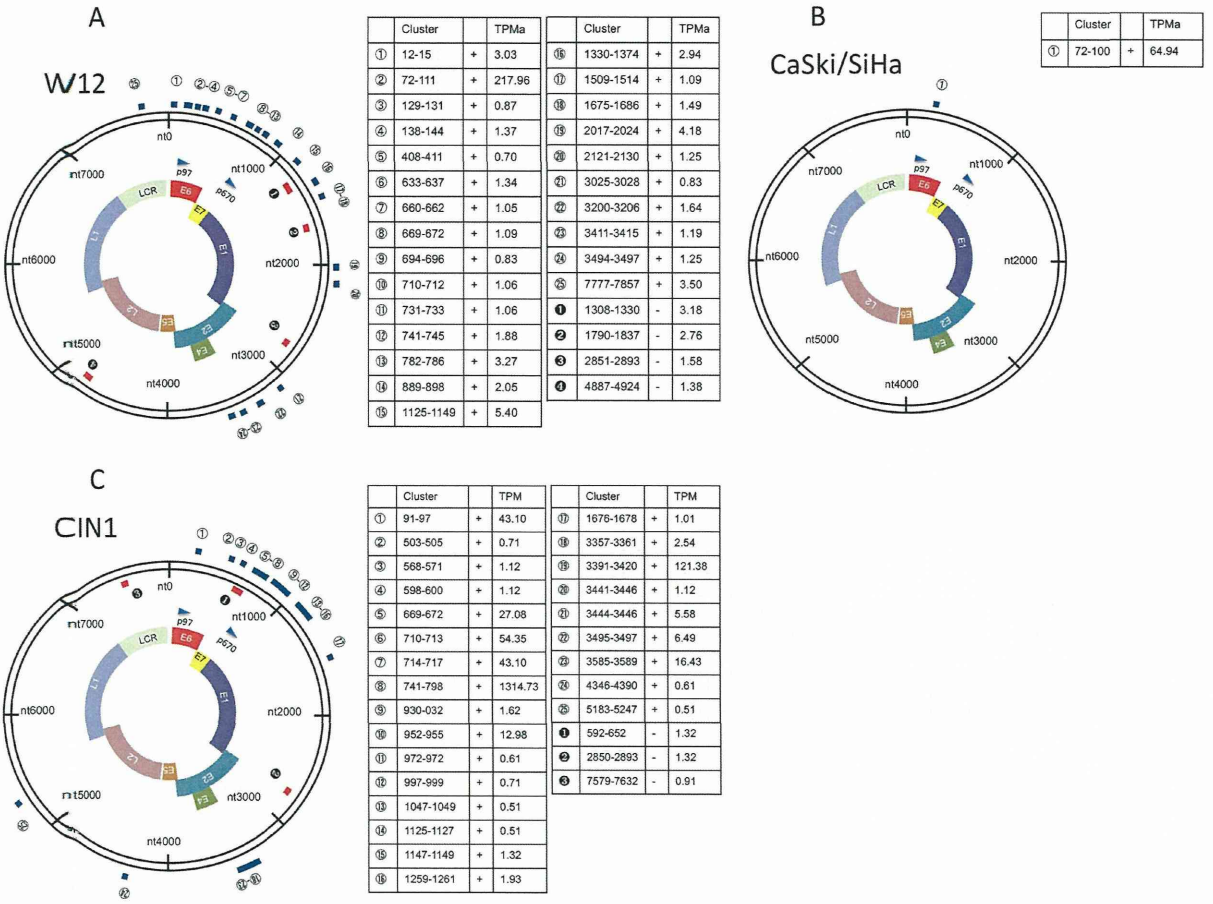
TABLE 1 Number of tags mapped to HPV16 genome

