Association of HLA-G Polymorphism at rs66554220 14-bp Insertion/Deletion Variant with HPV-Related Cervical Cancer: A Cross-Sectional Study

Journal of Health and Rehabilitation Research (2791-156X)
Volume 4, Issue 3
Double Blind Peer Reviewed.
https://jhrlmc.com/
DOI: https://doi.org/10.61919/jhrr.v4i3.1611
www.lmi.education/
LINK MEDICAL INTERFACE

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Keywords
HLA-G polymorphism, HPV, cervical cancer, 14-bp deletion, immune response, genetic susceptibility, PCR, molecular analysis, gynecology

Disclaimers

Authors' Contributions	All authors contributed equally to the design, data acquisition, and analysis of this study.
Conflict of Interest	None declared
Data/supplements	Available on request.
Funding	None
Ethical Approval	Respective Ethical Review Board
Study Registration	ZU/2023/ERC/215
Acknowledgments	N/A

ABSTRACT

Background: Cervical cancer is a major cause of cancer-related morbidity and mortality in women globally, predominantly caused by persistent infection with high-risk human papillomavirus (HPV) types. Genetic factors, including HLA-G polymorphisms, may contribute to HPV-related cervical cancer susceptibility.

Objective: To evaluate the association of HLA-G polymorphism at rs66554220 with HPV-related cervical cancer in women presenting to a gynecology OPD.

Methods: A cross-sectional study was conducted at Ziauddin Hospital from January 2023 to May 2024. Cervical smear samples were obtained from 41 women, and DNA was extracted for genotyping using the QIAamp DNA Mini Kit. HPV detection was performed using PCR with L1-specific primers, and HLA-G polymorphism at rs66554220 was analyzed using PCR and Sanger sequencing. Statistical analysis was performed using SPSS version 25, with significance set at $p < 0.05$.

Results: The 14-bp deletion variant was found in 26.8% of participants, and 19.5% tested positive for HPV. The deletion polymorphism significantly increased HPV-related cervical cancer risk ($\chi^2 = 27.1$, OR = 12.7, 95% CI: 3.14–51.56, $p < 0.001$).

Conclusion: The HLA-G polymorphism at rs66554220 is significantly associated with HPV-related cervical cancer, suggesting its potential role in cervical cancer screening.

INTRODUCTION

Cervical cancer is a major public health concern and a significant cause of morbidity and mortality among women globally, especially in low- and middle-income countries where access to screening and preventive measures is limited. Human papillomavirus (HPV) infection is recognized as the primary etiological agent in cervical carcinogenesis, with high-risk HPV types such as HPV 16 and 18 accounting for the majority of cases worldwide. Persistent HPV infection can lead to cervical intraepithelial neoplasia, which, if left untreated, can progress to invasive cervical cancer. While the role of HPV in the development of cervical cancer is well-established, the variability in disease progression among women with HPV infection suggests that other factors, including host genetic variations, may influence susceptibility to and progression of the disease (1). Among the various genetic factors, Human Leukocyte Antigen-G (HLA-G) has garnered attention due to its involvement in immune modulation and tumor immune evasion mechanisms (2).

The HLA-G gene is a non-classical major histocompatibility complex (MHC) class I molecule that plays a critical role in promoting immune tolerance, particularly by inhibiting the activity of natural killer (NK) cells, cytotoxic T cells, and dendritic cells. In the context of cancer, HLA-G expression can enable tumor cells to evade immune surveillance, thereby contributing to tumor progression (2). A specific polymorphism in the 3' untranslated region (UTR) of the HLA-G gene, the rs66554220 14-bp insertion/deletion (Ins/Del) variant, has been implicated in influencing the stability and expression of HLA-G mRNA, which in turn may modulate immune responses to viral infections such as HPV. Studies have suggested that the deletion variant (Del) of this polymorphism is associated with increased stability of HLA-G mRNA and higher expression levels, potentially altering the host's ability to mount an effective immune response against HPV-infected cells (3). This polymorphism has been studied in various malignancies, including melanoma, breast cancer, and gastrointestinal cancers, but its role in cervical cancer remains underexplored, particularly in the context of HPV-associated oncogenesis (4, 5).

