Dense Genotyping of Immune-Related Loci Identifies Variants Associated with Clearance of HPV among HIV-Positive Women in the HIV Epidemiology Research Study (HERS)

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Abstract

Persistent high-risk human papillomavirus (HR-HPV) is a necessary and causal factor of cervical cancer. Most women naturally clear HPV infections; however, the biological mechanisms related to HPV pathogenesis have not been clearly elucidated. Host genetic factors that specifically regulate immune response could play an important role. All HIV-positive women in the HIV Epidemiology Research Study (HERS) with a HR-HPV infection and at least one follow-up biannual visit were included in the study. Cervicovaginal lavage samples were tested for HPV using type-specific HPV hybridization assays. Type-specific HPV clearance was defined as two consecutive HPV-negative tests after a positive test. DNA from participants was genotyped for 196,524 variants within 186 known immune related loci using the custom ImmunoChip microarray. To assess the influence of each single-nucleotide polymorphism (SNP) with HR-HPV clearance, the Cox proportional hazards model with the Wei-Lin-Weissfeld approach was used, adjusting for CD4 count, low risk HPV (LR-HPV) co-infection, and relevant confounders. Three analytical models were performed: race-specific (African Americans (n = 258), European Americans (n = 87), Hispanics (n = 55), race-adjusted combined analysis, and meta-analysis of pooled independent race-specific analyses. Women were followed for a median time of 1,617 days. Overall, three SNPs (rs1112085, rs11102637, and rs12030900) in the MAGI-3 gene and one SNP (rs8031627) in the SMAD3 gene were associated with HR-HPV clearance (p < 10⁻⁷). A variant (rs1633038) in HLA-G were also significantly associated in African American. Results from this study support associations of immune-related genes, having potential biological mechanism, with differential cervical HR-HPV infection outcomes.

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Introduction

HPV DNA is present in 99.7% of all cervical cancer, the third most common cancer in women worldwide, with HPV types 16, 18, 31 and 45 being the most predominant HR-HPV types [1–5]. HPV is a common sexually transmitted infection and the majority of those infected are able to clear the infection naturally and only a small proportion will progress to cervical cancer [6,7]. A persistent infection of a HR-HPV type is considered the most important factor for development of pre-cancer high-grade lesions and progression to cervical cancer [8]; although, it is not a sufficient cause. Further, while cervical cancer is a definitive end to the stages of progression associated with HPV infection, it is important to understand the earlier biological processes of HPV persistence in the host.

The factors that lead to the development of a persistent HPV infection in some women, but not others, remain unclear. The role of host genetics that regulate biological mechanisms of immune response may contribute to the differential responses to infection and HPV clearance among women. To our knowledge, most research on host genetics including genome-wide association studies (GWAS) have focused on cervical cancer as the outcome [9,10], and few have investigated the influence on HPV persistence, the intermediate phenotype to cervical cancer. Even
with the limited genetic epidemiology studies of HPV infection as an outcome, the study designs have been predominantly cross-sectional, comparing genetic variants between women with HPV-positive cervical cancer and randomly selected controls [11,12]. Since persistence of HPV is time-dependent, longitudinal studies assessing HPV over time would be more appropriate to examine the true association. Several studies implicate immune evasion [13–15] involving genetically mediated determinants of the localized cell-mediated immune response in the host to be an important factor in the pathogenesis of HPV infection [16,17]. Specifically, human leukocyte antigens (HLA) variants (DRB1*13 and DRB1*1501-DQB1*06) have been shown to be associated with cervical cancer [10,18] and possibly HPV infection [19]. Further, even among women who naturally clear HPV infection, there are differences in time to clearance suggesting the role of the host immune system. While HPV persistence is necessary for development of most cervical premalignant and cancers, the role of immune-related genes (such as those in the ImmunoChip) are biologically meaningful in relation to viral pathogenesis and may or may not be involved in the development or progression of pre-cancer lesions. The knowledge of immune response will complement our understanding of the pathogenesis of HPV. Our objective was to assess the association of host genetic variants in immune-related genes with clearance of HR-HPV using the Human ImmunoChip in HIV-positive African Americans, Hispanics, and European women.

Materials and Methods

Ethics Statement

Written consent was obtained from all participants (parental written permission was obtained for minorities wherever required) and the study protocols for the parent study and this sub-study was approved by institutional review boards (IRB) at all sponsoring organizations and conformed to human-experimentation guidelines set forth by the United States Department of Health and Human Services. All protocols including the genetic work was finally reviewed and approved by the University of Alabama at Birmingham IRB.