| Cell line | Bar code | No. of tags mapped to HPV16 genome | No. of tags mapped to hg19 genome | Tags per million (TPM) |
|---|---|---|---|---|
| CaSki-1 | GTA | 548 | 9,632,333 | 56.89 |
| CaSki-2 | ACC | 664 | 13,139,414 | 50.53 |
| CaSki-3 | CAC | 494 | 11,535,883 | 42.79 |
| SiHa-1 | AGT | 1,504 | 12,064,850 | 124.66 |
| SiHa-2 | GCG | 991 | 9,050,850 | 109.49 |
| W12-1 | TAC | 5,750 | 15,955,328 | 350.95 |
| W12-2 | GCT | 4,019 | 11,517,132 | 348.96 |
| W12-3 | ATG | 3,928 | 12,018,142 | 326.84 |
| CIN1 | ATG | 20,181 | 9,861,351 | 2,046.47 |

2024, nt 12 to 15, nt 1330 to 1322, and nt 741 to 745, some of which were previously identified (26). The TC at nt 90 to 97 (Fig. 2A) corresponds to the p97 promoter, while those at nt 129 to 131 and nt 138 to 144 had probably leaked from the P97 promoter (21). The TC at nt 1125 to 1149, detected only in W12 cells (Fig. 2B), is probably a TSS of E8-E2 (27, 28), and the TC at nt 12 to 15 corresponds to a promoter upstream of p97, indicating limited E1 transcription (Fig. 2D) (27). The TCs at nt 741 to 745 would be a TSS of E1ÊE4, corresponding to the p670 promoter (Fig. 2F) (3). Most interesting, however, was the previously unreported TC at nt 1330 to 1322, which is a potential antisense cluster, highly expressed in W12E cells (Fig. 2E). In addition, we identified another new TC at nt 2017 to 2024 (Fig. 2C).

To verify these novel transcripts, W12 RNA with or without poly(A) was reverse transcribed using a ReverTra Ace qPCR RT kit (Toyobo), and 3′ rapid amplification of cDNA ends (3′ RACE)




| | Cluster | | TPMa |
|---|---|---|---|
| ① | 12-15 | + | 3.03 |
| ② | 72-111 | + | 217.96 |
| ③ | 129-131 | + | 0.87 |
| ④ | 138-144 | + | 1.37 |
| ⑤ | 408-411 | + | 0.70 |
| ⑥ | 633-637 | + | 1.34 |
| ⑦ | 660-662 | + | 1.05 |
| ⑧ | 669-672 | + | 1.09 |
| ⑨ | 694-696 | + | 0.83 |
| ⑩ | 710-712 | + | 1.06 |
| ⑪ | 731-733 | + | 1.06 |
| ⑫ | 741-745 | + | 1.88 |
| ⑬ | 782-786 | + | 3.27 |
| ⑭ | 889-898 | + | 2.05 |
| ⑮ | 1125-1149 | + | 5.40 |

| | Cluster | | TPMa |
|---|---|---|---|
| ⑯ | 1330-1374 | + | 2.94 |
| ⑰ | 1509-1514 | + | 1.09 |
| ⑱ | 1675-1686 | + | 1.49 |
| ⑲ | 2017-2024 | + | 4.18 |
| ⑳ | 2121-2130 | + | 1.25 |
| ㉑ | 3025-3028 | + | 0.83 |
| ㉒ | 3200-3206 | + | 1.64 |
| ㉓ | 3411-3415 | + | 1.19 |
| ㉔ | 3494-3497 | + | 1.25 |
| ㉕ | 7777-7857 | + | 3.50 |
| ❶ | 1308-1330 | - | 3.18 |
| ❷ | 1790-1837 | - | 2.76 |
| ❸ | 2851-2893 | - | 1.58 |
| ❹ | 4887-4924 | - | 1.38 |

