Role of Human Leukocyte Antigen Allele Sharing in Human Papillomavirus Infection Transmission Among Heterosexual Couples: Findings From the HITCH Cohort Study

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**Background.** Human leukocyte antigen (HLA) polymorphism influences innate and adaptive immune responses. Among heterosexual couples in the HPV Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) cohort study, we examined whether allele sharing in a couple predicted the partners’ infections with the same human papillomavirus (HPV) type.

**Methods.** We tested genital samples from 271 couples for 36 HPV genotypes by polymerase chain reaction. We used direct DNA sequencing to type HLA-B07, -DRB1, -DQB1 and -G. Generalized estimating equations were used to examine the associations between the extent of allele sharing and HPV type concordance in which at least 1 of the partners was HPV positive.

**Results.** We identified 106 different HLA alleles. The most common HLA alleles among couples were G*01:01:01 (95.6%), G*01:01:02 (60.1%), DQB1*03:01 (57.2%), and DRB1*07:01 (46.9%). Allele sharing was as follows: 19.6% shared none, 43.2% shared 1 only, 25.1% shared 2, and 12.5% shared 3–5. Irrespective of HLA class, grouped or in combination, the extent of allele sharing was not a significant predictor of type-specific HPV concordance in a couple (odds ratio, 1.1 [95% confidence interval, .5–2.1], for 3–5 vs none).

**Conclusions.** We found no evidence that the extent of allele concordance influences the likelihood of HPV transmission in newly formed heterosexual couples.

**Keywords.** HPV; HLA; transmission; heterosexual; cervical; couple.

Persistent human papillomavirus (HPV) infection causes 5% of all cancers worldwide. Nearly 10% of all female cancers, particularly cervical cancer, are caused by HPV [1, 2]. HPV is a common sexually transmitted infection in young women and men. Genital HPV infections are mostly transient and clear spontaneously in 12–24 months after acquisition [3, 4]. Characteristics that affect transmission of HPV infection in heterosexual couples are mostly behavioral, hormonal, or virus related [5]. Host genetic variation, particularly human leukocyte antigen (HLA) polymorphism, is an important driver in HPV-associated cervical carcinogenesis [6]. However, little is known about the role of HLA polymorphism in the transmission of HPV within sexually active couples.

HLA genes influence innate and adaptive immune responses. The different HLA genes are classified into class I (HLA-A, -B, and -C) and class II (HLA-DRB and -DQB) alleles and the class Ib (HLA-G) alleles [7]. These different HLA alleles cluster in various genes that mediate antigen presentation and cell-mediated immune response by facilitating the recognition and clearance of virus-infected cells [8]. Sharing of HLA-B alleles seems to facilitate transmission of human immunodeficiency virus type 1 (HIV-1) between serologically discordant heterosexual partners [9]. Likewise, risk of vertical transmission of HIV-1 is increased with HLA allele concordance between mother and child [10]. On the other hand, concordance of HLA-G alleles between mother and infant did not seem to affect vertical transmission of HPV infection between the mother and her neonate [11].

Among heterosexual couples in the HPV Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) cohort study, we examined whether HLA-B07, -DRB1, -DQB1 and -G allele sharing in a couple predicted the partners'
infections with the same HPV type. Our hypothesis was that HLA allele concordance would facilitate transmission of HPV infection by lowering the likelihood of HLA-mediated rejection of exfoliated HPV-harboring cells exchanged during sex.

**MATERIALS AND METHODS**

The HITCH study is a longitudinal cohort investigation conducted at McGill University from May 2005 to January 2011 that enrolled young female university and junior college students (aged 18–24 years) and their male partners (at least 18 years old) whose sexual activity was initiated within the previous 6 months prior to enrollment. Study procedures have been described previously [12, 13]. In brief, participants completed computerized self-administered questionnaires and provided biologic samples for HPV assessment. Participants were asked to abstain from oral, vaginal, and anal sex for 24 hours prior to clinic visits. Women self-collected vaginal specimens using a Dacron swab and a clinic nurse collected penile and scrotal samples at each clinic visit for the men. The Linear Array HPV genotyping assay (Roche Molecular Systems) was used to detect 36 mucosal HPV genotypes (6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89). β-globin DNA was coamplified to assess DNA integrity. The ethical review committees of McGill University, Concordia University, and Université de Montréal approved the study. All participants provided written informed consent.

