Int J Clin Exp Pathol 2018;11(2):748-756
www.ijcep.com /ISSN:1936-2625/IJCEP0062778

Original Article

Association of HLA-DRB1/DQB1 polymorphism with high-risk HPV infection and cervical intraepithelial neoplasia women from Shanghai

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Received August 1, 2017; Accepted September 28, 2017; Epub February 1, 2018; Published February 15, 2018

Abstract: Persistent human papillomavirus (HPV) infection is the main causative agent for cervical intraepithelial neoplasia (CIN) and cancer. Variability in host immunogenetic factors is important in determining the overall cellular immune response to the HPV infection. This study was carried out to confirm the association of human leukocyte antigen (HLA) class II DRB1 and DQB1 alleles with CIN and HPV persistent infections in women from Shanghai in a case-controlled study. A total of 170 patients, including 105 HPV positive patients and 65 HPV negative women (control) participated in the study. HybriBio's proprietary flow-through hybridization technique was used to perform HPV genotyping. Low-resolution PCR-sequence specific priming (PCR-SSP) was used to genotype HLA class II for DRB1 and DQB1 loci. Binary and multivariate logistic regression analysis highlighted the association of specific alleles with CIN and HPV persistent infections after adjusting for the confounding factor of age. HLA-DQB1*02 and *06 is significantly associated with increased risk of HPV16 persistent infection (P_c < 0.013). HLA-DRB1*09 is significantly associated with increased risk for CIN, whereas the -DRB1*16 exhibit protective to CIN (P < 0.05). Significant association is found for HLA-DQB1*04 and *06 with increased risk for CIN (P < 0.05). There were possible associations of specific HLA class II alleles either with risk of persistent HPV infection or with developing CIN.

Keywords: HLA-DRB1/DQB1, polymorphism, persistent human papillomavirus infection, cervical intraepithelial neoplasia

Introduction

Cervical cancer is the second most frequent case of cancer in women with more than 500,000 new cases leading to about 270,000 deaths worldwide annually, among which occur in 40 million CINs and 160 million HPV infections [1, 2]. Cervical cancer is one of the 10 most common diseases affecting women with approximately 75,500 new cases (15.1% of all cervical cancer worldwide) and 34,000 deaths (12.6%) per year in China annually [3, 4]. Persistent HPV infection plays an important role in the development of CIN and cervical cancer [5]. HPV persistence is defined as the shortest duration of HPV positivity period as 6 to 12 months for most studies [6]. Although the average national estimates of the cervical cancer burden in China are low, the burden may be underestimated because the prevalence of the human papillomavirus (HPV) is high (16.8%) [7, 8]. HPV types 16 and 18 are predominant genotypes contributing to cervical cancer worldwide, while other high-risk (HR) genotypes such as HPV 31, 45 and 58 are mainly associated with CIN and cervical cancer [9, 10]. In Asian countries, HPV18 is not the most common genotype, and our previous results suggested that HPV16, 52 and 58 are the most common genotype in women from Shanghai [11-13].

Interestingly, the incidence of HR-HPV infection far exceeds the number of individuals who develop HPV-associated CIN and cervical cancer, with 95% of HR-HPV infections of the cervix resolving spontaneously within 1 to 2 years as a result of cell-mediated immunity, which indicates that HPV infection is a necessary but not

sufficient risk factor for persistent infection and CIN from the transient infections [14, 15]. Host genetic differences in the effective host immune response may influence the risk for cervical cancer among those infected with HPV [16]. Consequently, it's important to identify biomarkers for distinguishing women with HPV positivity who might develop persistent infection and CIN from the transient infections.

Over the past few decades, researchers have found that the most important Single nucleotide polymorphisms on the genetic susceptibility of cervical cancer were located in 6q12 by candidate gene association and genome-wide association studies, within the human leukocyte antigen (HLA) [17, 18]. The human major histocompatibility complex (MHC) is a multigene including the highly polymorphic human leucocyte antigen (HLA) class I (HLA-A, HLA-B, HLA-C) and II genes (HLA-DR, HLA-DQ, HLA-DP) that code different types of glycoproteins. These glycoproteins are specialized in the presentation of short peptides derived from infectious agents or self-proteins to T lymphocytes, and play a key role in both the cellular and humoral immune responses [19, 20]. The HLA-II (DRB1) gene contains many mutations, and these mutations result in changes of the amino acid sequence of HLA-II. Studies have reported that HLA-II (DRB1) is strongly associated with cervical cancer [21]. Polymorphisms in HLA-II complex variation susceptibility to long-term viral infections such as HIV, EBV, hepatitis B and C have been reported [22-26]. The correlation between HLA-II gene subtype and high risk HPV persistent infection has not been reported in Shanghai, China.

