HLA-G alleles impact the perinatal father-child HPV transmission

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Abstract

Background

The host factors that influence the father-to-child human papillomavirus (HPV) transmission remain unknown. This study evaluated whether human leukocyte antigen (HLA)-G alleles are important in father-to-child HPV transmission during the perinatal period.

Methods

Altogether, 134 father-newborn dyads from the Finnish Family HPV Study were included in the analyses. Oral, semen and urethral samples from the fathers were collected before the delivery, and oral samples from their offspring at delivery and postpartum at birth, day-3, at 1-, 2- and 6-month follow-up visits. HLA-G alleles were tested by direct sequencing. Unconditional logistic regression was used to determine the associations between the father-child HLA-G allele and genotype concordance and the father-child HPV prevalence and concordance at birth and during follow-up.

Results

HLA-G allele G*01:01:03 concordance was associated with father's urethral and child's oral high-risk (HR)-HPV concordance at birth (OR 17.00, 95%CI:1.24-232.22). Controversially at postpartum period G*01:01:03 discordance was associated with father's urethral and child's oral HR-HPV concordance (OR 6.67, 95%CI:1.08-40.97). HLA-G allele G*01:04:01 concordance increased the father's oral and child's postpartum oral any- and HR-HPV concordance, with OR 7.50 (95%CI:1.47-38.16) and OR 7.78 (95%CI:1.38-43.85), respectively. There was no association between different HLA-G genotypes and HPV concordance among the father-child dyads at birth or postpartum.

Conclusion

The HLA-G allele concordance appears to impact the HPV transmission between the father and his offspring. This suggests that the father might have an important regulatory role in the natural history of his child's oral HPV infection, which should be further explored.

Background

Human papillomavirus (HPV) infection is furthermost known as the accountable factor for the development of cervical cancer in women [1, 2]. However, HPV also encompasses a great worldwide burden of diseases in men including medical problems from benign warts to different HPV related cancers such as anal, penile and oropharyngeal cancers [3]. In children HPV infection is known to cause benign warts as also juvenile-onset recurrent respiratory papillomatosis (JoRRP), which could be life-threatened if it is led untreated [4, 5].

Even though HPV infection is one of the most common sexually transmitted infection, non-sexual routs of transmission as vertical and horizontal transmission and autoinoculation have been emerged [6, 7]. Evidence suggest that newborn can acquire HPV infection via vertical transmission from the mother or father [8–11]. Prenatal transmission from the mother to child occurs during pregnancy as an intrauterine transmission [7, 12]. A recent study showed that mother's persistent HPV16/18 infection is also associated with preterm birth [13]. Perinatal transmission occurs at the time of delivery and immediately thereafter; it is tough to result mainly from a contact with the infected maternal genital tract [7].

Father's role as a source of HPV infection to the newborn is less known. As HPV DNA has been isolated from the vas deferens, seminal fluid, and spermatozoa [14–16] the peri-conceptional transmission (time around fertilization) from the male partner is at least theoretically possible [7]. Postpartum infection (time after delivery) of newborn could have been transmitted vertically from either father or mother and horizontally from other care givers via kissing or digital contacts [7].

Even though different modes of transmission have been identified, child's early-life exposure for HPV infection and genetical as immunological co-factors that facilitate the susceptibility for an infection remains mostly unexplored. Human leukocyte antigen G (HLA-G) is one of those immunological co-factors that is supposed to impact the natural history of HPV as other viral infections. In general, HLA-G molecules take part in innate and adaptive immune responses and in immune escape in cancer progression [17, 18] and infectious diseases [19][20]. HLA-G is classified as a member of the non-classical human leukocyte antigen (HLA) class Ib since it differs from classical HLA-class I molecules by modulation of the immune response and by having low degree of polymorphism as restricted tissue distribution [21]. By the expression of placental cells HLA-G plays a significant role in maternal-fetal interface [22]. The impact of mother-child HLA-G gene concordance to vertical transmission of HPV infection have been investigated before [23] but no studies of the role of HLA-G in father-child HPV transmission have been published. Consequently, our aim was to evaluate whether HLA-G alleles are important in father-to-child HPV transmission during the perinatal period.

