Polish Journal of Microbiology
2021, Vol. 70, No 4, 501–509
https://doi.org/10.33073/pjm-2021-047

ORIGINAL PAPER

Identification of Genetic Variants of Human Papillomavirus in a Group of Mexican HIV/AIDS Patients and Their Possible Association with Cervical Cancer

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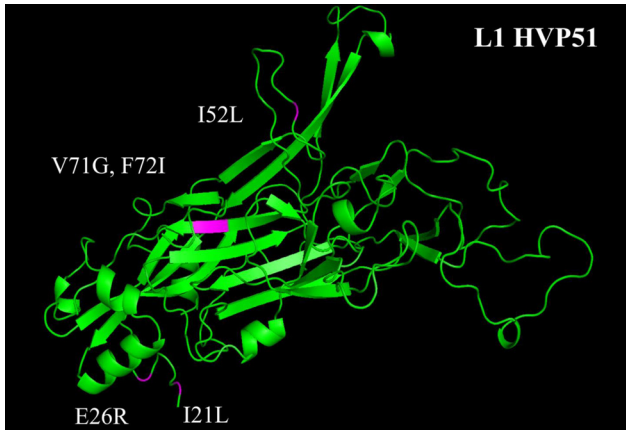
Submitted 11 September 2021, accepted 16 November 2021, published online 20 December 2021

Abstract

Infections caused by the human immunodeficiency virus (HIV) and human papillomavirus (HPV) cause thousands of deaths worldwide each year. So far, there has been no consensus on whether there is a direct relationship between the incidence of neoplasms and the immunosuppression caused by HIV that could help understand if coinfection increases the likelihood of cervical cancer. The objective of the study was to identify the presence of genetic variants of HPV in a group of HIV-positive women and their possible association with cervical cancer. Cervical samples were taken from HIV-positive patients for cytological analysis to identify the HPV genotype by polymerase chain reaction (PCR) and sequencing. The most prevalent L1 capsid protein mutations in the HPV genotype were analyzed *in silico*. Various types of HPV were identified, both high-risk (HR) and low-risk (LR). The most prevalent genotype was HPV51. Analysis of the L1 gene sequences of HPV51 isolates showed nucleotide variations. Of the samples analyzed in Puebla, Mexico, HPV51 had the highest incidence (17.5%, 7/40). Different mutations, which could be used as population markers, were detected in this area, and they have not been reported in the L1 databases for HPV51 in Mexico. Genotypes 6, 14, 86, 87, 89, and 91, not detected or reported in samples from patients with HPV in Mexico, were also identified. Data from the population analyzed suggest no direct relationship between HIV immunosuppression and cervical cancer, regardless of the high- or low-risk HPV genotype. Furthermore, it is possible to develop regional population markers for the detection of HPV based on the mutations that occur in the sequence of nucleotides analyzed.



K e y w o r d s: cervical cancer, human immunodeficiency virus, human papillomavirus, polymorphism

Introduction

The importance of the human papillomavirus (HPV) as an etiological factor in cervical cancer (CC) has been recognized since the 1980s (Muñoz et al. 1994). In developing regions, CC is the second most common type of cancer. In 2018, it caused approximately 311,000 deaths worldwide (WHO 2020). In America, 3.8 million cases were diagnosed in the same year, and about 1.3 million died (www.paho.org). According to GLOBOCAN

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(https://gco.iarc.fr), 4,121 women died from CC in Mexico in 2018, 1.3% of all CC-related deaths worldwide.

HPV belongs to the family Papillomaviridae, which comprises non-enveloped viruses with a double-stranded DNA genome of approximately 8,000 base pairs (bp). There are 228 different types of papillomaviruses registered in the International HPV Reference Center (www.hpvcenter.se) (Bruni et al. 2019). Papillomaviruses are classified into low-risk (LR) and high-risk (HR) types based on their association with cancer (Egawa and Doorbar 2017). It is thus crucial to identify the viral genotype with which a patient is infected. Since people who are immunosuppressed due to infection with the human immunodeficiency virus (HIV) have a high incidence of neoplasms (Goedert et al. 1998; Frisch et al. 2001), immunosuppressed women infected with some type of oncogenic HPV have a greater probability of developing cervical cancer (Clifford et al. 2005).