In this study, we performed a case-controlled study to explore the association between the immunogenotype of HLA genes and the risk of HR-HPV persistent infection and CIN in women from Shanghai.

Materials and methods

Clinical samples

We investigated the association of HLA class II (DRB1 and DQB1) alleles with susceptibility to HPV persistent infection and HPV-associated CIN in a hospital-based case-control study. A total of 105 patients, comprising of 78 CINs and 27 HPV positive without lesion cases, participated in the study. The patients were recruited from Cervical Disease Centre of Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine (Shanghai, China), with histopathology confirmed pre-cancer of the uterine cervix. The patients had a mean age of 41.2±12.3 years, whereas the controls without HPV infection were 42.8±11.2 years old. The age and ethnicity matched the control group consisting of 65 healthy women with no self or familial history of any neoplastic diseases were selected from patients who came into the Cervical Disease Centre of Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine (Shanghai, China) for routine check-ups.

Ethics approval and consent to participate

This study was approved by the ethics committee of the University of Shanghai First Maternity and Infant Health Hospital (No: KS 1533), Tongji University School of Medicine. Written, informed consent had been obtained from the reported patients.

Genomic DNA isolation

DNA from cervical cell brush samples was purified by silica gel columns (TIANamp Genomic DNA Kit No: 3304-9) according to the manufacturer's procedure. Final elution of DNA was performed in 50 μL of distilled water. And the concentration (C) ≥ 80 ng/μL was used to the latter experiment.

HPV detection and typing

The HPV GenoArray test kit (HybriBio Ltd) was used to perform Human papillomavirus genotyping [13]. It was used in both DNA amplification and HybriBio's proprietary flow-through hybridization technique. HPV Blot contains 21 types of genotypes, including 5 low-risk types (6, 11, 42, 43, and 44), 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), and 2 intermediate-risk types (CP8304 and 53) common in Chinese people.

HLA typing

Low-resolution PCR-sequence-specific priming (SSP) was used for the amplification of HLA DR-DQ alleles in both the cases and the controls (Morgan™ HLA SSP DRB Typing Kit, DQB Low SSP Morgan™ Kit) according to the manufacturer's instructions.

Table 1. HLA-DQB1* alleles associated with HPV Persistent Infection

HLA-DQB1	HPV16 (N=47)		no-HPV16 (N=58)		Total Cases (N=105)		Controls (N=65)		*P* values	OR	95% CI	p_c value
	n	Af (%)	n	Af (%)	n	Af (%)	n	Af (%)				
*02	23	24.47	11	9.48	34	16.19	12	9.23	**0.003**[a]			**0.013**
									0.633[b]			
									0.067[c]			
									0.031[d]			
*03	37	39.36	52	44.83	89	42.38	66	50.77	0.231[a]			
									0.46[b]			
									0.716[c]			
									0.043[d]	**0.393**	**0.159-0.972**	
*04	5	5.32	7	6.03	12	5.71	8	6.15	0.067[a]			
									0.125[b]			
									0.054[c]			
									0.685[d]			
*05	6	6.38	18	15.52	24	11.43	23	17.69	0.384[a]			
									0.477[b]			
									0.359[c]			
									0.83[d]			
*06	23	24.47	28	24.14	51	24.29	21	16.15	**0.009**[a]	**4.198**	**1.432-12.31**	**0.013**
									0.212[b]			
									0.03[c]	**2.327**	**1.083-5.002**	
									0.1[d]			

n, n=2N, number of alleles; Af, allelic frequency; OR, odds ratio; CI, confidence interval; OR, odds ratio; CI, confidence interval; P_c, corrected *P* value after applying Bonferroni's correction; *P* value, probability from logistic regression analysis after adjusting for the confounding factor of age comparing the haplotype frequency distribution among the following: [a]HPV16 infection cases versus controls; [b]no-HPV16 infection versus controls; [c]total cases versus controls; and [d]HPV16 infection versus no-HPV16 infection. Bold type refers to statistically significant results.

Statistical analysis

Binary and multivariate logistic regression analysis was applied to compare the number of cases and controls who were positive for HLA DR-DQ alleles. Allelic frequencies; odds ratios (OR) with respective 95 per cent confidence intervals were estimated using the SPSS software version 20.0 (SPSS, Chicago, Il, USA). Multivariate analysis highlighted the association of specific alleles with CIN and HPV persistent infection after adjusting for the confounding factor of age. $P_c < 0.013$ is considered statistically significant.