Methods

Finnish Family HPV Study The Finnish Family HPV (FFHPV) Study is a longitudinal cohort follow-up study conducted at Turku University Hospital and University of Turku, Finland. At baseline, a total of 329 families with pregnant women (in their third trimester), fathers-to-be and later their newborns participated to the original study. They were followed up for six years to assess dynamics of HPV infection between family members as described previously [24, 25]. The present study includes 132 fathers and 134 offspring from the FFHPV study. The cohort represents Caucasian origin as the Finnish population has the same ethnic background.

HPV genotyping Semen, urethral and oral scapings from the fathers and oral scrapings from the newborns were collected for HPV testing with a Cytobrush (MedScand, Malmö, Sweden) as described earlier [9]. Fathers HPV samples were collected at baseline before delivery. Newborns oral follow-up

samples were collected at delivery and postpartum at day 3 as 1-, 2- and 6-month follow-up visits. HPV genotyping was performed by the Multimetrix kit (Multimetrix, Progen Biotechnik GmbH, Heidelberg, Germany) identifying 24 different low risk (LR) and high risk (HR) HPV genotypes (LR-genotypes: 6, 11, 42, 43, 44 and HR-genotypes: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82) [26].

HLA-G typing DNA from father's and newborn's frozen whole blood samples were extracted for HLA-G typing by using the MagNAPure 96 System (Roche). Determination of HLA-G alleles was done by direct DNA sequencing exploring exons 2–4 (1718 bp) of HLA-G gene regions as described before [27].

Statistical analyses

STATA SE15.1 (StataCorp College station TX, USA) was used for all statistical analyses. Study cohort included 134 father-child dyads, 132 fathers and their 134 offspring (two dyads of twins) both parties having HLA-G allele determination available. Only those HLA-G alleles and genotypes that were identified both among the fathers and children and were ≥ 3% prevalent among fathers and/or children were included in the analyses. HLA-G alleles were explored both in high- and low-resolution groups. HLA-G concordance for a specific HLA-G allele were considered if father and his child both had at least one specific allele; in other words, HLA-G allele concordance was defined if both parties was heterozygous or homozygous for this allele. If one party had an allele and other miss the allele the dyad was count as HLA-G discordant for the allele.

In low resolution analyses only one allele group G*01:01+ (including HLA-G alleles G*01:01:01, G*01:01:02, G*01:01:03 and G*01:01:14) was available while there were four low resolution genotype groups: 01:01+/01:01+, 01:01+/01:03+, 01:01+/01:04+, 01:01+/01:06+. In low resolution analyses HLA-G allele concordance were divided to four groups by number of shared alleles (1 = discordant for the allele; 2 = 2 shared alleles, 3 = 3 shared alleles, 4 = 4 shared alleles).

In HPV genotyping analyses HPV species were classified as either LR- or HR groups [28]. Multiple-type HPV infections were sorted out as individual HPV genotypes. Child's oral HPV status was counted as the point HPV prevalence as followed 1) at birth covering oral samples at delivery and at day 3 (at discharge) and 2) at postpartum covering samples taken at 1-, 2- and 6 months.

In assessing HPV concordance (HPV+/+ or HPV -/-), only those father-child dyads who had an opportunity for HPV infection (i.e. both parties having HPV sample available) were considered. HPV concordance in relation to any-, HR- and LR-HPV types were defined if both father and child had any-, HR- or LR-HPV positive HPV sample. HPV discordance denoted if one party (father or child) had a positive and other party had a negative HPV sample. HPV prevalence among father-child dyads was calculated as HPV positive (for any-, LR- or HR HPV) if at least one party, father or child, had at least one positive (any-, LR- or HR-) HPV sample.