Several studies have shown that HIV-infected women co-infected with LR-HPV and HR-HPV have a two- to seven-fold greater risk of developing low- and high-grade neoplastic intraepithelial lesions, and even CC, compared to HIV-negative women (Mbulawa et al. 2009; Yamada et al. 2008; Videla et al. 2009). In 2018, Hispanic women with HIV were reported to have a higher incidence of HPV-associated CC compared to other ethnic groups (Ortiz et al. 2018). The present study aimed to identify the presence of genetic variants of HPV in a group of HIV-positive Mexican women undergoing antiretroviral therapy. The polymorphisms of the most prevalent genotype were identified. In some areas of Mexico, HPV51 predominates over other genotypes (Gallegos-Bolaños et al. 2017; Jácome-Galarza et al. 2017; Campos et al. 2019).

Experimental

Materials and Methods

Study population. It was a cross-sectional and descriptive study. It was approved by the review committee of the Hospital General de Puebla and participating patients signed an informed consent form (143/2009). Forty female patients from the Centro Ambulatorio para la Prevención y Atención en SIDA e Infecciones de Transmisión Sexual, in Puebla, Mexico (CAPASITS-SSA), were selected through their clinical records. It was done by considering the last CD4+ lymphocyte count and the last HIV viral load measurement, as long as they were not taken more than six months before enrollment in the study. The HIV viral load measurement and the CD4+ lymphocyte count were performed by the hospital's clinical analysis service per the corresponding diagnosis, treatment, and follow-up guidelines of the World Health Organization (WHO) and the country's health authorities (WHO 2009; 2010). HIV-positive patients were classified into two main groups based on the number of CD4+ cells, one with > 350 cells/mm^3 and the other with < 350 cells/mm^3. This threshold was the main criterion for the initiation of antiretroviral therapy and was significantly associated with more rapid HPV clearance (Sabin and Phillips 2009; Kang and Cu-Uvin 2012).

Biological material. Two endocervical exfoliation samples were taken. One for cervical cytology analysis (a thin prep) and one for DNA extraction and PCR amplification.

Cervical cytology. A clean, non-lubricated vaginal mirror and an Ayre spatula were used to collect endocervical secretions. The smears were placed on previously labeled glass slides and fixed with 95% ethanol. After staining using the Papanicolaou method, the smears were analyzed in the Cytopathology Department of the Medical School of the Benemérita Universidad Autónoma de Puebla. Possible cellular abnormalities found by the thin prep were analyzed and classified according to the Bethesda classification system as Type I (negative), negative for intraepithelial lesion or malignancy; Type II (inflammatory process), reactive cellular changes associated with radiation, intrauterine contraceptive device, glandular cells status post hysterectomy, cellular changes consistent with viral activity, *Trichomonas vaginalis*, fungal organisms, etc.; Type III (LSIL): low-grade squamous intraepithelial lesions; Type IV (HSIL), high-grade squamous intraepithelial lesions (Nayar and Wilbur 2015).

HPV Amplification Assays by Polymerase Chain Reaction. For the collection of cervical samples and DNA extraction, the QIAamp Fast DNA tissue kit® with dacron swabs and transport buffer (Qiagen®) was used following the manufacturer's instructions. For the amplification reaction, the QIAGEN Multiplex PCR kit® was used following the manufacturer's instructions, with the following general primers: MY09/11 and GP5+/GP6+. These primers amplify conserved sequences of the HPV L1 gene of both high and low-risk types. The primers for the actin gene were used as an internal control (Manos 1991; Qu et al. 1997). For the identification of HPV types in the amplified samples, the PCR products were sequenced with the dideoxy method using an Abi Prism 310 Sequencer (Applied Biosystems) and the primer GP5+ in all sequencing reactions. The sequences obtained were aligned using the Basic Local Alignment Search Tool (BLAST) of the NCBI platform to determine the similarity of the regions of interest (Madden 2008).