Study Population

Participants from the HIV Epidemiology Research Study (HERS) cohort were included in this study [20,21]. HERS is a multicenter, prospective study established by the Centers for Disease Control and Prevention (CDC) to examine the natural history of HIV in women. Women aged 16–55 with documented HIV status and high-risk behaviors were recruited between April 1993 and January 1995. The exclusion criteria in the parent study were as follows: i) had no identified HIV risk behavior; ii) had risk history of HIV in women. Disease Control and Prevention (CDC) to examine the natural diseases [22,23]. The genotyping of the samples was processed at two different laboratory facilities, and this was adjusted for in the statistical models.

Genotyping

Genomic DNA was extracted from stored PBMC and genotyped using the Human ImmunoChip, an iSelect HD custom genotyping array (Illumina, Inc.). The ImmunoChip is a custom SNP microarray developed by a consortium of specialists in the fields of immunology and inflammation. The microarray chip contains densely spaced 196,524 SNP variants (5,001 non-synonymous coding, 1,926 synonymous coding, and 4,065 in the untranslated region (UTR)), previously reported from GWAS and candidate gene studies of major autoimmune and inflammatory diseases [22,23]. The genotyping of the samples was processed at two different laboratory facilities, and this was adjusted for in the statistical models.

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73,017 in European Americans, and 68,264 in Hispanics that had a minor allele frequency less than 5% (rare variants) that were also removed in the analysis of each ethnic group, respectively. Fourth, there were 1234 SNPs in African Americans, 442 SNPs in European Americans, and 347 SNPs in Hispanics that deviated from HWE (p-value < 0.001), and thus were also removed from the analyses. Further, kinship between the individuals was also assessed in KING software [24], and two of the African American individuals were determined to be genetically related. However, one of the individuals had a lot of missing data and the relatedness seems likely due to specimen contamination; this individual was removed from the analyses (removal of both individuals did not change the results of the analysis). There were no major differences with the genotype call rates, minor allele frequency between the two genotyping facilities; however, they were adjusted for in all our analyses. After applying the QC methods above, there were 258 African Americans with 117,694 SNPs, 87 European Americans with 116,239 SNPs, and 55 Hispanics with 120,845 SNPs included in the analysis.

The same QC methods mentioned above for each ethnic group separately were then applied to the combined analysis which contained all three ethnic groups. For the combined analysis of all three distinct race (described below), there were 5190 SNPs removed because of low genotyping calls and an additional 66,536 rare variants (<0.05%) across any one ethnic group and were removed; thus, 123,861 SNPs were available for analysis. Since SNPs in the ImmunoChip are mostly in the fine-mapped regions with high linkage disequilibrium (LD), correction for multiple SNPs in the ImmunoChip are mostly in the fine-mapped regions.

### Results

The average age at baseline of the 400 HIV-positive women included in the study was 34 years and their median baseline CD4+ count was 426.3 cells/mm³ [interquartile range (IQR): 262.3–546.1 cells/mm³]. Women were followed for a median time of 1,617 days (range 324–1729 days). Among the 400 women, there were 1052 HR-HPV infections, and 668 (64%) cleared during follow up. The most common HR-HPV types were HPV18 (n = 99), HPV16 (n = 88), HPV51 (n = 88), HPV58 (n = 83), and HPV52 (n = 79). Of the 668 infections that cleared during follow up, the average time to clearance was 457.9 days (median 322 days). Among the HR-HPV infections that cleared during follow-up, the average CD4+ count was 385.1 cells/mm³ (median 336.7 cells/mm³). Among the HR-HPV infections that persisted during follow-up, the average CD4+ count was 251.1 cells/mm³ (median 212.9 cells/mm³).

