Genome-wide associated variants of neurocognitive disorder among people with and without HIV of Us Research Program

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BACKGROUND

- Advances in antiretroviral therapy (ART) have transformed the landscape of **clinical neurocognitive complications** associated with chronic HIV infection.
- Nearly **50%** of people with HIV (PWH) experience some form of HIV-associated **neurocognitive disorder**, such as asymptomatic neurocognitive disorder and mild neurocognitive disorder.
- Increased susceptibility to neurocognitive disorder could be due to **divergence in host genetics**.

Gap 1: The role of host genetic factors in HIV neuropathogenesis and cognitive impairment has been clouded by the critical issue of a **lack of reproducibility** among various studies.
Gap 2: Previous studies and reproducibility have been limited due to relatively small sample sizes, disproportionate focus on Caucasian populations and young adults, and lack of specificity and clarity regarding disease outcome measures and diagnoses.

Study aim: To identify and compare the host genetic factors associated with cognitive impairment in PWH versus exactly matched people without HIV (PWoH).

METHODS

Data source:

- We used multi-sourced data (i.e., electronic health records [EHR], survey data, and genomic data) from the latest **All of Us (AoU) controlled tier data, version 8**, which included participants enrolled from May 6, 2018, to October 1, 2023.

Study population: PWH (All confirmed/probable HIV cases without any history of cognitive disorder prior to HIV diagnosis) and **PWoH (**For each PWH, we used an exact matching approach to match 10 cases of PWoH based on sex, age, race, and ethnicity).

***Cognitive disorder** was identified based on the International Classification of Diseases, Ninth/Tenth (ICD-9/10) Revision diagnostic codes; **Confirmed and probable HIV cases** were determined by a predefined comprehensive HIV phenotyping algorithm based on ICD codes, drug exposure, lab results, and survey data.*

The interplay between host genetics and HIV infection may influence cognitive vulnerability through multiple biological pathways.

METHODS

Statistical analysis

- We conducted a **genome-wide association study (GWAS)** and **gene-environmental interaction analysis** among PWH (n = 13,013) and matched PWoH (n = 112,132).
- GWAS was adjusted for age, sex, race, ethnicity, and the top five principal components to account for population stratification, with a genome-wide significance threshold of $p < 5\times10^{-8}$ and the suggestive significance threshold of $p < 1\times10^{-5}$.
- All analyses were conducted in **a secure informatics workspace** provided by NIH that enables users to access and analyze the AoU

RESULTS

- In both total sample and subset of PWoH, three genome-wide significant SNPs have been identified, including rs429358 (Gene: APOE, $p = 8.8\times10^{-18}$), rs769449 (Gene: APOE, $p = 1.48\times10^{-12}$), and rs4420638 (Gene: APOC1, $p = 8.15\times10^{-10}$).
- Among PWH, three suggestively significant variants located in the MPLH and TH genes were associated with cognitive impairment.
- The gene-environment interaction analysis identified 143 SNP x HIV status interactions reaching the genome-wide significant threshold ($p < 5\times10^{-8}$), with the top six genes of these significant variants including CACNA1B, ADAMTS9, MYH9, NAGA, and STIM1.

Table 1. Demographic characteristics of the study population

	PWoH	PWH
Cognitive disorder		
No	110740 (98.8)	13844 (98.8)
Yes	1392 (1.2)	169 (1.2)
Sex		
Female	57041 (50.9)	6784 (48.4)
Male	55091 (49.1)	7229 (51.6)
Age (Mean [SD])	58.96 (15.25)	59.23 (14.87)

RESULTS

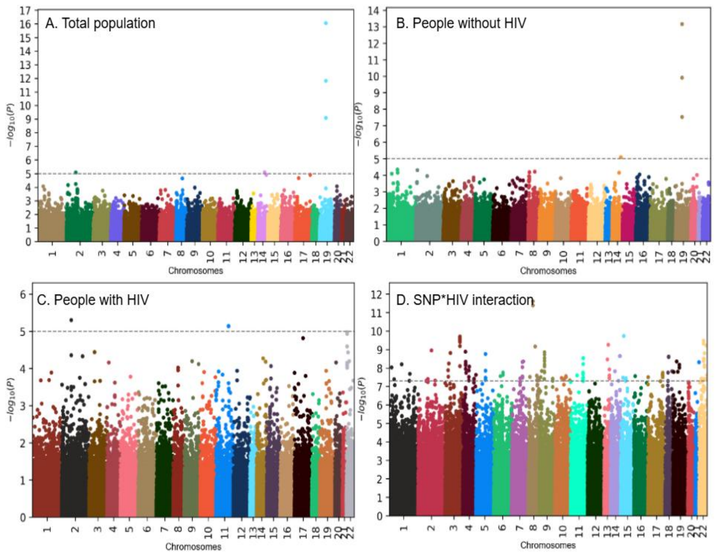


Figure 1 Manhattan plots of SNPs associated with cognitive disorder among (A) the total population, (b) PWoH, (C) PWH, and (D) the SNP*HIV interaction (*Notes: the significance threshold was 5×10^{-8} for the interaction analysis and 1×10^{-5} for others.)*

CONCLUSIONS

- Consistent with prior literature, we identified genome-wide significant associations in **APOE and APOC1,** which are well-established risk factors for Alzheimer's disease and cognitive decline among the total sample and PWoH.
- In contrast, only suggestively significant associations were observed in **MPLH and TH**, pointing to potentially distinct genetic mechanisms contributing to cognitive disorder in the context of HIV.
- The **interplay between host genetics and HIV infection** may influence cognitive vulnerability through multiple biological pathways.
- These findings could contribute to the precision intervention targeting PWH with an elevated risk of cognitive impairment

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