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GENETICALLY PREDICTED GENE EXPRESSION AND HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

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CHARTER
CNS HIV Anti-Retroviral Therapy Effects Research
CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Objective

To estimate the genetically-determined component of gene expression within the CHARTER cohort using genotypes known to influence expression within whole blood, and to explore how these genes and their pathways influence CHARTER neuroconigitive phenotypes.

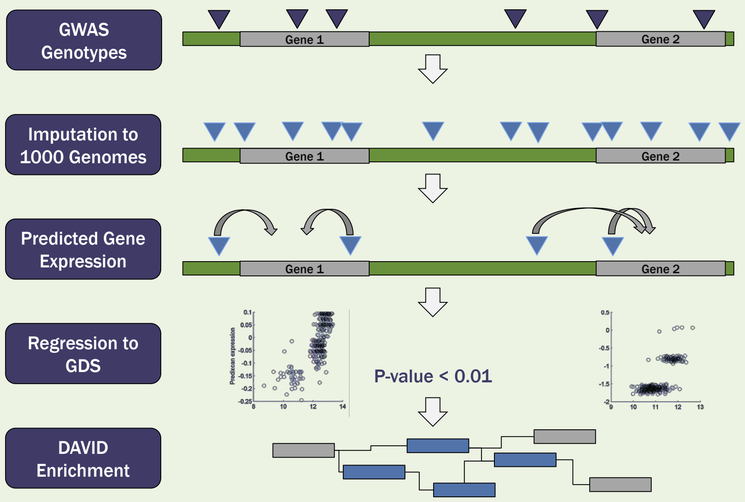
Background & Significance

HIV-Associated Neurocognitive Disorder (HAND) is a term established to capture a spectrum of neurocognitive (NC) deficits associated with HIV infection. The genetic underpinnings of HAND are poorly understood. CHARTER is a U.S.-based observational study of neuro-HIV outcomes in ambulatory, HIV+ adults who underwent standardized, comprehensive NC assessment (2003-7) and were assigned a Global Deficit Score (GDS) [normal (GDS<0.5) or impaired (GDS≥0.5)]. In this study, we investigated the impact of genetic variants known to alter the expression of genes in whole blood on GDS outcomes.

Hypotheses

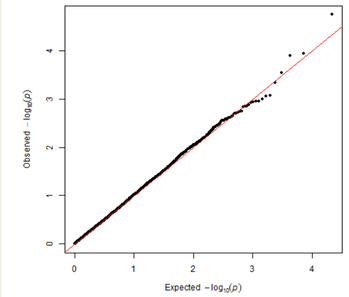
- We hypothesize that genetically-predicted gene expression traits will associate to neurocognitive phenotypes measured by GDS in the CHARTER cohort
- We further hypothesize that significantly associated genes will be enriched for iron-related and mitochondrial mechanisms

Method



We used CHARTER genome-wide association study (GWAS) data (imputed to the 1000 Genomes reference) to predict gene expression using an approach called PrediXcan (Gamazon et al). It estimates the genetically regulated component of gene expression using reference panels from studies of expression quantitative trait loci (eQTL). In this study, Gene/Tissue Expression data and CHARTER genome-wide genotype data were used to model the expression profile of 11,000 genes. We then evaluated associations of these "imputed" gene expression traits with two CHARTER NC phenotypes (continuous GDS and GDS impairment). Because of difficulties estimating gene expression traits in African American and Hispanic populations, **we restricted this analysis to 440 individuals of European descent**. We performed regression analyses to identify predicted gene expression values that associate to continuous GDS and GDS impairment, adjusting for population effects and known clinical covariates (comorbidity status, current CART use, plasma viral load, nadir CD4+ T-cell count).

