

Molecular characterization of human papillomavirus and mouse mammary tumor virus-like infections in prostate cancer tissue and relevance with tumor characteristics

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Received November 10, 2021; Accepted January 11, 2022

DOI: 10.3892/mco.2022.2530

Abstract. The suspected roles of human Papillomavirus (HPV) and mouse mammary tumor virus (MMTV) infections in prostate tumor development were recently reported. To detect the frequency of HPV and MMTV-like infections and clinical correlates of tumor characteristics, DNA samples from 50 men treated at Teaching Hospital of Rabat City (Morocco) between June 2017 and February 2019, were genotyped and confirmed by Sanger sequencing. Eight infections of HPV18 and two infections of MMTV-like were detected, and 50% of patients were at a Gleason score of 6. A significant association between Gleason score and HPV or MMTV-like infection was noted ($P=0.0008$); 90% of patients with viral infections presented with T1 and T2 pathological stage tumors. Yet, no significant differences were found between infected and noninfected men regarding other pathological parameters including prostate-specific antigen (PSA), tumor histological stage, age at diagnosis

and radical prostatectomy treatment ($P=0.2179$, 0.4702 , 0.8101 , and 0.9644 , respectively). The molecular evolution of HPV and MMTV in comparison with previously aligned sequences was discussed. Our findings provide a highlight on the correlations between the clinical-pathological parameters of prostate tumors and HPV and MMTV infections. Prospective studies with a wide sample size are needed for more statistical clarification of the association between viral infections with prostate tumor criteria.

Introduction

Prostate cancer is the second most frequently diagnosed malignancy (after lung cancer) in men worldwide, accounting for 1,276,106 new cases and causing 358,989 deaths (3.8% of all deaths caused by cancer in men) in 2018 (1). Risk factors can increase the risk of prostate cancer among men which include age, obesity, smoking, and inheritance of risk alleles. Notably, prostate cancer incidence and mortality vary through different ethnic backgrounds. Among the many risk factors causing prostate cancer, several studies suggest that virus infections might be important risk factors (2). The role of human papillomavirus (HPV) in human tumors has been intensively studied for decades; the virus has been suggested to contribute seriously to the incidence of ovarian, uterine, and other female reproductive system tumors. HPV 16 and 18 contribute to malignant tumors especially cervical cancer, and these two types are considered high-risk for 70% of all cancers caused by HPV in general compared to other types of HPV, and these two types affect about 20% of the adult population in Western countries (3-5).

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Key words: prostate cancer, mouse mammary tumor virus, human papillomavirus, prostate-specific antigen, gleason score, molecular evolution

Yet, there is some confusion regarding the presence of HPV infections in prostate cancer tissues and its role in the entire tumorigenesis process (6,7), as research has confirmed the presence of HPV in both cancerous and healthy tissues. HPV infections have been frequently detected in prostate cancer tissues but the infection frequencies detected vary significantly. The most frequently detected high-risk HPVs in prostate tumors are HPV types 16 and 18 (8-10).

In addition, the retrovirus mouse mammary tumor virus (MMTV) has been suggested to induce or accelerate carcinogenesis of healthy breast tissues by proviral integration (11), but the implications of MMTV in various human tumors such as prostate cancer remain unclear.

The correlation between the presence of HPV 18 and MMTV infections in prostate cancer tissues and clinical tumor criteria has not been previously analyzed in Moroccan men. The present study aimed to detect viral infections of high risk HPV 18 and MMTV-like in prostate cancer tissues and to find correlations between these viral infections and tumor clinical criteria.

Materials and methods

Prostate tissue specimens. A total of 50 fresh prostate biopsies were obtained from 50 men who were evaluated at the Teaching Hospital of Rabat City (Morocco) between June 2017 and February 2019. Histological samples were obtained to confirm a diagnosis of the presence of prostate adenocarcinoma. Biopsies were obtained according to standard protocols by physicians directly. Along with the biopsies, every sample had the relevant attached clinical and pathological parameters including: age, date of diagnosis, date of biopsy, Gleason score, prostate-specific antigen (PSA) concentration of prostate tumors, and the vital status of the patients. The clinical characteristics of the prostate cancer patients are provided in Table I.