Nucleotide and amino acids sequence analysis. The nucleotide and amino acid sequences of positive samples

were compared against GenBank using Blast. A multiple alignment of these sequences was performed (ClustalW Multiple Alignment v1.4) using BioEdit Sequence Alignment Editor version 7.0.9.0. (Hall 1999): For the analysis of nucleotides, the sequence MH577959.1 (Xu et al. 2019) was used as a reference. For the analysis of amino acid sequences, the sequence ARQ82736.1 was used (Oliveira et al. 2017). See the attached key resources table.

Homology modeling. The L1 structure of HPV51 was generated from amino acid sequences ARQ82736.1 in the I-TASSER platform (Roy et al. 2012; Yang and Zhang 2015). The preliminary sequence alignments were performed using the local meta-threading server of I-TASSER (Wu and Zhang 2007) to generate a list of templates for modeling (i.e., 3IYJ, 3OFL, 2R5K, and 1DZL). In addition to the sequence alignment, I-TASSER uses the TM-align structural alignment program to match the first I-TASSER model to all structures in the Protein Data Bank (PDB) library. For this monomer, the PDB codes used were 3IYJ, 1DZL, 2R5I, and 2R5K. The model validation outcome on the same website gave no hints of bad/unusual geometrical features. The visualization was performed using the program PyMOL (TM) 1.7.4.5 Molecular Graphics System, Version 2.0 Schrödinger, LLC.

Statistical analysis. Descriptive statistics were used for quantitative and categorical variables. The Pearson's *chi*-squared test was used to check whether the prevalence of HPV infection increased with age or the presence of certain genotypes. The age of the patients was stratified into groups of < 45 years, 45–54 years, and > 54 years (Lazcano-Ponce et al. 2001; Tharcisse et al. 2020). The interaction between high-risk genotypes in each group of patients was also analyzed. Spearman's Rho or Pearson's tests were used to assess the correlation between the variables of viral load, CD4+ cell count, and low and high-risk subtypes of HPV. The statistical analysis was performed using IBM® SPSS® Statistics version 25.0. See the attached key resources table.

Results

Presence of HIV and immunological status of the patient. Clinical features. The analysis of the patients' clinical history showed they had been infected with HIV for an average of 4.6 years after AIDS diagnosis and had been under antiretroviral treatment for an average of 3.46 years. Table I describes the age and the last measurement of CD4+ cells.

HPV prevalence. Amplification assays showed that 77.5% (31/40) of the study population were positive for some HPV type, while 22.5% (9/40) were negative. The following types of HR-HPV were found in 37.5%

Table I
Clinical characteristics of the patients.

Patient age	HIV viral load (copies/ml)	CD4+ (cell/ml)	Pap cytology[1]	HPV type[2]
Group I[3]				
45	< 50	744	I and II	90 (LR)
30	< 50	726	I and II	ND
23	5,840	655	I	11 (LR)
30	< 50	602	I and II	97 (LR)
17	90,800	580	I and II	51 (HR)
42	< 50	521	I	ND
44	< 50	506	I	66 (HR)
50	400	503	I and II	16 (HR)
35	< 50	485	I	16 (HR)
27	< 50	481	I and II	51 (HR)
37	< 50	410	IV	51 (HR)
42	< 50	405	I	11 (LR)
60	57	388	I	58 (HR)
29	< 50	380	I and II	70 (LR)
31	4,940	364	I and II	ND
Group II[3]				
35	< 50	317	I and II	ND
35	< 50	294	IV	ND
24	1,170	282	I and II	ND
30	< 50	280	III	54 (LR)
42	< 50	258	I and II	102 (LR)
49	< 50	255	I and II	6 (LR)
35	< 50	208	I	84 (LR)
32	369	180	I	51(HR)
36	13,900	175	I and II	51 (HR)
37	< 50	161	III	81 (LR)
28	67	160	I and II	ND
24	74,620	146	I and II	ND
51	< 50	132	III	51 (HR)
37	73	127	IV	81 (LR)
48	5560	104	I and II	6 (LR)
43	< 50	103	I and II	86 (LR)
37	ND	102	I	56 (HR)
31	< 50	76	III	52 (HR)
23	> 100,000	70	I and II	6 (LR)
34	822	65	III	58 (HR)
63	451	63	I and II	ND
44	5,140	60	I and II	51 (HR)
25	95200	30	I and II	81 (LR)
41	ND	22	III	33(HR)
31	> 100,000	16	I and II	70 (LR)

