

CCL3L1 Gene Copy Number in the Northeast AIDS Dementia (NEAD) Cohort and the National NeuroAIDS Tissue Consortium (NNTC)



*Amanda Brown, *Richard Skolasky, *Ned Sacktor, #Karen Marder, +Bruce Cohen, ^Giovanni Schifitto, *Jason Creighton, *Liping Guo and *Justin McArthur
*Johns Hopkins University School of Medicine, Baltimore, MD; #Columbia University, New York, NY; +Northwestern University, Chicago, IL; ^University of Rochester, Rochester, NY.

BACKGROUND

The use of HAART in the developed world has led to a dramatic decline in the incidence of HIV-dementia and a shift toward milder forms of impairment, which collectively are called **HIV-associated neurocognitive disorders (HAND)**. While neuropsychological definitions have been updated, there is an independent need for surrogate markers that would permit the identification of individuals at risk for the development of **HAND**. Early identification would allow improved treatment regimens and monitoring to be implemented.

Host genetics contribute to HIV resistance, susceptibility or to disease progression. Specific mutations in MCP-1 and its receptor CCR2, alterations in the promoter of TNF α and the E4 isoform for ApoE have been shown to render individuals more susceptible to HIV-D. Gonzalez et al., reported that a CCL3L1 chemokine gene copy number below the ethnic group average increased risk for HIV infection and the development of key AIDS-defining illnesses that included HIV-D.

The aim of this study was to determine whether CCL3L1 copy number in self-defined ethnic groups could differentiate individuals with different types of **HAND**.

METHODS

Genomic DNA was obtained from two sources: The NEAD Cohort and the NNTC.

The NEAD Cohort

- Established in 1982-Columbia, Johns Hopkins, Northwestern and Rochester Universities
- 90% on HAART
- 24% Mild-moderate cognitive impairment
- 69% Severe cognitive impairment
- Very advanced disease
- Mixed cortical and subcortical features with milder phenotype
- Frequent transitions and reversals

The NNTC

- Established in 1998 to collect, store and distribute samples of nervous tissue, CSF, blood and other tissues from HIV-infected individuals at centers in Los Angeles, San Diego, Galveston and New York.
- Comprehensive neuropsychiatric data are gathered antemortem.
- Funded by 1U01MH083545-01

METHODS (continue)

- Methods are based on Gonzalez et al., Science 307:1434 (2005).

•DNA was isolated using the QiaAmp Blood and Tissue Mini Kit (Qiagen).

•CCL3L1 and beta-globin copy numbers were determined on triplicate samples by qPCR.

•The relative quantitation method based on a standard curve generated with DNA from A431 cells that have a diploid CCL3L1 copy number was used.

•Data were analyzed using repeated measures, analysis of variances with significance defined as $p < .05$.

RESULTS

1. Significant differences in CCL3L1 copy number between African-Americans and Caucasians and between Hispanics and Caucasians were found.

	Mean (standard deviation)	p value
African American	2.7 (1.25)	$p < .001$
Caucasians	1.45 (0.74)	
Hispanics	2.95 (1.26)	$p = .002$

2. No significant differences in CCL3L1 copy number across neurocognitive groups was detected.

Copy Number by Neurocognitive Group

Mean (standard deviation)

Unimpaired	MCMD	HAD
2.31 (1.1)	2.41 (1.29)	2.52 (1.34)

AAN Dementia Classification	Race	N	Mean	Std Dev	Min	Max
Not impaired	White	48	1.24	0.67	0.39	2.93
	Black	155	2.53	0.97	0.54	4.72
	Hispanic	22	3.29	1.04	0.53	4.15
MCMD	White	59	1.39	0.71	0.32	2.93
	Black	167	2.78	1.23	0.56	6.29
	Hispanic	20	2.58	1.36	0.70	4.15
HAD	White	40	1.77	0.79	0.56	3.17
	Black	137	2.70	1.39	0.57	8.49
	Hispanic	11	2.84	1.4	0.61	4.03

3. Among Hispanics there was a trend (not significant) toward lower copy number with increasing HAND severity that was not observed with African-Americans or Caucasians.

CONCLUSIONS

These results suggest that CCL3L1 copy number cannot serve as a predictive marker for identifying patients at risk for developing specific HAND subtypes.

ACKNOWLEDGMENTS

We acknowledge the generous participation of patients and staff of the NEAD cohort and NNTC and the funding sources: NIH R01 NS049465, P03MH075673 and 1U01MH083545-01.