| | Cluster | | TPMa |
|---|---|---|---|
| ① | 72-100 | + | 64.94 |

| | Cluster | | TPM |
|---|---|---|---|
| ① | 91-97 | + | 43.10 |
| ② | 503-505 | + | 0.71 |
| ③ | 568-571 | + | 1.12 |
| ④ | 598-600 | + | 1.12 |
| ⑤ | 669-672 | + | 27.08 |
| ⑥ | 710-713 | + | 54.35 |
| ⑦ | 714-717 | + | 43.10 |
| ⑧ | 741-798 | + | 1314.73 |
| ⑨ | 930-032 | + | 1.62 |
| ⑩ | 952-955 | + | 12.98 |
| ⑪ | 972-972 | + | 0.61 |
| ⑫ | 997-999 | + | 0.71 |
| ⑬ | 1047-1049 | + | 0.51 |
| ⑭ | 1125-1127 | + | 0.51 |
| ⑮ | 1147-1149 | + | 1.32 |
| ⑯ | 1259-1261 | + | 1.93 |

| | Cluster | | TPM |
|---|---|---|---|
| ⑰ | 1676-1678 | + | 1.01 |
| ⑱ | 3357-3361 | + | 2.54 |
| ⑲ | 3391-3420 | + | 121.38 |
| ⑳ | 3441-3446 | + | 1.12 |
| ㉑ | 3444-3446 | + | 5.58 |
| ㉒ | 3495-3497 | + | 6.49 |
| ㉓ | 3585-3589 | + | 16.43 |
| ㉔ | 4346-4390 | + | 0.61 |
| ㉕ | 5183-5247 | + | 0.51 |
| ❶ | 592-652 | - | 1.32 |
| ❷ | 2850-2893 | - | 1.32 |
| ❸ | 7579-7632 | - | 0.91 |

FIG 1 Clustered TSSs of the HPV16 genomes of cervical cell lines of different grades. CAGE tags of HPV16 genes from each cell lines are quantitatively visualized. The data are representative of the results determined with the respective cell lines. The CaSki and SiHa cultured cells, representing a transcriptional program characteristic of the conditions in a tumor, were cultured in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 1% penicillin-streptomycin. W12E (20863) is an HPV16-positive cell line derived from a CIN1 lesion (23). W12E (20863) cells were cocultured with mitomycin C-treated 3T3 fibroblast feeder cells. (A) Circular map depicting viral transcripts identified by Paraclu clustering. CAGE tags were clustered for HPV16 genes from W12E cells. Regions containing over 0.5 tags per million (TPM) in all samples were selected as tag clusters (TCs) and mapped to the circular HPV16 genome. (B) We defined regions containing over 0.5 TPM in the sample as TCs. Then, CAGE tags were clustered for HPV16 genes from the CaSki and SiHa cells. (C) CAGE tags were clustered for HPV16 genes from a CIN1 clinical sample. Notably, we found 25 positive-strand TCs and 4 negative-strand TCs in W12E cells (A), whereas only 1 positive-strand TC was found in CaSki or SiHa cells (B). TPMa, the average number of TPMs.

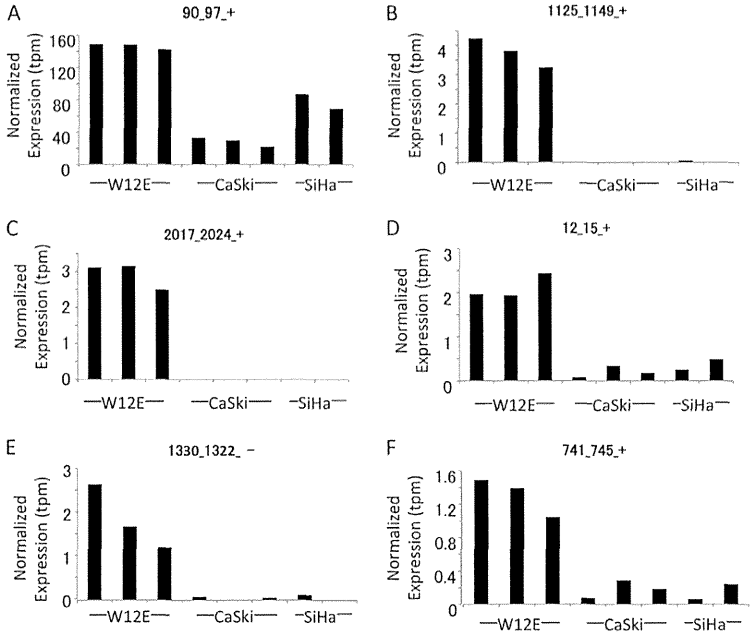
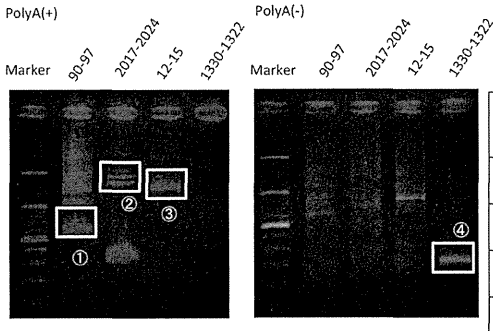



