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A meta-analysis of association of Human Leukocyte Antigens A, B, C, DR and DQ with Human Papillomavirus 16 infection

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ABSTRACT

Human Papillomavirus (HPV) induced cervical cancer (CaCx) is a major health problem in women from both developing and developed regions of the world. This virus accounts for > 95% of the CaCx cases with a preponderance of HPV type −16 (65%). Paradoxically HPV-16 is prevalent even in the cervix of healthier women and anti HPV-16 T-cell response is considered critical for the viral clearance. Studies on HLA association with HPV-16 infection and cervical cancer have yielded varied HLA associations in different epidemiological settings. To validate these associations, we performed a meta-analysis of HLA-A, B, C, DR and DQ association with HPV-16 infection. Of the 1409 studies retrieved, 26 qualified for meta-analysis based on stringent inclusion and exclusion criteria.

HLA-B*47, B*57, DRB1*10, DRB1*15 and DQB1*0303 were significantly associated with HPV-16 infection (OR = 3.4, 1.8, 1.5, 1.1 and 1.5 respectively). HLA-B*49, B*39, A28 (serotype), C*04 and DRB1*13 were negatively associated with HPV-16 (OR = 0.5, 0.6, 0.7, 0.7, and 0.7 respectively). Certain HLA alleles such as B*07, DRB1*15, DRB1*11 and DRB1*07 showed weakly positive associations. A comprehensive analysis coupling HPV-16 antigenic diversity and the HLA variation in various global populations shall provide further insights into the immunogenetic predisposition to HPV-16 and shall help identify host-parasite co-evolution.

1. Introduction

Cervical Cancer (CaCx) is the fourth common type cancer in women, with 270,000 deaths reported in 2015 (WHO, 2018). The major causative agent of CaCx is the Human papillomavirus (HPV) infection. HPV can however cause a wide range of manifestations ranging from genital warts, skin lesions to oral and cervical malignancies. Taxonomically, HPV has been classified based on the genetic variations of their capsid protein L1 (de Villiers et al., 2004). Further, based on the nature of the disease caused, HPV strains have been broadly classified into two groups: High Risk (HR) (HPV types- 16, 18, 31, 35, 39, 45, 51, 52, 56, 59, 66, 68, 69, 73 and 82) and Low Risk (LR) (types – 6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81) (Chan et al., 1995; Munoz et al., 2003). The HR HPVs generally cause pre-malignant lesions and cervical & oral malignancies, while the LR types cause non-malignant lesions and warts (Pillai et al., 2009). HPV-16 and 18 put together account for 80% of CaCx cases world over (Li et al., 2011). Paradoxically, these are also seen in 4–7% of cytologically normal women (Bruni et al., 2010).

HPV-16 has a tropism for keratinocytes and infects the basal layers of stratified squamous epithelium. Though the virus is initially cleared off by innate and adaptive immune mechanisms, suboptimal $CD4^+$ & $CD8^+$ T cell responses, persistent sub-clinical viral infection and the integration of the viral genome into the host cell are considered as precipitating factors leading to cancer (Garcia-Chacon et al., 2009; Zheng and Baker, 2006). It is known that in most of the viral infections including HIV, Hepatitis-B, Dengue etc., Major Histocompatibility Complex (MHC) restriction phenomenon and Cytotoxic T-lymphocyte (CTL) generation are considered as an important contributor in developing resistance or disease (Leslie et al., 2006). The MHC of humans called Human Leukocyte Antigen (HLA) is categorised into two major classes: HLA Class I (HLA-A, B and C) present intracellular pathogen and altered self-antigens to $CD8^+$ T cells while HLA Class II (HLA-DR, DP, DQ) present exogenous antigens to $CD4^+$ T cells. At the populations level individuals possess a variety of HLA alleles, hence do they respond the same way to a given antigen. HLA genes, the most polymorphic loci in the human genome, are highly disparate among the various continental and regional populations.

Many studies have reported HLA Class I and Class II allele associations with both CaCx and HPV-16 infection. HLA-B*07, B*44, B*51 and B*57 associations with HPV related cervical cancers have been

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reported in various populations, and these associations transcended the ethnic barrier (Bhattacharya and Sengupta, 2007; Chan et al., 2006; Hernandez-Hernandez et al., 2009; Zehbe et al., 2003). Among HLA A alleles, A*32, A*01 and A*02 alleles were associated with HPV-16 while A*11 was negatively associated (Saito et al., 2007; Zehbe et al., 2003). Among the class II HLA alleles, HLA DRB1*01, DRB1*08, DRB1*10, DRB1*15 were positively associated with HPV-16 (Chan et al., 2007; Kohaar et al., 2009; Madeleine et al., 2002; Mahmud et al., 2007; Saito et al., 2007; Wu et al., 2007) while DRB1*13 was negatively associated (Kohaar et al., 2009; Saito et al., 2007). HLA DQB1*05, DQB1*06 and DQ9 serotype (DQB1*0303) were associated with HPV-16 infection (Chan et al., 2007; de Araujo Souza et al., 2008; Kohaar et al., 2009; Saito et al., 2007). While some associations were valid in many studies, some other associations were not consistent in different populations. For example HLA-B*07 has shown a positive association with HPV-16 in East Indian, Chinese and Japanese populations, while it showed a negative association in Minnesotan and Mexican populations (Bhattacharya and Sengupta, 2007; Chan et al., 2006; Hernandez-Hernandez et al., 2009; Saito et al., 2007; Zehbe et al., 2003). Similarly HLA DRB1*15 showing a positive association in Indian, Chinese and Canadian populations was not identified in American, French and the Dutch studies (Bontkes et al., 1998; Chan et al., 2007; Hildesheim et al., 1998; Kohaar et al., 2009; Mahmud et al., 2007; Sastre-Garau et al., 1996). Thus a given allele showing a consistent association in various populations shall be interpreted as HLA dependent phenomenon may be responsible for the disease, while varied alleles showing associations in disparate populations may mean involvement of these different alleles in the disease association or a locus in strong linkage to these alleles as responsible for the disease. This need to be however interpreted in the context of the prevalence of various HPV clades in the circulation, cross reactivity, HPV-16 antigenic variation at the population level in different continents.

