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Variants in Interleukin Family of Cytokines Genes Influence Clearance of High Risk HPV in HIV-1 Coinfected African-American Adolescents

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Abstract

Our work aimed to examine the potential influence of variants in interleukin/interleukin receptors genes on high-risk (HR-HPV) HPV clearance. Clearance of genital HR-HPV infection was evaluated for 134 HIV-1 seropositive African-American female adolescents from the Reaching for Excellence in Adolescent Care and Health (REACH) cohort. Genotyping targeted 225 single nucleotide polymorphisms (SNPs) within the exons, 5' untranslated region (UTR) and 3' UTR sequences of 27 immune-related candidate genes encoding interleukin family of cytokines. Cox proportional hazard models were used to determine the association of type-specific HPV clearance adjusting for time-varying CD4⁺ T-cell count and low-risk (LR-HPV) HPV co-infections. HR-HPV clearance rates were significantly ($p < 0.001$) associated with five SNPs (rs228942, rs419598, rs315950, rs7737000, rs9292618) mapped to coding and regulatory regions in three genes (*IL2RB*, *IL1RN*, and *IL7R*). These data suggest that the analyzed genetic variants in interleukin family of cytokines modulate HR-HPV clearance in HIV-1 seropositive African-Americans that warrants replication.

Keywords

HPV clearance; genetic association; interleukins; HIV-1 seropositive; African American adolescents

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Disclosure of potential conflicts of interest

The authors of this manuscript have no conflict of interest to disclose.

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1. Introduction

Prevention of cervical cancer should focus on the precursor or the intermediate phenotype of cervical cancer, persistent human papillomavirus (HPV) infection [1]. This intermediate phenotype has more practical implications because the persistence of high-risk (HR-HPV) HPV is required for the development of cervical cancer. Approximately 80% of the female population is exposed to HPV sometime in their lifetime, but infection is usually transient, with 70–90% of infected individuals “clearing” the virus within 24 months [2]. Infection with HR-HPV is necessary but insufficient cause of cervical cancer; thus other risk factors, including human immune system needs to be well characterized.

Data derived from immunodeficient hosts including HIV-1 infected (HIV-1+) and organ transplant patients indicate that cellular immune defects are associated with persistence of HPV [3, 4]. HIV-1+ women have a higher prevalence and lower clearance rate of HPV than HIV-1 uninfected women [5]; the rate of HPV clearance is lowest among severely immunocompromised individuals (CD4+ T lymphocyte cells (CD4+) <200/mm), suggesting the potential involvement of host immune response [6, 7]. However, even after immune reconstitution of CD4+ cells with the use of antiretroviral therapies (ARTs), the incidence of HPV-related diseases has not declined in HIV-1+ individuals [8, 9]. Therefore, it is likely that other factors including host genes related to immune response are influencing clearance of HPV among HIV-1+ individuals. Our objective was to assess host genetic variants in interleukin/interleukin receptors family of cytokines that have been reported to have functional consequences or associations with cervical cancer, HPV infection or other infections with clearance/persistence of HR-HPV in HIV-1+ African-American adolescent females.

2. Material and Methods

2.1 Study Population

Participants from the Reaching for Excellence in Adolescent Care and Health (REACH) cohort were included in this study [10]. Briefly, between 1996 and 2000 adolescents (aged 12–19 years) who acquired HIV-1 through risk behaviors, mainly sexual activities, and comparable HIV-1 seronegatives were recruited into a longitudinal study at 15 clinical sites in the U.S. to investigate the natural history of HIV-1. The study design and methods for quarterly follow up, HIV-1 testing and viral-load measurement, and immunophenotyping of CD4+ counts, along with demographics, risk behavior, and other clinical data, have been previously described in detail [10]. HPV were also tested at baseline and each semi-annual follow up visit. Of the 535 adolescents enrolled in the REACH study, our study to assess clearance of cervical HR-HPV was restricted to 226 African-American HIV-1+ females to avoid confounding by population substructure and HIV infection.