[1] – Pap cytology results according to the Bethesda classification system (2014 update) (Nayar 2015), see experimental procedures
[2] – HPV type (HR – High Risk, LR – Low Risk, ND – not determined)
[3] – CD4+ cell count results were classified into two groups, Group 1: > 350 cells/mm^3 and Group 2: < 350 cells/mm^3

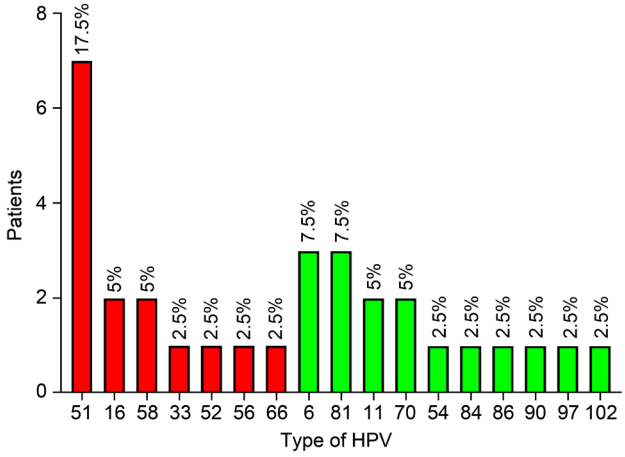

Fig. 1. HPV genotype frequency detected by PCR. Red bars – HR-HPV types, green bars – LR-HPV.

(15/40) of the samples: 16, 33, 51, 52, 56, 58 and 66. The most frequent types were HPV 51 (17.5%, 7/40), 16 and 58 (both 5%, 2/40), 33, 52, 56 and 66 (each with 2.5%, 1/40). The following LR-HPV types were found in 40% of the samples: 6, 11, 54, 70, 81, 84, 86, 90, 97 and 102. The most frequent types were HPV 6 and 81 (both 7.5%, 3/40), followed by 11 and 70 (both 5%, 2/40), 54, 84, 86, 90, 97 and 102 (2.5% each, 1/40) (Table I, Fig. 1 and 2).

Pap cytology, HPV and CD4+ lymphocytes status. As can be seen in Table I and Fig. 2, nine (22.5%) patients presented some type of high or low grade cervical intraepithelial neoplasia, five were positive for some type of HPV-HR (33, 51, and 52), four were positive for some type of HPV-LR (54 and 81), and in only one patient with HGSIL the associated type of HPV could not be identified. Thus, no relationship was found between the type of HPV, its risk level, and the age of the patients (< 45, 45–55, and > 55 years) (Fig. 2).

As mentioned, HIV-positive patients were classified into two groups based on the number of CD4+ cells, one with > 350 cells/mm^3 and the other with < 350 cells/mm^3. It was found that 15 patients out of 40 (37.5%) had CD4+ cell counts > 350 cells/mm^3, while 25/40 (62.5%) had < 350 cells/mm^3 (Table I). According to the CDC classification system (CD4+ ≥ 500; CD4 + 200–499; CD4+ < to 200), and the presence of LR and HR-HPV genotypes was evaluated. According to Spearman's test, there was no relationship between the prevalence of HPV subtypes and the CD4+ cell count (Kamps et al. 1994).

HPV51 Nucleotide sequence analysis. A multiple alignments of the identified HPV sequences was performed (Fig. 3). Several nucleotide substitutions could be observed in the primary sequence of the L1 protein from clinical samples. The analyzed sequences were translated, and the polymorphisms were identified through multiple alignments (Fig. 4).