Required ethical approval was obtained from the Committee of Biomedical Research Ethics in Morocco (no. 3/2018/30 April/2018). All patients consented to participate in the study and their information was handled as anonymous according to the ethical standards.

DNA extraction and genotyping. DNA samples were obtained from prostate cancer tissues; ≤ 25 mg of prostate tissue was placed into a sterile microcentrifuge tube, and DNA was extracted from the tissue samples using pure link Invitrogen Genomic DNA Mini Kit (Thermo Fisher Scientific, Inc.), according to the manufacturers' protocol. DNA extraction was performed at the place of biopsy collection (Research and Biosafety Laboratory, Mohammed V Construction Teaching Hospital, Morocco). Processing and genotyping took place at the Oncology and Virology Laboratory at the Faculty of Sciences and Techniques at Mohammedia, Morocco. DNA was quantified using the Nanodrop spectrophotometer (Thermo Fisher Scientific, Inc.). Samples with a DNA concentration of 20-50 ng/ μ l or above were selected to perform polymerase chain reaction (PCR). To evaluate the quality and integrity of the extracted DNA, a 268-bp fragment of the housekeeping β -globin gene was amplified using the GH20/PCO4 primer set as previously described (12). Oligonucleotides for β -globin amplification are provided in Table SI.

HPV detection (Fig. S1). The Specific HPV L1 gene was targeted by PCR using specific primers described elsewhere (13). The PCR reaction consisted of 25 μ l total volume PCR reaction containing genomic DNA (8 ng), 2X *Taq* PCR Master Mix kit (Qiagen USA), 2 μ mol forward and reverse primers. PCR amplification was performed using a Perkin Elmer 2400 Thermal Cycler® (PerkinElmer, Inc.).

The amplification procedure for HPV-L1 gene amplification was as follows: initial denaturation at 94°C for 3 min, followed by 35 cycles of denaturation at 94°C for 1 min, annealing at 43°C for 1 min, and extension at 72°C for 1 min and final extension at 72°C for 10 min. HPV16 and 18 provided by the biology and medical research unit (CNESTEN) Rabat, Morocco were used as positive PCR control and Ultra-pure water as negative PCR control. Primers set data used in HPV-L1 gene amplification are provided in Table SII.

MMTV-like detection. The 356-bp env sequence of MMTV-like virus as described previously (14,15) was targeted by PCR using specific primers: forward, GTAACACAGGCA GATGTAGG and reverse, GTATGAAGCAGGATGGGT AGA. The conditions for PCR were as follow: initial denaturation at 94°C for 3 min, followed by 35 cycles of denaturation at 94°C for 1 min, annealing at 54°C for 1 min, and extension at 72°C for 1 min and a final extension at 72°C for 10 min. Primer sequences and amplicon size expected of MMTV amplification are provided in Table SIII.

Sequence identification and molecular evolution analysis. PCR product sizes were confirmed by gel electrophoresis for 1.5 h at 70 V on 2% agarose. PCR products were purified using ExoSAP-IT™ Express PCR Product Cleanup (Thermo Fisher Scientific, Inc.). Last purification was performed using BigDye XTerminator® Purification Kit (Thermo Fisher Scientific, Inc.). Bidirectional Sanger sequencing was performed using BigDye Terminator v1.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Inc.).

Forward and reverse PCR primers used in PCR were used in Sanger sequencing performed by Genetic Analyzer 3130 (Applied Biosystems). All purification and sequencing were performed at the Innovation Centre Facility, Sidi Mohammed Bin Abdullah University of Fez (Fez, Morocco). Sequence identity recognition was performed by NCBI blast tools: <https://blast.ncbi.nlm.nih.gov/moleblast/moleblast.cgi>. In addition, the phylogeny analysis of the genotypes of the viruses was performed using MSA viewer built in NCBI-Blast tools, method: fast minimum evolution, max sequence differences=0.75.

