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Human Papillomavirus 16 (HPV16) in the Middle East and North Africa: Molecular, Epidemiology and Clinical Characterization

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Abstract

Human papillomavirus (HPV) is the main cause of sexually transmitted infections, globally. Clinical characterization and Phylogenetic analysis of HPV can be useful in improving the preventive and management measures in the Middle East and North Africa (MENA). The objectives of our study were to estimate the prevalence of HPV16 and its associated human cancers and to evaluate phylogenetic clustering proportions as a measure of viral domestic transmission in the MENA region. Gen-Bank was the source of all HPV16 sequences that had been collected in the MENA region; also, the sequence metadata (if obtainable) was retrieved. The probable phylogenetic clusters were identified using Neighbour Joining phylogenetic analysis. The total number of available HPV16 sequences was 997 (which presented just a total of 9 MENA Countries) dispersed as follows: Iran had the highest number of HPV16 sequences (n = 664, 66%), followed by Morocco (n = 176, 17.6%), and Turkey (n= 64, 6.42%)

The findings demonstrated that the MENA have high incidence of HPV 16 infection in females as well as high frequencies of the HPV 16 genotypes (sequences linked to the E6 gene) associated with cervical cancer in the MENA. On the other hand, it was noted that the number of HPV16 available sequences in the MENA region has increased over time. Analysis of the HPV16 clusters revealed that transmission of HPV 16 was between the countries of the MENA region, such as (Morocco and Algeria), (Morocco and Iran) and (Iran, Morocco, and Algeria).

Keyword: Human Papillomavirus; Middle East and North Africa; Epidemiology, phylogenetic; E6 gene; L1gene, HPV16

1. Introduction

Human papillomavirus (HPV) is a small, double-stranded DNA virus responsible for causing both skin-related and sexually transmitted diseases. It belongs to the Papillomaviridae family. (Tommasino, 2014) .HPV is notably one of the most common causes of sexually transmitted infections globally, with both men and women facing a 50% chance of acquiring the virus at least once in their lifetime. (Handler et al., 2015). In addition, HPV has the ability to infect both cutaneous and mucosal epithelial tissues, including those of the skin, upper respiratory tract, and anogenital region.(Tommasino,2014)

The homologous nucleotide sequence of the L1 protein has been used to identify over 200 genotypes of HPV. A phylogenetic tree was constructed, classifying HPV types into five genera: α, β, γ, μ, and v. (Bernard et al., 2010 and de Villiers, 2013). The α genus (mucosal)includes about 30 HPV types linked to the infection of the mucosal epithelial tissues of the oral and anogenital tracts, as well as benign cutaneous HPV types that cause skin warts. Mucosal HPV types are categorized as low-risk (LR) or High-risk (HR) based on their oncogenic abilities. Infections caused by LR-HPVs (HPV 6 and HPV11) comprise recurrent respiratory papillomatosis, skin warts, and benign gynecological papillomas (Ouda et al., 2021 and Lacey, Lowndes, and Shah 2006).

Furthermore, HR-HPVs (types -16, -18, -31, -33, -35, -39, -45, -51, -52, -55, -56, -58, -59, -68, -73, -82, and -83) have oncogenic ability and are associated to develop the human cancer (Bernard et al., 2010). HR-HPVs are subsequently demonstrated to be linked to a subset of further genital cancers in addition to colorectal, breast, head, and neck, cancers (Brianti, De Flammineis, and Mercuri, n.d.; Delgado-García et al., 2017). Specifically, in cervical cancer, HPV 16 and HPV 18 are often prevalent, with over 96% of these cancers testing positive for both virus types(Smith et al., 2007and Muñoz et al., 2003)

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On the other hand, multiple studies (in vitro and in vivo) revealed the β HPV genus to have oncogenic properties (Gabet et al., 2008 and Michel et al., 2006). Nevertheless, the μ, γ, and v genera are implicated in skin tropism but have no identified roles in oncogenesis (Tommasino, 2014).