Unconditional logistic regression was used to determine the associations (OR) between 1) within father and his child shared HLA-G alleles or genotype and 2) father-child HPV concordance and prevalence. In

high resolution HLA-G allele analyses the father-child dyads with both parties being negative for these specific alleles served as a reference, whereas in low resolution group analyses HLA-G allele discordant father-child dyads served as a reference. Significance level of 0.05 was used (two-tailed) and 95% confidence intervals (CI) were calculated.

Results

The mean age of the fathers were 28.8 years (range 19–46 years). Overall, nine different HLA-G allele with 19 different genotype combinations were identified among fathers and their offspring. Only those seven alleles and five genotypes that were ≥ 3% prevalent and were identified in both among the fathers and the children were included in the analyses. The most common HLA-G allele found was the wild-type G*01:01:01; 86.4% (n = 114) of the fathers and 85.8% (n = 115) of children had the allele. The second most common allele among father was G*01:01:02; 36.4% (n = 48) of the fathers and 32.8% (n = 44) of the children had the allele. The most common HLA-G genotype among the fathers and children was G*01:01:01/01:01:01; 37.1% (n = 49) and 36.6% (n = 49); followed by G*01:01:01/01:01:02; 23.5% (n = 31) and 21.6% (n = 29), respectively. Figure 1 shows allele sharing (Fig. 1a) and genotype concordance (Fig. 1b) among 134 fathers-child dyads. The most shared allele was the G*01:01:01, for which 73,9% (n = 99) of dyads shared at least two common alleles, (i.e. both were at least heterozygous for the allele), followed by other alleles that were shared between 2.2% (n = 3) and 22.4% (n = 30) among the dyads. The most commonly concordant genotype between father-child dyads was the G*01:01:01/01:01:01; 25.4% (n = 34). Overall, 37.3% (n = 50) of the father-child dyads had any concordant HLA-G genotype.

When the influence of HLA-G alleles on HPV concordance was evaluated, those father-child dyads who both tested positive for a particular allele (both the father and offspring had at least one allele) were compared to those dyads with discordant HLA-G alleles (only the father or the child had the allele). The father-child dyads with both parties missing the allele served as the reference. Sharing of different alleles was compared to the HPV concordance of father's three anatomical baseline (before birth) HPV status (semen, urethral and oral) and child's oral HPV status at birth and postpartum as seen in Table 1. HLA-G allele G*01:01:03 concordance was associated with father's urethral and child's oral HR-HPV concordance at birth (OR 17.00, 95% CI 1.24-232.22). Controversially at postpartum period G*01:01:03 discordance was associated with father's urethral and child's oral HR-HPV concordance (OR 6.67, 95% CI 1.08–40.97). HLA-G allele G*01:04:01 concordance increased the father's oral and child's postpartum oral any- and HR-HPV concordance, with OR 7.50 (95% CI:1.47–38.16) and OR 7.78 (95% CI:1.38–43.85), respectively. When HLA-G genotype concordance was compared to the HPV concordance, no association was observed between different HLA-G genotypes and HPV concordance among the father-child dyads at birth or postpartum period.

The association between father-child HLA-G allele sharing and common HPV prevalence of fathers and/or children is shown in Table 2. HLA-G allele G*01:01:03 discordance increased the risk of fathers' urethral and/or children's oral any- and HR-HPV prevalence at birth with OR 5.47 (95% CI 1.11–26.89) and 6.76 (95% CI 1.37–33.35), whereas G*01:01:03 concordance increased the risk of fathers' oral and/or

children's oral HR-HPV prevalence at birth with OR 8.81 (95% CI 1.00-77.94). G*01:06 allele concordance increased the LR-HPV prevalence of fathers' semen/urethral and/or children's oral sites at birth; OR ranging between 12.00 (95% CI 1.03-140.19) and 16.15 (95% CI 1.37-190.72). No association was seen between HLA-G allele sharing and fathers' and/or children's postpartum HPV prevalence as shown in **Table S1** (see Additional file 1).