Other common causes of inconsistencies in HLA genetic association studies across the globe include variations in the sample size, ethnicity, case-control selection, stages of the disease and other unknown confounders. In this regard, meta-analysis offers an efficient way to overcome such variations and to identify meaningful patterns in the data compiled from multiple and disparate studies. Higher sample size in meta-analysis in general gives increased statistical power (Blettner et al., 1999). The study reported here presents the results of our meta-analysis on the HLA-A, B, C, DR, and DQ allele association with HPV-16 infection. To our knowledge our paper presents for the first time a comprehensive meta-analysis of association of major HLA Class-I and II alleles with HPV-16 infection.

2. Materials and methods

2.1. Literature search strategy

We performed a Literature search in PubMed and SCOPUS databases, using the key words “Human Papillomavirus AND Human Leukocyte Antigen”, “HPV AND HLA”, “Cervical cancer AND HLA”. A total of 1409 studies showed up and we applied stringent inclusion and exclusion criteria for selecting the articles for meta-analysis.

2.2. Article selection and meta-data extraction

The articles were selected only if these were case-control designs on HPV-16 infection and HLA allele association. Studies that showed association of HLA alleles with persistent HPV-16 infection (HPV-16 + ve for at least 2 years), cervical neoplasia with HPV-16 or cervical malignancy with HPV-16 were included in the meta-analysis. Exclusion criteria were (i) articles not having case-control study design, or ill-defined cohorts (ii) studies without HPV-16 genotyping information, (iii) association studies on non-HLA genes and HLA genes other than HLA-A, B, C, DRB & DQB (iv) Review Articles and (v) articles written in non-English language. The selected studies were scaled as per the guidelines of Newcastle-Ottawa scale for the assessment of the quality of non-randomized studies in meta-analyses (Stang, 2010; Wells et al., 2014). The meta-data thus compiled included number of cases & controls, HLA-A, B, C, DRB, DQB genotypes and allele frequencies, Odds ratios (OR) and its 95% Confidence Interval (CI) and the population on which the study was performed.

2.3. Statistical analysis

The association of HLA-A, B, C, DRB and DQB alleles with HPV-16 infection was determined by Odds Ratio (OR) and its 95% CI. The reliability of the combined OR was tested using *Z*-statistic and a 2 tail *P* value of ≤ 0.05 was considered to be significant. Heterogeneity analysis was performed using Q and I^2 statistics (Bowden et al., 2011; Higgins and Thompson, 2002). Fixed effect model of meta-analysis was used if heterogeneity was low (P value of Q test ≥ 0.05 and $I^2 < 50\%$) while random effect model was used if heterogeneity was high (P value of Q test ≤ 0.05 and $I^2 > 50\%$) (Borenstein et al., 2010; Mantel and Haenszel, 1959). The meta-analysis was represented using forest plots. Publication bias between studies was tested using Egger's test and Begg's test (Begg and Mazumdar, 1994; Egger et al., 1997). Publication bias was considered to be low/nil if the P value of these tests were non-significant ($P \geq 0.05$). All statistical analyses were performed using Metafor package in R v3.4.3 (R Core Team, 2017; Wolfgang, 2010).

3. Results

3.1. Study selection and their characteristics

A total of 1409 studies that reported associations of Human Leukocyte Antigen (HLA) polymorphisms with Human Papillomavirus (HPV) infection were retrieved and meta-analysis performed as per the PRISMA guidelines for meta-analysis (Liberati et al., 2009). The year of publication of the screened articles ranged from 1985 to 2017. The flow chart of selection of studies for the meta-analysis is given in Fig. 1. A total of 26 studies comprising 2386 cases and 8392 controls qualified for meta-analysis (Supplementary Table 1). The NOS scale for the selected 26 studies ranged from 7 to 9.

3.2. Meta-analysis of HLA – Class I genes in HPV-16 infection

The present analysis defined 16 HLA- A, 28 HLA-B and 6 HLA-C locus alleles. Of the three HLA-class I loci, alleles belonging to HLA-B locus showed many significant association with HPV-16 infection (Table 1). The alleles with significant positive associations were HLA-B*07 (OR:1.31/*p*-value:0.018), B*14 (OR:1.53/p-value:0.033), B*41 (OR:2.42/p-value:0.043), B*44 (OR:1.24/p-value:0.034), B*47 (OR:3.40/p-value:0.007) and B*57 (OR:1.76/p-value:0.001) (Fig. 2, Supplementary Fig. 1, Table 1). The Odds were thus the highest with B*47 with higher significance, though B*57 showed the highest significance of OR. Significant negative associations were found with B*08 (OR:0.789/ p- value:0.045) and B*39 (OR:0.617/*p*-value:0.011), indicating a protection against or non-susceptibility to HPV-16 infection (Table 1).

HLA A alleles predominantly did not show significant associations with HPV-16. HLA-A*23, A*32 and A*29 alleles showed low, non-significant association (OR ranging from 1.2–1.3, Table 2, Supplementary Fig. 1). HLA A28 serotype (OR:0.696/*p*-value:0.05) and C*04 showed negative associations (OR:0.733/p-value:0.022) (Supplementary Figs. 1, 2). Bonferroni correction for multiple comparisons showed that only HLA-B*57 retained the significance of the OR among the Class-I alleles (Tables 1, 2).