The HPV genome measures around 8 kb and has 8 or 9 open-reading frames (ORFs) on the same DNA strand (13). The HPV genome is split into three distinct regions: an early part, which includes the early genes (E1, E2, E4, E5, E6, and E7); a late part, which includes the late genes (L1 and L2); and a non-coding region, known as the long control region (LCR) found between ORFs L1 and E6. (13). The L1 ORF encodes the Main capsid protein L1, which has 55 KDa (Buck, Day, and Trus 2013 and Akhatova et al., 2022). Additionally, the L1 OR is the most conserved genomic sequence. As a result, it is utilized for the phylogenetic categorization of viral types or subtypes (de Villiers ,2013 and de Villiers et al., 2004).

Interestingly, the two major HPV oncoproteins are E6 and E7, and the variants of the E6 and E7 genes in HPV-16 are linked to ongoing HPV infection and cancer development (Cornet et al., 2012). Despite HPV-16 being the most common cancer-causing genotype globally, the type-specific prevalence of medically significant HR-HPVs differs by geographic area (Burk, Harari, and Chen 2013 and Guan et al., 2012). The three most prevalent HPV types found in 74.5% of cervical cancer in Sub-Saharan Africa are HPV-45, HPV-18and HPV-16 (in ascending order of prevalence, whilst the HPV subtypes associated with cancer are generally similar across countries (Cornet et al., 2012 and Cornet et al., 2013).

Numerous studies conducted that, globally revealed the prevalence of HPV infection subtypes in human cancers varied. , demonstrating an association between HPV prevalence and geographical location(Smith et al., 2007 and Fernandes et al., 2020). Thus, studying viral transmission in a region such as the MENA region which shares similar cultural, demographic, and economic characteristics as a whole could be helpful in the epidemiological exploration of virus distribution(Athamneh et al.,2023).

There is a limited data about HPV16 prevalence or HPV16 infection and human cancers as well as the HPV16 transmission in the MENA. Hence, the objectives of our study were to estimate the prevalence of HPV16 and its associated human cancers and to evaluate phylogenetic clustering proportions as a measure of viral domestic transmission in the MENA region.

2. Methodology

2.1. Source of data

A search was performed using the GenBank search tool, part of the National Institutes of Health (NIH) genetic sequence database (www.ncbi.nlm.nih.gov/genbank) to retrieve all available HPV16 sequences collected from the following MENA region countries: Qatar, Egypt, Iraq, Iran, Kuwait, Saudi Arabia (KSA), Somalia, Jordan, Algeria, Bahrain, Oman, Turkey, Morocco, Palestine, Mauritania, Tunisia, Lebanon, Syria, Libya, UAE, Sudan, and Yemen. The search concluded on April 7, 2023, when available metadata for the sequences were also obtained, including information such as the individual's sex, the country and year of sequence collection, sample data, and the viral gene analyzed. The algorithm used to retrieve the HPV16 sequences, along with the demographic and clinical characterization, is presented in. (Figure 1)

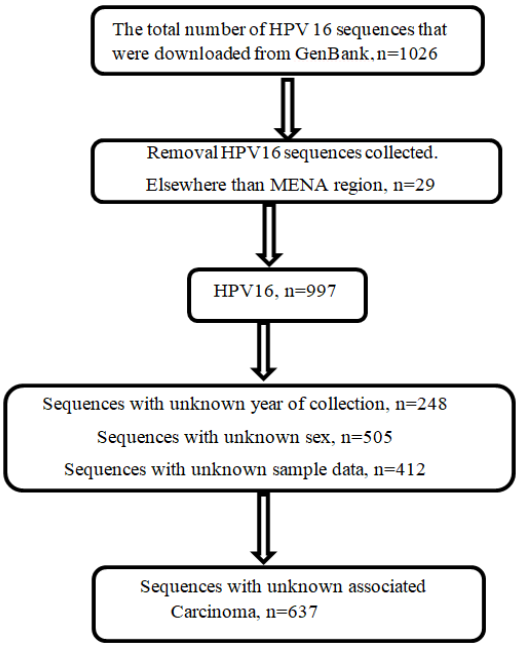

Figure1: The MENA HPV16 sequence selection algorithm served as the foundation for clinical and demographic characterization. MENA: Middle East and North Africa; HPV: Human Papilloma Virus

