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Protective *interleukin-28B* genotype affects hepatitis C virus clearance, but does not contribute to HIV-1 control in a cohort of African–American elite controllers/suppressors

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Abstract

We tested the hypothesis that a single nucleotide polymorphism (SNP) located near the *interleukin-28B* gene is associated with the control of hepatitis C virus and HIV-1 replication in elite controllers/suppressors. We show here that the protective genotype is not overrepresented in elite controllers/suppressors compared with HIV-1-seronegative patients and HIV-1-infected patients with viral loads more than 10 000 copies/ml. Thus, it appears that this SNP is not associated with the elite control of HIV-1 infection.

The mechanisms involved in the control of hepatitis C virus (HCV) and HIV-1 infection remain unclear. The C/C genotype of a single nucleotide polymorphism (SNP) near the *interleukin-28B* (*IL28B*) gene has recently been associated with successful treatment [1,2] and spontaneous clearance [3] of HCV infection. Although HIV-1 is not spontaneously cleared, viral replication is controlled to a level below the limit of detection by commercial assays in a cohort of patients known as elite controllers/suppressors [4–6]. A recent study has shown that elite controllers/suppressors are also more likely to clear HCV infection [7], suggesting that common mechanisms may be involved in the control of the two polymorphic RNA viruses. *IL28B* encodes a type III interferon, which may suggest a role for innate immunity in HCV clearance. Such an innate immune response could potentially be involved in the control of other viruses including HIV-1. A recent study has documented that, in primary infection, elite controllers/suppressors have peak viral loads that are 1–2 logs lower than that typically seen in patients who develop progressive disease [8]. Peak viremia precedes the development of the adaptive HIV-specific immune response, thus a strong innate immune response may be involved in the early control of HIV-1 replication in elite controllers/suppressors. Although it has recently been shown that the protective *IL28B* genotype does not affect the rate of CD4⁺ T-cell decline in HIV-1-infected patients [9], it is not known whether it plays a role in the elite control of HIV-1 replication. We, thus, examined the *IL28B* SNP in a well characterized cohort of 25 African-American elite controllers/suppressors, of whom 13 were seropositive for HCV. We hypothesized that the protective C/C allele would be overrepresented in this cohort compared with a cohort of patients with progressive HIV-1 disease if this SNP played a role in the elite suppression of HIV-1 replication.

HCV status was determined for all patients. A third-generation enzyme immunoassay was used to determine the antibody status and quantitative HCV-RNA level was determined on all HCV-seropositive patients (Roche COBAS TaqMan 1.0 assay, Roche Molecular Systems, Branchburg, New Jersey, USA) with a limit of detection of 35 IU/ml). Liver disease stage was determined by histologic evaluation. Liver biopsy specimens were read by a single pathologist and staged/graded according to the METAVIR scoring system. Genotyping for *IL28B* was performed as previously described [3].

Of 25 African–American elite controllers/suppressors in our cohort, 13 were HCV seropositive. Five of these patients had no detectable HCV-RNA, which was confirmed by repeat testing (Table 1). A recent study has shown a higher rate of HCV clearance in elite controllers/suppressors than in HCV-monoinfected patients and in co-infected patients with progressive HIV-1 disease [7]. The clearance rate in our cohort (five of 13 HCV-seropositive elite controllers/suppressors or 38.5%) is similar to that seen by Sajadi *et al.* [7] and significantly higher than the rate of HCV clearance in a large study of African–American patients. In the remaining eight patients, a broad range of HCV-RNA levels was observed. The magnitude of HCV-RNA viremia was relatively low (<200 000 IU/ml) in three persons, but was high (>1 000 000 IU/ml) in the other five (Table 1). Among the elite controller/suppressor patients with chronic HCV infection, serum alanine aminotransferase levels were modestly elevated (34–83 U/l /l), consistent with liver inflammation. Histologic evaluation was performed in six viremic patients, of whom one (elite controller/suppressor 4) had established cirrhosis. Interestingly, the *human leukocyte antigen-B*57* (*HLA-B*57*) allele has been implicated in the control of HIV-1 [4] and HCV infection [10] and is clearly overrepresented in our cohort compared with the general African–American population [11]. Three of the five elite controllers/suppressors who cleared HCV viremia in our cohort were *HLA-B*57*-positive, but several *HLA-B*57* patients also had very high HCV-RNA levels (Table 1). Taken together, the broad spectrum of liver disease seen in our cohort strongly suggests that elite control of HIV-1 does not necessarily lead to control of HCV infection.

We next determined the frequency of the protective C/C genotype in HCV-positive and HCV-negative patients in our cohort. Two of five patients who cleared HCV infection were positive for the C/C *IL28B* genotype. This is consistent with studies finding that this genotype is overrepresented in patients who clear HCV [3]. In order to determine whether this genotype also played a role in the control of HIV-1 replication, we looked at the frequency in the entire cohort and compared it with the frequency seen in HIV-1-positive and HIV-1-negative African–American patients from the AIDS Link to the Intravenous Experience (ALIVE) cohort. Overall, only four of 25 elite controllers/suppressors in our study [16.0%, 95% confidence interval (CI) 1.76–31.58%) were positive for the protective genotype. This frequency is similar to that seen in HIV-1-infected patients with viral loads more than 10 000 copies/ml (47/275 = 17%, 12.56–21.44%) and seronegative patients at high risk for HIV infection (62/308 = 20%, 15.65–25.61%) in the ALIVE cohort. Notably, similar frequencies have been reported in other cohorts of HCV-infected African–Americans (30/191 = 15.7%, 95% CI 10.55–20.87% [2] and 58/232 = 25.0%, 95% CI 19.43–30.57% [3]). This lack of overrepresentation of the protective C/C genotype in elite controllers/suppressors compared with HIV-1-infected patients with substantial levels of HIV-1 viremia suggests that the *IL28B* SNP does not play a significant role in the elite control of HIV-1 replication.