3.2.1. Heterogeneity analysis

Of the 28 HLA-B alleles, 27 of them showed low heterogeneity

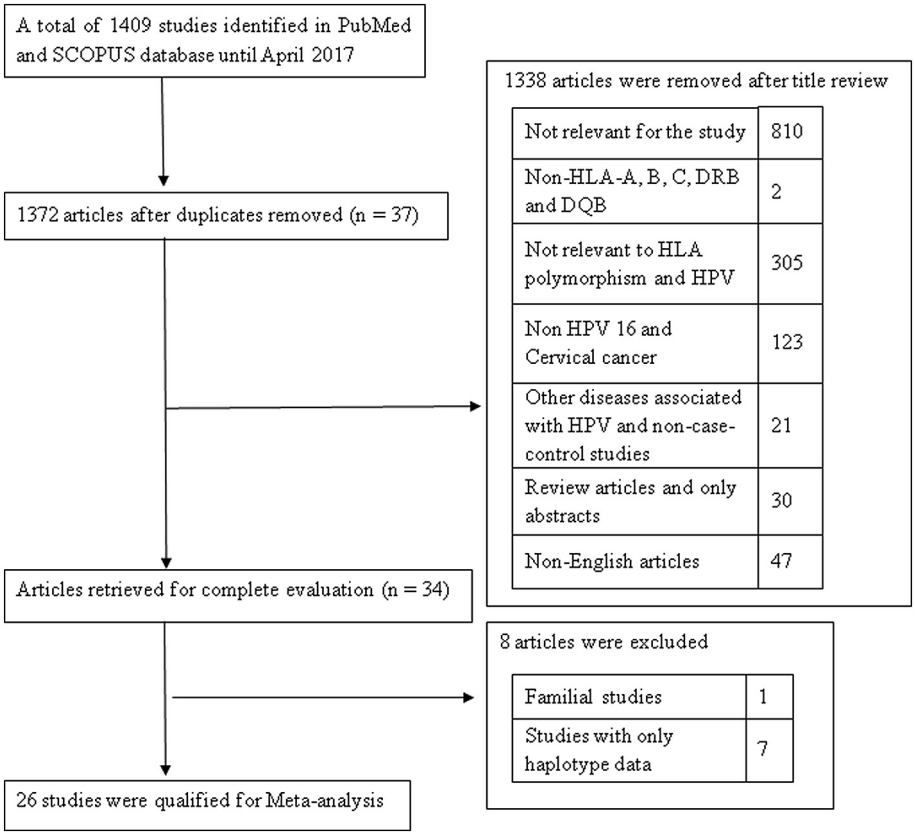

Fig. 1. Flow chart of literature search and selection of articles for meta-analysis based on inclusion and exclusion criteria following PRISMA guidelines.

among studies with I^2 ranging from 0 to 50.8 (Table 1). HLA-B*58 showed a high I^2 value of 73.66 respectively along with significant Heterogeneity *P*-values, suggesting a high heterogeneity among the studies used for meta-analysis. None of the other HLA-B alleles were significant in Egger's test, Begg's test and Heterogeneity P- values, though B*07 showed near significant H P-value of 0.071. Among the other Class I genes, A*02, A*24, C*01 and C*03 showed high I^2 value (> 50) (Table 2). Thus a random effect model was used for the meta-analysis for these alleles. The *P* value of the Egger's test and Begg's test for heterogeneity was not significant for all the HLA-A, B and C alleles tested (Tables 1, 2).

3.3. Meta-analysis of HLA – class II genes in HPV-16 infection

15 HLA-DRB1 alleles and 7 HLA-DQB alleles were included for the present meta-analysis. HLA-DRB1*10 showed a relatively high and a significant odds ratio of 1.5 (p-value = 0.017), while HLA-DRB1*13 showed a significantly low odds ratio of 0.7 (p-value < 0.0001) (Table 3, Fig. 3). Further, DRB1*07, DRB1*11 and DRB1*15 showed a very significant odds ratio of 1.2 (p- value < 0.003). Bonferroni correction for P-value showed HLA DRB1*07, DRB1*13 and DRB1*15 still retained the significance (Table 3). The heterogeneity among the studies taken up for HLA-DRB meta-analysis was low with I^2 ranging from 0 to 50.5, while DRB1*09 allele alone showed a high heterogeneity (I^2 = 70.25) (Table 3, Fig. 3). The Egger's test P value was significant for the alleles DRB 1*14, 1*07 and DR17 (DRB1*0301/0304) suggesting significant heterogeneity among the studies (Table 3). It was found that the heterogeneity was lost for DRB1*07 upon removal of Chinese samples from analysis (Supplementary Fig. 2).

HLA-DQB1*0303 (DQ9 serotype) showed a significantly high odds ratio of 1.5 (Fig. 3). The remaining 6 DQB alleles showed a positive association with odds ratio ranging from 0.8–1.1 and none of them were statistically significant (Table 3). The heterogeneity of the studies were low for the DQB alleles with I^2 value ranging from 0 to 53.5, with the exception of DQB1*06 with a high I^2 of 68.12 (Table 3). The Egger's P value and the Begg's P value were not significant for any of the DQB alleles (Table 3).

4. Discussion

HPV-16 normally infects the basal keratinocytes of the cervical epithelium and the viral gene expression leads to amplification of the viral genome, and the viral assembly takes place predominantly in the upper layers of the epithelia. The time lag from initial infection to the appearance of visible lesion may vary from days to months (Garcia-Chacon et al., 2009; Koutsky et al., 1992). The variation in the time and progression of the disease has been attributed to adaptive immune response, particularly T cell response, among many other factors. CD4+ T cells, specific to HPV E2 and E6 antigens are important to clear low grade HPV infection while CD4+ T cell response against E7 antigen is important to prevent neoplasia (Dillon et al., 2007; Peng et al., 2007). The hall mark of adaptive immune response is the presentation of antigenic peptides to the T cell by the HLA molecules.

The human MHC locus is the most polymorphic locus in the human genome (Fernandez Vina et al., 2012). Various alleles of the HLA exhibit different affinities to various antigenic peptides, which are considered to be one of the key causes for differential susceptibility to diseases among humans. Many association studies have shown contrasting associations of HLA alleles with HPV infection.