2.2. Analysis of the MENA Region's Domestic HPV16 Transmission

Phylogenetic tree based on Neighbour Joining (NJ) method analysis of 444 bp sequence of the E6 gene. Root sequence (GenBank NC_001526 accession). The E6 gene is crucial in HPV-related cancer development

The BLAST tool was used to find similar HPV16 GenBank sequences. The most ten similar sequences were found and added to the final NJ analysis along with the MENA region's sequences. (24). Excluded from the analysis were sequences having stop codons and those with the same accession number.

2.3. Statistical analysis

Analysis was performed with IBM SPSS Statistics. The associations between qualitative variables were appraised through the use of the chi-square ($\chi 2$).

3. Results

3.1. The MENA HPV16 Molecular Dataset's characteristics

The sequences were collected between 2004 and 2022, with the total number of HPV16 sequences being 997 sequences (that represented just a total of 9 MENA Countries) were dispersed as follows: Iran had the highest number of HPV16 sequences. (n = 664, 66.6%), followed by Morocco (n = 176, 17.65%), and Turkey (n= 64, 6.42%) as shown in (Figure 2).

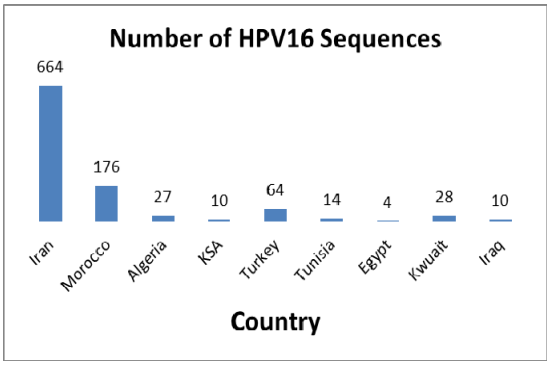

Figure 2: The total number of HPV16 MENA sequences stratified per country. HPV16: Human Papilloma Virus16; MENA: Middle East and North Africa; KSA: Kingdom of Saudi Arabia.

3.2. HPV16 sequences prevalence in the MENA region by sex

There were 492 HPV 16 sequences in total with known sex in the MENA region. Females had a high percentage of the available HPV 16 sequences (n=481,98%), as seen in (Figure 3)

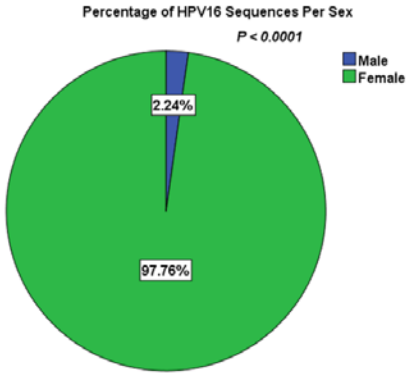

Figure3: percentage of whole HPV16 sequences per sex in the MENA region; HPV16: Human papillomavirus 16; MENA: Middle East and North Africa

3.3. percentage of the HPV16 genes that were analyzed in the MENA region.

The whole number of available HPV16 sequences with known analyzed genes in the MENA region was 988; the L1 gene had the largest percentage of these genes (41.72%), followed by the E6 gene (38%) However, the E5 gene had the lowest proportion (10%). as shown in (Table1).

Table1. The percentage of HPV16 analyzed genes in the MENA region; N: Number of the HPV16 analyzed genes; %: the percentage of analyzed genes; HPV16: Human Papillomavirus 16; MENA: Middle East and North Africa

HPV16 gene	**N**	%
L1	408	41.29%
L2	6	0.61%
E1	5	0.50%
E5	1	0.10%
E6	379	38.36%
E7	62	6.30%
LCR	127	12.85%

3.4. prevalence of carcinoma-related HPV16 in the MENA region

The total number of available HPV16 sequences that related to the cancer was 360, the most common carcinoma in the MENA region was cervical carcinoma (293:82%), followed by Oropharyngeal squamous cell carcinomas (26:7.28%) as shown in (Table 2). Compared to other cancers, cervical carcinoma had a significantly high percentage in the MENA region (Figure 4).