**HLA Typing**

Purified DNA from enrollment genital specimens collected at enrollment was used for HLA typing. HLA class I (B*07) was typed using polymerase chain reaction with sequence-specific primers as described previously [14]. HLA-DQB1 and -DRB1 alleles were determined by sequence-based typing with the Allele SEQR DRB1 and Allele SEQR DQB1 assays (Abbott Molecular Diagnostics), respectively. HLA-G alleles were determined through direct DNA sequencing of the nucleotide regions encompassing the HLA-G exons 2–4 (1718 bp) as described previously [15]. The HLA-G 3’ untranslated region (UTR) genetic variants including the 14 bp deletion/insertion polymorphism was determined by DNA sequencing according to the protocol [16].

**Statistical Analysis**

Stata 12.0 software (StataCorp, College Station, Texas) was used for all statistical analyses. Genital HPV types, belonging to the genus *Alphapapillomaviridae*, were categorized into 3 subgenera based on their phylogenetic relatedness, as follows: subgenus 1: HPV types that cause genital warts or asymptomatic infections (6, 11, 40, 42, 44, and 54); subgenus 2: HPV types that have possible, probable, or proven carcinogenic effects (16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, and 82); and subgenus 3: HPV types that cause mostly commensal vaginal infections (61, 62, 71, 72, 81, 83, 84, and 89) [17]. We combined the results for HPV type-specific positivity at enrollment and 4-month follow-up visits to derive a period prevalence estimate of HPV type-specific infections in females and males. Type-specific HPV concordance among partners in each couple (dyad) was restricted to couples positive for that type. For the sake of statistical precision, we only considered HLA alleles that were present in at least 5% of female or male participants. We analyzed type-specific HPV concordance overall and grouped by HPV phylogenetic groups among couples according to the extent of allele sharing by HLA class and for all HLA polymorphisms combined. We used unconditional logistic regression for HLA level sharing and generalized estimation equations with logistic link for grouped HPV types.

**RESULTS**

We identified a total of 106 different HLA alleles among the evaluable 271 female and male participants. Table 1 shows the alleles that were prevalent in at least 5% of the participants. Since 3 possibilities exist for each individual—that is, allele is absent, heterozygous (or heteroallelic), or homozygous (homoallelic)—there are $3 \times 3 = 9$ possible combinations of allele sharing per couple. The most common HLA alleles among couples were G*01:01:01 (95.6%), G*01:01:02 (60.1%), DQB1*03:01 (57.2%), and DRB1*07:01 (46.9%), followed by other alleles that were present between 0% (not shown in table) and 37.6% among the couples. The HLA-G*14bp deletion occurred in 86.3% of the couples and the different HLA-G 3’UTR single-nucleotide polymorphisms (SNPs) ranged between 8.5% and 94.8%.

The number of couples by shared HLA alleles is shown in Table 2. To be sharing an HLA allele, the dyads both had to have at least 1 allele of a specific HLA type. The HLA alleles were grouped into different groups based on inclusiveness of the HLA classification. First, we considered sharing only for classical class I and II HLA loci (HLA-B*07, -DRB1, and -DQB1). A second grouping included sharing of nonclassical class I HLA-G loci. A third grouping considered the extent of allele sharing without distinction of HLA class. We further considered sharing of HLA-G alleles combined with the 3’UTR variants by creating 2 different sets as follows. The first set included the 3’UTR 14 bp +3142 C/G and +3187 G/A together, based on knowledge of alleles that are in linkage disequilibrium. The second HLA-G group had all the HLA-G alleles and all HLA-G 3’UTR SNPs. The range of shared alleles varied between 0 and 6. Allele sharing among couples with all HLAs was as follows: 19.6% shared no alleles, 43.2% shared 1 only, 25.1% shared 2, and 12.5% shared between 3 and 5.