The Manhattan plots (Figures 1A–D) summarize the results from the association between HR-HPV clearance and the SNPs in the ImmunoChip (Q-Q plots - Figures S1A–D). All significant hits based on the K-effective method described above are presented for the three analytical models in Table 1 (race-adjusted analysis, race-specific analysis, and the pooled analysis). Results for all of the SNPs assessed can be found in Table S1. In the race-adjusted analysis, three SNPs that are in LD (rs1112085, rs11102637, and rs12030900) in the MAGI3 gene were associated with HPV clearance. HIV-positive women infected with HR-HPV that have minor allele A for SNP rs1112085, located on chromosome 1, had a HPV clearance rate 1.51 times (p = 1.14 × 10⁻⁰⁷) higher than those with the G wild type allele, controlling for CD4+ count, LR-HPV infection(s), 10 PCs, and genotyping facility (Table 1). When assessing this SNP (rs1112085) in the three races separately (Table 1), in African Americans and European Americans the minor allele was associated with higher clearance rates (HR = 1.49, p = 4.07 × 10⁻⁰⁵; HR = 1.53, p = 0.01, respectively), while no association was detected between this SNP and HR-HPV clearance among Hispanics (HR = 0.98, p = 0.91). In the pooled analysis using the meta-analysis approach, the same minor allele was associated with higher clearance rates (HR = 1.33, p = 0.03). Likewise, a SNP (rs8031627), located on chromosome 15 in the SMAD3 gene, was also significantly associated with higher clearance rates in the race-adjusted analysis (HR = 1.53, p = 8.04 × 10⁻⁰⁷) and the pooled analysis (HR = 1.49, p = 1.78 × 10⁻⁸⁶). When analyzed among the separate races, the SNP (rs8031627) was significantly associated with clearance in Hispanics (HR = 1.76, p = 0.0005) and African Americans (HR = 1.44, p = 0.003); a similar hazard ratio was seen in European Americans, but it was not statistically significant (HR = 1.34, p = 0.08).
A SNP (rs1633038) located on chromosome 6 in the HLA-G gene region, was significantly associated with higher clearance rates (HR = 1.89, p = 3.48 × 10^{-10}) in African Americans, although this was not observed in Hispanics or European Americans separately. Several other SNPs presented in Table 1 were significantly associated with clearance; however, to date, biological relevance of these SNPs and HPV is unclear.

Discussion

We report several variants in immune related genes that are associated with clearance of HR-HPV infection in African Americans, Hispanics, and European Americans HIV-positive women after accounting for the effects of CD4+ count, other LR-HPV co-infection(s), population stratification, and genotyping facility. In particular, CD4+ has been a major factor with HPV persistence/clearance among HIV patients; thus it was adjusted as a time-varying covariate. Also, none of the top hits in table 1 was associated with CD4+ change over time of infection, suggesting that these are independent SNP associations. The most significant association with time to clearance of HR-HPV in the adjusted analysis was seen with several SNPs located on chromosome 1 within the MAGI3 gene region: rs1112085, rs11102637, and rs12030900 (in LD). The minor alleles for these SNPs in LD were associated with faster time (days) to clearance. MAGI-3 is part of the membrane-associated guanylate kinases (MAGUK) family of proteins that have inverted domain structure, and are part of the PDZ domain-containing proteins, which are localized between epithelial cells [30,31]. The E6 protein of HPV inhibits cellular apoptosis or growth arrest [32]. Several in vivo studies have shown that HR-HPV E6 proteins target MAGI-1,-2,-3 proteins for degradation [30,31,33]. This degradation process appears to be necessary for cell transformation [31,34]. Women in our cohort that had the minor allele for the SNPs in the intragenic region of MAGI-3 cleared the HPV infection faster than those with the major allele, and we hypothesize that these genetic variants may interact with HPV differently and therefore affect time to clearance.

Another interesting finding was that the minor allele for SNP rs8031627 located on chromosome 15 in the SMAD3 gene was significantly associated with higher clearance rates in the adjusted analysis. SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signaling pathways including TGF-β signals [35,36], which inhibits the proliferation of most epithelial cells [36]. The E7 protein of HPV has been shown in vivo to block SMAD3 by binding to its target sequence of DNA, which then also inhibits TGF-β for inhibiting DNA synthesis [36]. Again,
Table 1. Cox proportional Hazard Ratios (HR) for the SNPS associated with time to clearance of high-risk (HR-HPV) HPV infection in the race-adjusted analysis, individual race-specific analysis, and pooled analysis of the three races separately.