Table 2: percentage of the HPV16 sequences that related to the carcinoma in the MENA region; HPV16: Human Papillomavirus16; MENA: Middle East and North Africa; N: Number of HPV16 sequences related to carcinoma cases; %: percentage of HPV16 sequences related to carcinoma cases

carcinoma group	N	%
Cervical carcinoma	293	81.2%
prostatic cancer	7	2%
Oropharyngeal squamous cell carcinomas	26	7.2%
Esophageal cancer	20	5.60%
Lung cancer	2	0.56%
Breast cancer	12	3.3%

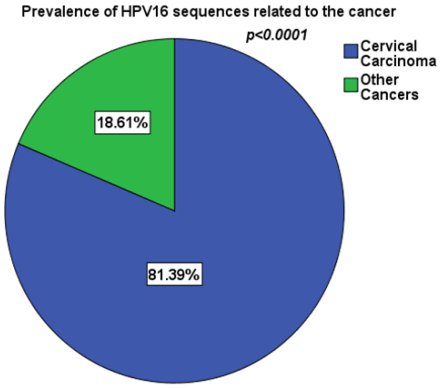

Figure 4: percentage of the HPV16 sequences that related to the cervical cancer and other cancers in the MENA region; HPV16: Human Papillomavirus16; MENA: Middle East and North Africa; other cancers: prostatic cancer Oropharyngeal squamous cell carcinomas, Esophageal cancer, Lung cancer, Breast cancer.

3.5. Prevalence of HPV16 sequences per sample data in the MENA region

The available HPV16 sequences with known sample data were divided into samples per anatomic region (Table 3) and samples from the patient group (Table 4). Regarding the samples per anatomic region, there were about 248 samples. Scientifically, the samples taken from the cervical region had a higher percentage compared to those taken from other regions as presented in (Figure 5). On the other hand, the total number of samples per patient group was about 337 samples (as documented at NCBI the samples were taken from patients with cancer or benign tumors in general without any details). A higher prevalence was noted in samples from patients with cervical cancer (293.87%), followed by those from patients with esophageal cancer (20.59%), as presented in (Table 4).

Table 3. prevalence of samples per anatomic region in the MENA region; MENA: Middle East and North Africa. Cervical region: cervix tissue, cervical scrape, cervical swab, pap smear, cervical smear; N: Number of HPV16 sequences identified in samples across various anatomic regions.; %: percentage of HPV16 sequences identified in samples across various anatomic regions.

samples per anatomic region	N	%
Cervical region	148	59.7%
oral cavity	14	5.64%
Larynx	36	14.50%
Tonsil	2	0.80%
Pharynx	5	2.00%
Saliva	6	2.40%
multiple region	36	14.50%
Genital	1	.0400%

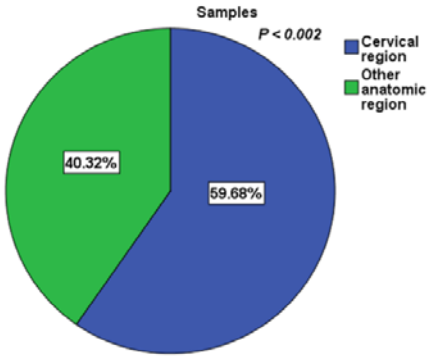

Figure5. Prevalence of samples that were taken from cervical region and other anatomic region in the MENA; MENA: Middle East and North Africa; other anatomic region: oral cavity, larynx, tonsil, pharynx, salivary gland, multiple regions, genital.

