IL28B Genotype Does Not Correlate with HIV Control in African Americans

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Abstract

Background: HIV-1 natural viral suppressors (NVS) are individuals that control HIV replication without antiretrovirals (also know as HIV elite controllers). We have recently shown that these individuals have an elevated rate of hepatitis C virus (HCV) clearance. Given the association of *IL28B* genotype, specifically the rs12979860 single nucleotide polymorphism (SNP) based CC genotype, with HCV clearance, we studied its association with HIV control in 172 African American HIV subjects and 173 race-matched controls.

Findings: The frequency of the CC genotype was 12.5% in the NVS, 14.7% in the LVL ("low viral load" cohort with 400–20,000 HIV-1 RNA copies/mL), 17.8% in the MHVL ("medium/high viral load" cohort with >20,000 HIV-1 RNA copies/mL), and 11.6% in an HIV-negative cohort. There was no statistical significance in the CC genotype distribution between these cohorts ($p = 0.48$ between the NVS and non-NVS HIV positive controls, $p = 0.85$ between NVS and HIV-negatives). We also did not observe any association between CC genotype distribution and HIV RNA viral load, as a continuous measure.

Conclusions: The *IL28B* CC genotype does not account for the noted HIV control in our specific NVS cohort. Further studies will be needed to determine if a common genetic factor can primarily account for any joint clearance of HCV and control of HIV. Clin Trans Sci 2011; Volume 4: 282–284

Keywords: HIV, HCV, natural viral suppressor, elite controller, *IL28B*

Introduction

In the past year, there have been several studies showing an association of sustained virologic response and spontaneous clearance of hepatitis C virus (HCV) in those with the CC genotype of the rs12979860 single nucleotide polymorphism (SNP) on chromosome 19q13, 3kb upstream of the *IL28B* gene, which encodes IFN-λ3.[1–3] Since discovery of IFN-λ,[4] its antiviral activity against West Nile virus (single-stranded virus),[5] and role in the response to double-stranded viruses have been demonstrated.[4] A remaining question is whether IFN-λ may also be responsible for the control of other viruses such as HIV-1.

HIV-1 natural viral suppressors (NVS) are individuals who control the replication of HIV-1 to undetectable levels in the absence of therapy.[6] We have recently demonstrated that NVS individuals appear to clear HCV infection at an elevated rate compared to controls.[7] Given the elevated clearance rates of HCV and control of HIV seen in the NVS, we undertook a study to determine if there was an association between the *IL28B* genotype and control of HIV-1 viral load.

Methods

Genotyping of the rs12979860 SNP was performed in 345 individuals who belonged to one of following four cohorts: (1) HIV-1 NVS: individuals with HIV-1 infection by both Western Blot and proviral DNA, and at least a 2-year period with <400 HIV-1 RNA copies/mL in the absence of highly active antiretroviral therapy (HAART);[7,8] (2) low viral load (LVL) cohort: individuals with 500–20,000 HIV-1 RNA copies/mL in the absence of HAART; (3) medium/high viral load (MHVL) cohort: individuals with >20,000 HIV-1 RNA copies/mL in the absence of HAART; and (4) HIV-negative group: race-matched controls infected with HCV[10] Thus, 172 HIV infected (48 NVS, 34 LVL, 90 MHVL) and 173 controls were tested. All participants were African Americans. This study was IRB approved, and all individuals provided informed consent.

Genotyping of the rs12979860 SNP for *IL28B* genotype was performed using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA) according to the manufacturer's protocol. Replicate genotyping in 8% of the samples resulted in >98% concordance rate.

Statistical approach: We used a linear regression model adjusting for age and gender to look at the association between the C allele under additive, recessive, and dominant genotype models with viral load as a continuous outcome. Fisher's exact test was used to compare genotype distributions within the four groups.

Results

The frequency of the CC genotype was 12.5% in the NVS, 14.7% in the LVL, 17.8% in the MHVL, and 11.6% in the HIV-negative groups. The CC genotype frequency in all cohorts was similar to that noted in two other African American cohorts (16%).[1,8] The SNP was in Hardy-Weinberg equilibrium in all groups. There was no statistical significance in CC genotype distribution between these groups ($p = 0.48$ between the NVS and non-NVS HIV patients, and $p = 0.85$ between the NVS and HIV-negatives by Fisher's exact test). Likewise, there was no correlation between HIV-1 RNA copies and CC genotype distribution ($p = 0.23$). There was no statistical significance between CC genotype distribution between HIV-1 positive and negative patients ($p = 0.26$). Although the above results were obtained using a recessive model, additive and dominant genetic models did not yield statistically significant results (data not shown). *Table 1* summarizes the demographics and genotype distribution across the four groups. Regarding HCV clearance in the NVS, 14% (1 of 7) of NVS who cleared HCV had the CC genotype, compared to 11% (2 of 22) who did not clear HCV ($p = 1.0$).