Table 3 summarized the association of father-child HLA-G genotype concordance, in both high- and low-resolution groups, and HPV prevalence of the fathers and/or children. No significant association was found in high resolution group, whereas in low resolution group G*01:01/01:04 concordance associated with greater HR-HPV prevalence of fathers' semen and/or children's oral sites at postpartum period, OR 7.00 (95% CI 1.14–42.97). Similarly, G*01:01/01:04 concordance increased the fathers' any urethral and/or children's postpartum any oral HPV prevalence with OR 6.50 (95% CI 1.05–40.13).

Discussion

According to our results certain HLA-G alleles appears to have the impact on father-child HPV concordance and prevalence in perinatal period. However, HLA-G genotypes did not show to influence the HPV concordance among the father-child dyads. The acquisition of HPV infection in early life is supposed to be facilitated by many complex immunological, genetical and epigenetical co-factors [29]. The father's role in child's early life exposure for HPV infection remains unclear. Only few studies have evaluated the father's role in perinatal HPV infection with controversial results [8, 9, 30]. The study with the Polish family cohort (146 parental couples and their newborns) showed that father's oral HPV16/18 infection increased the newborn's oral HPV16/18 infection at birth [8]. With our Finnish Family cohort, Rintala and colleagues showed that the newborn's genital HPV positivity associated with mother's oral HR-HPV detected before delivery whereas the newborn's oral HPV positivity at the age of six months associated with father's oral HR-HPV detected before delivery [9]. In both studies, type-specific concordance was not analyzed. In addition, another recent study with our Finnish Family cohort showed that the incident oral HR-HPV infection for a child were predicted by HR-HPV seropositivity of the father [11]. In contrast, Smith and coworkers showed HPV transmission from parents to newborn to be rare in American population in Iowa, as only one of 574 mother-child dyads and none of 68 father-child dyads had concordant HPV type [30].

The role of HLA-G in vertical HPV transmission is even less studied. To our knowledge there is only one previous study with the same Finnish Family HPV cohort that has evaluated the HLA-G and vertical mother-to-child HPV transmission [23]. In that study HLA-G allele or genotype concordance did not show any impact to mother-to-child genotype specific HPV transmission [23]. To date, no studies on HLA-G in father-child HPV concordance or transmission have been reported. HLA-G in vertical human immunodeficiency virus (HIV) transmission is more studied than HLA-G in vertical HPV transmission. Several studies have shown HLA-G polymorphism to influence the risk of mother-to-child HIV

transmission [31–36]. With regard of mother-child HLA-G concordance the data is controversial and sparse. One small prospective cohort study (N = 34) run in New York City suggested that mother-child discordance in exon 2 associate with a reduced risk of perinatal HIV infection [31]. However, two larger studies have not found association between HLA-G allele concordance and vertical mother-to-child HIV transmission [32, 36]. To best of our knowledge no studies with HLA-G and father-to-child transmission of HIV nor other viruses have been published before.

In this study with our cohort of fathers and their newborns we identified only nine different HLA-G alleles. To date overall 94 HLA-G alleles have been identified (IPD-IMGT/HLA Database) [37]. Relatively low number of different HLA-G alleles we found was expected considering that Finnish population has a quite restricted and homogenous gene pool due to historical isolation. The most common allele observed among both fathers and their offspring in our cohort was the wildtype G*01:01:01 as it was in other studies with Canadian, Black South African and Kenyan populations [32, 36, 38].