Table 4. prevalence of samples per patients' group in the MENA region; MENA: Middle East and North Africa; n: number of the sequences of sample per patients' group; %: percentage of the sequences

sample per patients' group	N	%
patient with cervical carcinoma	293	87.00%
patient with prostatic cancer	7	2.07%
patient with benign prostatic hyperplasia	3	0.89%
patient with Breast cancer	12	3.60%
Esophageal cancer	20	5.93%
lung cancer	2	0.60%

3.6. Prevalence of HPV16 genes that are associated with cancer in the MENA region.

The total number of HPV16 sequences that span apart of E6, L1or L2 genes that were associated with cancers in the MENA region was about 360 sequences. The E6 gene was linked with the highest percentage of cervical carcinoma (224,62.2%), followed by the L1gene (64,17.8%) and L2 gene (5,1.38%). The L1gene was associated with other cancers such as lung cancer (2,0.5%), prostatic cancer (7,1.94%), oropharyngeal squamous cell carcinomas (26,7.2%), esophageal cancer (20,5.5%) and breast cancer (12,3.33%) as presented in (Table 5) A significantly higher prevalence of sequences associated with the E6 gene related to cervical carcinoma was observed compared to other gene sequences, p <0.0001, as illustrated in (Figure 6)

Table 5. Percentage of HPV16 sequences that related to (E6,L1and L2genes) and associated with cancers in the MENA region; HPV16: Human papilloma virus 16 ; MENA :Middle East and North Africa; n:number of the HPV16 sequences; %:percentage of the HPV16 sequences

HPV gene	cervical carcinoma (n, %)	Lung cancer (n, %)	Prostatic cancer (n, %)	Oropharyngeal squamous cell carcinomas (n, %)	Esophageal cancer (n, %)	Breast cancer (n, %)
E6	224,62.2%	0	0	0	0	0
L1	64,17.8%	2,0.05%	7,1.94%	26,7.2%	20,5.5%	12,3.33%
L2	5,1.38%	0	0	0	0	0

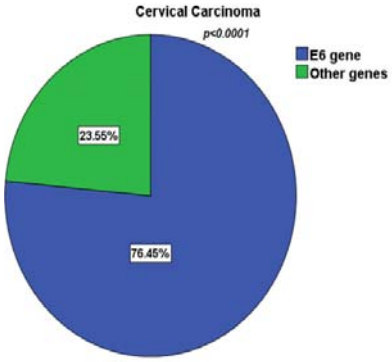

Figure 6. Prevalence of HPV16 sequences related to E6 gene and other genes that were associated with cervical carcinoma in the MENA region; HPV16: Human papilloma virus 16; MENA: Middle East and North Africa; other genes: L1 and L2.

3.7. Variations over time in the number of MENA region HPV16 sequences that are available.

The total number of HPV16 sequences with a known year of collection was 749. We excluded 248 HPV 16 sequences that did not have the dates of collection; there was a significant temporal change in the number of HPV16 MENA sequences that were available. Nonetheless, there was an increase in the number of sequences, particularly between 2012 and 2022, as shown in Figure7.

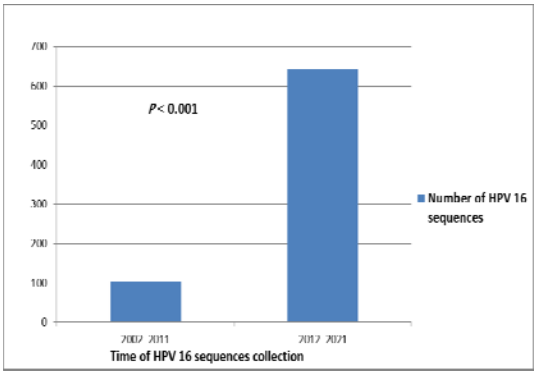

Figure7.HPV16 sequence number in the MENA region over time. HPV16: Human papillomavirus16; MENA: Middle East and North Africa.

3.8. Potential domestic transmission of HPV16 in the MENA

Neighbour Joining analysis was performed to assess the proportion of HPV16 sequences that are probably linked in transmission clusters suggesting domestic transmission, which found the proportion of phylogenetic clustering. According to the size of the cluster, each cluster was classed as a dyad (2 sequences), a small network (3-14 sequences), or a large network (at least fifteen sequences). For the E6 gene, the overall number of sequences contained within domestic phylogenetic clusters was 15/332 (4.52%). Clusters included dyads (n=1, 6.6%), small networks (n=11,73%), and large networks (n=3,20%). Some of the clusters are limited only to one country of the MENA region; for instance, the dyad (Iran (1)), 2 out of 11 of the small networks (Morocco (3), and Iran(3)),1 out of the 3 of the large networks (Morocco (22)) . On the other hand, some of the small and large networks included the United States and one or more of MENA countries.

