Poster # 260

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HLA Gene Loci Associated with HIV Load in CSF and Blood Plasma in the CHARTER Cohort

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

Objective

Determine whether polymorphic genes associated with lower loads of HIV-1 in blood plasma exhibit a similar association with the load of HIV-1 in cerebrospinal fluid (CSF) samples obtained from the Central Nervous System (CNS).

Background & Significance

Certain polymorphic genes in the human histocompatibility locus (HLA) are associated with heightened control of HIV replication in the blood plasma of patients not taking combinatorial antiretroviral therapy (cART) during acute early infection (see Carrington, M, Walker BD. Ann Rev Med 63:131-145, 2012). Several aspects of these genetic associations remain to be elucidated: 1) It is not clear whether these genotypes are associated with the control of HIV-1 replication in the CNS, a body compartment that is associated with brain dysfunction. 2) Associations between HLA genotype and HIV control vary markedly between different ancestries, and implications for gene based therapies in various kinds of patients need to be explored further. 3) Whether the genes influence HIV replication in patients with good viral suppression on cART is not established. We compared key HLA genotypes with the level of HIV-1 RNA in cerebrospinal fluid and blood plasma of 567 infected subjects in the CHARTER cohort, which contains patients with varied racial and treatment backgrounds.

Hypotheses

Hypothesis 1: White subjects who are treatment naive and have the protective HLA alleles *HLA-C*-35/C* {rs9264942} or HLA-B*5701{rs2395029} will exhibit better control of HIV-1 in cerebrospinal fluid (CSF) and blood plasma.
Hypothesis 2: White subjects who are treated with cART will not exhibit an association between the HLA gene loci and control of HIV-1 RNA in blood and CSF.
Hypothesis 3: No associations with the genes will be present in treated or untreated African Americans (in accord with prior reports).

Method

Subjects. 567 subjects were followed longitudinally in the CHARTER cohort, which is composed of HIV infected patients from a variety of ancestries and cART treatment histories.
Specimens. Blood and CSF were collected at entry and regularly thereafter.
HIV loads. The HIV RNA concentration in blood plasma and CSF was assayed using Roche Amplicor.
Genotyping. Genomic DNA was isolated from blood and HLA alleles *HLA-C*-35/C* {rs9264942} or HLA-B*5701{rs2395029} were measured using polymerase chain reaction.
Statistics. The statistical tests that were used are as shown in the tables.

Results

cART Naïve Subjects	Viral Load Type	Mean VL (TT)	Mean VL (CT)	Mean VL (CC)	P-value (CC vs CT&TT)
Overall					
N (CSF) = 73	CSF	2.70	2.76	2.77	0.88
N (Plasma) = 83	Plasma	4.0	4.02	3.78	0.24
Ancestry					
European					
N (CSF) = 43	CSF	2.93	2.81	2.73	0.61
N (Plasma) = 48	Plasma	4.45	4.30	3.60	0.034*
African					
N (CSF) = 27	CSF	2.51	2.7	2.87	0.39
N (Plasma) = 31	Plasma	3.52	3.53	4.12	0.32

The HLA-C -35 CC haplotype was associated with low plasma HIV RNA, but not CSF HIV RNA loads in treatment naïve whites but not Africans (above). A similar result was obtained for HLA-B5701 (at right). In patients treated with cART the association was absent (below). An unexpected link was observed between the HLA-C -5 CC haplotype and higher-than-expected viral loads only in Africans . Wilcoxon Rank Sum Test above. Fisher's exact test below..

Subjects on cART	Viral Load Type	Viral load TT	Viral load CT	Viral load CC	P-value (CC vs CT& TT)
Overall					
N (CSF) = 342	CSF<LLQ	118	145	30	0.45
	CSF≥LLQ	22	20	7	
N (Plasma) = 383	Plasma < LLQ	99	114	22	0.40
	Plasma ≥ LLQ	57	73	18	
Ancestry					
=European					
N (CSF) = 183	CSF < LLQ	54	88	22	0.48
	CSF ≥ LLQ	9	9	1	
N (Plasma) = 205	Plasma < LLQ	46	68	17	0.51
	Plasma ≥ LLQ	26	41	7	
=African					
N (CSF) = 147	CSF < LLQ	58	53	7	0.022
	CSF ≥ LLQ	13	10	6	
N (Plasma) = 164	Plasma < LLQ	49	43	4	0.012*
	Plasma ≥ LLQ	27	30	11	

Results

cART Naïve subjects	HIV load type	N	Viral load in HLA-B5701 negative (0) and positive (1) subjects		P-value
			0	1	
Overall	CSF	85	2.78 (1) 2.53 [1.7 – 3.69]	2.57 (1) 2.34 [1.7 – 3.17]	0.54
	Plasma	85	4.06 (1.08) 4.2 [3.41 – 4.76]	3.25 (1.08) 3.08 [2.38 – 4.14]	0.076
European	CSF	49	3.08 (0.99) 3.31 [2.39 – 3.8]	2.48 (0.99) 1.7 [1.7 – 3.23]	0.2
	Plasma	49	4.49 (1.01) 4.58 [4.17 – 4.93]	3.19 (1.01) 2.61 [2.3 – 4.34]	0.032 *
African	CSF	32	2.38 (0.87) 1.84 [1.7 – 2.78]	2.98 (0.87) 2.98 [2.98 – 2.98]	0.37
	Plasma	32	3.36 (0.84) 3.39 [2.71 – 4.08]	3.55 (0.84) 3.55 [3.55 – 3.55]	0.95

Mean (SD) and Median [IQR] are reported. Wilcoxon rank-sum test

Conclusions

1. Results from the CHARTER cohort confirm that ancestry and cART both influence whether the protective HLA alleles were associated with control of HIV-1 replication:
2. Whites not treated with cART: The protective HLA alleles were associated with stronger control of HIV-1 replication in blood plasma, but NOT in the CSF of these subjects.
3. Whites treated with cART: The protective HLA alleles were not associated with stronger control of HIV-1 in plasma or CSF because the genetic influence was weaker than cART.
4. African Americans not treated with cART: Unlike treatment naïve whites, the HLA alleles were not associated with stronger control of HIV-1 in plasma or CSF. That agrees with prior observations of plasma HIV-1 set point.
5. African Americans treated with cART: Unexpectedly, a "protective" HLA allele in Africans on cART was linked with HIGHER HIV RNA in plasma and CSF (worse control). Africans with those alleles might achieve improved HIV control by intensifying cART.

References

Carrington, M, Walker BD. Immunogenetics of spontaneous control of HIV. Ann Rev Med 63:131-145, 2012

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