Genetic Associations With CD4 Recovery in People With HIV After Initiation of Antiretroviral Therapy

Roxane Rohani [1, 2], Qin Hui [3], Jennie T. Mather [4], Lishomwa C. Ndhlovu [5], Michael H Chung [6], Kris Ann K Oursler [7, 8], Boghuma K. Titanji [6], Todd Hulgan [9, 10], Brian Agan [11,12], Yan V. Sun [3,4], Vincent C. Marconi [3,4, 6]
for the VA Million Veteran Program

353

[1] Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL; [2] Department of Pharmacy, Captain James Lovell Federal Health Care Center, North Chicago, IL; [3] Rollins School of Public Health, Emory University, Atlanta, GA; [4] Atlanta Veterans Affairs Medical Center, Atlanta, GA; [5] Department of Medicine, Division of Infectious Diseases, Weill Cornell Medicine, New York, NY; [6] School of Medicine, Emory University, Atlanta, GA; [7] Virginia Tech Carilion School of Medicine, Roanoke, VA; [8] Salem Veterans Affairs Health Care System, Salem, VA; [9] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; [10] Veterans Affairs-Tennessee Valley Healthcare System, Nashville, TN; [11]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD; [12] Henry Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD

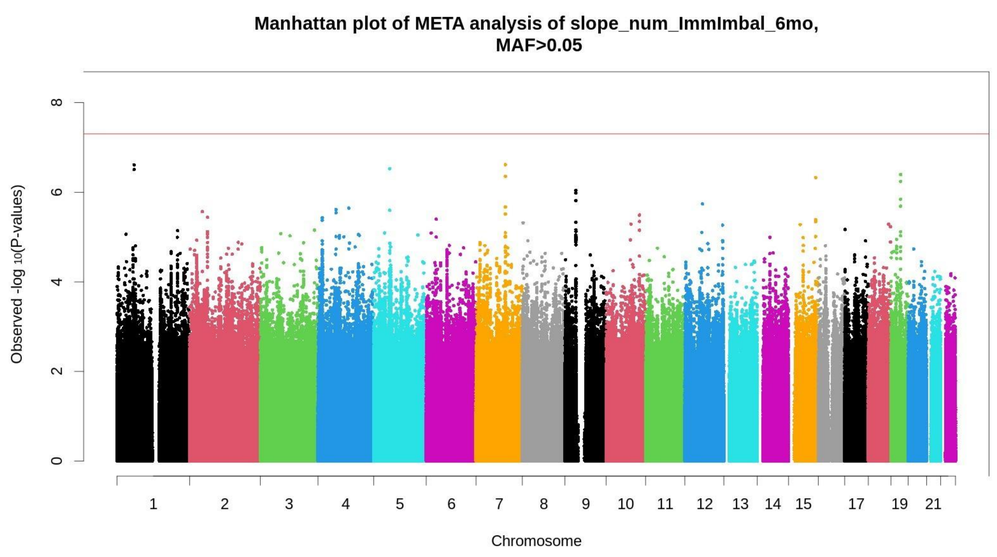
BACKGROUND

- CD4+ T-cell recovery varies among people with HIV (PWH) who are virologically suppressed on antiretroviral therapy (ART) and as result immunological non-responders experience greater rates of morbidity and mortality.
- Our objective was to identify the genetic predictors of CD4 recovery measured by the slope of longitudinal CD4+ T cell counts within two years after ART initiation in PWH virologically suppressed on ART.
- We hypothesized that select single nucleotide polymorphisms (SNPs) would be associated with CD4 T cell slope in PWH initiating ART.

METHODS

- A genome-wide association study (GWAS) was performed on blood samples from PWH enrolled in the Million Veteran Program (MVP).
- HIV infection was defined by 1 inpatient or 2 outpatient HIV ICD codes, or a detectable HIV-1 plasma RNA viral load, or ART prescribed for > 31 days.
- Individuals had at least 2 CD4 counts: one at baseline (up to 6 months prior to ART) and others within 2 years after ART.
- We evaluated SNP associations with CD4 slope adjusting for age at ART initiation, sex, and 10 principal components using linear regression.
- After standard quality control procedures, the TOPMed-imputed SNPs were used in ancestry-specific GWAS of common variants (minor allele frequency>5%).
- A meta-analysis was conducted to evaluate multi-ancestry associations.
- We considered a P-value of $5x10^{-8}$ as the genome-wide significance threshold.

One chromosome 7 locus close to *TRIM56 gene* and one chromosome 9 locus mapped to *TOMM5 gene* were associated with *diminished CD4 T cell recovery*



SNP ID	CHR	Beta	P-value	Direction (EUR/AFR/HIS)
7:100724452:C:T	7	-0.0456	2.42×10^{-7}	-/-/-
7:100723894C:T	7	-0.043	4.40×10^{-7}	-/-/-
9:37587092:T:C	9	-0.0532	9.11×10^{-7}	-/-/-
1:58932989:A:C	1	-0.0764	2.44×10^{-7}	NA/-/NA
15:92952940C:G	15	-0.0953	4.71×10^{-7}	NA/-/NA
19:33045844:A:G	19	0.0438	4.01×10^{-7}	NA/+/+
19:33044514:C:G	19	0.043	5.73×10^{-7}	NA/+/+
1:58927043:T:A	1	0.0768	3.11×10^{-7}	NA/+/NA

RESULTS

- A total of 4192 PWH (48% African Americans, 97% male) were included in the GWAS.
- Mean age at ART initiation was 49 years and mean nadir CD4 T cell count was 358 cells/µl.
- Median intercept and slope were 394 cells/µl and 43 cells/µL/year, respectively.
- Although no SNP meeting significance was identified in the multi-ancestry GWAS of CD4 slope, two common variants were associated at P-value $<1x10^{-6}$, with consistent directionality of association in all three ancestral groups: European, African and Hispanic Americans.
- One chromosome 7 locus, close to TRIM56 gene (rs7786422, β= -0.0456; p= 2.42×10^{-7}), and one chromosome 9 locus, mapped to TOMM5 gene (rs10973430, β= -0.0532; p= 9.11×10^{-7}) were associated with diminished CD4 T cell recovery.

CONCLUSIONS

- In the first study of PWH in MVP, we did not identify significant associations with CD4+ T-cell slope after ART initiation, possibly limited by sample size.
- However, we found several sub-threshold genetic associations.
- TRIM56 has inhibitory effects on viral replication.
- TOMM5 is part of a complex in mitochondrial outer membrane, acting as an entry point for viral proteins.
- A replication study using a larger sample size is needed.

ACKNOWLEDGEMENTS

- The authors are grateful for the participants and staff for their contributions to the study.
- The authors thank Erna A. Clyburn for coordinating this study.
- The authors are thankful for MVP Program Office, MVP Executive Committee, MVP Co-Principal Investigators, MVP Core Operations, and MVP Publications and Presentations Committee.
- This project was supported by MVP042 I01BX006008.

The views expressed are those of the authors and do not reflect the official views of the Uniformed Services University of the Health Sciences, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense, Defense Health Agency, the Departments of the Army, Navy or Air Force, and U.S. Government.