Small network[1] :(Guatemala (1), Morocco (1), USA (4) and Iran (8)), small network[2]: (Morocco (1), Guatemala (1), USA (1), and Iran (4)), small network[3]:(Iran (3), Guatemala (1), Morocco (1), and USA (2),

Small network[4]: (Iran(5), Guatemala(1), and USA(2)) ,small network[5] : (Iran(3), Morocco(1), USA(2), and Algeria(1)), small network[6]: (Iran(3), Guatemala(1), Morocco(1),Japan(1) and USA(1)), small network[7]: (Iran(4),USA(2),Morocco(1)),small network[8]: (Algeria(2),Morocco(2)),small network[9] :(Morocco(3),Algeria(1),Iran(10))

Large network[1]: (Morocco (19), and USA (1)), large network [2]: Morocco (10), Iran (19)

A portion of the transmission clusters that originated in the MENA region were collected in two or more countries.: Iran and Morocco (small and large network), Iran, Morocco, and Algeria (small network), Algeria and Morocco (small network). The JN tree, which was utilized to determine the probable transmission clusters in the MENA area was supplied in (Supplementary Materials).

4. Discussion

There is limited data about the phylogenetic examination of HPV transmission in the MENA region, previous studies only covered one country or a region of one country. Investigating the HPV prevalence and phylogenetic of HPV transmission in the MENA region may show trends that might direct preventative measures (Fernandes et al., 2022). Nevertheless, in most MENA countries, there is no HPV infection testing because of stigmatization based on religious or traditional norms, potentially resulting in limited sample sizes alongside low incidence rates of HPV infection, and miscalculating the actual number of cases (Obeid et al., 2020).

The study's main finding was the observation of a high percentage of HPV16 sequences in females as well as a high prevalence of HPV16 sequences that related to cervical cancer in the MENA region, which led to an increase in the prevalence of samples that had been taken from the cervical region. This result seems plausible, considering the prior evidence showed that the prevalence of cervical cancer associated with HPV16 had increased in the MENA region (Obeid et al., 2020).

Significantly, a high prevalence of HPV16 sequences related to the E6 gene that were associated with cervical cancer in the MENA region. This result is consistent with the previous evidence which demonstrated that the two primary HPV oncoproteins are E6 and E7, and variants in the E6 and E7 genes in HPV-16 are linked to ongoing HPV infection and the development of cancer(Cornet et al., 2012 and Mirabello et al., 2017).There are several sequence variants (known as single nucleotide polymorphisms, or SNPs) within the E6/E7 gene region in cervical pre-cancers/cancers as compared to controls(Mirabello et al., 2016).

Another intriguing observation was the high prevalence of gene (L1) analysis in the MENA region. However, it is well known that L1 ORF is the most conserved region out of the eight ORFs in the HPV genome. Hence, it is utilized to detect the new HPV types (29).

Regarding the rising number of HPV16 MENA sequences over time , this may indicate a rise in interest in understanding the molecular epidemiology of HPV associated with human cancers (such as head and neck, or cervical cancer) in the region (Obeid et al., 2020 and McLaughlin, Bultas, and Shorey 2012), which has resulted in generating more sequences that were becoming available for study. This heightened attention is a result of observations of an increase in the prevalence of human cancers associated with HPV in the MENA region (Fernandes et al., 2022 and Obeid et al., 2020).

On the other hand, Asiri et al. reported that in a systematic review and Meta–analysis, the prevalence of HPV had the lowest rate between 2015 and 2019; Asiri and her colleagues detected the prevalence of different genotypes of HPV that were associated with Head and Neck cancer and depend on extracting their data on the published studies published on PubMed, and Google Scholar databases between 1998 and 2019(31), but in our study we depend on extracting our data on HPV 16 sequences downloaded in the NCBI which are associated with different types of cancer. However, other studies are advised to approve this result.