The type- and subgenus-specific HPV infection prevalence of the dyads is shown in Table 3. HPV-16 had the highest prevalence (22.88%), followed by HPV-84 (20.30%). Among types that were prevalent in at least 5% of the dyads, concordance varied from 26.32% for HPV-40 to 71.43% for HPV-82. Subgenus 3 had the highest concordance among partners (56.08% [95% confidence interval, 46.78%–65.39%]).
Table 1. Prevalence of Different Human Leukocyte Antigen (HLA) Alleles and the HLA-G 3’ Untranslated Region Single-Nucleotide Polymorphisms Among 271 Heterosexual Couples in the Human Papillomavirus Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) Cohort Study

| HLA                | Ab/Ab | Ab/Het | Ab/Hom | Het/Ab | Het/Het | Het/Hom | Hom/Ab | Hom/Het | Hom/Hom | Total |
|--------------------|-------|--------|--------|--------|---------|---------|--------|---------|---------|-------|
| B*07               | 169   | 44     | 0      | 43     | 14      | 0       | 1      | 0       | 0       | 271   |
| DRB1*01:01        | 222   | 20     | 1      | 26     | 2       | 0       | 0      | 0       | 0       | 271   |
| DRB1*03:01        | 180   | 33     | 2      | 43     | 10      | 0       | 3      | 0       | 0       | 271   |
| DRB1*04:01        | 216   | 30     | 0      | 21     | 3       | 0       | 1      | 0       | 0       | 271   |
| DRB1*04:04        | 237   | 18     | 0      | 15     | 0       | 0       | 1      | 0       | 0       | 271   |
| DRB1*07:01        | 144   | 63     | 3      | 43     | 16      | 1       | 1      | 0       | 0       | 271   |
| DRB1*11:01        | 208   | 27     | 4      | 27     | 3       | 0       | 2      | 0       | 0       | 271   |
| DRB1*11:04        | 224   | 20     | 2      | 21     | 3       | 0       | 1      | 0       | 0       | 271   |
| DRB1*15:01        | 177   | 41     | 2      | 37     | 11      | 0       | 3      | 0       | 0       | 271   |
| DRB1*16:01        | 243   | 13     | 1      | 11     | 1       | 1       | 0      | 0       | 1       | 271   |

Abbreviations: Ab, absent; Het, heterozygous; HLA, human leukocyte antigen; Hom, homozygous.

Only alleles with >5% prevalence among female or male participants are included.

Table 2. Number of Couples With Shared Human Leukocyte Antigen (HLA) Alleles or Shared HLA-G 3’ Untranslated Region Single-Nucleotide Polymorphisms in the Human Papillomavirus Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) Cohort Study

| No. of Shared Alleles | No. of Couples Sharing Alleles According to Inclusiveness of HLA Classification | No. of Couples Sharing HLA-G 3’ UTR SNPs |
|-----------------------|------------------------------------------------------------------------------------------------|----------------------------------------|
|                       | HLA-B*07, DRB1, -DQB1 Loci | HLA-G Loci | All HLA Loci | HLA-G: 14 bp, +3142 C/G, +3187 G/A | HLA-G: 14 bp and All 8 Different SNPs |
| 0                     | 160 | 92 | 53 | 66 | 65 |
| 1                     | 64  | 161 | 117 | 85 | 77 |
| 2                     | 42  | 18 | 67 | 58 | 46 |
| 3                     | 5 | ...  | 28 | 62 | 33 |
| 4                     | ...  | ...  | 5 | ...  | 38 |
| 5                     | ...  | ...  | 1 | ...  | 11 |
| 6                     | ...  | ...  | ...  | ...  | 1 |