Statistical analysis. We compared the frequency of HPV18 and MMTV-like infections among the subset of Moroccan men with tumor characteristic categories. Comparisons between infected and non-infected men against tumor characteristics of the prostate cancer (Gleason score, PSA concentrations, tumor stage, and age at diagnosis) were based on 2x2 or more Chi-squared analysis or Fisher's exact test to test for statistical significance. All statistical tests were two-sided, and all P-values of 0.05 or less were considered statistically significant. All analyses were conducted using the Minitab 17 (Coventry, UK).

Table I. Clinical characteristics of the prostate cancer patients (n=50).

Characteristics	n (%)
Age at diagnosis/surgery (years)	
≤60	7 (14)
>60	37 (74)
Unknown	6 (12)
Preoperative PSA, ng/ml	
<2.5	1 (2)
2.5-10	10 (20)
≥10.0	33 (66)
Unknown	6 (12)
Pathological Gleason score	
<7	11 (22)
7 (3+4)	6 (12)
7 (4+3)	8 (16)
>7	11 (22)
Unknown	14 (28)
Pathological T-stage	
pT1	14 (28)
pT2x	17 (34)
pT3x	3 (6)
pT4	5 (10)
Unknown/pTx	10 (20)
Radical prostatectomy	
Yes	16 (32)
No	21 (42)
Unknown	13 (26)
Alcohol consumption	
Yes	10 (20)
No	32 (64)
Unknown	8 (16)
Smoking	
Yes	18 (36)
No	24 (48)
Unknown	8 (16)

PSA, prostate-specific antigen.

Results

Positive viral infections in prostate cancer tissues were determined (Fig. 1). Of the 50 patients diagnosed with prostate cancer, 8 (16%) patients were confirmed to be infected by the high-risk human papillomavirus (HPV) 18 (Fig. 1B and C), and 2 (4%) patients were infected by MMTV-like virus (Fig. 1D). No patient was infected with the two viruses at the same time.

As determined from Table II, the age of diagnosis varied among those infected by HPV 18 (58-75 years). The PSA concentrations also varied significantly (6.56-26.16 ng/ml). While the Gleason score for 50% of these patients was 6; the

Gleason parameter was unknown for 1 patient. Three patients were not analyzed for Gleason score. One patient was treated by radical prostatectomy, three patients were treated by hormone therapy, and 1 patient was treated by both. Regarding tumor stage at the time of biopsy, 4 men presented with stage 1 tumors, 3 presented with histological stage 3 tumors, and 1 patient had third stage tumor.

Those infected by the MMTV-like virus were aged 57 and 61 years. Both patients had low PSA concentrations (8.09 and 7.27 ng/ml). One patient presented with a Gleason score of 6 and was treated by radical prostatectomy and presented with early stage 2 after histological evaluation of the tumor. The other patient was not analyzed for Gleason score and presented with tumor stage one at the time of biopsy, and was not treated at the place of therapy.

The clinical characteristics of the 10 men infected by HPV 18 or MMTV-like viruses are documented in Table II.

To explore the relevance between tumor parameters and infections by HPV 18 or MMTV-like virus, statistical significance tests were performed (Table III). Five patients infected by HPV 18 or MMTV-like had a Gleason score of 6. In contrast, 5 non-infected patients had the same Gleason score. There was a significant difference between Gleason score and infection by one of the two viruses analyzed ($P=0.0008$). Regarding PSA, 4 infected patients had a low PSA concentration less than 10 ng/ml, and 4 had a moderate rate of PSA concentration and 2 patients presented with a high PSA concentration (>20 ng/ml). In contrast, 7 prostate cancer patients among the 40 men not infected by any virus presented with a low PSA concentration, and 27 out of 50 had a PSA concentration more than 10 ng/ml. No significant differences between viral infections and PSA concentration was noted ($P=0.2179$).

