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BRIEF REPORT

Toll-like Receptor Polymorphism Associations With HIV-1 Outcomes Among Sub-Saharan Africans

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Objective. We evaluated Toll-like receptors (TLRs) single nucleotide polymorphisms (SNPs) for associations with HIV-1 acquisition, set-point and disease progression in African couples.

Methods. Seven candidate and 116 haplotype-tagging SNPs (tagSNPs) were genotyped in 504 HIV-1 infected cases, and 343 seronegative controls.

Results. *TLR9* 1635A/G was associated with reduced HIV-1 acquisition among HIV-seronegative controls with high but not low HIV-1 exposure (odds ratio [OR] = 0.7; $P = .03$ and OR = 0.9, $P = .5$, respectively). *TLR7* rs179012 and *TLR2* 597C/T reduced set-point; the latter modified by time since HIV-1 acquisition. *TLR8* 1A/G reduced disease progression.

Conclusions. TLR SNPs impact HIV-1 outcomes with epidemiologic factors modifying these relationships.

Keywords. Acute Infection; Genetics; Heterosexual HIV-1 transmission; Progression; Risk Factors; Viral load; Toll-like Receptors; HIV-1 set-point; HIV-1 acquisition.

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Disparities in susceptibility to HIV-1 acquisition and control of viremia and disease progression following infection are partially explained by human genetic variation (ie, *CCR5-Δ32* and *HLA* alleles). Toll-like receptor (TLR) genes may alter HIV-1 outcomes by influencing recognition of pathogen-associated molecular patterns and initiating innate immune responses that vary longitudinally and may contribute to functional impairment and immune exhaustion. *TLR* single nucleotide polymorphisms (SNPs) have been associated with clinical HIV-1 outcomes, however, discrepant results underscore the need for validation [1–7]. Furthermore, these studies have generally not included populations from Africa, where HIV-1 is most prevalent and where different *TLR* variant frequencies may modify HIV-1 associations. To better understand TLR-mediated responses against HIV-1, we evaluated *TLR* SNP associations with heterosexual HIV-1 acquisition, set-point and disease progression among African HIV-1 serodiscordant couples.

METHODS

Participant Selection

Participants came from prospective HIV-1 serodiscordant heterosexual couple cohorts from sub-Saharan Africa: the Partners in Prevention HSV-2/HIV-1 and Couples Observational Studies. Both studies assessed HIV-1 transmission quarterly over 1–2 years of follow-up and collected longitudinal behavioral and laboratory data from both partners as previously described [8, 9]. Human subjects research review and approval was obtained at the University of Washington, study sites and affiliated institutions. All participants provided written informed consent.

We used a nested case-control study to analyze *TLR* SNP associations with HIV-1 acquisition. We matched 129 HIV-1 transmitting couples to 246 non-transmitting couples based on HIV-1 exposure scores, which increased with HIV-1 levels of infected partners, frequency of unprotected sex, decreasing age, female gender, and lack of male circumcision [9, 10]. Other factors such as treatable sexually transmitted infections were not modeled due to low prevalence among uninfected participants. To increase representation of HIV-1 seronegative individuals, we included additional seronegative participants having the highest persistent HIV-1 exposure levels in these cohorts. For this analysis, HIV-1 seroprevalent cases included participants with HIV-1 at study enrollment (unknown infection date) whereas seroconverter cases acquired HIV-1 during follow-up.

HIV-1 Set-point and Disease Progression

Plasma HIV-1 RNA levels were determined using the COBAS AmpliPrep/COBAS TaqMan HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN), with a quantification limit of 240 copies/mL. For seroconverters, HIV-1 set-point was defined as the average $\log_{10}$ plasma HIV-1 RNA measurement taken 4–18 months after infection (median = 6 measurements per person). For seroprevalent cases, set-point was based on consecutive measurements within 1 $\log_{10}$ copies/mL determined before antiretroviral therapy (ART) initiation or CD4 count < 200 cells/mm^3 (median = 4 measurements per person). HIV-1 disease progression among seroprevalent cases was defined as time to (1) ART initiation, (2) CD4 count < 200 cells/mm^3, or (3) death from medical causes.