The present meta-analysis showed both significant positive (HLA-B*07, B*57, B*47, DRB1*10, DRB1*15 and DQB1*0303) and negative (protective effect) (B*08, B*39, A28 (serotype), C*04, C*06, DRB1*12, DRB1*13) associations with HPV-16 (Tables 1, 2, 3). This variation in the positive and negative association of HLA alleles with the HPV-16 infection, may account for the observed differences in CD4+ and CD8+ T cell responses and Th1 (antibody production) response to HPV

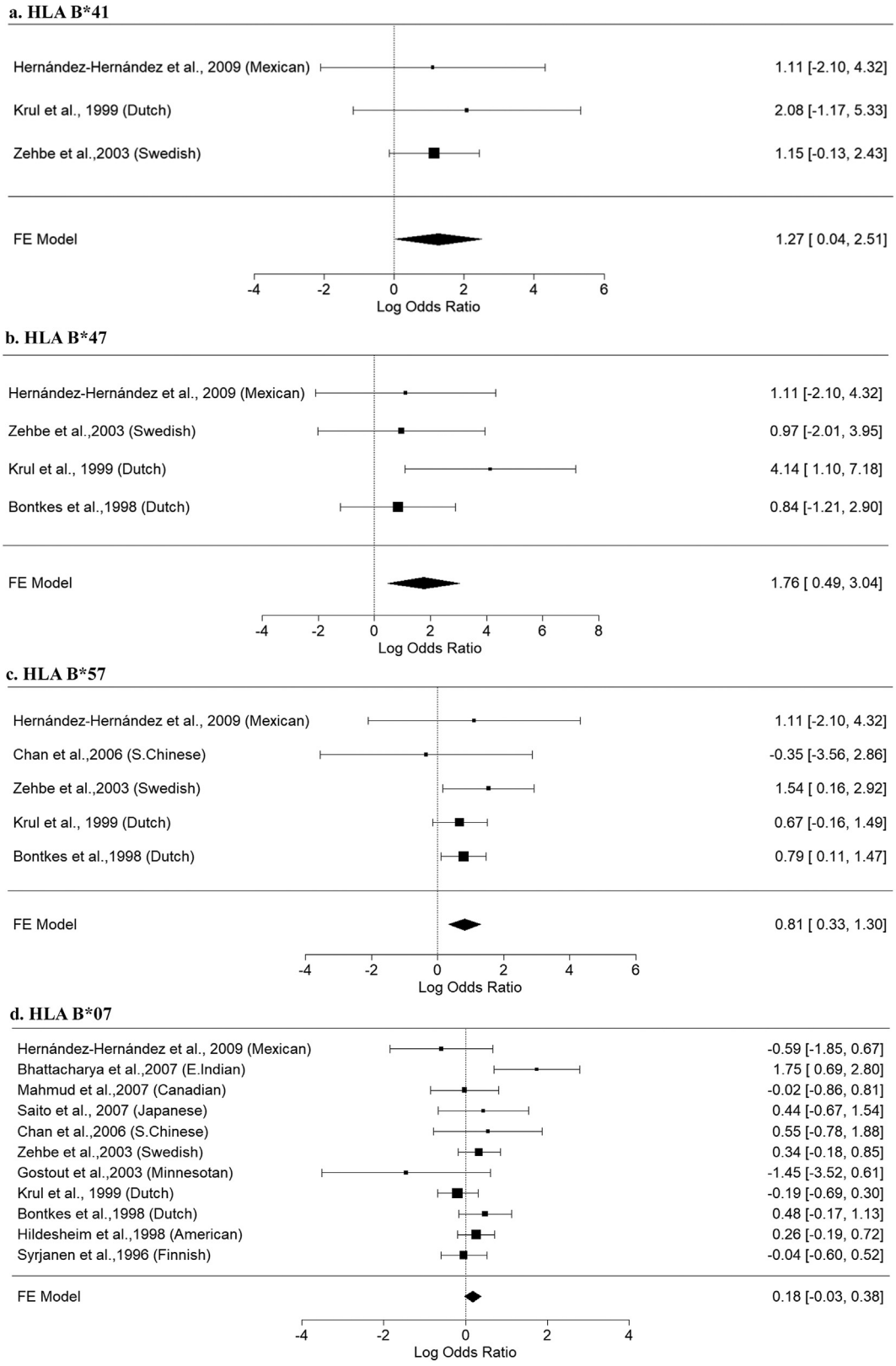

Fig. 2. Forest plot depicting association of (a) HLA B*41, (b) HLA B*47, (c) HLA B*57 and (d) HLA B*07 with HPV-16 infection.
Footnotes for Fig. 2: HLA B*41, B*47 and B*57 showed significant association with HPV-16 while B*07 showed meagre association. The associations are expressed as Log-odds ratio along with their 95% Confidence interval in the forest plot.

Table 1
Meta-analysis of associations between HLA-B alleles and HPV-16.