Results

HPV typing

Of the 105 women with identified persistent HPV infection, HPV type 16 was the most common type (44.8%, 47/105). HPV co-infection with two or three different types were 40, 38.1%. Women with HPV 16/52/58 co-infection were 34, 32.4%, and 65 HPV negative women participated in the study. (**Tables 1** and **2**) **Figure 3** depicts the representative gel picture for low-resolution PCR-SSP analysis for the HLA DRB1-DQB1 region.

Distribution of HLA-DRB1 and HLA-DQB1* alleles in case-controlled study population*

HLA DRB1 and DQB1 typing was completed in all 105 cases (HPV positive) and 65 controls (HPV negative). There were 14 HLA-DRB1 and 5 HLA-DQB1 alleles identified among 170 women, including 105 cervical patients and 65 control subjects (**Figures 1**, **2**). The allelic distribution for the HLA DQB1 locus revealed DQB1*03 was the most frequent allele both in cases (42.4%; 89/210) and in controls (50.8%; 66/130). The allelic distribution for the HLA DRB1 locus revealed DRB1*09 was the most frequent allele in HPV-positive cases (19.1%; 40/210) and controls (16.9%; 22/130).

Table 2. HLA-DRB1* alleles associated with HPV Persistent Infection

HLA-DRB1	HPV16 (N=47)		no-HPV16 (N=58)		Total Cases (N=105)		Controls (N=65)		*P* values	OR	95% CI	p_c value
	n	Af (%)	n	Af (%)	n	Af (%)	n	Af (%)				
*01	1	1.06	4	3.45	5	2.38	1	0.77	0.526			
									0.27			
									0.188			
									0.736			
*02	1	1.06	0	0	1	0.48	0	0	1.0			
									0.107			
									1.0			
*03	9	9.57	4	3.45	13	6.19	5	3.85	1.0			
									0.155			
									1.0			
									1.0			
*04	10	10.64	12	10.34	22	10.48	18	13.85	1.0			
									0.772			
									0.103			
									1.0			
*07	12	12.77	8	6.9	20	9.52	11	8.46	1.0			
									0.898			
									0.372			
									1.0			
*08	8	8.51	12	10.34	20	9.52	7	5.38	1.0			
									0.824			
									0.177			
									1.0			
*09	16	17.02	24	20.69	40	19.05	22	16.92	1.0			
									0.228			
									0.067			
									1.0			
*10	1	1.06	3	2.59	4	1.9	3	2.31	1.0			
									0.448			
									0.154			
									1.0			
*11	5	5.32	10	8.62	15	7.14	13	10	1.0			
									0.641			
									0.45			
									1.0			
*12	9	9.57	6	5.17	15	7.14	15	11.54	1.0			
									0.768			
									0.427			
									1.0			
*13	2	2.13	2	1.72	4	1.9	9	6.92	1.0			
									0.643			
									0.532			
									1.0			
*14	6	6.38	10	8.62	16	7.62	11	8.46	1.0			
									0.353			

									0.751			
									1.0			
*15	14	14.89	18	15.52	32	15.24	10	7.69	1.0			
									0.625			
									0.285			
									1.0			
*16	0	0	3	2.59	3	1.43	5	3.85	1.0			
									0.186			
									0.04	**0.187**	**0.038-0.927**	**0.013**
									1.0			

n, n=2N, number of alleles; Af, allelic frequency; OR, odds ratio; CI, confidence interval; OR, odds ratio; CI, confidence interval; ud, undetermined. P_c, corrected *P* value after applying Bonferroni's correction; *P* value, probability from logistic regression analysis after adjusting for the confounding factor of age comparing the haplotype frequency distribution among the following: [a]HPV16 infection cases versus controls; [b]no-HPV16 infection versus controls; [c]total cases versus controls; and [d]HPV16 infection versus no-HPV16 infection. Bold type refers to statistically significant results.

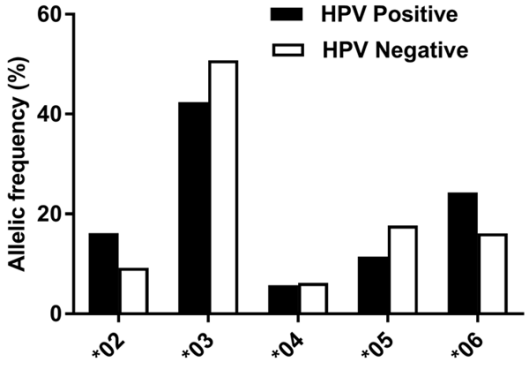

Figure 1. Distribution of HLA-DRB1* alleles in case-control study population. 14 HLA-DRB1 alleles were identified among 170 women, including 105 HPV-positive patients and 65 HPV-negative subjects from Shanghai. The HLA-DRB1*09 was the most frequent allele in HPV-positive cases (19.1%; 40/210) and controls (16.9%; 22/130).