Abbreviations: HLA, human leukocyte antigen; SNP, single-nucleotide polymorphism; UTR, untranslated region.
Under the assumption that HPV type and subgenus concordance implies transmission episodes within couples, we examined the effect of allele sharing on concordance among the 271 couples that were HPV positive. Allele prevalence could be complete (i.e., both partners harboring the allele or partial) with only 1 member of the couple being positive for the allele. Table 4 shows odds ratios (ORs) of HPV infection concordance for the latter 2 categories relative to complete absence of the allele in the couple for HLA-B*07, -DRB1, and -DQB1 alleles. Similarly, Table 5 shows the equivalent results for HLA-G alleles and 3’UTR SNPs. A few entries in both tables indicated significant associations between allele sharing and concordance (2 in Table 4 and 5 in Table 5). However, given the numbers of associations examined in Table 4 (22 alleles × 4 HPV concordance outcomes × 2 sharing levels = 176 ORs) and in Table 5 (similar calculation for 15 alleles × 120 ORs), the 7 flagged associations...
| HLA Allele | Level of Allele Sharing* | All HPVs | Subgenus 1 | Subgenus 2 | Subgenus 3 |
|------------|-------------------------|----------|------------|------------|------------|
| **B*07**   | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.07 (.74–1.55) | 1.12 (.53–2.39) | 1.13 (.72–1.76) | 0.82 (.43–1.56) |
|            | 2                       | 2.52 (.74–1.55) | 2.74 (.24–31.47) | 2.59 (.85–78.88) | 3.18 (.34–29.34) |
| **DRB1*01:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.00 (.63–1.60) | 0.93 (.35–2.50) | 0.86 (.49–1.52) | 1.42 (.62–3.24) |
|            | 2                       | 2.57 (.36–18.32) | 1.28 (.08–21.02) | ND         | ND         |
| **DRB1*03:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.46 (.98–2.17) | 1.42 (.62–3.27) | 1.28 (.80–2.03) | 1.65 (.83–3.29) |
|            | 2                       | 1.23 (.46–3.29) | 1.40 (.09–23.05) | 1.11 (.35–3.54) | 1.20 (.30–4.79) |
| **DRB1*04:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.02 (.66–1.59) | 0.45 (.19–1.05) | 1.10 (.66–1.86) | 1.66 (.74–3.75) |
|            | 2                       | 1.17 (.21–6.59) | NC         | 1.24 (.08–19.98) | 1.77 (.16–20.19) |
| **DRB1*04:04** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.12 (.63–2.02) | 0.29 (.06–1.42) | 1.20 (.60–2.38) | 1.80 (.57–5.70) |
|            | 2                       | ...      | ...        | ...        | ...        |
| **DRB1*07:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 0.82 (.57–1.17) | 1.14 (.56–2.33) | **0.63 (.41–.96)** | 1.02 (.55–1.90) |
|            | 2                       | 0.96 (.45–2.05) | 0.91 (.15–5.76) | 0.73 (.30–1.80) | 1.48 (.40–5.44) |
| **DRB1*11:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.13 (.75–1.70) | 1.55 (.70–3.43) | 1.05 (.65–1.70) | 1.09 (.55–2.19) |
|            | 2                       | 3.51 (.36–34.27) | ND         | ND         | ND         |
| **DRB1*11:04** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.14 (.73–1.80) | 0.96 (.38–2.45) | 1.22 (.70–2.11) | 1.06 (.52–2.20) |
|            | 2                       | ND       | ND         | ND         | ND         |
| **DRB1*15:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.30 (.90–1.88) | 1.35 (.62–2.94) | 1.51 (.97–3.24) | 1.12 (.60–2.10) |
|            | 2                       | 0.89 (.31–2.52) | 0.44 (.09–2.19) | 1.46 (.41–5.18) | 1.17 (.61–2.23) |
| **DQB1*02:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.21 (.82–1.80) | 1.09 (.48–2.50) | 1.15 (.73–1.83) | 1.27 (.64–2.51) |
|            | 2                       | 1.03 (.36–2.98) | 1.32 (.08–21.72) | 1.04 (.30–3.67) | 0.87 (.20–3.73) |
| **DQB1*02:02** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.01 (.69–1.48) | 1.26 (.60–2.66) | 0.80 (.51–1.27) | 1.17 (.61–2.23) |
|            | 2                       | 0.81 (.36–1.80) | 0.83 (.19–3.66) | 0.73 (.27–1.97) | 0.98 (.26–2.87) |
| **DQB1*03:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 0.98 (.67–1.43) | 0.98 (.46–2.09) | 0.99 (.63–1.55) | 1.05 (.56–1.99) |
|            | 2                       | 0.63 (.33–1.19) | 1.36 (.41–4.44) | 0.58 (.27–1.22) | 0.50 (.15–1.70) |
| **DQB1*03:02** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 0.77 (.52–1.14) | 0.71 (.33–1.52) | 0.79 (.49–1.26) | 0.89 (.45–1.75) |
|            | 2                       | 0.79 (.30–2.05) | ND         | 1.19 (.41–3.47) | 0.52 (.08–3.26) |
| **DQB1*03:03** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 0.85 (.52–1.41) | 1.60 (.55–4.66) | 0.76 (.42–1.36) | 0.79 (.33–1.88) |
|            | 2                       | ND       | ND         | ND         | ND         |
| **DQB1*04:02** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.01 (.58–1.78) | 0.82 (.26–2.63) | 1.37 (.71–2.66) | 0.57 (.23–1.43) |
|            | 2                       | 1.15 (.14–9.27) | ND         | 1.26 (.08–20.25) | ND         |
| **DQB1*05:01** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.12 (.77–1.64) | 1.08 (.51–2.29) | 0.97 (.61–1.52) | 1.84 (.85–3.15) |
|            | 2                       | 1.14 (.31–4.17) | 0.65 (.06–74.9) | 1.93 (.40–9.39) | 0.47 (.04–5.45) |
| **DQB1*05:02** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
|            | 1                       | 1.03 (.57–1.87) | 1.59 (.51–4.95) | 0.83 (.39–1.76) | 0.57 (.23–1.43) |
|            | 2                       | 2.40 (.38–15.20) | ND         | 5.36 (.49–58.90) | ND         |
| **DQB1*05:03** | 0                       | 1.0      | 1.0        | 1.0        | 1.0        |
Table 4. Continued