Structural analysis of the polymorphisms of HPV51. There are reports of crystallized structures in the L1 region of different HPV types such as 16 and 18, but they had not been reported for HPV51. The L1 monomer of HPV51 was used to check whether the mutations found in patient samples in the present study corresponded to previously reported mutations (Bishop et al. 2007) in HPV16. The results showed that

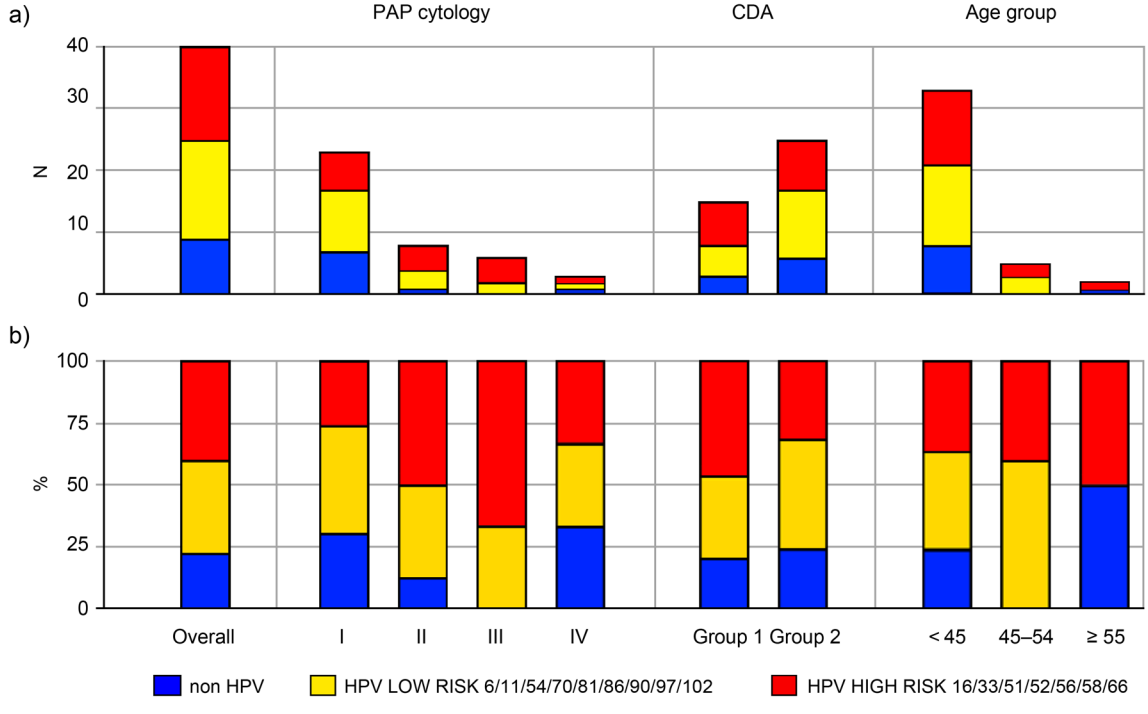

Fig. 2. Frequency of HPV types. a) Raw data, b) calculated percentage. Age was classified into three groups: < 45, 45–54, ≥ 55 years.