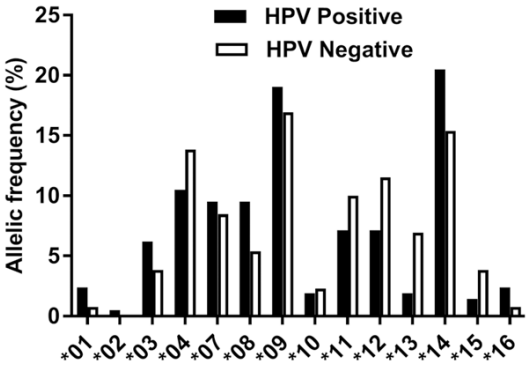

Figure 2. Distribution of HLA-DQB1* alleles in case-control study population. 5 HLA-DQB1 alleles were identified among 170 women, including 105 HPV-positive patients and 65 HPV-negative subjects from Shanghai. HLA-DQB1*03 allele was the most frequent allele both in cases (42.4%; 89/210) and in controls (50.8%; 66/130).

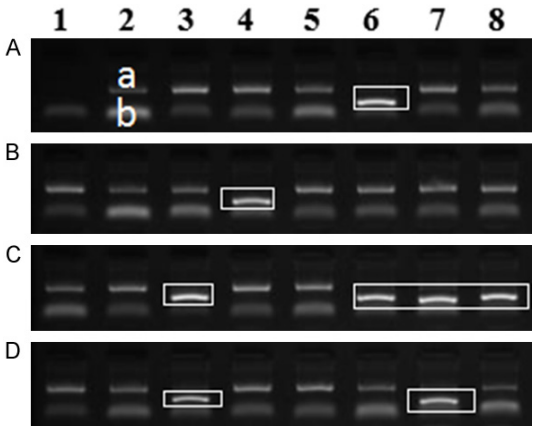

Figure 3. A representative 2% agarose gel picture showing PCR products of low resolution PCR-SSP analysis for the HLA DR-DQ region. (A-C): Correspond to HLA DRB1* alleles; (D): Corresponds to HLA DQB1* alleles, a corresponds to control band, b corresponds to control band Primer dimer band. 1 (A), contamination control. The internal control fragment is 600 bp in size. The DNA fragments amplified by allele- or group-specific primer pairs are designed to have a size in the range between 70-275 bp (shown in white rectangle). Refer to the worksheet for the exact size of the specifically amplified DNA fragment in each reaction tube. The positive wells of (A-C) are 6, 12, 19, 22, 23, 24; the positive wells of (D) are 3, 7. Document the positive reactions for the test and determine the HLA types by using the worksheet provided.

HLA-DRB1/DQB1 polymorphisms associated with HPV persistent infection

HLA-DQB1*02 and *06 were significantly associated with increased risk for HPV16 persistent infection (P_c < 0.013). A positive association was also established for the DQB1*02 and *03 allele with respect to HPV infection, for the

Table 3. HLA-DQB1* alleles associated with Cervical Intraepithelial Neoplasia

HLA-DQB1	Cases (N=78)		Controls (N=65)		*P* values	OR	95% CI
	n	Af (%)	n	Af (%)			
*02	21	13.46	12	9.23	0.06		
*03	63	40.38	66	50.77	0.688		
*04	10	6.41	8	6.15	0.014	2.195	1.176-4.097
*05	18	11.54	23	17.69	0.342		
*06	44	28.21	21	16.15	0.017	2.677	1.195-5.998

n, n=2N, number of alleles; Af, allelic frequency; OR, odds ratio; CI, confidence interval; *P* value, probability from logistic regression analysis after adjusting for the confounding factor of age comparing the haplotype frequency distribution among CIN and controls.