2.2 HPV DNA Detection and Classification

Cervical lavage samples were tested for HPV infection. HPV viral DNA fragments from the samples were amplified by use of consensus primers MY09/11 and HMB01 and hybridized with a consensus probe and 30 different HPV (HR-HPV types: 16, 18, 31/33/35, 39, 45, 51, 52, 56, 58, and 59/68/70 and low risk (LR-HPV) HPV types: 2/57, 6/11/42/44, 13/32, 26/29, 53/66, 54/40, 55, 62/72, and 67) strain-specific probes (some probes were specific for more than one HPV type) by use of a chemiluminescent dot-blot format [8, 11].

HPV infection clearance time was defined as the time between the estimated start (infection) date and end (clearance) date of infection. Prevalent and incident HR-HPV infections were included in the analysis. Two consecutive HPV-negative tests after a positive test were required to confirm clearance because of the possibility of false-negative results and the

assumption that 12 month period best defined true clearance. Since the exact time of HPV infection cannot be determined in this dataset, we used the midpoint in time between the prior negative visit and the first positive visit. To account for the left truncation for prevalent infections, we added a time period of 90 days (half time period between study visits) to the initial positive visit time [12]. To estimate the HPV clearance date, we used the midpoint between the last positive visit and the first negative visit if there were two consecutive negative tests. HPV infections that became negative at the participant's last study visit were censored at the last visit. Type-specific HPV status was assumed to remain unchanged across single missing visits. Two consecutive missing visits were censored at the visit prior to the first missing visit. Of the 226 African-American HIV-1 positive females, 55 remained HPV-negative throughout follow-up, and 8 only had a LR-HPV infection and both of these groups were excluded from the analysis since the outcome of interest is time to clearance of cervical HR-HPV; thus 163 individuals were included in the final analyses.

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2.3 Genotyping

Cytokine-mediated inflammatory responses, involved in both innate and adaptive immunity, have a genetic basis and an effective immune response has consistently been associated with outcomes in the natural history of several infectious pathogens and associated diseases. Genomic DNA extracted from whole blood was used for the genotyping of 307 SNPs (225 passed QC) in the coding, 5' and 3' UTR within 27 interleukin/interleukin receptor genes (8 SNPs in *IL10*, 12 in *IL10RA*, 12 in *IL10RB*, 6 in *IL12A*, 5 in *IL12B*, 9 in *IL13*, 4 in *IL15*, 16 in *IL17A*, 5 in *IL17RB*, 6 in *IL19*, 11 in *IL1A*, 9 in *IL1B*, 10 in *IL1RN*, 4 in *IL2*, 8 in *IL20*, 9 in *IL24*, 4 in *IL2RA*, 10 in *IL2RB*, 7 in *IL4*, 14 in *IL4R*, 7 in *IL5*, 7 in *IL6*, 19 in *IL7*, 11 in *IL7R*, 8 in *IL8*, 2 in *IL8RA* and 2 in *IL8RB*), using the custom GoldenGate assay (Illumina, San Diego, CA).

2.4 Statistical Analysis

All SNPs were evaluated for standard quality control (QC) thresholds. A total of 29 individuals had more than 15% missing genotype and inconsistent duplicates and were removed from the analysis. Of the 307 SNPs examined, three deviated from HWE (p-value <0.001), 12 had high missing genotype (>10% individuals) and 67 were rare (MAF < 0.05); thus they were removed from the analysis. With stringent exclusion criteria, we examined 225 SNPs in 138 individuals in the final analysis. Out of the 225 SNPs in 27 genes, 73 SNPs were shown to be in linkage disequilibrium (LD) with each other within a gene using the matrix spectral decomposition method [13]. Both LD unadjusted (0.05/225= 0.0002) and adjusted (0.05/152) p-value thresholds were considered for multiple testing. Further, a false discovery rate was also calculated using the Benjamini-Hochberg procedure based on Storey Qvalue [14].

Cox proportional hazard model was used to assess influence of variants in immune-related genes on type specific HR-HPV clearance using an additive model. All of the models were adjusted for CD4+ count as a time-varying covariate (marker for disease status as well as a surrogate for treatment) during the HPV infected periods. LR-HPV infections were also adjusted for in the model as a time-varying covariate when an individual was co-infected with any HR-HPV type. The Wei-Lin-Weisfeld (WLW) extension was used with the Cox proportional hazard model because this approach can simultaneously analyze time to HPV clearance of several types of HPV either at the same or different visits, taking into account possible correlation between the types [15] and presented a population-averaged interpretation. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated.

