Human Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

HLA-G and vertical mother-to-child transmission of human papillomavirus infection

Karolina Louvanto[a,b,c,*], Michel Roger[d], Marie-Claude Faucher[d], Kari Syrjänen[a,e], Seija Grenman[a], Stina Syrjänen[c,f]

[a] Department of Obstetrics and Gynaecology, Turku University Hospital, University of Turku, Kiinanmyllynkatu 13, 20520 Turku, Finland
[b] Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK
[c] Department of Oral Pathology and Radiology, University of Turku, Lemminkäisenkatu 2, 20520 Turku, Finland
[d] Centre de Recherche du CHUM et Département de Microbiologie, Infectiologie et Immunologie, Université de Montréal, 2900, boul. Édouard-Montpetit, Montréal H3T 1J4, Canada
[e] Department of Clinical Research, Biohit Oyj, Laippatie 1, 00880 Helsinki, Finland
[f] Department of Pathology, Turku University Hospital, Kiinanmyllynkatu 10, 20520 Turku, Finland

ARTICLE INFO

Keywords:
HLA-G
Human papillomavirus
Vertical transmission
Mother
Newborn

ABSTRACT

Role of host factors in transmission of human papillomavirus (HPV)-infection from mother to her offspring is not known. Our aim was to study whether human leukocyte antigen (HLA)-G allele concordance among the mother–child pairs could facilitate vertical transmission of HPV, because HLA-G may contribute to immune tolerance in pregnancy. Altogether, 310 mother-child pairs were included from the Finnish Family HPV study. Overall, nine different HLA-G alleles were identified. The HLA-G genotype concordance of G*01:01:01/01:04:01 increased the risk of high risk (HR)-HPV genotype positivity in cord blood and infant's oral mucosa. The mother-child concordance of G*01:01:02/01:01:02 increased the risk of oral HPV positivity with HR-HPV genotypes both in the mother and offspring; OR 2.45 (95%CI 1.24–4.85). Discordant HLA-G allele for G*01:04:01 and for G*01:06 was significantly associated with infant's oral low risk (LR)-HPV at birth, OR 3.07 (95%CI 1.01–9.36) and OR 5.19 (95%CI 1.22–22.03), respectively. HLA-G had no association with HPV genotype-specific concordance between the mother and child at birth nor influence on perinatal HPV status of the child. Taken together, our results show that HLA-G molecules have a role in predicting the newborn's likelihood for oral HPV infection at birth.

1. Introduction

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infection (STI) worldwide [1]. The prevalence is shown to be highest among women and men around their sexual debut, and nearly all sexually active women and male will be infected with HPV in their lifetime [1,2]. However, HPV-infection can be transmitted in early life by vertical transmission from a mother to her child [3–6]. This transmission could occur in fertilization, during pregnancy (prenatal), at delivery or during the perinatal period [3,4]. Acquisition of HPV-infections in early life is most likely dependent on a combination of epigenetic, immune and genetic factors of the child acting in concert with endogenous and exogenous co-factors and viral load [7]. Most HPV-infections among adults are transient, whereas infections in early life may lead to long-term consequences such as HPV-related cancer [3,8,9]. If HPV-infections are acquired in early life, this will certainly impact the protective effect of prophylactic HPV vaccines (currently given to adolescent girls) which should be considered while designing the future policies of vaccination and screening programs.

Human Leukocyte Antigen (HLA)-G interferes with HPV-infection; its prevalence, persistence and progression to cervical cancer [10–13]. HLA-polymorphism influences the innate and adaptive immune response by antigen presentation and are crucial to the cell-mediated immune (CMI) response by clearing the virus [14]. These different HLA-types are divided into classical and non-classical, where HLA-G alleles represent the non-classical class Ib [15]. HLA-G is highly tissue-specific and has a very low degree of polymorphism compared to the other HLA-molecules [16]. Recent studies have revealed HLA-G to play a