Nine out of 10 infected by viruses were at an early histological stage of the tumor (T1 or T2), at the same time 22 out of 40 of noninfected men treated for prostate cancer also presented with early tumor stage T1 or T2. No significant differences between viral infections and tumor stage were noted ($P=0.4702$). A total of 80% of the prostate cancer patients infected by viruses had an age range of more than 60 years. In addition, the majority of those not infected had the same range of age. No significant differences between viral infections and age at diagnosis/surgery was noted ($P=0.8101$). Three prostate cancer patients (30%) infected by HPV 18 or MMTV-like viruses were subjected to radical prostatectomy while 13 non-infected patients (33% of the study group) were subjected to radical prostatectomy. Eighteen patients were treated with hormone therapy or other types of medication. A phylogenetic pairwise tree for MMTV-like was constructed using the sequence data already registered in NCBI databases in comparisons with our study sequence (Fig. 2A and B).

The molecular evolution homology with other HPV 18 genotypes and MMTV-like is reported in Fig. 2A and B. Certain homologies of our sequence are demonstrated with genotypes found in the NCBI database. Our sequence meets the reference sequence at 4067-4078 base pair (bp), the taxonomic classification of papillomaviruses in origin based on nucleotide similarity of the L1 gene.

Table II. Clinical characteristics of the 10 men infected by HPV or MMTV viruses.

ID	HPV 18+ve (Yes/No)	MMTV+ve (Yes/No)	Age at diagnosis (years)	PSA (ng/ml)	Gleason score ^a	Treatment	Pathological T-stage
PR-04	N	Y	57	8.09	6	RP	T2a
PR-01	Y	N	72	18.92	6	RP+HT	T1c
PR-03	Y	N	67	24.25	0	-	T3
PR-08	N	Y	61	7.27	0	-	T1c
PR-05	Y	N	67	17	6	HT	T2b
PR-06	Y	N	67	11.8	6	HT	T1c
PR-07	Y	N	75	9.99	-	-	T2b
PR-18	Y	N	70	19.31	6	HT	T1c
PR-10	Y	N	58	6.56	0	HT	T2b
PR-13	Y	N	63	26.16	-	RP	T1c

HPV, human papillomavirus; MMTV, mouse mammary tumor virus; PSA, prostate-specific antigen. Treatment: RP, radical prostatectomy; HT, hormone therapy. ^aScore of 0 for Gleason score=not analyzed.