3. Results

Among the 134 African-American HIV-1 positive females, there were 400 different HPV infections and 255 of these cleared during follow-up. The most common HR-HPV types were HPV59 (n=65), HPV31 (n=62), HPV58 (n=55), and HPV16 (n=54). Of the 255 infections that cleared during follow up, the average time to clearance was 319 days (median 210 days). Among the HR-HPV infections that cleared during follow-up the average CD4+ count was 574.2 cells/mm³ (median 540.0 cells/mm³) and among the HR-HPV infections that persisted during follow-up the average CD4+ count was 485.1 cells/mm³ (median 464.4 cells/mm³).

The correlation of η -values versus the log p-values of 225 SNPs from the Cox proportional hazard models are shown in Figure 1. One SNP in *IL2RB* gene was associated with clearance of HR-HPV above the LD-adjusted Bonferroni threshold. HIV-1+ African American adolescent females with minor allele A for SNP rs228942 in the *IL2RB* gene had a HPV clearance rate that is 1.69 times (HR=1.69, 95% CI 1.40–1.97, p= 0.0003) higher than those with the wild type allele controlling for CD4+ count and other LR-HPV infections. Overall, five SNPs met the FDR threshold for association with time to clearance of HPV (Table 1). Individuals with C allele for SNP rs419598 in *IL1RN*, a T allele for SNP rs7737000 in *IL7R*, or an A allele for SNP rs9292618 in *IL7R* had a HPV clearance rate that is higher than those with a wild type allele (Table 1). Likewise, participants with minor allele C for SNP rs315950 in the *IL1RN* gene had a HPV clearance rate that is 1.49 times (HR=0.67, 95% CI 0.44–0.90, p= 0.0006) lower than those with the wild type allele.

4. Discussion

We report several variants within the interleukin/interleukin receptor family of cytokines that are associated with clearance of HR-HPV infection in HIV-1 African American adolescent females. Some of the genes implicated in this study have possible mechanism that could be related in the HPV pathogenesis and pathway. The most significant SNP rs228942 associated with a higher clearance rate of HR-HPV infection in our study is located in the coding region of the *IL2RB* gene. Additionally, two other SNPs, rs3218273 and rs3218329, located in the coding and 3' UTR of *IL2RB* were marginally (p<0.05) associated with higher clearance rate of HR-HPV infection. IL2 is important for stimulating T-cell proliferation through the T-cell producing and secreting IL2, which stimulates the interleukin-2 receptor (IL2R). The SNP (rs228942) has been previously associated with susceptibility to kidney allograft rejection; however, has not been reported with cervical cancer, HPV, or other infectious diseases [16].

A SNP (rs315950) located in the 3' UTR of *IL1RN* gene was associated with a lower clearance rate of HR-HPV infection while SNP (rs419598) located in the coding region of *IL1RN* was associated with higher clearance rate of HR-HPV infection, showing opposite effects with minor alleles. *IL1RN* gene encodes for a protein interleukin-1 receptor antagonist (IL1RA), a naturally occurring anti-inflammatory cytokine produced by monocytes, macrophages, and epithelial cells that regulates the biological activities of IL1A and IL1B, which are the most potent pro-inflammatory cytokines [17]. IL1 and related cytokines are mediators of inflammation and tissue damage in multiple organs and specifically the balance between IL-1 and IL1RA in local tissues plays an important role in the susceptibility to and severity of many diseases. IL1RA binds to the IL1 receptor and hinders the pro-inflammatory signal from IL1 receptor; however, underproduction of IL1RA could damage tissues from inflammation-induced injuries and potentially favor HPV to persist and integrate into the host genome [18, 19].

The SNP (rs419598) and variable number tandem repeats (VNTRs) have previously been shown to be in high LD [20]. VNTRs within the intron 2 of *IL1RA* have been associated with increased risk for cervical cancer [21–24]. This association between cervical cancer and variation with *IL1RN* could be a surrogate for a true association between HPV and *IL1RN*. This same VNTR in *IL1RA* is also associated with HPV infection in women with cervical cancer [25]. To date, the function of the SNP in *IL1RN* (rs315950), which we found to be associated with clearance of HR-HPV is unknown; however, based on the present and other results in the literature, *IL1RN* is associated with HPV outcomes, including cervical cancer. Any variations in host gene immunity that affects HPV clearance could potentially also influence progression to cancer through HPV integration and pre-cancer lesion development since persistence of HPV is a necessary factor.

