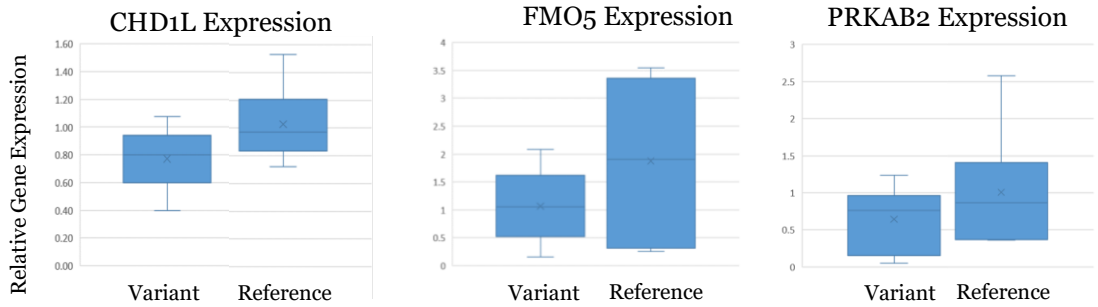
Differential gene expression in <u>stimulated CD4+ T cells</u> normalized against TBP, RPL13A, and SDHA expression



Relative gene expression was calculated using multiple housekeeping genes for CD4+ T cells and monocytes as previously described[5,6].

We detected no significant differences in CD4+ T cells (N=21). There was a trend for higher *CHD1L* expression in stimulated CD4+ T cells of individuals carrying the reference allele but this was not statistically significant ($p < 0.15$).

Differential gene expression in <u>monocytes</u> normalized against HPRT1 and SDHA expression



There is a non-significant trend ($p < 0.11$) that *CHD1L* has decreased expression in individuals with the variant allele in monocytes (N=12). Increasing the sample size may improve our power to determine significant differences.

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Results – RNA Sequencing

We used RNA-sequencing to ask whether *CHD1L, PRKAB2,* and/or *FMO5* are likely to act in a signalling cascade. If these genes are modulating pathway expression, genes acting downstream of *CHD1L, PRKAB2,* or *FMO5* would likely have differential expression.

Stimulated CD4+ T cells		
Gene ID	Log2FC	Adj P-value*
STAG3L1	0.61	0.036
PRKAB2	0.14	0.995
FMO5	-0.09	0.995
CHD1L	-0.06	0.995

Unstimulated CD4+ T cells		
Gene ID	Log2FC	Adj P-value*
ITM2B	-0.19	0.036
PRKAB2	0.08	0.999
FMO5	0.23	0.999
CHD1L	0.14	0.999

*adjustment using Bonferonni correction

We observed no significant differences in expression of *CHD1L, PRKAB2,* or *FMO5* in stimulated or unstimulated CD4+ T cells (N=21).

We observed no significant differences in gene expression for genes in pathways associated with *CHD1L, PRKAB2,* or *FMO5.*

Summary

1. There were no significant differences of *CHD1L, PRKAB2,* or *FMO5* expression in CD4+ T cells (N=21) or monocytes (N=12)
2. There is a non-significant trend ($p < 0.15$) for decreased *CHD1L* expression in stimulated CD4+ T cells and monocytes of individuals carrying the variant allele
3. There is no significant difference in expression pathways downstream of genes in the chromosome 1 region
4. It is unlikely that gene expression changes in CD4+ T cells are driving decreased HIV spVL

References

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