| HLA Allele | Level of Allele Sharing* | All HPVs          | Subgenus 1          | Subgenus 2          | Subgenus 3          |
|-----------|-------------------------|-------------------|---------------------|---------------------|---------------------|
| 1         |                         | 1.34 (1.70–2.56)  | 0.91 (0.75–2.28)    | 1.09 (0.51–2.32)    | 2.93 (1.90–9.22)    |
| 2         |                         | 1.41 (1.34–5.85)  | 3.99 (0.43–37.01)   | 0.95 (0.17–5.16)    | 0.90 (0.57–14.36)   |
| DQB1*06:02|                         | 1.00 (1.0)        | 1.00 (1.0)          | 1.00 (1.0)          | 1.00 (1.0)          |
| 1         |                         | 1.09 (0.75–2.15)  | 1.15 (0.52–2.53)    | 1.19 (0.76–2.15)    | 1.05 (0.55–2.00)    |
| 2         |                         | 1.04 (0.48–2.26)  | 0.53 (0.13–2.11)    | 1.69 (0.66–4.31)    | 0.83 (0.20–3.52)    |
| DQB1*06:03|                         | 1.00 (1.0)        | 1.00 (1.0)          | 1.00 (1.0)          | 1.00 (1.0)          |
| 1         |                         | 0.82 (0.47–1.44)  | 0.74 (0.23–2.40)    | 0.95 (0.48–1.87)    | 0.72 (0.29–1.82)    |
| 2         |                         | 0.76 (0.29–5.19)  | 0.40 (0.08–1.99)    | 0.60 (0.23–2.85)    | 1.70 (0.29–9.98)    |
| DQB1*06:04|                         | 1.00 (1.0)        | 1.00 (1.0)          | 1.00 (1.0)          | 1.00 (1.0)          |
| 1         |                         | 1.32 (0.78–2.25)  | 1.09 (0.43–2.76)    | 1.85 (0.98–3.49)    | 0.77 (0.26–2.24)    |
| 2         |                         | 0.77 (1.12–4.91)  | ND                  | ND                  | ND                  |

Significant ORs are shown in bold. Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; HPV, human papillomavirus; ND, not determined; OR, odds ratio.