HLA Allele	N studies	N-cases/N-controls	I^2	H P value	OR (95% CI)	OR P value	OR Bonferroni adjusted P value	Egger's *P* Value	Begg's P value
B*07	11	856/5313	17.600	0.071	1.131 (0.982–1.303)	0.018	0.504	0.949	1.000
B*08	6	514/4451	0.000	0.750	0.789 (0.626–0.995)	0.045	1	0.639	0.719
B*13	7	550/4589	0.000	0.568	1.257 (0.978–1.614)	0.074	1	0.467	0.562
B*14	4	298/4005	27.720	0.332	1.53 (1.035–2.262)	0.033	0.924	0.252	0.750
B*18	6	514/4451	0.000	0.319	0.973 (0.705–1.342)	0.866	1	0.680	0.469
B*27	7	550/4589	0.000	0.700	1.001 (0.76–1.319)	0.993	1	0.423	1.000
B*35	7	550/4589	13.990	0.345	0.93 (0.772–1.121)	0.448	1	0.642	0.562
B*37	5	419/4263	0.000	0.463	1.116 (0.686–1.817)	0.659	1	0.537	0.817
B*38	5	419/4263	0.000	0.480	1.185 (1.77–1.261)	0.407	1	0.547	0.483
B*39	6	455/4401	0.000	0.939	0.617 (0.426–0.894)	0.011	0.308	0.779	0.469
B*40	5	420/3290	18.360	0.330	0.912 (0.742–1.12)	0.379	1	0.777	0.817
B*41	3	210/1565	0.000	0.869	2.417 (1.026–5.693)	0.043	1	0.568	0.333
B*44	6	455/4401	0.000	0.247	1.239 (1.017–1.51)	0.034	0.952	0.675	0.469
B*45	4	315/4159	0.000	0.962	0.916 (0.393–2.134)	0.839	1	0.065	0.083
B*46	3	245/2836	4.110	0.272	1.077 (0.793–1.461)	0.635	1	0.989	1.000
B*47	4	298/4005	9.700	0.327	3.399 (1.4–8.248)	0.007	0.196	0.542	0.333
B*48	4	349/2940	0.000	0.315	0.874 (0.507–1.509)	0.629	1	0.512	0.750
B*49	3	210/1565	0.000	0.714	0.535 (0.202–1.42)	0.209	1	0.637	0.333
B*50	5	419/4263	0.000	0.497	0.728 (0.343–1.544)	0.408	1	0.055	0.817
B*51	6	455/4401	50.880	0.077	1.145 (0.909–1.442)	0.250	1	0.744	0.719
B*52	6	455/4401	0.670	0.371	1.1 (0.72–1.68)	0.659	1	0.619	1.000
B*53	4	407/3963	0.000	0.671	1.331 (0.654–2.71)	0.431	1	0.220	0.083
B*55	6	455/4401	0.000	0.584	0.971 (0.644–1.464)	0.887	1	0.886	0.719
B*56	5	367/1961	0.000	0.994	1.046 (0.619–1.769)	0.866	1	0.392	0.233
B*57	5	419/4263	0.000	0.787	1.757 (1.256–2.457)	0.001	0.028	0.975	1.000
B*58	4	315/4159	73.660	0.003	1.502 (0.576–3.921)	0.406	1	0.651	0.750
B*61	3	193/1340	24.55	0.21	1.538 (1.039–2.276)	0.0314	0.8792	0.789	1
B15[#]	7	550/4589	45.870	0.098	0.836 (0.694–1.007)	0.059	1	0.873	1.000

Significant positive associations of HLA-B alleles with HPV-16 infection were seen in HLA-B*07, B*14, B*41, B*44, B*47, and B*57 alleles. The HLA-B alleles, B*08 and B*39 were found to have a protective effect against HPV-16 infection. Except HLA-B*58 (I^2 = 73.66), all other alleles were found to show low heterogeneity among studies (I^2 values ranged from 0 to 50.8).
H-P value: P value of heterogeneity test; # Only serotype information available; OR: Odds Ratio.

16 infection.

Of the many alleles positively associated with HPV-16 (Table 1), HLA B*07 is a very common allele in the general population (Fernandez Vina et al., 2012; Zhao et al., 2013) that is associated with both HPV-16 infection and familial cervical cancer (Fig. 2) (Qiu et al., 2011). Only the studies by Hernandez-Hernandez et al. (2009) and Gostout et al. (2003) showed negative association of HLA B*07 with the disease. Bhattacharya and Sengupta (2007) showed a very strong association of

Table 2
Meta-analysis of associations between HLA-A and C alleles and HPV-16.

HLA Allele	N studies	N-cases/N-controls	I^2	H-P value	OR (95% CI)	OR-P value	OR -Bonferroni adjusted *P* value	Egger's P Value	Begg's P value
A*01	6	423/4799	44.080	0.134	1 (0.823–1.215)	1.000	1.00	0.979	1.000
A*02	6	423/4799	89.080	< .0001	0.869 (0.525–1.436)	0.583	1.00	0.930	0.719
A*03	6	423/4799	0.000	0.772	1.018 (0.845–1.225)	0.854	1.00	0.582	0.469
A*11	6	423/4799	49.920	0.104	0.942 (0.763–1.162)	0.578	1.00	0.080	0.272
A*23	3	194/3901	47.120	0.157	1.26 (0.735–2.159)	0.400	1.00	0.668	1.000
A*24	5	328/4611	88.460	0.001	0.737 (0.348–1.559)	0.424	1.00	0.265	0.483
A*25	3	194/3901	0.000	0.440	0.992 (0.492–1.999)	0.982	1.00	0.411	0.333
A*26	5	328/4611	0.000	0.783	1.111 (0.768–1.607)	0.576	1.00	0.987	1.000
A*29	4	292/4473	0.000	0.675	1.161 (0.787–1.712)	0.453	1.00	0.624	1.000
A*30	6	365/4679	0.000	0.878	0.974 (0.619–1.534)	0.911	1.00	0.333	0.469
A*31	5	328/4611	0.000	0.691	0.974 (0.619–1.534)	0.911	1.00	0.341	0.817
A*32	5	329/4541	35.370	0.174	1.219 (0.843–1.763)	0.293	1.00	0.996	1.000
A*33	5	328/4611	36.980	0.229	0.81 (0.576–1.14)	0.227	1.00	0.249	0.233
A10[#]	3	277/3789	0.000	0.733	0.993 (0.702–1.403)	0.967	1.00	0.055	0.333
A28[#]	4	289/4089	40.910	0.217	0.696 (0.485–1)	0.050	0.8	0.256	0.750
A9[#]	3	277/3789	57.990	0.088	1.047 (0.747–1.466)	0.791	1.00	0.241	1.000
C*01	3	254/2787	85.550	0.001	1.084 (0.522–2.249)	0.829	1.00	0.742	1.000
C*02	3	254/2787	48.160	0.195	0.943 (0.67–1.329)	0.739	1.00	0.980	1.000
C*03	3	254/2787	75.970	0.021	0.907 (0.595–1.381)	0.648	1.00	0.625	1.000
C*04	3	254/2787	44.970	0.159	0.733 (0.562–0.955)	0.022	0.13	0.889	1.000
C*05	3	254/2787	0.000	0.546	0.703 (0.451–1.095)	0.119	0.71	0.686	1.000
C*06	3	254/2787	34.810	0.231	0.741 (0.532–1.032)	0.076	0.46	0.749	1.000