Discussion

The rs12979860 CC genotype is a powerful determinant of spontaneous HCV clearance and its frequency varies significantly across populations.[1] Our hypothesis was that the CC genotype would account for a significant part of the previously observed

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Cohort	Age (median)	Sex	Race	HIV viral load (median)	HIV risk factor	C/C	C/T	T/T	C allele frequency	T allele frequency
NVS $n = 48$	49 (range 30–68)	50% M 50% F	100% AA	<50 (range <50 to 273)	54% IDU 46% S	12.5%	54.2%	33.3%	39.6%	60.4%
LVL $n = 34$	46 (range 21–63)	53% M 47% F	100% AA	3080 (range 233–19,600)	39% IDU 61% S	14.7%	52.9%	32.4%	41.1%	58.9%
MHVL $n = 90$	48 (range 22–60)	54% M 46% F	100% AA	100,000 (range 24,584–667,000)	38% IDU 62% S	17.8%	47.8%	34.4%	41.7%	58.3%
HIV negative $n = 173$	50 (range 27–70)	35% M 65% F	100% AA	N/A	55% IDU*	11.6%	54.9%	33.5%	39%	61%

Demographics and frequency of the C/C, C/T, and T/T alleles for SNP rs12979860 of the NVS and other cohorts. There was no statistically significant difference among any of the four cohorts by recessive, allelic, and dominant models. By the recessive model, $p = 0.48$ between the NVS and non-NVS HIV groups, and $p = 0.85$ between the NVS and HIV-negative group by Fisher's exact test. NVS (natural viral suppressors) = HIV-1 patients with viral loads <400 copies/mL without treatment. LVL (Low Viral Load) = HIV-1 patients viral loads 500–20,000 copies/mL without antiretrovirals. MHVL (Medium/High Viral load) = HIV-1 patients with viral loads >20,000 copies/mL. HIV negative = HIV-1 negative and HCV positive race-matched (African American) control cohort. M = male, F = female, AA = African American. IDU = injection drug use, S = sexual.

*A total of 55% of the HIV-negative group had a history of IDU.

Table 1. Demographics, clinical characteristics, and genotype distributions in the four cohorts.

joint HIV control and HCV clearance. However, in this study, there was no statistically significant difference or evidence of trend in genotype distribution between the NVS and the other HIV-positive and HIV-negative cohorts. In addition, there was no correlation between CC genotype or allele frequency and HIV-1 viral load. While our study is not sufficiently powered to rule out a weak or modest effect of *IL28B* polymorphisms on HIV control, our results suggest that the *IL28B* CC genotype does not account for the joint HIV and HCV control seen within our cohort.

Similarly, in a smaller study with 25 African Americans similar to NVS, Salgado et al. found no difference between the rs12979860 CC genotype in their NVS cohort (16% CC genotype) and other HIV-infected subjects (17% CC genotype).[9] Another recent study by Martin et al. did not find an association with HIV progression in a Caucasian cohort (though they did not have an NVS group).[10]

Of the seven NVS described previously that have cleared HCV infection,[7] only one had the CC genotype (14%). While this by no means contradicts the role of CC genotype in increasing the ability to clear HCV, it suggests that the CC genotype does not explain the heightened HCV clearance in the NVS. Taken together, our data suggest that our measured *IL28B* genotype does not account for the specific joint clearance of HCV/HIV noted in our NVS cohort. Although within the context of a genetic association study, the overall number of patients studied was small, one of the strengths of the study include using the largest African-American NVS cohort available, as well as using race and demographically matched controls. Moreover, our primary goal was to test if *IL28B* genotype could account for part of the intriguing NVS status and joint HCV clearance noted in our cohort, as opposed to ruling out any effect of *IL28B* genotype on HIV.

In short, this study provides validation of the previous small single null study by Salgado et al.,[9] which also aimed to test the important hypothesis that *IL28B* genotype may in addition to HCV clearance, act as a crucial mediator of NVS status in African Americans. Further genetic studies using larger cohorts, as well studying the immune response in relation to the *IL28B* genotype should help definitively understand whether *IL28B* polymorphisms have any role in the control of HIV infection.

Conclusion

In conclusion, although some NVS can effectively control two agents of chronic viral infection (HCV and HIV), the *IL28B* rs12979869 CC genotype does not appear to be a primary mediator of a potential common pathway for viral clearance and/or suppression of HIV-1 and HCV. Further studies are highly warranted to help identify potential genetic factors that may account for part of the critically important NVS status.

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The authors declare that they have no competing interests.

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