Table 4. HLA-DRB1* alleles associated with Cervical Intraepithelial Neoplasia

HLA-DRB1	Cases (N=78)		Controls (N=65)		*P* values	OR	95% CI
	n	Af (%)	n	Af (%)			
*01	2	1.28	1	0.77	0.0620		
*02	0	0	0	0			
*03	8	5.13	5	3.85	0.161		
*04	16	10.26	18	13.85	0.0920		
*07	14	8.97	11	8.46	0.1940		
*08	18	11.54	7	5.38	0.113		
*09	33	21	22	17	0.031	0.078	0.008-0.79
*10	4	2.56	3	2.31	0.074		
*11	11	7.05	13	10	0.155		
*12	8	5.13	15	11.54	0.217		
*13	1	0.64	9	6.92	0.406		
*14	16	10.26	11	8.46	0.699		
*15	24	15.38	10	7.69	0.0880		
*16	1	0.64	5	3.85	0.032	0.1	0.009-0.807

n, n=2N, number of alleles; Af, allelic frequency; OR, odds ratio; CI, confidence interval; *P* value, probability from logistic regression analysis after adjusting for the confounding factor of age comparing the haplotype frequency distribution among CIN and controls.

DQB1*06 allele in HPV16 infection compared with no-HPV16 infection cases. After application of Bonferroni's correction, statistical significance were not retained (P_c=0.013) (**Table 1**). A positive association was also established for the DRB1*16 allele in HPV16 infection compared with no-HPV16 infection cases. After application of Bonferroni's correction, statistical significance were not retained (P_c=0.013) (**Table 2**).

HLA-DRB1/DQB1 polymorphisms associated with CIN

HLA-DQB1*04 and *06 were significantly associated with increased risk for CIN ($P < 0.05$) (**Table 3**). Significant association was found for HLA-DRB1*09 with increased risk for CIN ($P < 0.05$). Conversely, the allele frequencies for DRB1*16 among cases was significantly lower than that among control subjects, thereby indicating their protective effect ($P < 0.05$) (**Table 4**).

Discussion

In this study, we identified the high risk HLAII allelic associated with HR HPV persistent infection. This is the first comprehensive study in women from Shanghai. Approximately 80% of the female population is exposed to HPV sometime in their life, but the infection is usually transient, with 70-90% of infected individuals 'clearing' the virus (HPV DNA undetectable by assays) within 6-12 months [27]. Fewer than 4% of individuals infected with HPV develop persistent infections and CIN and even fewer proportion (1-2%) will progress to cervical cancer [28, 29]. Therefore in addition to HPV infection, other viral risk factors and host susceptibilities are required to initiate the transformation process [30, 31]. Significant associations were observed in the major histocompatibility complex region on chromosome 6 for influenza A virus, Epstein-Barr virus, JC polyomavirus, and Merkel cell polyomavirus. And common HLA-DRB1 haplotypes showed virus-specific patterns of humoral-response regulation [32].

In our study, of the 105 women with identified persistent HPV infection, HPV type 16 was the most common type (44.8%, 47/105). The frequency of HPV52 and HPV58 was 24.8% and 20%. HPV co-infection with two or three differ-

ent types were 40, 38.1%. Women with HPV 16/52/58 coinfection were 34, 32.4%. Our previous results suggested that HPV16 and 52, instead of HPV18, are the top two prevalent types in China [13, 33, 34].

There were 14 HLA-DRB1 and 5 HLA-DQB1 alleles identified among 170 women, including 105 cervical patients and 65 control subjects. The allelic distribution for the HLA-II locus revealed DRB1*09, and DQB1*03 was the most frequent allele in Shanghai population. HLA-DQB1*02 and *06 were significantly associated with increased risk for HPV16 persistent infection (P_c < 0.013). These results indicate that the HLAII allele is closely related to the persistent HPV infection.

HPV persistent infection is an essential factor in the development of cervical cancer, but not all of the persistent infections develop into cervical cancer. Some patients have persistent infection for many years but malignant transformations have not occurred. So we speculate that this may be related to the different HLA gene subtype. Sankhadeep Dutta1's data suggest persistent HPV16/18 infection in the cervix due to the presence of the HLA-DQB1*03 [35]. Hu JM's study suggests that HLA-DRB1*1501 and DQB1*0602 alleles may influence the immune response to HPV16 infection and decrease the risk of ICC among Uighurs and Hans in Xinjiang, China [36].

Our results show that HLA-DRB1*09, DQB1*04 and *06 were significantly associated with increased risk for CIN (P < 0.05). Conversely, the allele frequencies for DRB1*16 among cases was significantly lower than that among control subjects, thereby indicating their protective effect (P < 0.05). This is consistent with the results of previous studies [37].

Our study indicates that different polymorphic human leukocyte antigen (HLA) genes are involved in the clearance and maintenance of HPV infection. To fully evaluate the effects of the HLA class II alleles on the natural course of HPV persistent and cervical lesions, prospective studies with larger sample sizes and longitudinal design may be needed in various ethnic populations [38].