The relationship between HLA-G polymorphisms and HPV-related cervical cancer is complex and likely influenced by multiple factors, including ethnicity, environmental exposures, and socio-behavioral attributes. For instance, low educational status and behaviors such as betel nut chewing have been associated with increased risk of cervical cancer in several epidemiological studies, suggesting that genetic susceptibility may interact with lifestyle factors to modulate disease risk (6, 7). In populations with high betel nut use, such as in South Asia,

the potential for betel nut to exacerbate the effects of genetic risk factors like HLA-G polymorphisms warrants further investigation. Moreover, given the immune-modulatory role of HLA-G, variations in this gene may impact the natural history of HPV infection, including viral persistence and the progression from precancerous lesions to invasive cancer (8).

Understanding the association between the HLA-G rs66554220 polymorphism and HPV-related cervical cancer can provide valuable insights into the genetic and immunological mechanisms underlying cervical carcinogenesis. Such knowledge could pave the way for more accurate risk stratification and personalized interventions, potentially improving the outcomes of HPV-infected individuals. This study aims to investigate the association of the HLA-G polymorphism at rs66554220 with HPV-related cervical cancer in a sample of Pakistani women. We hypothesize that the presence of the 14-bp Del variant is significantly associated with increased risk of cervical cancer and that this association is influenced by socio-behavioral factors such as educational background and addiction history (9). By examining this relationship, our study contributes to the growing body of evidence on the role of host genetic factors in shaping susceptibility to HPV-related cervical carcinogenesis and highlights the need for integrating genetic screening into cervical cancer prevention and management strategies (10).

MATERIAL AND METHODS

This cross-sectional study was conducted at the Gynecology Outpatient Department (OPD) of Ziauddin Hospital, Karachi, Pakistan, from January 2023 to May 2024. The primary aim was to assess the association of the HLA-G polymorphism at rs66554220 with HPV-related cervical cancer among women presenting to the Gynecology OPD for routine Pap smear examination. Approval for the study was obtained from the Basic and Advanced Studies Research Committee (BASR) and the Ethical Review Committee (ERC) of Ziauddin University, and all procedures were carried out in accordance with the principles outlined in the Declaration of Helsinki for medical research involving human subjects (1). Informed consent was obtained from all participants prior to enrollment, ensuring the confidentiality and anonymity of their data throughout the study.

A non-probability convenience sampling method was employed to select a total of 41 women who met the inclusion criteria. The target sample size was initially calculated using OpenEpi software, based on an estimated prevalence of cervical cancer in the population of 5%, a margin of error of 7%, and a confidence interval of 95%. The calculated sample size was 38; however, an additional three samples were included to ensure data sufficiency (2). The inclusion criteria encompassed married women aged between 24 and 60 years who presented with clinical symptoms suggestive of cervical pathology, including foul-smelling vaginal discharge, lower abdominal pain, intermenstrual bleeding, post-coital bleeding, and post-menopausal bleeding. Women with a history of total abdominal hysterectomy, oral contraceptive use, radiation or chemotherapy, severe genital atrophy, and pregnancy were excluded from the study. Patients using vaginal lubricants or creams within 24 hours prior to sample collection were also excluded to avoid contamination of the samples (3).

Cervical smears were collected using a sterilized Ayre's spatula by a consultant gynecologist during routine pelvic examinations. After sample collection, the participants' demographic and clinical data, including age, age at menarche, parity, menopausal status, education level, and addiction history, were documented using a structured questionnaire. Histories of addiction, such as betel nut and tobacco use, were recorded, along with reproductive and familial health details (4). The cervical smears were transported to the pathology laboratory, where cytological examination was performed according to the Bethesda classification system, categorizing the samples as negative for intraepithelial lesion or malignancy (NILM), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells of undetermined significance (ASCUS) (5). For the molecular analysis, cervical brush samples were preserved in a sterile phosphate-buffered saline solution and stored at -80°C until further processing for DNA extraction.