Genotyping

DNA was isolated from archived blood using Puregene DNA purification (Qiagen, Valencia, CA), with genotyping using an Illumina Custom Oligo Pooled Assay for 124 SNPs (9 in *TLR2*, 13 *TLR3*, 22 *TLR4*, 40 *TLR7*, 25 *TLR8*, 3 *TLR9*, 4 *MYD88*, and 8 *TIRAP*). These included seven candidate SNPs previously associated with HIV-1 infection and 116 haplotype-tagging SNPs (tagSNPs) chosen to represent common variation across *TLR* genes (Supplementary Table 1). Haplotypes were inferred from the Yoruba HapMap population, and tagSNPs with minor allele frequency >5% were selected. Overall, six SNPs were excluded for >10% missing results (n = 3), for being monomorphic (n = 1), or failing Hardy-Weinberg Equilibrium (n = 1) or X-linked autosomal tests (n = 1). Of 847 genotyped samples, 15 were excluded for X-chromosome sex discrepancies and 5 for >10% genotypic missingness.

Statistical Analysis

HIV-1 acquisition analyses compared *TLR* genotypes in all seropositive cases to seronegative controls using logistic regression. Secondarily, an 'extreme phenotype design' was restricted to highly exposed seronegative controls to improve sensitivity [10]. Set-point analyses were performed using linear regression among all seropositive individuals, with interaction analyses by seroconverter or seroprevalent HIV-1 status to assess differential effects of *TLR* polymorphisms by time since infection. Finally, we determined associations of *TLR* variants with disease progression using Cox regression and Kaplan-Meier curves.

Regression models were conducted in the R GenABEL package (http://www.genabel.org/) and were adjusted for sex, age, acyclovir use and population stratification using principal components from a separate study [9]. X-chromosome SNP associations were evaluated combining all participants and separately for males and females. Evaluation of candidate SNPs represents confirmatory analyses of factors previously implicated in HIV-1 infection, therefore, we report uncorrected *P*-values for those SNPs. For exploratory analyses of 111 *TLR* tagSNPs we calculated Bonferroni-corrected *P*-values with a significance cutoff of $P_{corrected} < .00045$ ($\alpha = .05$). Since different inheritance models lack independence, we did not adjust *P*-values for testing multiple models.

RESULTS

Study Participants

Among genotyped individuals, 343 were HIV-1 seronegative controls (243 with high and 100 with lower exposure) and 504 were seropositive cases (129 seroconverter and 375 seroprevalent) (Supplementary Table 2). Approximately 75% of cases and controls were from East Africa. Overall, cases and controls had similar sex distributions with 160 (47%) controls and 265 (52%) infected cases being female ($P = .2$). HIV-1 exposure scores ranged from 0 to 7 and were similar among seroconverters and highly exposed controls (median = 5 [IQR: 3–5] vs 5 [IQR: 5–6]) but were lower among low exposure controls (2 [IQR: 1–3], $P < .001$). Highly exposed controls were similar to seroconverters in age (31 vs 30 years, $P = .4$), but had lower prevalence of male circumcision (33% vs 43% $P = .2$) and increased frequency of any unprotected sex (50% vs 44%, $P = .3$). Compared to low exposure controls, highly exposed controls were more likely to report unprotected sex (50% vs 22%, $P < .001$) and to have HIV-1 infected partners with higher HIV-1 levels (5.0 vs 3.9 $\log_{10}$ copies/mL, $P < .001$).

Follow-up among HIV-1 seronegative controls was similar among participants with high and low exposure (21 [IQR: 15–24] vs 21 months [IQR: 18–24], respectively). Among, HIV-1 seroconverters, median time before the first seropositive HIV-1 test was 9 months (IQR: 3–15) and median post-seroconversion follow-up was 12 months (IQR: 12–12). Median follow-up for HIV-1 seroprevalent cases was 22 months (IQR: 17–24).

TLR Associations With HIV-1 Acquisition

Comparing HIV-1 infected cases to all seronegative controls, the candidate *TLR9* 1635G allele was associated with reduced HIV-1 acquisition risk (OR = 0.8; 95% CI, .6–.9; $P = .04$). The association was stronger when cases were compared to highly exposed controls (OR = 0.7, 95% CI, .5–.9; $P = .03$) but was lost when compared to low exposure controls (OR = 0.9, 95% CI, .6–1.5; $P = .5$) (Figure 1*A*).