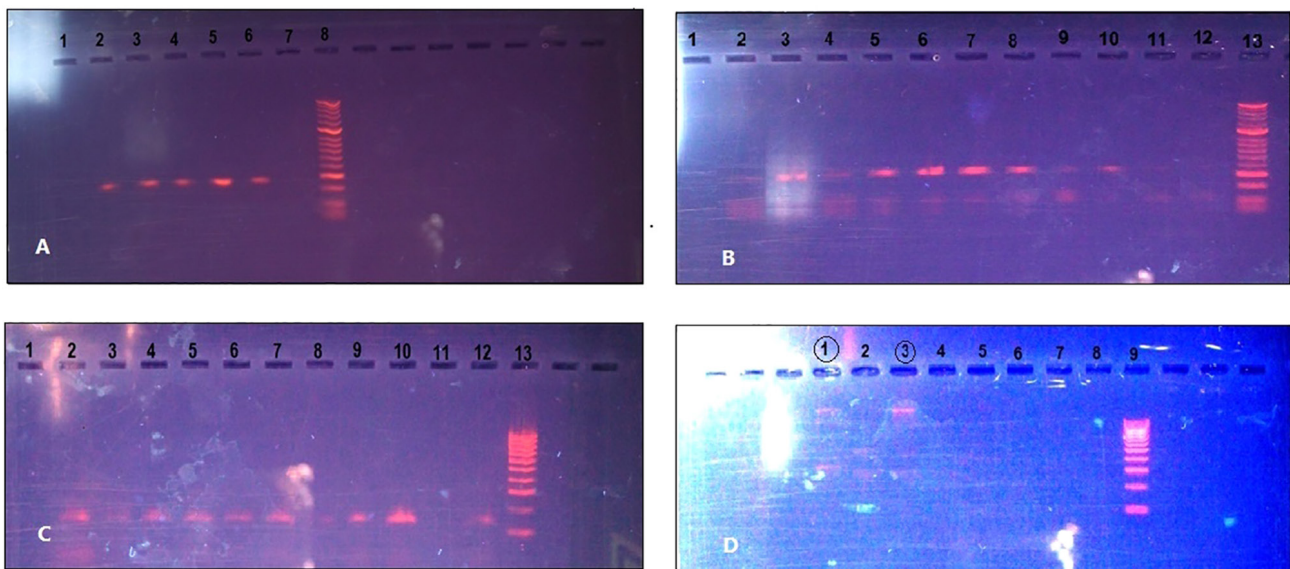


Figure 1. Positive viral infections in prostate cancer tissues. (A) 268 base pair (bp) β -globin fragments on gel (lanes 2-6, β -globin fragments; lane 7, negative control; lane 8, 50-bp DNA ladder). (B) HPV L1 450-bp fragment by MY09/MY11 primers on gel (lane 1, empty; lanes 3, 4 and 10, positive samples; lanes 2, 9 and 11, negative samples; lane 12, negative control; lane 13, 50-bp DNA ladder). (C) HPV L1 142-bp fragment by GP5+/GP6+ primers on gel (Lane 1, negative control; lanes 2-10 and 12, HPV fragments; lane 13, 100-bp DNA ladder). (D) MMTV-like (MMTV1 and 2 primers) on gel (lanes 1 and 3, suspected positive samples; lanes 4-8, negative; lane 9, 100-bp DNA ladder). HPV, human papillomavirus; MMTV, mouse mammary tumor virus.

Discussion

Human papillomavirus (HPV) infections in healthy and cancerous prostate tissues have been previously reported, but vary in regards to infection frequencies among prostate cancer patients, with no absolute confirmation concerning a susceptibility role of HPV infections in prostate tumor development (16,17). The present study findings concerning HPV 18, well-described as a high-risk genotype, reported 8 HPV 18 infections (out of the 50 prostate cancer patients) in the prostate cancer biopsies. Two mouse mammary tumor virus (MMTV) infections in the same subset of subjects were identified; MMTV infections in prostate cancer tissues have been rarely reported to date (18).

The association between tumor parameters and viral infections was also discussed, revealing a significant association between viral infections and Gleason score ($P=0.0008$). The majority of infected men (5 patients) had a Gleason score of 6. From the pathological angle, scores of 6 or less describe cancer cells that look similar to normal cells and indicate that the cancer is likely to grow slowly. Furthermore, the tumor pathological stage for 90% of the infected patients was at stage one or two (T1 50%, T2 40%) which indicate that the prostate tumors were in the early stages of development. This indicates that viral infections were presented at an early stage as the tumors were being initiated. This led us to conclude that there is a possible

Table III. Association between prostate tumor criteria and HPV 18, MMTV-like infected vs. non-infected patients.

Tumor characteristics	Infected by HPV or MMTV-like ^a (n=10)	Not infected (n=40)	P-value ^b
Pathological Gleason score			0.0008
=6	5	5	
>6	0	25	
Unknown	5	10	
PSA			0.2179
<10	4	7	
10-20	4	10	
>20	2	17	
Unknown	0	6	
Pathological T stage			0.4702
T1	5	9	
T2	4	13	
>T3	1	7	
Unknown	0	11	
Age at diagnosis/surgery			0.8101
≤60 years	2	5	
>60 years	8	28	
Unknown	0	7	
Radical prostatectomy			0.9644
Yes	3	13	
No	4	18	
Unkown	3	9	