Results



No genes meet Bonferroni significance

122 genes significant at p<0.01

Nominally significant genes used in DAVID enrichment analysis

Table 1. Results from DAVID Enrichment Analysis of 122 significant genes

ANNOTATION CLUSTER 1	ENRICHMENT SCORE: 2.71				
DAVID Category	Term	Gene Count	%	P-Value	Fold Enrichment
Gene Ontology Term	oxidation-reduction process	14	12.1	7.36E-05	3.78
Keywords	Oxidoreductase	11	9.48	0.0015	3.35
Keywords	Iron	7	4.55	0.0009	3.83
Keywords	Monooxygenase	4	3.44	0.0132	8.06
ANNOTATION CLUSTER 2	**ENRICHMENT SCORE: 1.25**				
DAVID Category	Term	Gene Count	%	P-Value	Fold Enrichment
Gene Ontology Term	oxidoreductase	6	5.17	0.0092	4.64
Keywords	FAD	3	2.58	0.12	4.83
Keywords	Flavoprotein	3	2.58	0.12	4.83
ANNOTATION CLUSTER 3	**ENRICHMENT SCORE: 1.24**				
DAVID Category	Term	Gene Count	%	P-Value	Fold Enrichment
Keywords	Iron	7	6.03	0.0097	3.83
Keywords	Metal	8	2.58	0.10	5.28
Keywords	Heme	3	2.58	0.16	4.03

While no genes were significant after multiple testing corrections, the top genes were Ankyrin Repeat Domain 44 (*ANKRD44*), insulin receptor substrate 2 (*IRS2*), and Activating Transcription Factor 3 (*ATF3*). Using a set of 122 genes associated to CHARTER phenotypes at p < 0.01, we performed gene pathway enrichment analysis (Table 1). Initial analysis suggests overrepresentation of iron ion binding and oxidoreductase activity. We then evaluated the cumulative effect of SNPs within these mechanisms on GDS (Table 2). All categories show statistical significance, and explain between 1.3% and 2.1% of variance in GDS within the CHARTER European-descent samples. We also found a significant enrichment for HIV-Interacting genes (p =0.016), based on a PrediXcan models which predict altered expression of 8 (of 17) genes shown in in Table 3.

Table 2. Cumulative Effects of DAVID Enrichments on GDS Outcome

Category	% Variance in GDS Explained	SE	P-value	# of SNPs
Iron Ion Binding	**1.8%**	**1.0%**	**0.0006**	**192**
Iron	**1.9%**	**1.1%**	**0.005**	**76**
Annotation Cluster 1	2.1%	1.2%	0.0002	188
Annotation Cluster 2	1.3%	0.9%	0.002	84
Annotation Cluster 3	1.5%	1.0%	0.01	103

Table 3. HIV-Host Interaction Genes Enriched within the 122 genes

HIV INTERACTION (PUBMED)	ENRICHMENT P-VALUE: 0.016
Symbol	Gene Name
ERGIC2	ERGIC and golgi 2(ERGIC2)
LIMD1	LIM domains containing 1(LIMD1)
SEH1L	SEH1 like nucleoporin(SEH1L)
SEL1L	SEL1L ERAD E3 ligase adaptor subunit(SEL1L)
SUN1	Sad1 and UNC84 domain containing 1(SUN1)
DOHH	deoxyhypusine hydroxylase/monooxygenase(DOHH)
NCOR1	nuclear receptor corepressor 1(NCOR1)
TIMM13	translocase of inner mitochondrial membrane 13(TIMM13)

Conclusions

Using PrediXcan, we have identified genes and pathways potentially influencing NC impairment in HIV-infected individuals. Based on these findings, we further hypothesize that individuals with altered regulation of HIV-interacting genes may be predisposed to HAND in the presence of HIV infection. This preliminary study provides further support for a role of iron transport in HAND pathogenesis and evaluates gene expression effects by modeling the mechanisms through which genetic variants influence NC impairment.

REFERENCES

Gamazon, et al., A gene based association method for mapping traits using reference transcriptome data Nature Methods, 2015

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CHARTER NEUROAIDS DATA RESOURCE

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