Abstract

Background:

HIV-1 exposed seronegative individuals (HESN) have been documented in diverse cohorts. Recent genome-wide studies capturing common genetic variation in European populations failed to identify HESN-associated single nucleotide polymorphisms (SNPs). We compared whole genome sequences (WGS) of African HESN and HIV-1 seroconverters (SC) in order to identify genetic variation underlying an HESN phenotype.

Methods:

HIV-1 exposure scores (ES) were generated through regression modeling of SC and HESN in the context of prospective follow-up of 3893 African HIV-1 serodiscordant couples. We selected 50 HESN with consistently high ES matched to 50 SC by gender and self-reported ethnicity. Complete Genomics, Inc. generated 100 WGS with a median of 49 reads per base obtained over these genomes. We evaluated 38 candidate SNPs previously reported as associated with HESN versus SC. We also evaluated 1) single SNP associations with HIV-1 acquisition using logistic regression, and 2) gene-level associations using two distinct algorithms (SKAT and Morris Zeggini). All analyses controlled for population stratification using the first 3 principal components. P-values are uncorrected for multiple comparisons.

Results:

Nearly 22 million high quality autosomal SNPs (454,176 exonic SNPs) were identified across 100 African WGS. Only one candidate (CCL2, rs1024610) was significantly associated with HESN compared to SC (P = 0.01, identified in 1 SC and 11 HESN); although, the power to evaluate some candidate variants was limited. The by-variant analysis identified 13 variants having 10 - 5P > 1.8 + 10 - 7; the by-gene analysis identified 36 genes with $10 - 3P > 1.34 \cdot 10 - 7$ (SKAT) or 28 genes with 10 - 3P > 4.2 + 10 - 5 (Morris-Zeggini).

Conclusion:

Our WGS analysis of African HESN and SC has identified variants not previously associated with HIV-1 acquisition phenotypes that are of high priority for further study. Among 38 candidate SNPs tested, only one was significantly associated with protection from HIV-1. We are currently validating these associations through genotyping in an independent cohort of HESN and SC.