Abbreviations: HPV, human papillomavirus; HLA, human leukocyte antigen; STI, sexually transmitted infection; HR, high-risk; LR, low-risk; FFHPV cohort, Finnish Family HPV cohort; PCR, polymerase chain reaction; CMI, cell-mediated immune

* Corresponding author at: Department of Obstetrics and Gynecology, Turku University Hospital, University of Turku, Kiinanmyllynkatu 4-8, 20521 Turku, Finland.
E-mail addresses: karolina.louvanto@utu.fi (K. Louvanto), michel.roger.chum@ssss.gouv.qc.ca (M. Roger), marie-claude.faucher.chum@ssss.gouv.qc.ca (M.-C. Faucher), kari.syrjanen@biohit.fi (K. Syrjänen), seija.grenman@tyks.fi (S. Grenman), stina.syrjanen@utu.fi (S. Syrjänen).

https://doi.org/10.1016/j.humimm.2018.03.002
Received 18 October 2017; Received in revised form 6 March 2018; Accepted 6 March 2018

significant role in female reproduction, including pregnancy complications like miscarriage, preterm birth, pre-eclampsia and recurrent spontaneous abortions [17]. On the other hand, HLA-G has also been associated with different cancers e.g. by facilitating their escape from immune surveillance [18].

With its preferential expression at the maternal-fetal interface and its immunosuppressive properties, HLA-G has proved to be important in the mother-to-child transmission of HIV-infection [19–22]. These studies have reasoned that children have a natural protection against HIV-transmission provided by a HLA-G polymorphism, as suggested by the fact that a large proportion of children remain HIV-1 uninfected even if their mother had not been on any antiretroviral therapy. Interestingly enough, it was discovered that the vertical transmission of HIV-1 virus from a mother to her child increases when both are HLA concordant [19,20,22].

In our Finnish Family HPV (FFHPV)-cohort, we recently described a close mother-child concordance in HPV-genotype distribution at birth [23]. The most likely transmission route to the child was speculated to be via placenta or cord blood [23]. In the present study, we investigated the impact of HLA-G and its allele concordance in the mother-to-child transmission of HPV in the mother-child pairs of the FFHPV-cohort. Our hypothesis was that HLA-G allele concordance would predict the vertical transmission of HPV.

2. Materials and methods

2.1. Finnish Family HPV-study

The FFHPV-study is a longitudinal cohort followed-up at University of Turku and Turku University Hospital, Turku(Finland) as described previously [24,25]. At baseline (36-week of pregnancy), 329 families were enrolled, comprising 329 mothers, 131 fathers and 331 newborns, subsequently followed up (FU) for 6 years. All the families were Caucasian origin, have the same ethnic background and are representative of Finnish population. The study protocol and its amendment (#2/1998 and #2/2006) have been approved by the Research Ethics Committee of Turku University Hospital. All parents gave their written consent for the study. The 310 mother-child pairs analyzed in the present study comprise a sub-cohort of the FFHPV-study.

2.2. Samples

Genital and/or oral scrapings from the mothers and their newborns were collected for HPV-testing with a cytobrush (MedScand, Malmö, Sweden) as described before [24,25]. HPV was detected with nested polymerase chain reaction (PCR) using My09/My11 and GP05+/GP06+-primers [26]. Every 8th sample was a negative control to detect any contamination during the isolation and PCR. HPV genotyping was done by Luminex-based Multimetrix kit (Progen Biotechnik GmbH, Heidelberg, Germany), which detects 24 low-risk (LR)- and high-risk (HR)-HPV genotypes (LR-HPV:6,11,42,43,44 HR-HPV: 16,18,26,31, 33,35,39,45,51,52,53,56,58,59,66,68,70,73,82) [27]. All HPV16 positive samples were retested using the original sample for nested PCR as above and tested for HPV16 with our in-house bead based assay as described earlier [27]. Genomic DNA for HLA-G typing was isolated from frozen blood of the mothers and their children using MagNA Pure 96 System (Roche). 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 by Ferguson et al. [10].