We showed HLA-G concordance with certain specific alleles to have an impact on HPV father-child concordance (in any-, LR- and HR-HPV groups) but if it indicates HPV transmission from father to child, is questionable. At least we showed that the type-specific father-child HPV concordance associated with HLA-G allele G*01:04:01. HLA- G*01:04:01 father-child concordance was related to the father's oral and child's postpartum oral any- and HR-HPV concordance. In this case, HPV type-specific concordance was seen in two father-child dyads with HR-HPV genotypes 33 and 70 (50% of concordant dyads had HR-HPV genotype specific concordance, data not shown). Further evaluations showed that if the mother's oral HPV status were also taken into account, the adjusted OR's for G*01:04:01 father-child concordance and the father's oral and child's postpartum oral any- and HR-HPV concordance remained statistically significant; adjusted OR:s 11.50 (95% CI 1.77–74.87) and 9.86 (95% CI 1.49–65.12), respectively (data not shown). This finding is suggestive for vertical father-to-child HPV transmission in this case. Interestingly, in the study of the same Finnish Family cohort with mother-child dyads, discordant mother-child HLA-G allele G*01:04:01 increased the risk for child's oral LR-HPV infection at birth [23].

According to our results HLA-G G*01:01:03 allele father-child concordance relates to father's urethral and child's oral HR-HPV concordance at birth. Controversially, when child's oral HPV status was determined at postpartum, association between G*01:01:03 allele discordance and father's urethral and child's oral HR-HPV concordance was seen. Moreover, HLA-G allele G*01:01:03 discordance seems to increase the risk of father's urethral and/or child's oral any- and HR-HPV positivity at birth, whereas G*01:01:03 concordance was associated with the higher risk of father's oral and/or child's oral HR-HPV positivity at birth. This contradiction remains unexplainable assuming that biologically HLA-G allele discordance is supposed to reduce risk of infection at any anatomical site. Therefore, we investigated separately the fathers' HPV prevalence at baseline (before birth) and children's HPV prevalence at birth; G*01:01:03 allele discordance seemed to increase solely the father's urethral any- and HR-HPV positivity but not child's oral HPV positivity at birth (data not shown). G*01:01:03 allele concordance lost the statistical significance when fathers' oral HR-HPV prevalence and children's oral HR-HPV prevalence at birth were explored separately, thus it did not show an impact on one or the other's oral HR-HPV prevalence alone (data not shown).

Interestingly in our recently published study we found the presence of men's allele G*01:01:03 to associate with an increased risk for urethral HR-HPV infections [39].

Allele G*01:06 concordance associated with the LR-HPV prevalence of fathers' semen as urethral and/or children's oral HPV at birth. When explored this association by fathers' and children's prevalence alone, G*01:06 concordance did not associate with alone father's semen or child's oral LR-HPV positivity at birth. However, G*01:06 concordance increased the father's urethral LR-HPV positivity, but not child's oral LR-HPV positivity at birth, when prevalence of fathers and children were analyzed separately (data not shown). Interestingly, the study of the Finnish Family cohort with mother-child dyads showed that G*01:06 mother-child discordance increased the child's oral LR-HPV positivity but had not impact on the mother's site [23].

The main limitation of this study is that we could not stratify analyses by HPV genotype due to relatively low sample size of fathers and newborns. A small sample size of fathers and children with uncommon HLA-G alleles may reduce the detection rate of significant associations between father-child HLA-G allele concordance and father-child HPV concordance.

For many it is still questionable whether child's HPV status at birth represent passive HPV contamination or a true infection. However, recently published study with the FFHPV cohort showed that part of the newborns born to seronegative mothers had a seroconversion to HPV6, HPV11, HPV16 and HPV18 recorded after birth [40]. According to this finding, there is a reason to suggest that newborns had acquired HPV infection somewhere in their body as they had created an immune response for HPV already in early infancy. In fact our previous findings by Koskimaa et al showed that HPV16-specific immune response exists among these unvaccinated and sexually naïve children [41–43]. The oral infection with LR HPV6 and HPV11 types is known to cause juvenile-onset recurrent respiratory papillomatosis [4]. Even if the JoRRP is rare, and the lesions it causes are benign, recurrent disease need repeated surgery and can persist into adulthood [4]. Given that, the consequences of newborn's exposure for HPV infection should not be ignored. Furthermore, the risk of genital precancerous lesions in adolescents and young adults based on vertical transmission is not fully understood. Better knowledge of natural history of HPV in early childhood is crucial to create the most effective preventive strategies for HPV-infections related diseases as to determine the optimal timing of the prophylactic HPV vaccination.