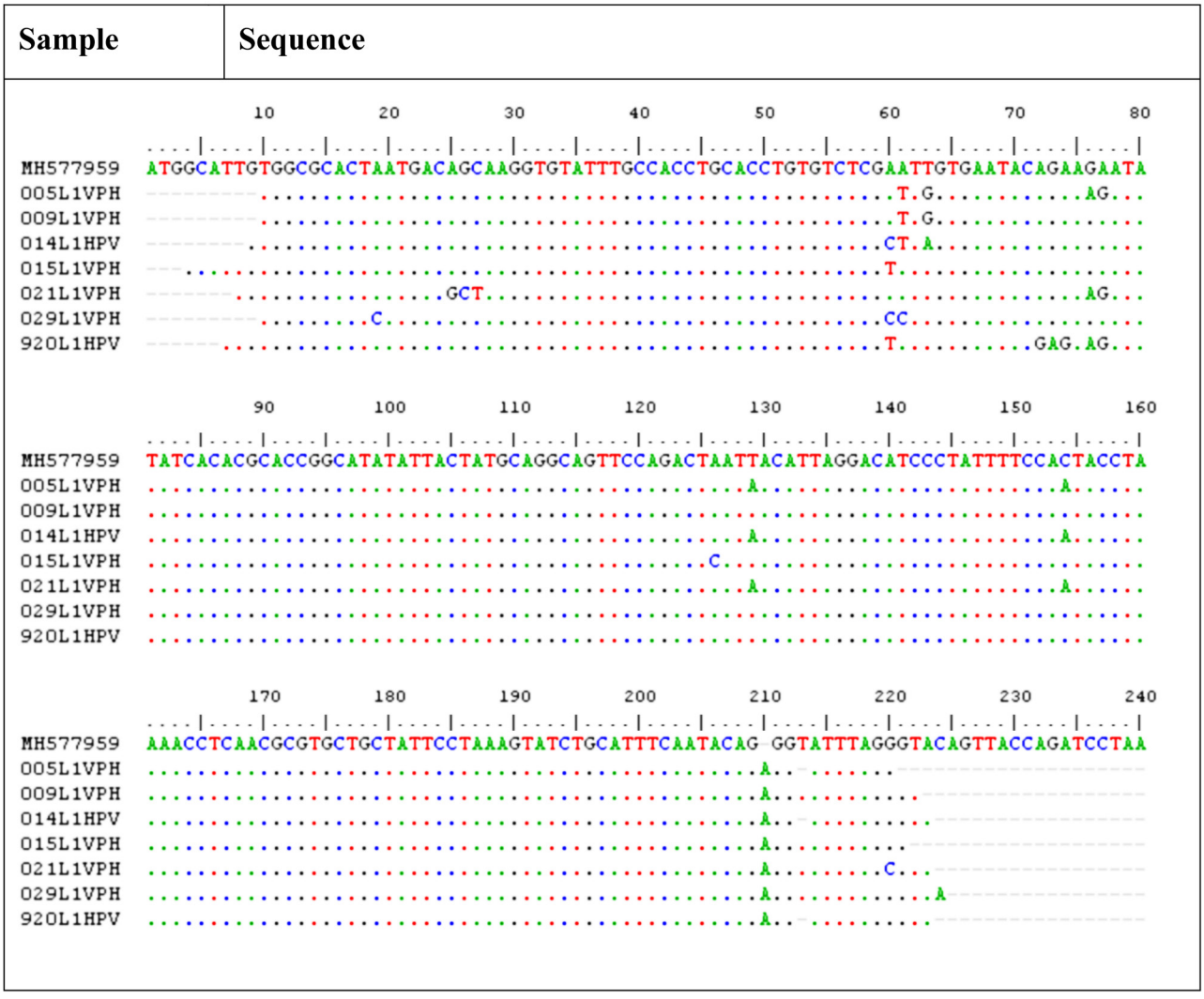

Fig. 3. Comparison of nucleotide sequences of the L1 gene of HPV51 from clinical samples. The figure shows nucleotide sequences of seven HPV51-positive clinical isolates. The reference sequence is at the top. The nucleotides from the clinical samples that were homologous to the reference sequence are shown as points. Capital letters indicate differences concerning the reference sequence. Sequence alignment was performed using ClustalW multiple alignment software v1.4.

