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Relationship of Genotype for HLA B*57 and *IFNL4* With Disease Progression in Female HIV Controllers

To the Editor—Dominguez-Molina et al [1] identified genetic associations of the HLA-B*57 allele group and interferon lambda 4 (*IFNL4*)–ΔG/TT genotype (rs368234815; formerly designated ss469415590) with CD4 T-cell decline in human immunodeficiency virus (HIV) controllers. To examine these associations in the Women's Interagency HIV Study (WIHS), we identified HIV-infected women (n = 178) with complete data for those genetic loci and the HIV controller phenotype. We defined this phenotype, per the International HIV Controllers Study [2], as ≥3 consecutive measurements of plasma virus load (VL) <2000 RNA copies/mL over a period of ≥12 months in the absence of antiretroviral therapy (ART). Genotyping and imputation methods for HLA-B and *IFNL4*-ΔG/TT in WIHS have been described elsewhere [3, 4].

The median age at enrollment for WIHS controllers was 36 years (interquartile range, 30–42 years) and most participants (n = 116; 65%) were African American (32 Hispanic, 24 white, 6 other). The median follow-up time was 14 years (range, 2–21). Fifty-one controllers (29%) never started ART. Controllers who did start ART did so after a wide range of follow-up time (median, 6 years; range, 1–20 years) and at a wide range of CD4 T-cell counts (median T-cell count, 396/μL; range, 12–973/μL).

To replicate the HIV progression phenotype used by Dominguez-Molina et al [1] ("subjects with $CD4^+$ T-cell counts >500 cells/mm^3 for >7 years after HIV diagnosis"), we studied the subset of WIHS HIV controllers (n = 145; 81%) who had been followed up for ≥7 years. Of these, 19 (13%) always had a CD4 T-cell count >500/mm^3 (>500/μL) and could be defined as long-term nonprogressors (LTNPs). In bivariate analysis (Table 1), we observed a significant positive association of the B*57 allele group with the LTNP phenotype among WIHS controllers (odds ratio [OR], 4.2; exact 95% confidence interval [CI], 1.4–13.1; $P = .006$), which remained significant after adjustment for age and race/ethnicity (adjusted OR, 6.0; exact 95% CI, 1.9–20.3; $P = .002$) in multivariable logistic regression analysis. We found no significant association between *IFNL4*-ΔG/TT genotype and being a LTNP among WIHS controllers (adjusted OR, 1.6; exact 95% CI, 0.4–5.6; $P = .63$).

Our data replicate the influence of HLA-B on CD4 T-cell counts in HIV controllers; however, no association of *IFNL4*-ΔG/TT genotype with the LTNP phenotype was observed. The number of HIV controllers with LTNP in WIHS is not large; therefore, our statistical power to assess *IFNL4*-ΔG/TT genotype was relatively low. In addition, WIHS participants differ from the populations studied by Dominguez-Molina et al [1] in at least 2 important ways. First, most WIHS controllers were African American, whereas the previous study was restricted to patients of European ancestry. However, given that *IFNL4*-ΔG/TT is a functional variant, rather than simply a genetic marker, it is not obvious why an association between *IFNL4*-ΔG/TT genotype and CD4 T-cell loss would not be seen across ancestral groups.

The study populations also differ with regard to sex: WIHS is restricted to women, whereas the populations studied by Dominguez-Molina et al are mostly male. The authors might examine whether the association of *IFNL4*-ΔG/TT genotype with CD4 T-cell loss among HIV controllers differs between men and women, because sex differences in *IFNL4*-ΔG/TT genotype associations with liver fibrosis have been observed [5].

Table 1. Genetic Associations With the LTNP Phenotype in WIHS HIV Controllers (n = 145)[a]

	HIV Controllers, No. (%)					
Genotype	LTNP Phenotype (n = 19)	HIV Progression (n = 126)	Unadjusted OR (Exact 95% CI)	Exact P Value	Adjusted OR (Exact 95% CI)[b]	Exact P Value
HLA-B*57	11 (58)	31 (25)	4.2 (1.4–13.1)	.006	6.0 (1.9–20.3)	.002
HLA-B*27	0 (0)	9 (7)	NE	.61	NE	.71
HLA-B*08	1 (5)	13 (10)	0.5 (.1–3.6)	.70	0.5 (.1–4.0)	.85
HLA-B*35	3 (16)	16 (13)	1.3 (.2–5.3)	.72	1.4 (.2–6.3)	.88
IFNL4-TT/TT[c]	5 (26)	35 (28)	0.9 (.2–3.0)	>.99	1.6 (.4–5.6)	.63

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LTNP: long-term nonprogressor; NE, not estimable; OR, odds ratio; WIHS, Women's Interagency HIV Study.

[a]The LTNP phenotype was defined as all CD4 T-cell counts >500/mm^3 (>500/μL) in women with ≥7 years of follow-up.

[b]Adjusted for age at enrollment and race/ethnicity (African American, Hispanic, white, or other)

[c]As in the study by Dominguez-Molina et al [1], the *IFNL4*-ΔG/TT genotype was analyzed as *IFNL4*-TT/TT vs *IFNL4*-TT/ΔG and *IFNL4*-ΔG/ΔG.

Notes

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Potential conflicts of interest. L. P. O and T. R. O. are inventors on patent applications filed by the National Cancer Institute for the *IFNL4*-ΔG/TT (rs368234815) genotype-based test. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Kuniholm et al

To the Editor—Kuniholm et al [1] interestingly replicated the influence HLA-B*57 on immunologic progression in human immunodeficiency virus (HIV) controllers, as we previously showed in a local Spanish cohort and validated in the international HIV controllers consortium cohort [2]. However, Kuniholm et al could not find an association of *IFNL4*-ΔG/TT with the long-term nonprogressor (LTNP) phenotype in a cohort composed mainly of African American women.

As Kuniholm and colleagues acknowledged, sex and race/ethnicity may be factors influencing this lack of association. Although *IFNL4*-ΔG/TT has been shown to be the functional variant, as the authors noted, the different genetic backgrounds can explain the different results. In addition, the authors acknowledged a small sample size; the LTNP phenotype was present in only 19 subjects. This fact, associated with the lower frequency of the genotype of interest in African Americans [3], may reduce even more the statistical power of the analysis. However, these results are quite interesting, and they prompted us to check our analysis based on sex differences. In the Spanish cohort, sex was associated only with LTNP phenotype in the study cohort, about 60% male, but HLA-B*57 and *IFNL4*-ΔG/TT were still independently associated with the LTNP phenotype.

In any event, the reanalysis considering only women of European ancestry did not have power, owing to the small sample size in the Spanish cohort. The proportion of women was even smaller in the validation cohort, in which 81.2% of the subjects were men. However, when only men were included, results replicated the previous findings with HLA-B*57 (adjusted odds ratio, 2.1; exact 95% confidence interval, 1.3–3.3; P = .004) and *IFNL4*-A/A (0.6; .4- .9; P = .02) genotype associated with LTNP phenotype. Moreover, as previously shown, this phenotype was associated with age (adjusted odds ratio, 0.96; exact 95% confidence interval, .93–.98; P = .001) and also interestingly with HLA-B*27 (2.0; 1.1–3.4; P = .02). Based on these observations further studies in a larger cohorts of HIV controller women with African American and European ancestry are needed to confirm the results presented by Kuniholm et al [1].

Notes

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