Conclusions

We showed that father-child HLA-G concordance might play some role in father-child HPV concordance and prevalence at birth and perinatal time. The regulatory role of HLA-G in child's susceptibility for HPV infection and the role of father in the transmission chain needs further investigations.

Abbreviations

HPV

human papillomavirus
HLA-G
human leukocyte antigen G
LR
low risk
HR
high risk

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol and its amendment (#3/1998, #2/2006 and 45/180/2010) have been approved by the Ethics Committee of Turku University Hospital. Written informed consent to participate was obtained from all adult participants. Written informed consent for child's participation was obtained from both parents of the child.

Consent to publish

Written informed consent for publication was obtained from both parents participated in this study.

Availability of data and materials

The datasets analyzed during the current study are available from the guarantor Karolina Louvanto on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

SS and SG conceived and designed the study. SS, MR and MCF did the HPV genotyping and HLA-G testing. SS, KS and KL collated the data. NS, KL, SS and KS interpreted the data. NS and KL did the statistical analyses. NS wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors gave final approval of the version to be published and have contributed to the manuscript. KL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

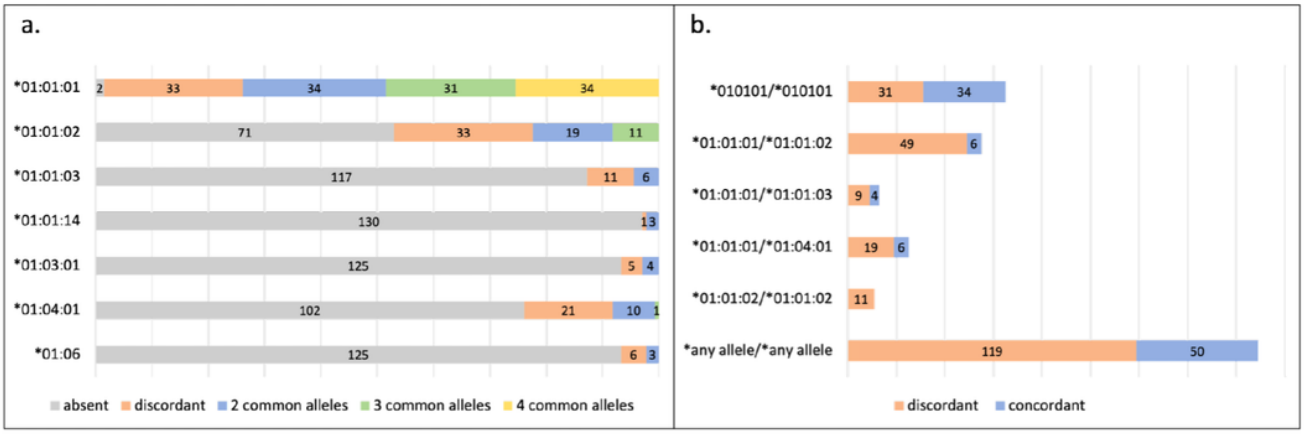

Figure 1

HLA-G (a) allele and (b) genotype concordance among the 134 father-child dyads from the Finnish Family HPV study. Stacked bar columns showing the HLA-G (a) allele sharing (absent = both missing the allele; discordant = one homo- or heterozygous for the allele and the other absent; 2 common alleles = both heterozygous for the allele; 3 common alleles= one heterozygous for the allele and other homozygous for the allele; 4 common alleles=both homozygous for the allele) and (b) genotype concordance (discordance = one having the genotype and the other missing the genotype; concordance = both having the same genotype) between the 134 father-child dyads from the Finnish Family HPV-Study. Those HLA-G alleles and genotypes that were ≥3% prevalent among the father-child dyads were included.

Supplementary Files

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