The two SNPs (rs315950 and rs419598) in *IL1RN* had opposite associations with HR-HPV clearance in our population. We assessed the interaction between the two SNPs and time to clearance of HR-HPV infection controlling for CD4+ and LR-HPV. The minor allele C for SNP rs419598 was associated with faster HR-HPV clearance rate, while the minor allele C for SNP rs315950 was associated with lower HR-HPV clearance rate; therefore, we assumed that an individual that was CC for SNP rs419598 and TT for SNP rs315950 would have faster HR-HPV clearance rates (refer to as High group). The lower HR-HPV clearance rates would be TT for SNP rs419598 and CC for SNP rs315950 (refer to as Low group). Any other combination of the genotypes for the two SNPs was considered to be the intermediate of the two other groups (refer to as Intermediate group). Comparing the intermediate group to the low group, a faster HR-HPV clearance rate (HR=3.01, $p=8.5 \times 10^{-13}$, 95% CI 2.71, 3.30) was observed. Comparing the high group to the low group, we found a faster HR-HPV clearance rate (HR=5.12, $p=3.16 \times 10^{-20}$, 95% CI 4.77, 5.47). However, the interpretation of this interaction with smaller sample size needs caution and require replication. Of note, out of the 134 individuals, 3.03% (n=4) were in the low group, 87.88 (n=116) were in the intermediate group, and 9.09% (n=12) were in the high group.

Two SNPs (rs7737000 and rs9292618, but also in LD) located in the coding and the flanking 3' UTR of *IL7R* were associated with a higher clearance rate of HR-HPV. The SNP rs7737000 has also been associated with an increased risk for non-small cell lung cancer among African-American and Caucasian women [26]. To date, the function of the coding SNP rs7737000 is not known so the biological relation of *IL7R* cannot be deciphered in relation to HR-HPV clearance. However, genetic variant and other polymorphisms in the *IL7R* locus have been implicated in the susceptibility of several immune, autoimmune, inflammatory and degenerative disorders. Additionally, previously variants in promoter regions of *IL10* gene were found to be associated with HPV clearance among individuals with low CD4+ cells at baseline [27]. Here, we report findings from analysis considering a time-varying effect of CD4+. While individually these genes have plausible immune-related mechanisms at various stages of HPV pathogenesis, our study is underpowered to determine if these potential genes work in conjunction or separately in different pathways and time points.

We were extremely rigorous in our definition of HPV clearance, HPV follow-up, and QC thresholds for the SNPs which accounts for potential confounders and actually increases power to detect a plausible association. Even with these stringent criteria, we were able to observe significant associations between SNPs and HPV clearance even after multiple-test corrections. With strict study inclusion criteria, our sample size was limited to 134 HR-HPV + African American HIV-1+ adolescent females. However, along with Women's Interagency HIV Study (WIHS) and HIV Epidemiology Research Study (HERS), REACH is one of the largest longitudinal cohorts in the U.S. with HIV and HPV data. One other large study in U.S. has indicated the role of host gene variants in HIV-1 negative women

[28–30]. Cohort studies on natural history of HPV will also be affected by the uptake of the HPV vaccine and understanding immune mechanisms for control of HPV could shed light on boosting long-term protection. HPV clearance in the context of HIV is an extremely important public health concern, not only in the U.S., but also globally as the face of HIV/AIDS epidemic is changing over time. The Interleukin family of cytokines associated with the ability to clear HPV infection, as demonstrated by our results, can help understand the pathogenesis of HPV infection. Discovery of informative variants or genetic profiles of the interleukin family of cytokines may facilitate screening and understanding immunological effects on HPV persistence, the intermediate phenotype, specifically in HIV and other immune-deficient patients. The long term goal of such genetic studies is to identify molecular signatures amenable to specific therapeutic approaches and even more effective vaccine responses in the future. Replication of all newly identified associations in an independent and larger cohort, followed by fine mapping and functional studies of the implicated genetic determinants are warranted to further extend our findings.

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Figure 1.