| SNP      | chr | position | Gene     | Race-Adjusted |          |          |          |          | African Americans |          |          |          | European Americans |          |          | Pooled Analysis* |
|----------|-----|----------|----------|--------------|----------|----------|----------|----------|------------------|----------|----------|----------|-------------------|----------|----------|------------------|
| rs1112085| 1   | 113742688| MAGI3    | 1.51         | 1.14E-07 | 0.98     | 0.91     | 1.49     | 4.07E-05         | 1.53     | 0.01     | 1.33     | 0.03              |
| rs11102637| 1   | 113793315| MAGI3    | 1.51         | 1.34E-07 | 0.98     | 0.91     | 1.47     | 5.78E-05         | 1.53     | 0.01     | 1.33     | 0.03              |
| rs12030900| 1   | 113775786| MAGI3    | 1.50         | 2.11E-07 | 0.98     | 0.91     | 1.47     | 7.49E-05         | 1.53     | 0.01     | 1.32     | 0.03              |
| rs8031627 | 15  | 65271173 | SMAD3    | 1.53         | 8.04E-07 | 1.76     | 0.0005   | 1.44     | 0.003            | 1.34     | 0.08     | 1.19     | 1.78E-06          |
| rs1633038 | 6   | 29848016 | HLA-G    | 1.61         | 2.5E-05  | 0.79     | 0.43     | 1.89     | 3.48E-07         | 1.35     | 0.20     | 1.34     | 0.22              |
| rs1125341 | 6   | 34894283 | UHRF1BP1 | 0.85         | 0.01     | 0.96     | 0.86     | 0.93     | 0.36             | 1.77     | 8.41E-08 | 1.18     | 0.51              |
| rs180327  | 11  | 116128869| BUD13    | 1.16         | 0.02     | 0.89     | 0.48     | 1.05     | 0.62             | 0.50     | 7.52E-09 | 0.77     | 0.30              |
| rs619054  | 11  | 116166023| APOA5    | 0.85         | 0.03     | 1.03     | 0.92     | 1.03     | 0.74             | 0.52     | 4.26E-07 | 0.81     | 0.41              |
| rs10952259| 7   | 149764996| GIMAP8   | 1.14         | 0.03     | 1.62     | 0.04     | 1.01     | 0.86             | 1.81     | 2.68E-07 | 1.42     | 0.12              |
| rs16852584| 4   | 40582748 | APBB2    | 1.10         | 0.45     | 0.53     | 0.05     | 1.06     | 0.69             | 3.36     | 4.3E-07  | 1.25     | 0.63              |
| rs17511504*| 6   | 111737220| LOC100128477 | 4.33  | | | | | | | | | |
| rs117611750**| 6 | 111892918 | REV3L   | 4.13         | 5.11E-07 | 5.11E-07 | 5.11E-07 |
| rs74833651**| 6 | 111894441 | REV3L   | 4.13         | 5.11E-07 | 5.11E-07 | 5.11E-07 |

*using meta-analysis approach;  
**Informative only in European Americans (e.g. MAF).  
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women in our cohort that had the minor allele for the SNP in UTR of SMAD3 cleared the HPV infection faster than those with the major allele. We hypothesize that the major allele variant may interact with HPV differently and therefore increase time to clearance.

Interestingly, the most significant association with time to clearance of HR-HPV in the African Americans analysis was with the SNP rs1633038 located on chromosome 6. The minor allele for SNP rs1633038 was associated with faster time (days) to clearance 1.9 times (HR = 1.89, p = 3.48 x 10^-7) in those that were homozygous for the minor allele had faster clearance compared to heterozygous and homozygous for the major allele. This SNP is located in chromosome 6 near the HLA-G gene region. HLA-G is a nonclassical HLA class Ib molecule that regulates the immune response through interaction with surface receptors on natural killer, T and antigen-presenting cells [37–40]. Several studies have reported associations between HLA-G polymorphisms and HPV infection susceptibility and persistence [39–41]. A 14 base pair deletion in the 3’ of HLA has also been shown to promote high-risk HPV infection and invasive cervical cancer in various populations [42–44]. In our study we report an association between a SNP near the HLA-G region and HPV clearance; however, specific HLA-G alleles could not be determined through the available data in this region. While there were some differences in minor allele frequency of the variants in table 1 among the three races, there did not seem to be any correlation with the strength of direction of the associations. Further research is warranted to validate these findings and to determine the function of the SNP or if it is in LD with known SNPs in other studies.