TLR Associations With HIV-1 Set-point

Median plasma HIV-1 set-point among all cases was 4.7 $\log_{10}$ copies/mL (IQR: 4.1–5.2) and was similar among seroprevalent (4.8; IQR: 4.4–5.3) and seroconverter cases (4.5; IQR: 3.6–5.0). The *TLR7* rs179012 G allele, a haplotype-tagging intronic SNP, was associated with 0.4 $\log_{10}$ copies/mL lower set-points (95% CI, .2–.6; $P_{corrected} = .03$), regardless of duration of infection (Table 1). This association was stronger among females ($\beta = -.5$;

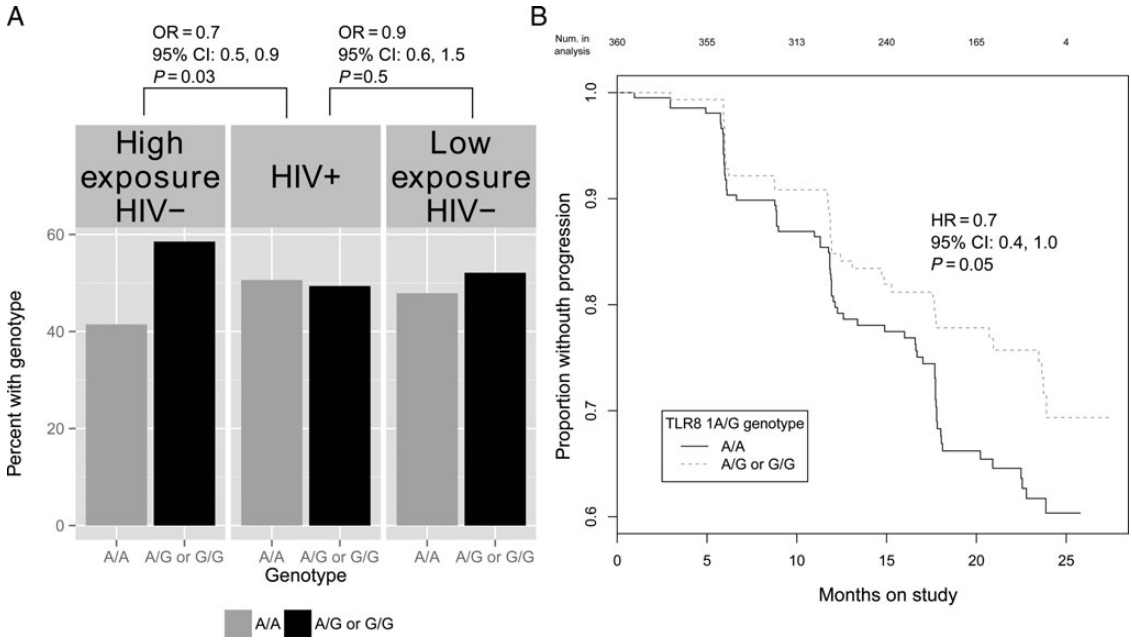

Figure 1. *A,* Frequency of the *TLR9* 1635A/G (rs352140) single nucleotide polymorphism by HIV-1 infection status and level of HIV-1 exposure. HIV-1 exposure scores were used to represent an individual's risk of infection at enrollment and were based on a Cox proportional hazards regression model that included HIV-1 plasma RNA levels of the infected partner, unprotected sex, age, sex, and male circumcision. *B,* Kaplan-Meier plot of HIV-1 progression by *TLR8* 1A/G (rs3764880) genotype. HIV-1 progression is defined as CD4 < 200 cells/mL^3, ART initiation, or death among HIV-1 seroprevalent cases with enrollment CD4+ T cell counts greater than 200.

95% CI, −.7,−.2; $P = .0002$) but not males (β = −.3; 95% CI, −.6, −.01; $P = .05$). Homozygosity of the candidate *TLR2* 597 T allele was associated with lower set-point among seroprevalent cases (β = −.4; 95% CI, −.1,−.7; $P = .005$), but not seroconverters (β = .3; 95% CI, −.4,1.1; $P = .4$)(interaction P-value = .02).

TLR Associations With HIV-1 Progression

At enrollment, HIV-1 seroprevalent cases with the candidate non-synonymous *TLR8* 1A/G polymorphism had higher median CD4+ T cells/mm^3 (442; IQR: 334–636) than those with the AA genotype (405; IQR: 325–535) and this association was significant under a dominant model of inheritance (β = 49.3; 95% CI, 2.6–96.1; $P = .04$). When evaluating associations with HIV-1 disease progression, *TLR8* 1A/G was protective among all participants (hazard ratio [HR] = 0.7; 95% CI, .4–1.0; $P = .05$) and was stronger among females (HR = 0.5; 95% CI, .3–.9; $P = .03$) (Figure 1*B*). This association remained after participants with ART initiation or death as their disease progression end-point were removed.