*0, allele not present in either partner; 1, presence in 1 partner; 2, presence in both partners.

could be due to chance. Moreover, no pattern emerged for the few identified associations. In the interest of conservatism, we repeated the analyses shown in Tables 4 and 5 for selected alleles but by rearranging the partner genetic categories as (1) allele not present in either partner or in 1 partner only; (2) presence in both partners (both heterozygous or 1 heterozygous and the other homozygous); (3) both partners homozygous. Again, no patterns of association emerged that could not be due to chance (Supplementary Table 1).

Finally, we evaluated the extent of HLA sharing irrespective of HLA class, grouped or in combination, and HPV concordance between the dyads (Table 6). There was no discernible pattern or trend of association between the extent of allele sharing and HPV type concordance, and the 5 entries in the table that were significant at the 5% level could have been due to chance, owing to the high number of associations examined.

**DISCUSSION**

The role of different host factors in transmission of HPV infections between heterosexual couples is not well known. Since antigen processing as the initiating step in immune response requires mediation via HLA [8], we hypothesized that HLA allele sharing between partners would facilitate transmission of HPV infections within heterosexual couples. Our HITCH cohort of young couples provides a suitable observational study design to study the role of HLA polymorphism on HPV transmission. As a strength, all HITCH couples had recently initiated their sexual relationship, when most HPV transmission episodes are known to occur [18, 19]. We also had high-resolution typing for 106 different HLA alleles investigated with substantial (48%) between-partner type-specific HPV concordance, our surrogate endpoint for considering that transmission had occurred.

We did not find evidence to support our hypothesis. Allele sharing, individually or in combination over multiple loci, was not statistically associated (beyond chance expectation) with presumed infection transmission using different HPV type groupings chosen according to biological behavior and pathogenetic propensity.

HLA genetic variation has been demonstrated to affect risk of HPV-related cervical cancer, especially with HLA class I and II loci molecules [6, 20–22]. Deletions in HLA-B alleles are associated with cervical carcinogenesis [6, 22]. A recent meta-analysis found the class II alleles HLA-DQR*02, -*03, and -*06:03 to decrease and HLA-DQB1*05, -*03:01, and -*04:02 to increase risk of cervical cancer [20], while a genome-wide study concluded HLA-DRB1*06:02 and -*15:01 to be major risk alleles in cervical carcinogenesis [6]. None of the above class I and II HLA alleles were associated with HPV transmission in our couples study.

The nonclassical class Ib HLA-G molecules have been suggested to play a prognostic or risk marker role because of HLA-G alleles’ relatively low polymorphism rate and restricted tissue distribution compared to other HLA molecules [23]. Different HLA-G alleles were shown to have a distinctive role in the reproductive system of females and males [24, 25] and also in other cancers and infections by facilitating their escape from immune surveillance [26]. HLA-G was shown to be important in mother-to-child transmission of HPV infection, mainly because of its preferential expression at the maternal-fetal interface and its immunosuppressive properties [10, 27–29]. A recent study investigated the role of HLA-G alleles in the vertical transmission of HPV infection but could not confirm HLA-G allele sharing to impact the HPV transmission between mother and child at birth or perinatally [11]. Few studies showed HLA-G*01:01:01, -*01:01:03, and -*01:01:05 and the HLA-G 14bp deletion to be associated with HPV infection or cervical cancer among women [15, 30–32]. Our results could not confirm HLA-G alleles to mediate risk of HPV transmission between partners.
In conclusion, our results do not support a role for HLA allele sharing in influencing transmission of genital HPV infection. HPV transmission within heterosexual couples is likely to be a more complex combination of host and environmental factors.

### Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The

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**Table 5. Association Between Within-Couple Sharing of Human Leukocyte Antigen G Alleles and 3’ Untranslated Region Single-Nucleotide Polymorphisms and Human Papillomavirus (HPV) Type Concordance by Subgenera Among the 271 Heterosexual Couples That Were HPV Positive**

| HLA-G Allele/Variant | Level of Allele Sharing | All HPVs | Subgenus 1 | Subgenus 2 | Subgenus 3 |
|----------------------|-------------------------|---------|------------|------------|------------|
| 01:01:01             | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.83   | 0.86       | 0.85       | 0.40       |
|                      |                          | (0.30–2.28) | (0.38–1.96) | (2.4–2.94) | (0.07–2.32) |
| 01:01:02             | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 1.01   | 3.29       | 0.79       | 0.95       |
|                      |                          | (0.69–1.47) | (1.52–7.15) | (5.0–1.24) | (5.0–1.81) |
| 01:01:03             | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.55   | ND         | 0.65       | 0.36       |
|                      |                          | (0.35–0.87) | (38–1.12)   | (1.12–1.03) |             |
| 01:03                | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 1.03   | 0.71       | 1.01       | 1.24       |
|                      |                          | (0.64–1.65) | (26–1.91)   | (58–1.78)  | (54–2.85)  |
| 01:04:01             | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.97   | 1.20       | 1.21       | 0.70       |
|                      |                          | (0.66–1.42) | (26–1.25)   | (77–1.90)  | (0.37–1.34) |
| 01:06                | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.98   | 0.49       | 0.96       | 0.67       |
|                      |                          | (0.60–1.62) | (2.2–1.09)  | (52–1.77)  | (30–1.50)  |
| 14 bp                | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 1.05   | 1.20       | 0.98       | 0.96       |
|                      |                          | (0.62–1.80) | (43–3.38)   | (51–1.87)  | (37–2.49)  |
| +3001 C/T            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 2.21   | 4.08       | 1.85       | 1.69       |
|                      |                          | (0.91–5.34) | (87–19.15)  | (71–4.84)  | (30–9.59)  |
| +3003 T/C            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 1.35   | 1.05       | 1.40       | 1.61       |
|                      |                          | (0.93–1.95) | (51–2.14)   | (91–2.17)  | (81–3.18)  |
| +3010 G/C            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.99   | 1.85       | 1.13       | 0.49       |
|                      |                          | (0.68–1.42) | (91–3.76)   | (73–1.74)  | (26–94)   |
| +3027 C/A            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 1.23   | 1.88       | 1.22       | 0.90       |
|                      |                          | (0.62–2.44) | (47–7.54)   | (54–2.76)  | (27–3.05)  |
| +3035 C/T            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.77   | 0.97       | 0.76       | 0.80       |
|                      |                          | (0.48–1.24) | (32–2.96)   | (44–1.32)  | (34–1.92)  |
| +3142 C/G            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.98   | 1.53       | 0.98       | 0.66       |
|                      |                          | (0.61–1.57) | (62–3.78)   | (55–1.34)  | (29–1.54)  |
| +3187 G/A            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 1.02   | 0.61       | 1.89       | 0.14       |
|                      |                          | (0.49–2.11) | (17–2.23)   | (76–4.69)  | (0.02–1.18) |
| +3196 C/G            | 0                       | 1.0     | 1.0        | 1.0        | 1.0        |
|                      | 1                       | 0.96   | 2.58       | 0.96       | 0.63       |
|                      |                          | (0.65–1.43) | (1.18–5.66) | (60–1.53)  | (32–1.24)  |
|                      | 2                       | 1.10   | 4.23       | 0.93       | 0.78       |
|                      |                          | (0.66–1.81) | (1.52–11.76) | (51–1.69)  | (34–1.79)  |

Significant ORs are shown in bold.

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; HPV, human papillomavirus; ND, not determined; OR, odds ratio.