We limited our analysis to clearance of HR-HPV infections since these types are most likely to be associated with cervical cancer risk. The underlying hypothesis with this approach is that the biology and pathogenesis of cancer-causing HR-HPV infections should be similar in relation to the host. While the model adjusted for the correlation between the HPV types, it did not produce hazard ratios specific to each HPV type. We were underpowered to assess HPV types separately; however the HERS cohort is one of the largest HIV-positive cohorts with over four years of HPV follow-up data in the United States. Our sample was comprised of 100 women (258 African Americans, 87 European Americans, and 55 Hispanics), which reduced the statistical power to detect significant findings after adjusting for multiple genetic testing, especially when analyzing the three races separately. However, we were able to observe several significant SNPs in the separate analyses for African Americans and European Americans. The ImmunoChip was designed for use in European populations and could be less informative for other ethnic groups if the disease-associated variants are not shared between them [23]. The sample sizes for European Americans and Hispanics were small, so any race-specific associations need further evaluations in larger cohorts. Several SNPs that were significantly associated in multiple races independently seem interesting, even for smaller sample size. Few other SNPs have been shown to be significantly associated with HPV clearance in another cohort of HIV+ adolescents (REACH); however, most were not included in the ImmunoChip and of the few included (e.g. rs228942 and rs9292618) [27], they were not significantly associated with HPV clearance in HERS. REACH comprised of adolescents also at early period of infection and HER only had adults, mostly after several years of infection and thus may indicate different network of immune-related genes involved in the two scenarios and will need caution in interpretation requiring further research.

Of note, the Q-Q plot (Figure S1 A–D) had high deviation (lambda values of 1.23, 1.49, and 1.57 in European Americans, African Americans and Hispanics, respectively) from the expected line. Caution is needed to interpret these associations as they might also be due to population stratification, repeated measures and the inter-relationships, the Cox proportional hazard model, or the nature of ImmunoChip SNPs that are in high LD within the fine-mapped regions, like MHC on chromosome 6 [45,46]. Women with multiple HPV infections were included in the Cox proportional hazard model with the WLW extension, which should account for the correlation between the individuals’ data being used multiple times, but this could have an effect on the Q-Q plot due to the population substructure. The ImmunoChip has dense coverage of the MHC region as well as other regions so this may explain the deviation. Since the SNPs are close together, they are in high LD and therefore result in similar p-values. To our knowledge, the majority of genetic studies model the association using logistic regression, and the same assumptions of the Q-Q plot may not hold for the Cox proportional hazard model. The results could reflect a true association since we are assessing the association between a virus and immune related genes; therefore, we would expect a complex network of genes to play a role in clearance of HR-HPV and our significant findings are biologically plausible. Such an approach and methods have not been used often, specifically with high density SNP analyses; thus, it is difficult to interpret the actual reason of the observed deviations.

This analysis assessing SNPs in immune related genes and their associations with HR-HPV clearance brought forth hypotheses regarding several significant SNPs and gene regions. While these SNPs are associated with HPV clearance, future studies could examine if they are also associated with progression of pre-cancer neoplasia in larger cohorts with adequate events during follow-up periods. The variants in the current ImmunoChip are based on a consortium of genes involved in autoimmune diseases, and do not represent the comprehensive genes involved in human immunity. However, future research is needed to validate these associations and finemap the gene regions (which are not as dense in ImmunoChip for most regions) to identify one or multiple rare variants in LD with the functionally associated SNPs in ImmunoChip, specifically with MAGI-3, SMAD3 and HLA-G or other biologically plausible genes, potentially involved with HPV clearance.

Supporting Information

Figure S1 Quantile-quantile (Q-Q) plot showing the association P-values of single nucleotide polymorphisms (SNPs) in the ImmunoChip with the time to clearance of HR-HPV. The X-axes display the expected −log10 P-value, the Y-axes display the observed −log10 P-value. (TIF)

Table S1 Results of Cox Proportional Hazard Ratios (HR) associated with time to clearance of high-risk (HR-HPV) HPV infection for all the SNPs in the ImmunoChip in the race-adjusted analysis (Adjusted), individual race-specific analysis (EA = European American, AA = African American, HIS = Hispanic), and pooled analysis (Meta Analysis) of the three races separately. (TXT)

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and other affiliated institutes.

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Conceived and designed the experiments: SLS CCK AMR SC RSK CSV KS JDS JJ. Performed the experiments: SLS. Analyzed the data: SLS HWW SS. Contributed reagents/materials/analysis tools: HWW CCK JS DJJ SS. Performed the experiments: SLS SS. Analyzed the data: SLS.

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