DISCUSSION

Innate immune responses through TLR signaling may be important in HIV-1 infection. We found that polymorphisms in *TLR2* and *TLR7* were associated with HIV-1 set-point, *TLR8* with disease progression, and *TLR9* with HIV-1 acquisition. These relationships may be modified by HIV-1 exposure levels and duration of HIV-1 infection, providing a potential context for understanding previous study results.

In our study, *TLR9* 1635A/G was 1.4-times more prevalent among HIV-1 exposed seronegative controls than infected cases. This is the first report of an association between this SNP and reduced HIV-1 acquisition, but is consistent with previous protective associations with HIV-1 progression and set-point [2, 6]. We did not find an association between this SNP and disease progression or set point. This may be due to differences in ethnicity (African vs Caucasian) or background characteristics (heterosexual, MSM or IDU) of these study populations. Perinatal HIV-1 transmission studies found this locus to associate with increased acquisition risk, possibly reflecting differences in heterosexual and vertical transmission [7]. One possible reason for protective effects of this SNP among adults is that it may overcome HIV-1 gp120 suppression of IFN-α responses to TLR9 agonists in pDCs, thereby maintaining production of antiviral and inflammatory responses against HIV-1 [11]. This association was more pronounced when comparing HIV-1 infected cases to controls with high, but not low, HIV-1 exposure, demonstrating that detection of host risk factors for sexual HIV-1 acquisition may be influenced by exposure levels among seronegative participants [10].

We found *TLR2* and *TLR7* SNP associations with HIV-1 set-point. The *TLR2* 597C/T SNP was associated with 0.4 $\log_{10}$ copies/mL lower viral load among HIV-1 seroprevalent cases but not among recent seroconverters, suggesting that effects of

Table 1. Associations Between TLR Polymorphisms and Plasma HIV-1 RNA Set-point Among All HIV-1 Seropositive Participants and Among HIV-1 Seroprevalent and Seroconverters Cases Separately

Gene Variant	Gender	Cases	N[a]	MAF[b]	Median HIV-1 RNA Set-point by Genotype (IQR)			Mean Difference in HIV-1 Set-point (95% CI)[c,d]	
				T	*CC*	*CT*	*TT*		
TLR2 rs3804099 (candidate SNP: 597 C/T, synonymous change in exon 3) Chromosome: 4	All	All	359	0.3	4.6 (4.3–5.2)	4.6 (4.1–6.2)	4.4 (3.9–4.9)	−0.20 (−.5, .09)	*P* = .2
		Prevalent	249	0.3	4.8 (4.5–6.2)	4.9 (4.4–5.4)	4.4 (3.7–4.7)	**-0.42 (−.72, -.13)**	***P* = .005**
		Incident	110	0.29	4.3 (3.7–4.9)	4.4 (3.7–5.0)	5.0 (4.1–5.3)	0.34 (−.42, 1.10)	*P* = .4
				G	*AA/A−*	*AG*	*GG/G−*		
	All	All	359	0.25	4.8 (4.4–5.3)	4.5 (3.9–5.0)	4.5 (3.9–4.9)	**−0.37 (−.56, −.19)**	***P* = .00008[e]**
		Prevalent	249	0.24	4.9 (4.5–5.4)	4.6 (4.3–5.0)	4.6 (4.0–4.9)	**−0.34 (−.54, −.15)**	***P* = .0006**
		Incident	110	0.28	4.7 (3.9–5.1)	4.1 (2.6–5.2)	4.4 (3.7–4.8)	−0.38 (−.79, .03)	*P* = .07
				G	*AA*	*AG*	*GG*		
TLR7 rs179012 (Intronic tagSNP) Chromosome: X	Female	All	193	0.23	4.9 (4.4–5.4)	4.5 (3.9–5.0)	4.6 (3.7–4.7)	**−0.49 (−.74, −.23)**	***P* = .0002**
		Prevalent	148	0.23	5.0 (4.6–5.0)	4.6 (4.3–5.0)	4.6 (3.9–4.7)	**-0.40 (−.64, −.15)**	***P* = .0001**
		Incident	45	0.26	4.8 (4.0–5.1)	4.1 (2.6–5.2)	3.6 (3.6–3.6)	−0.64 (−1.36, .09)	*P* = .08
				G	*A−*		*G−*		
	Male	All	166	0.26	4.8 (4.3–5.2)		4.5 (4.0–4.9)	**−0.29 (−.58, −.01)**	***P* = .05**
		Prevalent	101	0.25	4.8 (4.5–5.3)		4.6 (4.0–5.0)	−0.26 (−.59, .08)	*P* = .14
		Incident	65	0.29	4.6 (4.0–5.1)		4.4 (3.9–4.8)	−0.22 (−.73, .29)	*P* = .41

[a] Includes HIV-1 infected participants for whom HIV-1 set-point met the definition of consecutive plasma HIV-1 RNA measurements within one $\log_{10}$ copies/mL and who had genotype data.