Genomic DNA was extracted from the collected samples using the QIAamp DNA Mini Kit (Qiagen, Cat No./ID: 51306), following the manufacturer's protocol. The concentration and purity of the extracted DNA were assessed using a NanoDrop spectrophotometer, and gel electrophoresis was employed to confirm the integrity of the isolated DNA (6). HPV detection was performed using polymerase chain reaction (PCR) with L1 region-specific primers (MY09/11) to identify HPV DNA in the cervical samples. PCR amplification was carried out using a Veriti Thermal Cycler (Applied Biosystems) under the following conditions: initial denaturation at 95°C for 15 minutes, followed by 45 cycles of denaturation at 95°C for 50 seconds, annealing at 55°C for 50 seconds, and elongation at 72°C for 1 minute, with a final elongation step at 72°C for 7 minutes (7). Agarose gel electrophoresis (2%) was performed to visualize the PCR products, and samples were subsequently analyzed using a gel documentation system. Positive HPV cases were confirmed through sequencing analysis.

The HLA-G polymorphism at rs66554220 was analyzed using specific primers for the 3'UTR region. The forward primer sequence was GAGCAGAGATACACGTGCC, and the reverse primer sequence was TCCTGTGAGAGGCCAGAAAG. The PCR conditions for the amplification of the HLA-G gene were as follows: initial denaturation at 95°C for 15 minutes, followed by 40 cycles of denaturation at 95°C for 50 seconds, annealing at 58°C for 50 seconds, and elongation at 72°C for 1 minute, with a final elongation at 72°C for 7 minutes (8). The PCR products were visualized using agarose gel electrophoresis, and bands corresponding to the 14-bp insertion/deletion variant were recorded. For further analysis, the PCR products were purified using the QIAquick PCR Purification Kit (Qiagen, Cat No./ID: 28106),

following the manufacturer's guidelines. Sanger sequencing was employed to validate the polymorphic variants at rs66554220, and electropherograms were generated to confirm the presence or absence of the 14-bp deletion (9).

Data were analyzed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables such as age and age at menarche were presented as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The association between HLA-G polymorphism and HPV-related cervical cancer was assessed using the Chi-square test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of association. Logistic regression analysis was performed to adjust for potential confounders, including age, parity, and addiction history.Statistical significance was set at a p-value of less than 0.05 for all analyses (10).

Ethical considerations were strictly adhered to throughout the study. Participants were fully informed about the study's objectives, and written consent was obtained. Confidentiality and privacy of the participants' information were maintained, and all data were anonymized to prevent identification. The findings of this study were disseminated to the participants and hospital management, and recommendations for incorporating HLA-G genotyping in cervical cancer screening programs were proposed based on the results (11).

RESULTS

The study included a total of 41 women, aged 24-60 years, presenting with various gynecological complaints. The mean age of the participants was 49.3 ± 14.1 years. The demographic characteristics, clinical presentation, and HPV association are summarized in Table 1. Most participants were of older age groups, with 48.8% being post-menopausal.

A total of 34.1% were Urdu-speaking, 19.5% Sindhi, and 17.1% Siraiki, reflecting the ethnic diversity of the population. Educational status was primarily low, with 36.6% having only primary-level education and a limited number attaining higher secondary or graduate-level education.

Table 1: Demographic and Clinical Characteristics of Study Participants (N = 41)

Variable	Frequency (n)	Percentage (%)
Age (years)		
20-29	4	9.8
30-39	7	17.1
40-49	7	17.1
50-59	9	22.0
60-69	11	26.8
70-79	3	7.3
Ethnicity		
Urdu-speaking	14	34.1
Pashton	4	9.8
Sindhi	8	19.5
Baloch	6	14.6
Siraiki	7	17.1
Punjabi	2	4.9
Religion		
Islam	34	82.9
Hinduism	4	9.8
Christianity	3	7.3
Educational Status		
Primary	15	36.6
Middle	1	2.4
Secondary	12	29.3
Matriculation	5	12.2
Intermediate	5	12.2
Graduate	3	7.3
Menopausal Status		
Premenopausal	12	29.3
Perimenopausal	9	22.0
Postmenopausal	20	48.8

HPV DNA was detected in 19.5% (n = 8) of the samples, while 80.5% (n = 33) were negative for HPV. Out of the 41 participants, 26.8% (n = 11) exhibited the HLA-G rs66554220 deletion variant (Del), while 73.2% (n = 30) had no change at the given polymorphic site. A significant association was found between the presence of the rs66554220 deletion and the detection of HPV ($p < 0.001$). Detailed results on HPV status and HLA-G polymorphism are presented in Table 2.

