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Study of Single Nucleotide Polymorphisms Associated with HIV-1 Set-Point Viral Load in Antiretroviral Therapy-Naïve HIV-Positive Participants of the START study

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BACKGROUND

- HIV-1 set-point viral load (spVL) is predictive of disease progression and shows variability across HIV-1-positive (HIV+) persons.
- Various factors may influence spVL including viral features, environmental exposure and host genetics.
- To identify single nucleotide polymorphisms (SNPs) associated with spVL, we performed a genome-wide association study (GWAS) on a subset of participants from the Strategic Timing of AntiRetroviral Treatment (START) study covering a demographically diverse population.

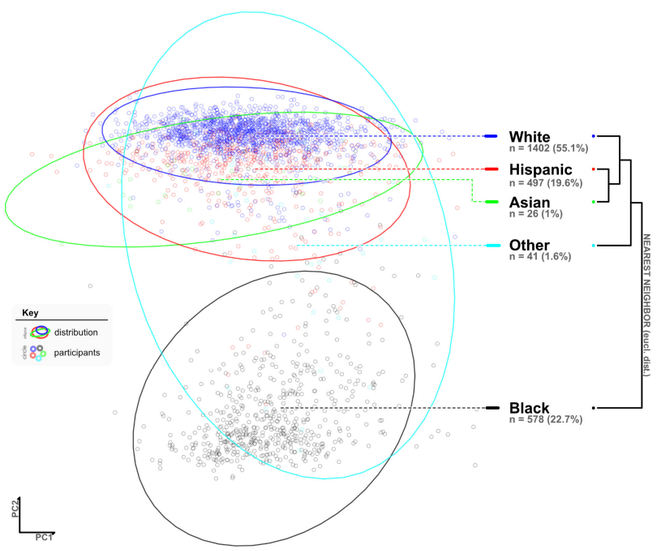

Figure 1. Population structure of the study participants
LEFT: The population structure is illustrated by a principal component analysis (PCA) plot. Each study participant is illustrated by a point that is coloured by race; blue = White, red = Hispanic, green = Asian, black = Black and aqua blue = other. Gaussian estimates are used to visualise the distributions of races in relation to one another (large ellipses). RIGHT: A nearest neighbour dendrogram, calculated on the Euclidean distance between population means, highlights the differences between races.

METHODS

- 4,864 HIV+ participants were included in the START trial, of which 2,547 consented to genomics and were genotyped. 2,544 had an HIV RNA (copies/mL) taken at study entry and were included in analysis. Participants were antiretroviral therapy (ART)-naïve and spVL was taken as log10(HIV RNA) at study entry.
- Genotypic data was generated on a custom content Affymetrix Axiom SNP array covering 770,558 probes, and the Ensembl Gene database, assembly GRCh37.p13, was used for annotation.
- Principal component analysis (PCA) was used to identify population structures, and analysis of variance (ANOVA) was performed to detect associations between SNPs and spVL.
- SNPs with zero variance or minor allele frequency (MAF) ≤0.05 were removed.

RESULTS

- Among the 2,544 participants, PCA showed distinct population structures with strong separation between Black (n=578) and non-Black (n=1966) participants, **Figure 1**. ANOVA was performed independently on both subsets.
- Two SNPs located in the Major Histocompatibility Complex (MHC) class I region of chromosome 6 reached genome-wide significance ($P < 5 \times 10^{-8}$) in the non-Black population: rs4418214 ($P = 1.74 \times 10^{-10}$), and rs57989216 ($P = 3.96 \times 10^{-8}$), **Figure 2**. Two additional SNPs, rs9264942 ($P = 5.99 \times 10^{-8}$) and rs7356880 ($P = 9.69 \times 10^{-8}$), in the same region approached significance.
- The minor alleles of all four SNPs were associated with lower spVL, **Figure 3**. While no SNPs reached genome-wide significance in the Black group, we observed similar trends toward lower spVL for both rs4418214 and rs57989216.

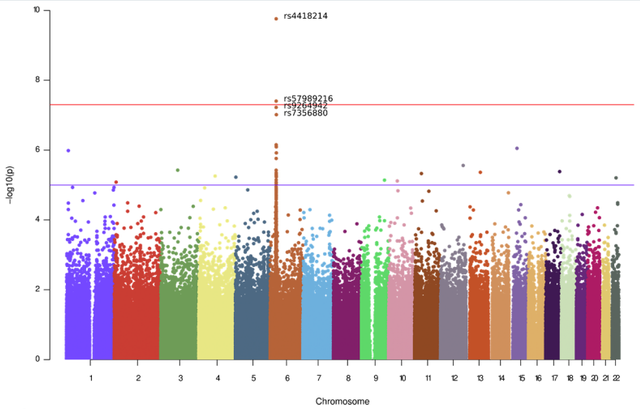

Figure 2. SNPs associated with spVL in the non-Black population
The Manhattan plot shows the association between SNPs and spVL in non-Black participants. Each SNP is represented by a point and plotted by chromosomal location (x-axis), and –log10(*P*) per SNP is shown on the y-axis. Genome-wide significance is indicated by the horizontal red line ($P = 5 \times 10^{-8}$).

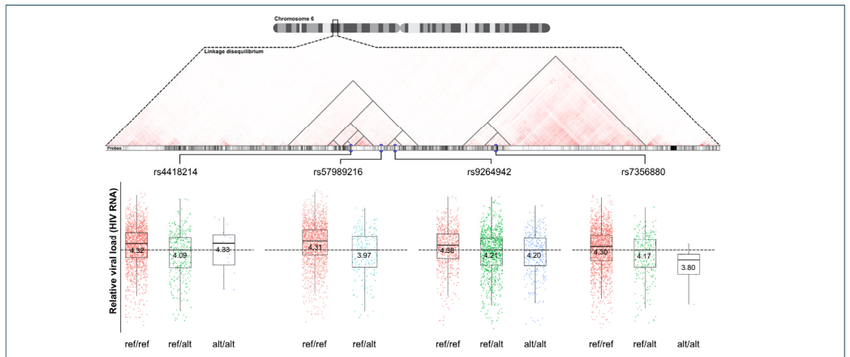

Figure 3. Summary of top four SNPs associated with spVL
TOP: The location of the four most significant SNPs in the MHC region of chromosome 6. MIDDLE: A heatmap of linkage disequilibrium (LD) highlighting local structures of SNPs in LD with one another. The black line annotations demonstrate the pyramidal, or tree-like, structure of SNP clusters in LD with one another. The positions of the top four SNPs are shown as blue points. The barcode below the heatmap shows the probe coverage of the Affymetrix array in that region, i.e. the SNPs we were able to test for association with spVL. BOTTOM: Boxplots of spVL distributions for each of the four SNPs and their different genotypes. Median log10(HIV RNA) is shown per genotype.

CONCLUSIONS

- In this study, we confirm the association of a previously reported SNP (rs4418214) and identify a novel candidate SNP (rs57989216) associated with lower spVL in a population of non-Black, ART-naïve HIV+ persons.
- Current findings suggest that the effects of these SNPs are consistent across race groups, but further studies are required to confirm this.
- Our results support previous findings that variation in the MHC class I region is a major host determinant of HIV-1 control.

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