Acknowledgements

This work was supported by Shanghai Science and Technology Committee Foundation (Grant NO. 15411967700, 16411950200, 17441902500), National Natural Science Foundation of China (Grant NO. 81572546, 81771529), Shanghai Natural Science Foundation (Grant NO. 15ZR1433300).

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.

[2] Sudenga SL and Shrestha S. Key considerations and current perspectives of epidemiological studies on human papillomavirus persistence, the intermediate phenotype to cervical cancer. Int J Infect Dis 2013; 17: e216-220.

[3] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.

[4] Zhao FH, Lewkowitz AK, Hu SY, Chen F, Li LY, Zhang QM, Wu RF, Li CQ, Wei LH, Xu AD, Zhang WH, Pan QJ, Zhang X, Belinson JL, Sellors JW, Smith JS, Qiao YL and Franceschi S. Prevalence of human papillomavirus and cervical intraepithelial neoplasia in China: a pooled analysis of 17 population-based studies. Int J Cancer 2012; 131: 2929-2938.

[5] Cho HW, So KA, Lee JK and Hong JH. Type-specific persistence or regression of human papillomavirus genotypes in women with cervical intraepithelial neoplasia 1: a prospective cohort study. Obstet Gynecol Sci 2015; 58: 40-45.

[6] Rositch AF, Koshiol J, Hudgens MG, Razzaghi H, Backes DM, Pimenta JM, Franco EL, Poole C and Smith JS. Patterns of persistent genital human papillomavirus infection among women worldwide: a literature review and meta-analysis. Int J Cancer 2013; 133: 1271-1285.

[7] Levin CE, Sharma M, Olson Z, Verguet S, Shi JF, Wang SM, Qiao YL, Jamison DT and Kim JJ. An extended cost-effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China. Vaccine 2015; 33: 2830-2841.

[8] Wang SM and Qiao YL. Implementation of cervical cancer screening and prevention in China--challenges and reality. Jpn J Clin Oncol 2015; 45: 7-11.

[9] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, Tous S, Felix A, Bravo LE, Shin HR, Vallejos CS, de Ruiz PA, Lima MA, Guimera N, Clavero O, Alejo M, Llombart-Bosch A, Cheng-Yang C, Tatti SA, Kasamatsu E, Iljazovic E, Odida M, Prado R, Seoud M, Grce M, Usubutun A, Jain A, Suarez GAH, Lombardi LE, Banjo A, Menéndez C, Domingo EJ, Velasco J, Nessa A, Chichareon SCB, Qiao YL, Lerma E, Garland SM, Sasagawa T, Ferrera A, Hammouda D, Mariani L, Pelayo A, Steiner I, Oliva E, Meijer CJLM, Al-Jassar WF, Cruz E, Wright TC, Puras A, Llave CL, Tzardi M, Agorastos T, Garcia-Barriola V, Clavel C, Ordi J, Andújar M, Castellsagué X, Sánchez GI, Nowakowski AM, Bornstein J, Muñoz N and Bosch FX. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet Oncology 2010; 11: 1048-1056.

[10] Jalal Kiani S, Shatizadeh Malekshahi S, Yousefi Ghalejoogh Z, Ghavvami N, Shafiei Jandaghi NZ, Shahsiah R, Jahanzad I and Yavarian J. Detection and typing of human papilloma viruses by nested multiplex polymerase chain reaction assay in cervical cancer. Jundishapur J Microbiol 2015; 8: e26441.

[11] Natphopsuk S, Settheetham-Ishida W, Pientong C, Sinawat S, Yuenyao P, Ishida T and Settheetham D. Human papillomavirus genotypes and cervical cancer in northeast thailand. Asian Pac J Cancer Prev 2013; 14: 6961-6964.

[12] Quek SC, Lim BK, Domingo E, Soon R, Park JS, Vu TN, Tay EH, Le QT, Kim YT, Vu BQ, Cao NT, Limson G, Pham VT, Molijn A, Ramakrishnan G and Chen J. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical intraepithelial neoplasia across 5 countries in Asia. Int J Gynecol Cancer 2013; 23: 148-156.

[13] Suman S, Yu YY, Xu X, Huang X, Zhao J, Han L, Wang K, Sun J, Li F. Distribution of HPV genotypes in Shanghai women. Int J Clin Exp Pathol 2015; 8: 11901-11908.

[14] Remy-Ziller C, Germain C, Spindler A, Hoffmann C, Silvestre N, Rooke R, Bonnefoy JY and Preville X. Immunological characterization of a modified vaccinia virus Ankara vector expressing the human papillomavirus 16 E1 protein. Clin Vaccine Immunol 2014; 21: 147-155.