2.3. Statistical analysis

Stata13.0 (Stata Corp., College Station, TX) was used for all statistical analyses. HPV types were categorized into two groups based on their phylogenetic relatedness: α1 group as LR-HPV (6,11,42,43,44) and α2 group as HR-HPV types (16,18,26,31,33,35,39,45,51,52, 53,56,58,59,66,68,70,73,82) [28]. HPV-status of the mothers (genital and oral) as well as that of the placenta and cord blood at birth was compared to the oral HPV-status of her child at birth and in perinatal period. In assessing the child's HPV prevalence at birth, the results of both the samples taken at delivery and those taken at day 2–3 (release from the hospital) were pooled, while the perinatal period covered the HPV-status at FU-visits at 1-, 2- and 6-months. HPV-prevalence was calculated as the proportion of HPV-positive mother-child pairs of all pairs. Calculating HPV-concordance, only those mother-child pairs were considered that have an opportunity for infection (i.e., both partners infected vs. those pairs having the opportunity for the infection). HLA-G concordance was considered when two alleles of the child matched the two alleles of the mother. If the mother was homozygous at HLA-G, she was also considered to be concordant with her child, because the child has no foreign HLA-G antigens.

HLA-G analyses were explored both in high and low resolution. The low resolution groups were G*01:01+ (including G*01:01:01, *01:01:02, *01:01:03, and *01:01:14) and G*01:04+ (including *01:04:01 and *01:04:04), respectively. To estimate the effect of each HLA-G genotype and allele, we included those HLA-genotypes and alleles that were > 3% prevalent between the mother and her child. The association between 1) within mother and her child sharing HLA-G genotype or alleles and 2) HPV prevalence and concordance (among the pairs that were HPV-positive), were analyzed using unconditional logistic regression for HLA level sharing. Analyses we done by using generalized estimation equations (GEE) model, clustered according to the cases id numbers and run in univariate mode with logistic link for grouped HPV-types [29].

3. Results

A total of nine different HLA-G alleles were identified among these 310 mother-child pairs, (Fig. 1b). The most common HLA-G alleles among the mothers and children was G*01:01:01; 83.9% (n = 260) and 84.8% (n = 263); followed by G*01:01:02; 39.7% (n = 124) and 37.0% (n = 115), respectively. The HLA-G genotype concordance and allele distribution among the 310 mother-child pairs are shown in Fig. 1. The most commonly shared allele was G*01:01:01, for which 76.5% (n = 237) of the pairs were at least both heterozygous, followed by other alleles that were shared between 0.3% (n = 1) and 23.2% (n = 72) among the pairs, respectively. The most commonly discordant allele between the pairs was G*01:01:02 by 30.3% (n = 94). From the HLA-G alleles a total of 22 different HLA-G genotypes were identified among the mother-child pairs. The most commonly concordant genotype between the mother and her child was G*01:01:01/01:01:01; 31.3% (n = 97) followed by G*01:01:01/01:01:02; 11.3% (n = 35), respectively. Overall, 58.4% of the mother-child pairs had a concordant HLA-G genotype (any genotype) (Fig. 1a).

The HPV genotype-specific prevalence among the mother and her offspring at birth and during the perinatal period have been reported earlier [23]. The prevalence of any oral HPV in newborn at birth and perinatal period was 32.1% (n = 99/308) and 38.2% (n = 116/304), respectively. HR-HPV genotypes were more common than the LR-HPV genotypes both in the mothers and the infants [23]. Any HPV concordance between a) the newborn's oral HPV, and b) mother's genital, c) mother's oral, d) placenta and e) cord blood was 10.3%, 25%, 10.5% and 4.8%, respectively (data not shown).

To investigate the impact of HLA–G genotype or allele in the mother-to-child HPV-transmission, both the genotype-specific HPV prevalence and concordance among the mother-child pairs were assessed. For different HLA-G alleles, we compared those mother-child pairs who tested positive for a particular allele (both the mother and child either heterozygous or homozygous) to those pairs with discordant HLA-G alleles (only the mother or the child had the allele). The mother-child pairs with both parties being negative for these specific alleles served as the reference.