[b] Minor allele frequency.

[c] Plasma HIV-1 RNA set-point $\log_{10}$ copies/mL.

[d] Mean differences and 95% confidence intervals from ordinary least squares regression models adjusted for sex, age, and population stratification. For *TLR7* rs179012, we report results under a dominant model of inheritance and a recessive model of inheritance for *TLR2* rs3804099.

[e] Bonferroni adjusted *P*-value = .03.

this SNP may vary over the course of infection. Although TLR2 recognizes bacteria, fungi, and parasites, it could influence responses to HIV-1 by enhancing chronic immune activation through translocation of gut-associated microbial factors [12].

TLR7 rs179012 was associated with 0.4 $\log_{10}$ copies/mL lower set-point among all HIV-infected participants. One hypothesis for similar *TLR7* associations during early and chronic infection is that trafficking of HIV-1 to early endosomes instead of lysozomes elicits chronic immune activation through persistent release of IFN-α in the absence of pro-inflammatory cytokines [13], resulting in more targets for HIV-1 throughout acute and chronic infection. A recent study of TLR signaling pathways suggests that responses to a TLR2 agonist varied by duration of infection; in contrast, TLR7 agonist responses were detectable during acute and chronic infection [14]. Further studies may elucidate how TLR signaling through these variant receptors impact plasma HIV-1 levels throughout infection.

Finally, consistent with previous studies, *TLR8* 1A/G was associated with slower HIV-1 progression due to CD4+ T cell decline [4]. This SNP is associated with elevated TNF-α, reduced IL-10 production, and elevated prostaglandin E2 and leukotriene B4, which are associated with reduced HIV-1 replication and disease progression [4].

An advantage of our study was having longitudinal data from both partners in heterosexual African HIV-1 serodiscordant couples, including chronically infected individuals, HIV-1 seroconverters, and HIV-1 exposed seronegative individuals with varying exposure levels. This allowed us to evaluate if *TLR* SNP associations differed by time since HIV-1 infection and to evaluate resistance to infection among highly exposed HIV-1 seronegative participants, which may help avoid spurious associations [10]. Several cohort limitations could have obfuscated associations. First, most HIV-1 seroprevalent participants had HSV-2, possibly confounding *TLR*-HIV-1 associations through synergistic effects of HSV-2/HIV-1. However, sensitivity analyses suggest that HSV-2 was not important in this analysis. Second, selecting tagSNPs from Yorubans could limit representation of common variants among East and southern Africans.

Two previous GWA studies, including one among participants from our study, did not identify *TLR* SNP associations with HIV-1 acquisition or set-point [9, 15], but did not consider *a priori* information regarding *TLR* associations with HIV-1 outcomes and applied rigorous multiple testing corrections for all SNPs. In our GWAS, we had 80% power to detect associations with relative risks >3.2 for variants with minor allele frequency = 5% and, thus, may have missed modest associations.

In the current candidate gene study, we sought to confirm associations for candidate SNPs and were powered to detect modest associations. Additionally, both GWA studies used standard GWAS chips designed for European populations and less than half of the variants considered in the current analysis of Africans were analyzed. Lower linkage disequilibrium in Africans could accentuate the impact of missed variants.

In summary, our results further suggest that *TLR* polymorphisms alter the course of HIV-1 acquisition and infection. However, validation in other study populations or through functional assays is needed. Research designed to evaluate functional mechanisms might test how these polymorphisms influence pro-inflammatory cytokine levels and IFN-α following stimulation with TLR agonists. An integrated evaluation of innate immune functional pathways mediating these phenotypes may identify new targets for HIV-1 preventative and therapeutic interventions.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. All authors participated in critical review of the report. R. M., A. B., M. B., and J. L. designed the study. C. C., G. d. B, G. J. S., A. R., N. M., and J. L. participated in patient recruitment. R. M., A. B., C. C., G. d. B, K. B. S., G. J. S., A. R., N. M., K. B., J. M, M. J. M., and J. L. were involved in data collection and analysis, and laboratory processing. R. M., A. B., and J. L. wrote the report. R. M. and A. B. did the statistical analyses. All authors reviewed and commented on the report at all stages and approved the final version.

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