Low and non-significant association with HPV-16 were observed in HLA-A alleles, A*23, A*32 and A*29. There were no HLA-A alleles found to have significant positive association with HPV-16 infection. Negative associations with HPV-16 infection were found in A28 serotype and C*04 allele. A higher I^2 value (> 50) was seen in HLA-A*02, A*24, A9[#] C*01 and C*03 alleles.
H-P value: P value of heterogeneity test; # Only serotype information available; OR: Odds Ratio.

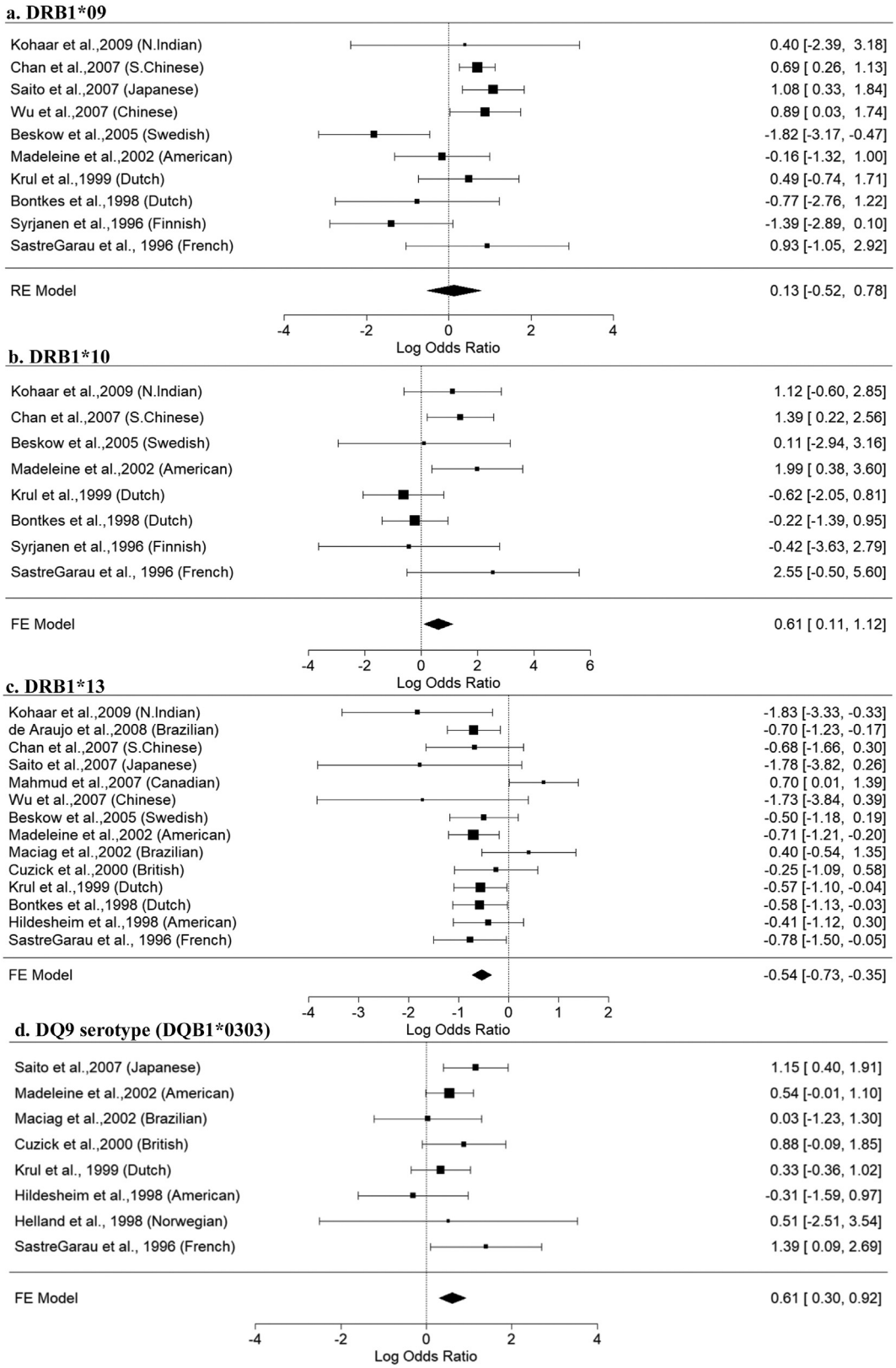

Fig. 3. Forest plot depicting association of (a) HLA DRB1*09, (b) HLA DRB1*10, (c) HLA DRB1*13 and (d) HLA DQB1*0303 (DQ9) with HPV-16 infection.
Footnotes for Fig. 3: HLA DRB1*10 and DQB1*0303 showed significant association with HPV-16 while DRB1*13 showed negative association. HLA DRB1*09 showed meagre association with contrasting results from different studies. The associations are expressed as Log-odds ratio along with their 95% Confidence interval in the forest plot.

Table 3
Meta-analysis of associations between HLA- DR and DQ alleles and HPV-16.