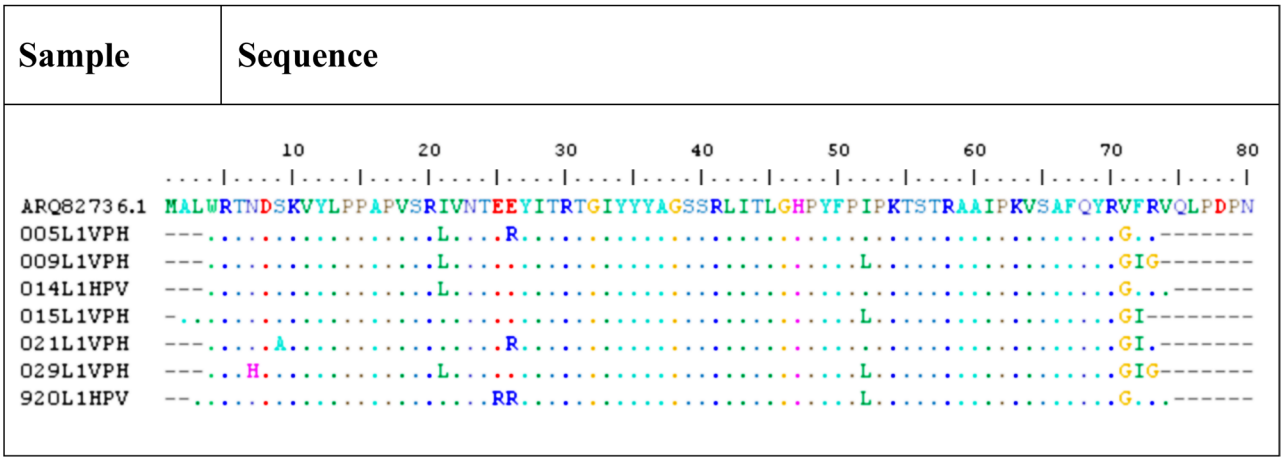

Fig. 4. Comparison of amino acid sequences of the L1 gene of HPV51 from clinical samples. The figure shows amino acids sequences of seven HPV51-positive clinical isolates. The reference sequence is at the top. The amino acids from the clinical samples that were homologous to the reference sequence are shown as points. Capital letters indicate differences with respect to the reference sequence. Sequence alignment was performed using ClustalW multiple alignment software v1.4.

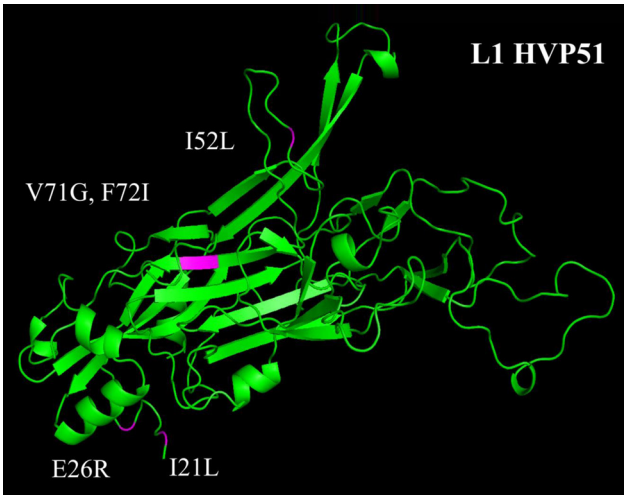

Fig. 5. The L1 monomer of HPV51. The I21L, E26R, I52L, V71G, and F72I mutations are highlighted in magenta.

the mutations found in the present work did not correspond to previously reported mutations. Fig. 5 shows the I21L, E26R, I52L, V71G, and F72I mutations.

Discussion

Cervical cancer is the third most common cancer affecting women in Mexico. The human papillomavirus is a factor associated with the development of this type of cancer. Furthermore, it has been reported that HIV-positive women have a higher prevalence of HPV and cervical cancer than HIV-negative women (Palefsky 2009). An HPV prevalence of 77.5% was found in the present study, which is very similar to what has been reported in other studies carried out in Mexico (Peralta-Rodríguez et al. 2012; Salcedo et al. 2014) and other countries (69–97.2%) (Sahasrabuddhe et al. 2007; Singh et al. 2009). The most common types of HPV in HIV-positive women in African countries such as Kenya and Togo have been reported to be: 16 (4.5%), 18 (3.1 to 8.6%), and 58 (3.6%) (Clifford et al. 2006; Menon et al. 2016; Nyasenu et al. 2019). Other authors have found that HPV types 52 (37.2%) (Clifford et al. 2006; Sahasrabuddhe et al. 2007; Menon et al. 2016; Abel et al. 2019; Nyasenu et al. 2019) and 45 (24.6%) (Desruisseau et al. 2009) have a higher prevalence. Moreover, it was found that HIV patients have a high prevalence (46.7–90.3%) of oncogenic HPV types (Sahasrabuddhe et al. 2007; Desruisseau et al. 2009; Menon et al. 2016; Vyankandondera et al. 2019).