*0, allele not present in either partner; 1, presence in 1 partner; 2, presence in both partners.*
Table 6. Associations Between Extent of Human Leukocyte Antigen Allele Sharing and Human Papillomavirus (HPV) Concordance Among the 271 Heterosexual Couples That Were HPV Positive

| Inclusiveness of HLA Groupings Shared | Alleles Shared per Couple | Age-Adjusted OR (95% CI)* |
|--------------------------------------|---------------------------|--------------------------|
|                                      | All HPVs | Subgenus 1 | Subgenus 2 | Subgenus 3 |
| HLA-B*07,-DRB1, and -DQB1            |          |            |            |            |
| 0                                    | 1.0      | 1.0        | 1.0        | 1.0        |
| 1                                    | 1.1 (.8–1.7) | 0.9 (.4–2.1) | 1.3 (.8–2.2) | 0.9 (.4–1.9) |
| 2–3                                  | 1.0 (.6–1.6) | 0.8 (.3–2.2) | 1.3 (.7–2.5) | 0.6 (.2–1.5) |
| HLA-G                                |          |            |            |            |
| 0                                    | 1.0      | 1.0        | 1.0        | 1.0        |
| 1                                    | 1.1 (.7–1.6) | 0.4 (.2–.7) | 1.1 (.7–1.7) | 1.9 (1.0–3.5) |
| 2                                    | 0.6 (.3–1.5) | 0.6 (.1–2.7) | 0.4 (.1–1.1) | 3.0 (5–16.7) |
| All HLAs                              |          |            |            |            |
| 0                                    | 1.0      | 1.0        | 1.0        | 1.0        |
| 1                                    | 1.6 (.7–1.9) | 0.7 (.2–1.8) | 1.1 (.6–2.0) | 1.5 (.7–3.3) |
| 2                                    | 1.0 (.6–1.7) | 0.8 (.3–2.4) | 0.9 (.5–1.8) | 1.2 (2–2.9) |
| 3–5                                  | 1.1 (.5–2.1) | 0.2 (.0–1.0) | 1.6 (.7–3.7) | 1.4 (.4–4.7) |
| HLA-G 3′UTR: 14 bp, +3142 C/G, +3187 G/A |          |            |            |            |
| 0                                    | 1.0      | 1.0        | 1.0        | 1.0        |
| 1                                    | 0.9 (.6–1.5) | 1.4 (.6–3.5) | 0.6 (.4–1.2) | 2.4 (1.0–5.7) |
| 2                                    | 0.8 (.5–1.3) | 0.9 (.3–2.5) | 0.9 (.5–1.6) | 0.8 (.4–1.9) |
| 3                                    | 0.7 (.4–1.2) | 2.4 (.9–6.3) | 0.6 (.3–1.1) | 0.8 (.4–1.8) |
| HLA-G 3′UTR: 14 bp and all 8 different SNPs |          |            |            |            |
| 0                                    | 1.0      | 1.0        | 1.0        | 1.0        |
| 1                                    | 1.0 (.6–1.6) | 1.5 (.6–3.7) | 0.7 (.4–1.3) | 2.6 (1.0–6.3) |
| 2                                    | 0.6 (.4–1.1) | 0.8 (.3–2.5) | 0.7 (.4–1.3) | 0.7 (.3–1.7) |
| 3                                    | 0.7 (.3–1.2) | 1.0 (.2–4.9) | 0.6 (.3–1.2) | 0.7 (.2–2.0) |
| 4                                    | 0.9 (.5–1.6) | 2.4 (.8–7.3) | 0.8 (.4–1.5) | 0.8 (.3–1.9) |
| 5–6                                  | 0.9 (.3–2.5) | 6.9 (.9–54.6) | 0.4 (.1–1.4) | 4.0 (4–36.9) |

Significant ORs are shown in bold.

*Results according to inclusiveness of HLA classification.

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; HPV, human papillomavirus; OR, odds ratio; SNP, single-nucleotide polymorphism; UTR, untranslated region.

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.

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