HLA Allele	N studies	N-cases/N-controls	I^2	H-P value	OR (95% CI)	OR-P value	OR -Bonferroni adjusted P value	Egger's P Value	Begg's P value
DRB1*01	12	1296/5811	0.000	0.486	0.988 (0.869–1.123)	0.850	1	0.448	0.947
DR103# (DRB1*0103)	3	509/1570	0.000	0.973	1.146 (0.607–2.162)	0.675	1	0.319	0.333
DR17# (DRB1*0301/0304)	5	694/1163	0.000	0.598	0.824 (0.677–1.002)	0.053	0.795	0.007	0.083
DR3# (DRB1*03)	6	528/4351	0.000	0.860	0.865 (0.721–1.037)	0.117	1	0.160	0.469
DRB1*04	14	1169/5196	0.000	0.729	0.914 (0.82–1.019)	0.104	1	0.511	1.000
DRB1*07	10	977/4775	0.000	0.475	1.226 (1.073–1.401)	0.003	0.045	0.032	0.073
DRB1*08	12	1258/5652	38.820	0.053	0.919 (0.764–1.106)	0.372	1	0.634	0.459
DRB1*09	10	1055/5024	70.250	0.004	1.096 (0.698–1.723)	0.690	1	0.112	0.108
DRB1*10	8	945/4788	42.690	0.112	1.53 (1.081–2.167)	0.017	0.255	0.769	0.720
DRB1*11	11	1163/5464	36.430	0.087	1.223 (1.05–1.424)	0.010	0.15	0.057	0.087
DRB1*12	9	960/4836	50.540	0.041	0.702 (0.55–0.898)	0.005	0.075	0.381	0.612
DRB1*13	14	1398/6154	39.710	0.039	0.689 (0.604–0.786)	< 0.0001	0.0015	0.463	0.747
DRB1*14	11	1163/5464	0.000	0.901	1.076 (0.88–1.314)	0.476	1	0.029	0.041
DRB1*15	12	1233/5579	32.370	0.065	1.197 (1.071–1.339)	0.002	0.03	0.772	0.737
DRB1*16	8	908/4914	0.000	0.574	1.081 (0.804–1.454)	0.606	1	0.824	0.720
DQB1*02	8	759/2611	0.000	0.501	0.892 (0.781–1.019)	0.093	0.651	0.720	0.905
DQB1*04	8	645/2439	53.540	0.045	1.1 (0.781–1.548)	0.586	1	0.698	0.548
DQB1*05	10	907/3006	48.660	0.050	0.966 (0.852–1.094)	0.585	1	0.827	1.000
DQB1*06	12	1030/3439	68.120	0.000	1.017 (0.828–1.248)	0.874	1	0.582	0.459
DQ7# (DQB1*0301/0304)	10	864/2866	40.530	0.098	1.096 (0.966–1.243)	0.156	1	0.240	0.108
DQ8# (DQB1*0302/0305)	7	623/2342	17.170	0.353	1.017 (0.851–1.215)	0.851	1	0.185	0.239
DQ9# (DQB1*0303)	8	677/2658	0.000	0.414	1.527 (1.235–1.888)	< .0001	0.0007	0.869	0.905

The odds ratio for HLA-DRB alleles ranged from 0.7 to 1.53, of which HLA-DRB1*13 was found to have a significantly low odds ratio. Except for DRB1*09 (I^2 = 70.25), the I^2 value for all other DRB alleles ranged from 0 to 50.5. Similarly, HLA-DQB1*0303 (DQ9 serotype) was found to be positively associated with HPV-16 infection (OR = 1.5) and was statistically significant.
H-P value: P value of heterogeneity test; # Only serotype information available; OR: Odds Ratio.

HLA B*07 with HPV-16 infection in normal individuals and those with CaCx (OR = 4.73 and 6.14 respectively) in East Indian populations (Bhattacharya and Sengupta, 2007). This allele HLA B*07 is associated with accelerated progression in HIV clade B infection (Kloverpris et al., 2014). Another allele that showed positive association in the present study is HLA B*57 which is a widely accepted marker for hypersensitivity to Abacavir and delayed progression of HIV infection to AIDS (Arrieta-Bolanos et al., 2014). The HLA C*04 and C*06 showed significant protective effect towards HPV-16 (Supplementary Fig. 2). The allele C*06 is a classical marker associated with Psoriasis (Strange et al., 2010).

Various alleles of Class I HLA genes act as ligands for killer-cell immunoglobulin-like receptors (KIRs) of NK Cells. Specifically, HLA B is the ligand for KIR3DL1, HLA C is the ligand for KIR2DL2, 2DS2 and 2DS3. NK-cell response is a crucial innate response in curtailing most viral infections. Epistatic interaction between Class-I HLA and the KIR genes and their allelic variation has been associated with the outcome of SIV infection in macaques and HBV infection in humans (Albrecht et al., 2014; Kalyanaraman et al., 2016). Thus one needs to analyse the observed association of Class I HLA alleles along with KIR genotypes to get further insights into the immune mechanism behind the association.

Among the HLA DRB alleles, DRB1*15 that showed significant positive association with HPV-16 (Table 3, Supplementary Fig. 2), has been strongly associated with multiple sclerosis, SLE and Good Pasteur's syndrome (Phelps and Rees, 1999; Shimane et al., 2013). 9 out of 12 studies in the present meta-analysis showed association of DRB1*15 with HPV-16 infection, 2 studies showed near 0 odds ratio while the study by Hildesheim et al. (1998) showed a protective effect of the allele in Americans (Supplementary Fig. 2) (Hildesheim et al., 1998). HLA DRB1*13 that showed protective effect against HPV-16 infection has also shown protective effect against auto immune disorders (Bettencourt et al., 2015).