[15] Ivansson EL, Juko-Pecirep I, Erlich HA and Gyllensten UB. Pathway-based analysis of genetic susceptibility to cervical cancer in situ: HLA-DPB1 affects risk in Swedish women. Genes Immun 2011; 12: 605-614.

[16] Gokhale P, Kerkar S, Tongaonkar H, Chaudhari H, Warke H, Salvi V, Mania-Pramanik J. Variations in immunogenetics, human papillomavirus (HPV) infection & predisposition to cervical cancer in Indian women. Indian J Med Res 2014; 140 Suppl: S36-43.

[17] Hosono S, Kawase T, Matsuo K, Watanabe M, Kajiyama H, Hirose K, Suzuki T, Kidokoro K, Ito H, Nakanishi T, Yatabe Y, Hamajima N, Kikkawa F, Tajima K and Tanaka H. HLA-A alleles and the risk of cervical squamous cell carcinoma in Japanese women. J Epidemiol 2010; 20: 295-301.

[18] Madeleine MM, Johnson LG, Smith AG, Hansen JA, Nisperos BB, Li S, Zhao LP, Daling JR, Schwartz SM and Galloway DA. Comprehensive analysis of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci and squamous cell cervical cancer risk. Cancer Res 2008; 68: 3532-3539.

[19] Gough SC, Simmonds MJ. The HLA region and autoimmune disease: associations and mechanisms of action. Current Genomics 2007; 8: 453-65.

[20] The MHC sequencing consortium. Complete sequence and gene map of a human major histocompatibility complex. Nature 1999; 401: 921-3.

[21] Chan PK, Cheung JL, Cheung TH, Lin CK, Siu SS, Yu MM, Tang JW, Lo KW, Yim SF, Wong YF, To KF, Ng HK, Chung TK. HLA-DQB1 polymorphisms and risk for cervical cancer: a case-control study in a southern Chinese population. Gynecol Oncol 2007; 105: 736-741.

[22] Delahaye-Sourdeix M, Urayama KY, Gaborieau V, Veenstra R, Foll M, Chabrier A, Benavente Y, Nieters A, Becker N, Foretova L, Maynadie M, Staines A, Smedby KE, Glimelius I, Lightfoot T, Cocco P, Galan P, Vatten LJ, Duell EJ, Kiemeney L, Roman E, de Sanjose S, Lathrop M, Melbye M, Brennan P, Diepstra A, van den Berg A, Hjalgrim H, Jarrett RF and McKay JD. A novel risk locus at 6p21.3 for Epstein-Barr virus-positive Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2015; 24: 1838-1843.

[23] Jiang DK, Ma XP, Yu H, Cao G, Ding DL, Chen H, Huang HX, Gao YZ, Wu XP, Long XD, Zhang H, Zhang Y, Gao Y, Chen TY, Ren WH, Zhang P, Shi Z, Jiang W, Wan B, Saiyin H, Yin J, Zhou YF, Zhai Y, Lu PX, Zhang H, Gu X, Tan A, Wang JB, Zuo XB, Sun LD, Liu JO, Yi Q, Mo Z, Zhou G, Liu Y, Sun J, Shugart YY, Zheng SL, Zhang XJ, Xu J, Yu L. Genetic variants in five novel loci including CFB and CD40 predispose to chronic hepatitis B. Hepatology 2015; 62: 118-128.

[24] Ranasinghe S, Cutler S, Davis I, Lu R, Soghoian DZ, Qi Y, Sidney J, Kranias G, Flanders MD, Lindqvist M, Kuhl B, Alter G, Deeks SG, Walker BD, Gao X, Sette A, Carrington M and Streeck H. Association of HLA-DRB1-restricted CD4(+)