Overall, our findings suggest that, although the protective *IL28B* allele contributes to the clearance of HCV infection in HIV-1-coinfected elite controllers/suppressors, it does not contribute to the control of HIV-1 infection in African–Americans. However, as most injection drug users acquire HCV infection much earlier than they became seropositive for HIV-1 [12], it is possible that the sequence of viral infection plays a role in the *IL28B*-

mediated control of viruses. Further studies are needed to elucidate the mechanisms by which *IL28B* contributes to the control of HCV infection, but not to HIV infection.

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M.S. performed genotyping of elite controller/suppressor samples and drafted the manuscript. G.D.K. provided samples and helped design the study. A.C. and A.R. helped design the study. Y.H. coordinated the study. J. A. performed statistical analysis. D.T. helped design the study and provided critical input. C.L.T. performed genotyping of chronic progressor samples. M.S.S. and J.N.B. conceived the study and drafted the manuscript. M.S.S. and J.N.B. contributed equally to the writing of the final article.

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Table 1
Clinical characteristics and *interleukin-28B* genotype in a cohort of 25 African-American elite controllers/suppressors

ES	HCV Ab	Age (years)	First HIV-positive test	HLA-A allele	HLA-B allele	CD4 cell counts (cells/ μ l)	HIV-RNA (copies/ml)	HCV-RNA (IU/ml)	Liver biopsy (METAVIR scores)	IL28B SNP
ES2	+	51	1986	02, 31	44, 5703**	399	<50	<35	ND	T/T
ES7	+	53	1994	30, 32	5703**, 81	1352	<50	<35	ND	C/C
ES8	+	55	2003	02, 03	44, 5703**	602	<50	<35	ND	C/C
ES13	+	65	1993	02, 23	15, 35	721	<50	<35	ND	C/T
ES34	+	52	1997	30, 68	42	1613	<50	<35	ND	T/T
ES3*	+	55	1991	25, 68	51, 5702**	728	<50	105 000	0	T/T
ES4	+	51	1996	02, 30	08, 44	783	<50	4 530 000	4	C/T
ES5	+	56	1990	23, 68	5703**, 58	839	<50	82 800	0	C/T
ES14	+	51	2002	30, 55	52, 78	939	<50	1 810 000	0	C/T
ES18	+	54	1998	23, 74	42, 5703**	1330	<50	183 000	ND	C/T
ES23	+	56	1986	03, 30	15, 5703**	750	<50	1 320 000	0	T/T
ES24	+	57	2009	24, 30	07, 5703**	2033	<50	27 800 000	1	C/C
ES31	+	56	2006	03	27, 5801	758	<50	1 370 000	ND	T/T
ES1	-	32	1999	24, 26	14, 27	850	<50	NA	NA	T/T
ES6	-	54	1996	23	15, 5703**	1139	<50	NA	NA	C/T
ES9	-	60	1999	02, 30	27, 5703**	1027	<50	NA	NA	C/T
ES12	-	44	2004	02	53, 5703**	1080	<50	NA	NA	T/T
ES15	-	33	1996	30, 33	07, 5703**	877	<50	NA	NA	T/T
ES19	-	59	1996	01, 30	07, 5703**	732	<50	NA	NA	C/T
ES22	-	49	2009	30, 31	15, 5703**	1180	<50	NA	NA	C/C
ES25	-	54	2002	30, 31	15, 5703**	579	<50	NA	NA	T/T
ES26	-	47	1998	02, 03	35, 5701**	242	<50	NA	NA	C/T
ES27	-	24	2006	01, 68	15, 5703**	1047	<50	NA	NA	C/T
ES32	-	34	2000	02, 74	07, 44	519	<50	NA	NA	C/T

ES	HCV Ab	Age (years)	First HIV-positive test	HLA-A allele	HLA-B allele	CD4 cell counts (cells/ μ l)	HIV-RNA (copies/ml)	HCV-RNA (IU/ml)	Liver biopsy (METAVIR scores)	IL28B SNP
ES36	–	62	2002	02, 11	51, 81	537	<50	NA	NA	T/T

Frequency of C/C genotype: ES ($n = 25$), 16% (1.76–31.58%); HIV-1-positive patients with viral load more than 10 000 copies ($n = 275$), 17% (12.56–21.44); HIV-1-negative patients ($n = 308$), 20% (15.65–25.61). +, positive; –, negative; Ab, antibody; ES, elite controllers/suppressors; HCV, hepatitis C virus; HLA, human leukocyte antigen; IL, interleukin; NA, not applicable; ND, not determined/not performed; SNP, single nucleotide polymorphism.

* ES3 was successfully treated with pegylated interferon and ribavirin.

** HLA-B*57 allele.