The HLA alleles show population specific distribution that is proposed to be a result of selective pressures and evolution that the population has undergone. Additionally, populations exhibit their specific HLA haplotypes which is a result of linkage among the HLA alleles. Analysis of HLA haplotypes and alleles among global populations suggest evolution of HLA alleles to be a dynamic process involving convergent evolutionary events (Fernandez Vina et al., 2012). Thus it is imperative to analyse HLA allele and disease association in the light of population included in the study before proposing general conclusions. Haplotype level analysis could not be performed in the present study as the availability of studies describing haplotypes was limited.

We performed the meta-analysis by stratifying the studies based on continental populations. Upon stratification, we found that HLA-B*57, DRB1*07 and DQB1*0303 showed significant association with HPV-16 infection in European populations (Supplementary Table 2). HLA DRB1*11 and DRB1*13 showed significant positive and negative associations respectively in East Asian population. But this association was not significant after performing Bonferroni correction (Supplementary Table 2). We could not perform the meta-analysis at the population level due to lack of multiple studies on the same population. The present meta-analysis included only Dutch, Swedish and Mexican populations in HLA-B*47 & B*41 and additionally South Chinese was included in HLA-B*57 (Fig. 2). Interestingly, the South Chinese population showed a negative association (OR = 0.8), while the Dutch, Swedish and Mexican populations showed a positive association with HLA-B*57 (Fig. 2). This discrepancy could probably be due to variation in HPV-16 strains between the East and the West or due to variation in HLA-B*57 subtypes or both. Negative association was found with HLA-B*49 and B*39 alleles (OR, p value = 0.5, 0.209; 0.6, 0.011, respectively). The analysis showed Mexican and the Dutch to have a negative association, while the Swedish showed a positive association between HLA-B*49 and HPV-16 infection. Further, the discrepancy could also be because the variation in associations between populations may be evident only at higher resolution of HLA allele genotyping. Most of the studies used in the present meta-analysis did not provide 4 digit or higher resolution of HLA typing. Thus we could perform the analysis only at the 2 digit level of HLA alleles.

Unlike the class I HLA alleles, the class II HLA alleles had a better global population representation encompassing the Europe, America, South Asia and East Asia. It is to be noted that majority of the studies that qualified for the meta-analysis had European and American populations only (Fig. 3, Supplementary Fig. 2). Only a few studies were

included from East Asian populations (Chinese and Japanese). Unfortunately, India that harbours one – sixth of the global population and very high HPV burden was represented only in 2 studies that too did not involve typing for all the HLA-B alleles (Bhattacharya and Sengupta, 2007; Das Ghosh et al., 2017). Although, they showed a very high association of HLA-B*07 and B*61 with HPV-16 (OR = 3.4, 2.5 respectively), the odds ratio under the FE model for B*07 and B*61 was only 1.2 and 1.5, respectively (Table 1).

The present meta-analysis was limited to associations of HLA alleles with HPV-16 infection and not with the grade of cervical cancer. We excluded papers from literature that did not have information on HPV-16 because no significant HLA association was obtained when meta-analysis was performed between HLA alleles and grade of cervical cancer or cervical neoplasia. This may be due to the complex heterogeneity in cervical oncogenesis caused by HPV (Crosbie et al., 2013; Kidd and Grigsby, 2008). It is also known that many HPV infections are cleared off and that only persistent HPV infection has a higher propensity to progress to cancer (Stanley, 2006). Thus the present study aimed to identify only the association of HLA alleles with persistent HPV16 infection. Analysis including all oncogenic HPV types and different grades of cervical cancer may further give insights on the immunogenetic predisposition to HPV medicated cervical cancer.

HPV-16 is one of the few pathogens that are pandemic in distribution. Phylogenetically the virus is classified into five major clades (A1-A3, A4, B, C and D). These clades show distinct geographic distribution. Clades A1-A3 are predominant in Europe, Asia and South America, A4 is restricted to East Asia, B and C is seen exclusively in Africa and D predominantly in North and South America (Cornet et al., 2012; Pimenoff et al., 2017). It is also noted that non-European lineages of HPV-16 exhibit persistent infection and are more frequent in high grade lesions (Villa et al., 2000). It was also shown that European women are more prone to persistence of European HPV-16 clade while African women to African clade of HPV-16 (Xi et al., 2006). This distinct phylogeographical distribution of HPV-16 and ethnicity specific patterns of viral virulence points directly to the ethnic variation in immune response to HPV. The implications of the geographical variation of HPV-16 genomic diversity and HLA allelic diversity will influence the design and effectiveness of vaccines. Currently approved vaccines for HPV include virus like particles made of L1 capsid protein (Monie et al., 2008). The long term efficacy of these vaccines are still being evaluated as the incubation time of HPV before causing cervical oncogenesis is decades long (Hariharan and Pillai, 2009; Stanley, 2006). One needs to take into consideration the geographical genetic variation of the pathogen and the host while evaluating the vaccine.

Phylo-geographic and population genetic variations in HLA allele distribution has also been well documented. For example HLA B57 is a common allele among Vellala population of South India is associated with Psoriasis in that population (Pitchappan et al., 1989). Similarly HLA DR10 was found in high frequencies in Irula of South India. The distribution of such alleles in the population is a result of human migration and regional expansion (Pitchappan, 2002). Likewise HPV-16 has evolved since the time of human evolution and has been postulated to have been transmitted from Archaic to modern humans (Pimenoff et al., 2017). Thus one can speculate that both HPV-16 and human HLA loci have been co-evolving giving rise to the present day picture of global distribution.

5. Conclusion

In conclusion, the large number of cases and controls used for the meta-analysis brought out the significant associations of HLA alleles with HPV-16. The present study showed that HLA-B*47, B*57, DRB1*10 and DQB1*0303 alleles were significantly associated with HPV-16 while DRB1*13 and DRB1*12 were negatively associated. Further studies correlating the HPV-16 genetic diversity and immunogenetic diversity of the host, shall shed further light into the molecular co-evolution of the host and the pathogen.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2018.12.026.

Conflict of interest

The authors declare no conflict of interest.

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