Several studies have long determined that the most common HPV types found in Mexico are HPV16, 18, 31 and 33 (Lazcano-Ponce et al. 2001; López Rivera et al. 2012; Aguilar-Lemarroy et al. 2015; Salcedo et al. 2015; Ortega-Cervantes et al. 2016). However, other genotypes have been detected with high frequency in some regions of Mexico. For example, HPV-31 is the most common type in cities such as Guanajuato and San Luis Potosí (López-Revilla et al. 2008), while genotype 58 is the most frequent in Yucatan (Canche et al. 2010). HPV has been found with a prevalence of 77.5% in Mexico, of which 37.5% corresponds to HR-HPV and 40% to LR-HPV types. Interestingly, the presence of uncommon HPV types has been identified in HIV-positive women such as types 54, 56, 70, 84, 86, 90, 97, and 102, both high and low risk (Table I) (Lazcano-Ponce et al. 2001; Montoya-Fuentes et al. 2001; López-Revilla et al. 2008; Salcedo et al. 2015). The present study found a high prevalence of HPV51 (17.5%) with various grades of the lesion (10% with grade I and II lesions; 2.5% in high- and low-grade intraepithelial neoplasia). The prevalence of HPV51 was thus three times higher than that of HPV16 and seven times higher than that of HPV33. It is consistent with the results of recent studies, which have also found a high prevalence of HPV51 in Mexico (Gallegos-Bolaños et al. 2017; Jácome-Galarza et al. 2017; Campos et al. 2019) and other countries such as Turkey (Gultekin et al. 2018), Greece (Argyri et al. 2018), Italy (Lillo et al. 2001), Tanzania (Mayaud et al. 2001), Kenya (Ferré et al. 2019; Omire et al. 2020) and Canada (de Pokomandy et al. 2018).

The present study results do not show an association between HPV types and the grade of the lesion. The variability in viral prevalence between studies may be due to the geographic location of the studied populations since it has been proposed that HPV types are differentially distributed among different populations and geographic locations (Yamada et al. 2008). As indicated above, there are different types of HPV in Mexico, and it is important to define the geographical distribution of these genotypes among the different regions of the country. A study on the phylogenetic classification of Alphapapillomavirus, including alpha-5 (HPV26, 51, 69, 82), determined that each genotype has an independent evolutionary history, that some regions of the capsid (L1) are more stable than others, and that certain variants are geographically related. Thus, it is important to determine specific polymorphisms (SNP's) and their geographical dispersion (Chen et al. 2018). Different mutations in the structure of the HPV16 L1 pentamer have been reported (Rodrigues et al. 2018) to affect the loops containing the epitopes recognized by neutralizing antibodies. These mutations also affect the conformation and composition of the epitopes and the antigenicity of the viral surface.

Since the crystallized structure of the L1 region of HPV51 has not been reported before, a monomer was generated by homology to check if the mutations found in the patient samples corresponded to mutations reported before (Bishop et al. 2007). Fig. 5 shows the three-dimensional model of these mutations (the I21L, E26R,

I52L, V71G, and F72I mutations are highlighted). The mutations do not structurally alter the monomer, nor are they located in the regions recognized by neutralizing antibodies. Thus, they could be used as population markers, given that these mutations have not been reported in the L1 databases for HPV51 in Mexico. Finally, there is clinical evidence that the CD4+ T-cell dependent response is effective in controlling HIV infection or replication, and it has been suggested that a greater number of CD4+ T-cells could help control HPV infection in HIV-positive patients (Montoya Guarín et al. 2006; Hanisch et al. 2013; Chambuso et al. 2020). The results of the present study do not suggest a similar role for the CD4+ cells in controlling high or low-risk HPV infection, the number of CD4+ cells, or the type and frequency of neoplastic cervical lesions, which is consistent with the results of other studies (Sopracordevole et al. 1996; Cardillo et al. 2001). It was possible to identify a high prevalence of HPV-51 with nucleotide variations that could be used to characterize the viral polymorphism present in this specific population group.

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Acknowledgments

This work was an inter-institutional effort. The authors are deeply grateful to all those who made this research possible.

Funding

This work received specific funding from the Secretaría de Educación Pública de México (PROMEP/103.5/08/1899).

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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