^aBased on infection of HPV or MMTV but not both. ^bChi-squared test or Fisher's exact test (excluding missing data). HPV, human papillomavirus; MMTV, mouse mammary tumor virus; PSA, prostate-specific antigen.

role of high-risk HPV genotypes or MMTV in the early development of prostate tumors. Yet, this result should be considered with restraint since other tumor criteria data especially the PSA concentration, tumor histological stage, age at diagnosis or radical prostatectomy treatment, were not significantly different between men infected by HPV 18 or MMTV-like vs. the non-infected men ($P=0.2179$, 0.4702 , 0.8101 , and 0.9644 , respectively). In addition; we considered the tumor stage as a clinical parameter, while radical prostatectomy was considered as a pathological indicators; thus, the result of HPV and MMTV infections in those men treated with radical prostatectomy should be given special attention than viral infections in the clinical stages.

High homology of our sequence is demonstrated with genotypes previously described by Tirosh *et al* (18). The research mentioned has described the complete genome of HPV 18. Our sequence meets the reference sequence at 4067-4078 base pair (bp), the taxonomic classification of papillomaviruses in origin was based on nucleotide similarity of the L1 gene sequence. Analyzing the molecular evolution tree, the homology of MMTV-like sequence was concluded to be similar to this described by Tsiagbe *et al* (19), providing the complete coding region of the superantigen gene (SAG) in mouse models, meeting perfectly at 784-800 of the reference sequence.

The comparisons were inclusive to the targeted sequence superantigen gene (SAG). The homology of the superantigen was notable with MMTV 3' LTR-derived superantigen gene, and endogenous MMTV (RCS-MTV) superantigen gene from SJL/J mouse strain (20,21), in addition to similarity with the sequence of the MMTV proviral DNA (from *Mus musculus* mammary gland) for gag-protease-pol polyprotein and env protein (19), and MMTV long terminal repeat region (22,23). Concerning HPV sequences, the similar homology was with HPV isolated from humans in the USA (Fig. 2A and B) (24).

The origin of viral infections in the prostate has been a point of argument for years. Taken in mind that the associations between viral infections and prostate tumors has not been perfectly established yet, the circulation of such viruses between males and females should be considered, and further studies concerning the assumed circulation are important. The present study results revealed that HPV 18 or MMTV-like infections were found in the prostate gland early in tumorigenesis. Therefore, other studies with a wide sample size aimed at explaining the relationship between viral infections, on the one hand, and Gleason score and other tumor parameters, on the other hand, could be statistically meaningful to further confirm our conclusion.