T cell responses with HIV immune control. Nat Med 2013; 19: 930-933.
[25] Urabe Y, Ochi H, Kato N, Kumar V, Takahashi A, Muroyama R, Hosono N, Otsuka M, Tateishi R, Lo PH, Tanikawa C, Omata M, Koike K, Miki D, Abe H, Kamatani N, Toyota J, Kumada H, Kubo M, Chayama K, Nakamura Y and Matsuda K. A genome-wide association study of HCV-induced liver cirrhosis in the Japanese population identifies novel susceptibility loci at the MHC region. J Hepatol 2013; 58: 875-882.
[26] Wank R, Thomssen C. High risk of squamous cell carcinoma of the cervix for women with HLA-DQw3. Nature 1991; 352: 723-725.
[27] Steenbergen RD, Snijders PJ, Heideman DA and Meijer CJ. Clinical implications of (epi) genetic changes in HPV-induced cervical precancerous lesions. Nat Rev Cancer 2014; 14: 395-405.
[28] Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998; 338: 423-428.
[29] Dalstein V, Riethmuller D, Pretet JL, Le Bail Carval K, Sautiere JL, Carbillet JP, Kantelip B, Schaal JP and Mougin C. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. Int J Cancer 2003; 106: 396-403.
[30] Shi Y, Li L, Hu Z, Li S, Wang S, Liu J, Wu C, He L, Zhou J, Li Z, Hu T, Chen Y, Jia Y, Wang S, Wu L, Cheng X, Yang Z, Yang R, Li X, Huang K, Zhang Q, Zhou H, Tang F, Chen Z, Shen J, Jiang J, Ding H, Xing H, Zhang S, Qu P, Song X, Lin Z, Deng D, Xi L, Lv W, Han X, Tao G, Yan L, Han Z, Li Z, Miao X, Pan S, Shen Y, Wang H, Liu D, Gong E, Li Z, Zhou L, Luan X, Wang C, Song Q, Wu S, Xu H, Shen J, Qiang F, Ma G, Liu L, Chen X, Liu J, Wu J, Shen Y, Wen Y, Chu M, Yu J, Hu X, Fan Y, He H, Jiang Y, Lei Z, Liu C, Chen J, Zhang Y, Yi C, Chen S, Li W, Wang D, Wang Z, Di W, Shen K, Lin D, Shen H, Feng Y, Xie X and Ma D. A genome-wide association study identifies two new cervical cancer susceptibility loci at 4q12 and 17q12. Nat Genet 2013; 45: 918-922.
[31] Stanley MA, Pett MR and Coleman N. HPV: from infection to cancer. Biochem Soc Trans 2007; 35: 1456-1460.
[32] Hammer C, Begemann M, McLaren PJ, Bartha I, Michel A, Klose B, Schmitt C, Waterboer T, Pawlita M, Schulz TF, Ehrenreich H and Fellay J. Amino acid variation in HLA class II proteins is a major determinant of humoral response to common viruses. Am J Hum Genet 2015; 97: 738-743.
[33] Zhong TY, Zhou JC, Hu R, Fan XN, Xie XY, Liu ZX, Lin M, Chen YG, Hu XM, Wang WH, Li L and Xiao HP. Prevalence of human papillomavirus infection among 71,435 women in Jiangxi Province, China. J Infect Public Health 2017; [Epub ahead of print].
[34] Zhao J, Guo Z, Wang Q, Si T, Pei S, Wang C, Qu H, Zhong J, Ma Y, Nie C and Zhang D. Human papillomavirus genotypes associated with cervical precancerous lesions and cancer in the highest area of cervical cancer mortality, Longnan, China. Infect Agent Cancer 2017; 12: 8.
[35] Dutta S, Chakraborty C, Mandal RK, Basu P, Biswas J, Roychoudhury S and Panda CK. Persistent HPV16/18 infection in Indian women with the A-allele (rs6457617) of HLA-DQB1 and T-allele (rs16944) of IL-1beta -511 is associated with development of cervical carcinoma. Cancer Immunol Immunother 2015; 64: 843-851.
[36] Hu J, Li L, Pang L, Chen Y, Yang L, Liu C, Zhao J, Chang B, Qi Y, Liang W and Li F. HLA-DRB1*1501 and HLA-DQB1*0301 alleles are positively associated with HPV16 infection-related Kazakh esophageal squamous cell carcinoma in Xinjiang China. Cancer Immunol Immunother 2012; 61: 2135-2141.
[37] Eiguchi K TS, Alonio LV, González JV, Leirós GJ, Fleider L, Vighi S, Padros K, Raimondi E, Teyssié A, Picconi MA. Association of DRB1 and DQB1 HLA class II polymorphisms in high-grade and neoplastic cervical lesions of women from Argentina. J Low Genit Tract Dis 2008; 12: 262-268.
[38] Matsumoto K, Maeda H, Oki A, Takatsuka N, Yasugi T, Furuta R, Hirata R, Mitsuhashi A, Fujii T, Hirai Y, Iwasaka T, Yaegashi N, Watanabe Y, Nagai Y, Kitagawa T, Yoshikawa H; for Japan HPV And Cervical Cancer (JHACC) Study Group. HLA class II DRB1*1302 allele protects against progression to cervical intraepithelial neoplasia grade 3: a multicenter prospective cohort study. Int J Gynecol Cancer 2012; 22: 471-478.