Phylogenetic clusters analyses showed that some of these clusters are limited to one country of the MENA countries. Strong evidence suggesting that HPV genomes are largely static and that sequence changes caused by mutation or recombination are uncommon occurrences. Also, the frequency of Mutational changes apparently is similar to that of the infected host organism's DNA genomes (de Villiers et al., 2004). Furthermore, there is a portion of the transmission clusters collected in Iran and Morocco (small and large network) as well as Iran, Morocco, and Algeria (small network), Algeria and Morocco (small network). This finding is in line with other research results reporting the inter-country transmission of various viruses in the MENA region (such as Hepatitis B virus, Hepatitis C virus and human immunodeficiency virus type 1). Most of the MENA countries share a sociocultural perspective that might inadvertently affect people's behaviour. In addition to some of the MENA countries neighboring each other, such as Morocco, and Algeria, this leads to an increase in the likelihood of viruses transmission in the MENA region(Athamneh et al., 2021, Sallam et al., 2017 and Athamneh et al., 2023).

Notably, most of the small and large networks connected the USA to one or more MENA countries (such as Iran, Algeria, and Morocco). Additionally, four countries (Iran, Guatemala, Morocco, and USA) repeated four times as small networks with different sizes (between 7 to 14 sequences). Additionally, another cluster comprises samples from (Iran, Guatemala, Morocco, Japan, and the USA). Interestingly, Iran is the 18th world's largest country, which is located in the Middle East, with more than 77 million citizens; it has land borders with Turkey, Turkmenistan, Pakistan, Afghanistan, Armenia, Iraq, and Azerbaijan, as well as marine borders with the UAE, Saudi Arabia, Kazakhstan, Russia, and Kuwait. Each one of these countries has endemic infectious illnesses that pose a risk for their neighboring countries, like Iran (34). The geographic position of Iran places it at the crossroads of several regions, making it susceptible to the transboundary spread of infectious diseases endemic to its neighboring countries. Each of these countries faces public health challenges due to endemic infectious diseases, which can easily spread across borders. However, these findings demonstrate the possibility that HPV16 is transmitted across these countries, due to the lack of HPV16 sequences available in many MENA countries and the variation in the number of HPV16 sequences among MENA countries; it is difficult to draw definitive conclusions about possible HPV16 transmission between these countries. Thus, an additional study is suggested to validate these results.

Despite the findings mentioned above, there were some limitations of the current study: First, many MENA countries lacked HPV16 sequences in GenBank (Lebanon, Syria, Bahrain, Palestine, Djibouti, Jordan, Yemen, Qatar, and Oman), in addition to the uneven distribution of HPV16 sequences among countries. Secondly, a portion of the sequences lacked essential metadata, including information on associated cancer, sample data, gender, and collection date. These limitations may have impacted the generalizability of the study results.

5. Conclusion

The clinical characterization of HPV16 in the MENA region has revealed several important findings. There is a notably high prevalence of HPV16 sequences that are strongly linked to cervical cancer in this region. Additionally, a significant number of HPV16 sequences related to the E6 gene, which plays a critical role in the development of cervical cancer, have been identified, further underscoring the virus's impact in the MENA region. This high prevalence has been associated with an overall increase in the number of HPV16 sequences observed in recent years. Moreover, phylogenetic analysis through the transmission cluster has highlighted the occurrence of inter-country transmission of HPV16 across different countries in the MENA region, suggesting that the virus spreads across borders, complicating control efforts. This inter-country transmission points to the need for coordinated regional efforts to manage HPV16 transmission effectively. Looking forward, future epidemiological research focusing on domestic transmission pathways of HPV16 within MENA countries is crucial. Identifying specific risk factors for the spread of HPV16 and evaluating the coverage and effectiveness of HPV vaccination programs in this region will provide valuable insights. Such research is essential to strengthen preventive measures and improve the overall management of HPV16-related diseases, particularly cervical cancer, in the MENA region.

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