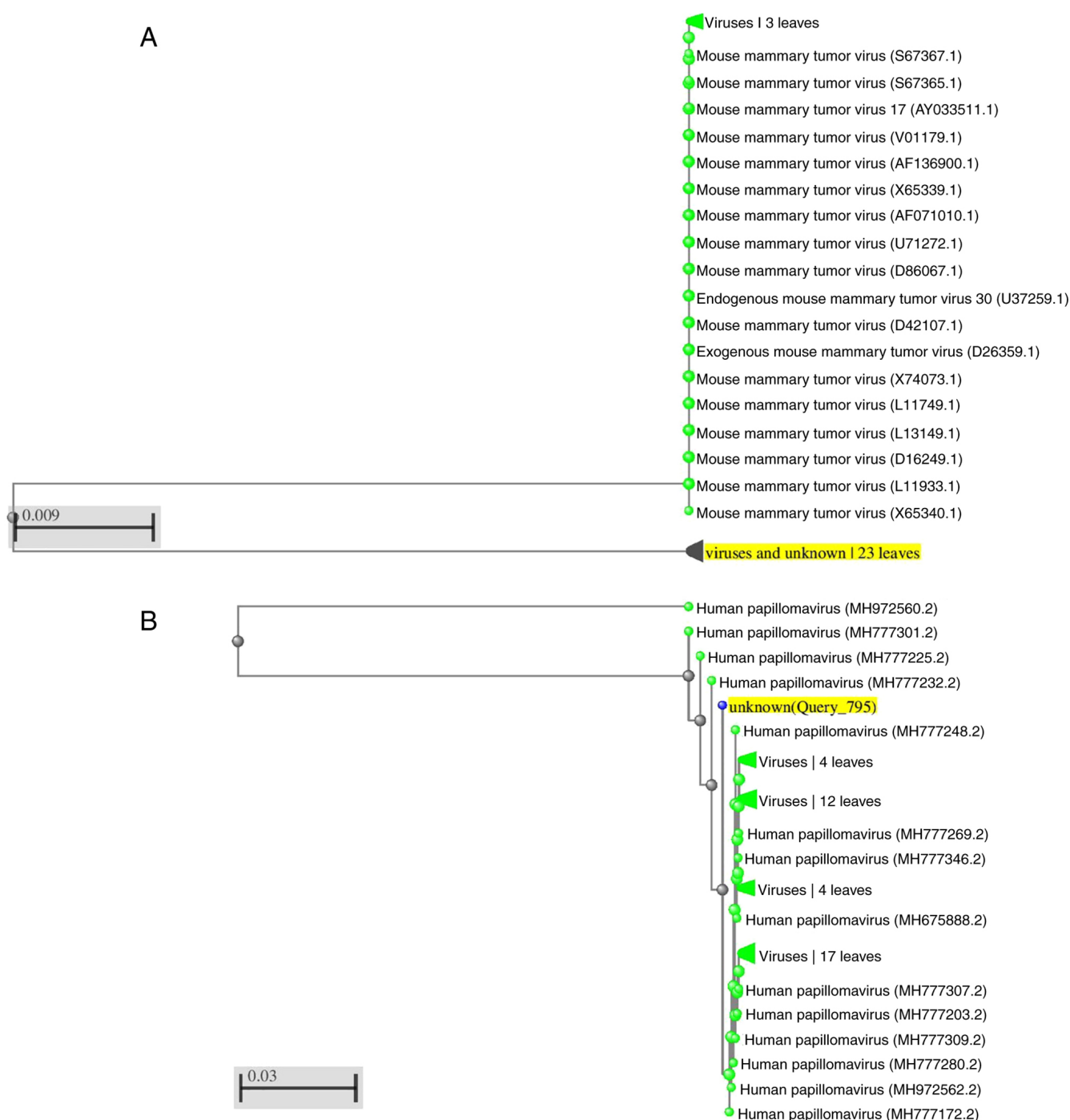


Figure 2. Distant tree pairwise alignment between HPV 18 (A) and MMTV-like (B) sequence results in this study and the database sequences already registered in NCBI GenBank. This analysis was performed using NCBI-Blast tools, method: fast minimum evolution, max sequence differences=0.75. The sequence results of this study are labeled in yellow color. HPV, human papillomavirus; MMTV, mouse mammary tumor virus.

Acknowledgements

The authors would like to thank the biopsy donors and their families, and many thanks to the members of the Virology, Oncology and Medical Biotechnology team at FSTM-Hassan II University of Casablanca, for all their efforts to support us during all work stages on this research.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BA and MME conceived and designed the experiments. BA, AL, MMz and MME optimized the experimental approach. BA, ML and YE performed the experiments. BA, ML, YE, IA and SIK analyzed all of the sequencing data and performed

the statistical analyses. MMr, AL and AA managed the sample collection and processing the data and supervised the place in which all samples were stored. Proofreading and technical assistance were carried out by BA, IA, MME and wrote the manuscript. All authors read and approved the manuscript and confirm the accuracy of the data and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Required ethical approval was obtained from the Committee of Biomedical Research Ethics in Morocco (no. 3/2018/30 April/2018). All patients consented to participate in the study and their information was handled as anonymous according to the ethical standards.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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