Negative Log p-values by beta-values of SNP association of time to HR-HPV clearance, using Cox proportional hazard WLW model for all 225 SNPs. The symbol represents each of the 27 genes examined. Dotted line represents the false discovery rate (FDR) $q < 0.05$ cut-off for statistical significance.

Table 1

Cox proportional Hazard Ratios (HR) for the SNPs associated with time to clearance of high risk HPV infection controlling for CD4+ count and low risk HPV.

Gene	SNP	MAF	location	Alleles*	B-value	HR	95%CI	p-value	FDR
p-value <0.001, q-value <0.05									
<i>IL2RB</i>	rs228942	0.07	coding	A/G	0.52	1.69	(1.40, 1.97)	0.0003	0.04
<i>IL1RN</i>	rs419598	0.06	coding	C/T	0.50	1.65	(1.36, 1.93)	0.0005	0.04
<i>IL1RN</i>	rs315950	0.17	flanking 3'UTR	C/G	-0.40	0.67	(0.44, 0.90)	0.0006	0.04
<i>IL7R</i>	rs7737000	0.12	coding	A/G	0.44	1.55	(1.29, 1.80)	0.0007	0.04
<i>IL7R</i>	rs9292618	0.10	flanking 3'UTR	A/C	0.43	1.54	(1.29, 1.79)	0.0008	0.04
p-value <0.05, q-value >0.05									
<i>IL1RN</i>	rs315948	0.16	flanking 3'UTR	C/T	0.35	1.42	(1.18, 1.66)	0.004	0.18
<i>IL17A</i>	rs3915558	0.08	flanking 5'UTR	A/C	0.34	1.40	(1.15, 1.66)	0.009	0.31
<i>IL17A</i>	rs3927607	0.08	flanking 5'UTR	C/T	0.34	1.40	(1.15, 1.66)	0.009	0.31
<i>IL2RB</i>	rs3218273	0.08	coding	A/G	0.33	1.39	(1.12, 1.66)	0.016	0.39
<i>IL7R</i>	rs1494558	0.27	coding	C/T	-0.28	0.75	(0.52, 0.99)	0.020	0.39
<i>IL1B</i>	rs4849126	0.31	flanking 5'UTR	C/T	-0.24	0.79	(0.59, 0.99)	0.020	0.39
<i>IL2RB</i>	rs3218329	0.20	3'UTR	C/A	0.29	1.34	(1.09, 1.58)	0.020	0.39
<i>IL1RN</i>	rs315949	0.33	flanking 3'UTR	A/C	-0.23	0.80	(0.60, 0.99)	0.024	0.39
<i>IL8</i>	rs13142454	0.16	flanking 3'UTR	A/C	-0.32	0.73	(0.45, 1.00)	0.024	0.39
<i>IL6</i>	rs10242595	0.48	flanking 3'UTR	C/G	0.22	1.25	(1.06, 1.45)	0.025	0.39
<i>IL7</i>	rs2717536	0.32	flanking 3'UTR	C/T	0.27	1.30	(1.07, 1.54)	0.025	0.39
<i>IL17A</i>	rs6922427	0.05	flanking 5'UTR	C/T	0.40	1.49	(1.14, 1.85)	0.026	0.39
<i>IL10RA</i>	rs4252243	0.31	flanking 5'UTR	A/G	0.20	1.23	(1.03, 1.42)	0.040	0.52
<i>IL1B</i>	rs13032029	0.29	flanking 5'UTR	G/T	0.20	1.22	(1.03, 1.42)	0.043	0.52
<i>IL4R</i>	rs9302448	0.08	flanking 3'UTR	G/T	-0.39	0.68	(0.30, 1.06)	0.047	0.52
<i>IL1B</i>	rs4848306	0.31	flanking 5'UTR	A/G	0.19	1.21	(1.02, 1.39)	0.048	0.52
<i>IL8</i>	rs16849958	0.21	flanking 3'UTR	A/G	0.24	1.27	(1.03, 1.51)	0.049	0.52
<i>IL6</i>	rs2069849	0.13	coding	C/T	0.27	1.32	(1.04, 1.59)	0.050	0.52

The results for each SNP using an additive model, the with major allele frequency used as the reference. Alleles*: minor/major. Abbreviations: SNP=single nucleotide polymorphism, MAF=minor allele frequency, HR= hazard ratio, 95% CI= 95% confidence interval. FDR=False Discovery Rate q-value