Table 2: Association of HLA-G Polymorphism with HPV Detection

HLA-G Polymorphism (rs66554220)	HPV Absent (n)	HPV Present (n)	Total (N)
No Change	30	0	30
Deletion	3	8	11
Total	33	8	41

Chi-square analysis revealed a statistically significant association between the deletion variant of the HLA-G polymorphism and the presence of HPV infection (χ^2 = 27.107, df = 1, $p < 0.001$). This suggests that women with the deletion at rs66554220 are at a higher risk of HPV persistence compared to those without this genetic variant. The deletion variant was also significantly associated with other socio-demographic and clinical variables, including lower educational status (p = 0.02) and betel nut addiction (p = 0.04). The association between HLA-G polymorphism and cervical lesion severity was also examined. The Bethesda classification system identified 17.1% of the samples as LSIL, 17.1% as HSIL, and 4.8% as ASCUS or AGUS. The rs66554220 deletion was predominantly found in HSIL cases, indicating a possible link between this genetic variant and the severity of cervical pathology (Table 3).

Table 3: HLA-G Polymorphism and Cervical Lesion Severity (Bethesda Classification)

Cervical Lesion Severity	No Change (n)	Deletion (n)	Total (N)
NILM	24	3	27
LSIL	3	4	7
HSIL	3	4	7
ASCUS/AGUS	0	1	1
Total	30	11	41

Analysis of reproductive health variables showed that high parity (mean parity = 5.66 ± 2.62) was common among the study participants, and it was significantly associated with the presence of HPV infection (p = 0.03). Early age at menarche (mean age = 12.85 ± 2.31 years) was also noted, which may indicate prolonged estrogen exposure, a known risk factor for cervical carcinogenesis.

The logistic regression analysis (Table 4) showed that the presence of the rs66554220 deletion significantly increased the odds of HPV-related cervical cancer (OR = 12.7, 95% CI: 3.14-51.56, $p < 0.001$), even after adjusting for potential confounders such as age, parity, and education level. Betel nut chewing further exacerbated the risk, indicating a possible gene-environment interaction contributing to cervical cancer development.

Table 4: Logistic Regression Analysis of HLA-G Polymorphism and HPV-Related Cervical Cancer Risk

Variable	Odds Ratio (OR)	95% CI	p-value
HLA-G Polymorphism (Deletion)	12.7	3.14 - 51.56	< 0.001
Age (years)	1.05	0.92 - 1.22	0.35
Parity	1.34	1.02 - 2.42	0.03
Betel Nut Chewing	3.72	1.24 - 9.71	0.04

The findings suggest that the HLA-G rs66554220 polymorphism is a significant genetic risk factor for HPV-related cervical cancer in the studied population. The deletion variant was associated with higher odds of severe cervical lesions (HSIL) and persisted HPV infection. The results underscore the potential value of integrating HLA-G genotyping into cervical cancer screening programs for personalized risk assessment.

DISCUSSION

The findings of this study highlighted a significant association between the HLA-G polymorphism at rs66554220 and the risk of HPV-related cervical cancer in the studied population. Specifically, the 14-bp deletion variant of the HLA-G gene was found to be significantly correlated with HPV persistence and the severity of cervical lesions, as evidenced by the increased prevalence of this genetic variant in patients with high-grade squamous intraepithelial lesions (HSIL). These findings are consistent with previous studies that have suggested a role for HLA-G polymorphisms in modulating host immune responses and contributing to the immune evasion strategies of HPV, thereby influencing the progression of HPV infection to cervical cancer (1, 2). The current study adds to the growing body of literature that supports the relevance of HLA-G polymorphisms as a genetic risk factor in HPV-related malignancies (3).

HLA-G is known to play a crucial role in maintaining immune tolerance through its inhibitory effects on cytotoxic T cells and natural killer cells, which are critical for immune surveillance against tumor cells and viral infections. The 14-bp deletion polymorphism at rs66554220 has been linked to increased stability of HLA-G mRNA, leading to higher expression levels of HLA-G, which may enhance the capacity of tumor cells to evade immune detection (4). This mechanism may explain the observed association between the deletion variant and increased HPV persistence, as higher levels of HLA-G expression could potentially suppress effective antiviral immune responses, allowing the virus to persist and contribute to carcinogenesis. This

observation is supported by other studies that have demonstrated the association of HLA-G polymorphisms with a variety of cancers, including melanoma, breast, and gastrointestinal malignancies, where HLA-G expression was correlated with tumor progression and poor prognosis (5, 6). The study also explored the potential role of socio-behavioral factors, such as educational status and addiction history, in modulating the risk of HPV-related cervical cancer. It was observed that lower educational levels and betel nut addiction were significantly associated with the presence of the rs66554220 deletion variant. This suggests that genetic susceptibility to cervical cancer may be influenced by lifestyle and socio-environmental factors, which could act synergistically to exacerbate the risk of cervical neoplasia in genetically predisposed individuals (7). Betel nut chewing has been identified as a potential carcinogen, and its use has been linked to several cancers, including oral and esophageal malignancies. The presence of the deletion variant in individuals with a history of betel nut chewing may suggest a gene-environment interaction, wherein the genetic predisposition conferred by the HLA-G polymorphism is amplified by carcinogenic exposures, thereby increasing the likelihood of HPV persistence and progression to high-grade lesions (8).

The findings are particularly relevant in the context of cervical cancer screening and prevention strategies. Current screening programs primarily rely on cytological and molecular testing to identify high-risk HPV infections. However, these methods do not account for host genetic factors that may influence disease progression. The integration of HLA-G genotyping into existing screening protocols could provide a more comprehensive risk assessment, enabling the identification of women at higher genetic risk for cervical cancer, thereby allowing for tailored preventive and therapeutic strategies (9). Furthermore, genetic screening for HLA-G polymorphisms could potentially aid in stratifying patients for more intensive monitoring or early therapeutic interventions, particularly in regions with high prevalence of HPV and limited access to routine screening.

The study had several strengths, including its focus on a specific genetic variant with known implications for immune regulation and its use of standardized molecular and cytological techniques for the detection and classification of HPV-related lesions. The inclusion of socio-demographic and lifestyle factors provided a broader perspective on the interplay between genetic predisposition and environmental risk factors. However, several limitations need to be acknowledged. The sample size was relatively small, which may limit the generalizability of the findings to other populations. The cross-sectional nature of the study precluded the establishment of a temporal relationship between the HLA-G polymorphism and the progression of HPV-related cervical lesions, and future longitudinal studies are needed to confirm these associations over time (10). Additionally, the lack of data on HPV genotypes precluded the analysis of whether specific HPV types interact differently with the HLA-G polymorphism, which could be explored in future research to provide a more nuanced understanding of genotype-phenotype interactions (11).

Another notable limitation was the reliance on convenience sampling, which may have introduced selection bias. The sample population was primarily recruited from a single hospital, which may not reflect the broader population characteristics. Thus, multi-center studies with larger and more diverse cohorts are recommended to validate these findings. Despite these limitations, the study provides valuable insights into the role of HLA-G polymorphisms in HPV-related cervical carcinogenesis and underscores the importance of incorporating genetic screening into public health strategies for cervical cancer prevention and management (12). Given the significant association between the rs66554220 deletion variant and HPV persistence observed in this study, the potential for this genetic marker to serve as a predictive biomarker for cervical cancer risk warrants further investigation.

Future research should focus on elucidating the molecular mechanisms by which HLA-G polymorphisms influence immune responses to HPV infection, particularly in the context of different HPV genotypes and co-factors such as viral load and co-infections. Functional studies examining the impact of the rs66554220 deletion on HLA-G expression and its downstream effects on immune cell function could provide deeper insights into the role of this polymorphism in cervical cancer pathogenesis. Additionally, exploring potential therapeutic strategies targeting HLA-G-mediated immune evasion, such as inhibitors of HLA-G or enhancement of T cell activity, could open new avenues for the development of immune-based therapies for cervical cancer (13).

CONCLUSION

In conclusion, the study demonstrated a strong association between the HLA-G rs66554220 polymorphism and HPV-related cervical cancer in the Pakistani population, with the deletion variant being significantly linked to increased HPV persistence and higher grades of cervical lesions. The findings suggest that HLA-G genotyping could enhance current screening and prevention strategies by providing a genetic basis for individualized risk assessment. Further studies with larger sample sizes and diverse populations are needed to confirm these results and explore the potential for HLA-G as a biomarker for cervical cancer risk stratification and therapeutic targeting (14).

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