FIG 2 Expression levels of the top 6 tag clusters (TCs) in W12E, CaSki, and SiHa cells. The top 6 expressed TCs were selected, and expression levels are indicated as tags per million (TPM) (25). Six TSS clusters were frequently found to be prominent in W12E cells, originating from nt 90 to 97 (90_97_+), nt 1125 to 1149 (1125_1149_+), nt 2017 to 2024 (2017_2024_+), nt 12 to 15 (12_15_+), nt 1322 to 1330 (1330_1322_−), and nt 741 to 745 (741_745_+).

was carried out using *Ex Taq* (TaKaRa) on the detected clusters found in clustering analysis of HPV16 genome expression, using the nt-97 cluster as a positive control.

To verify RNA without poly(A), a 3′ preadenylated DNA adaptor sequence was ligated at the 3′ end of RNA. To increase specificity, we carried out first RACE and second RACE experiments. Primer pairs for each peak [oligo(dT)] adaptor are shown in Fig. 3. The PCR conditions for the first RACE and second RACE exper-




| Bands | Coordinate |
|---|---|
| 1 | 97-226^3391-3761 polyA(+) |
| 2 | 2017-3761 polyA(+) (lower band)<br>2017-4230 polyA(+) (upper band) |
| 3 | 12-226^3358-4230 polyA(+) |
| 4 | 1330-997 polyA(-) |

Primer sequence of 3′ RACE and polyA(-) RT

| Peaks | 1st/ 2nd RACE | Primers |
|---|---|---|
| nt90-97 | 1st<br>2nd | 5′-GCGACCCAGAAAGTTACCAC-3′<br>5′-ATGCACAGAGCTGCAAACAAC-3′ |
| nt2017-2024 | 1st<br>2nd | 5′-GGATTGTGCAACAATGTGTAG-3′<br>5′-CAAATGAGTATGAGTCAATGG-3′ |
| nt12-15 | 1st<br>2nd | 5′-CGGTTGAACCGAAACCGGTTAG-3′<br>5′-TATGCACCAAAAGAGAACTGC-3′ |
| nt1330-1322 | 1st<br>2nd | 5′-TTGCCATACCCGCTGTCTTCGC-3′<br>5′-ATTATTGTCTACACATCCAC-3′ |
| polyA(+) | 1st<br><br>2nd | 5′-CAAGCAGAAGACGGCATACGATT TTTTTTTTTVN-3′<br>5′-CAAGCAGAAGACGGCATACGA-3′ |
| polyA(-) | 1st<br>2nd | 5′-CATCATTGATGGTGCCTACAG -3′<br>5′-CATCATTGATGGTGCCTACAG -3′ |
| polyA(-) RT-primer | | 5′- CCGATCTCACCTCCTGCATCATTGATG GTGCCTACAG -3′ |
| 3′adaptor | | 5′- rApp-CTGTAGGCACCATCAAT-ddC -3′ |

FIG 3 Validation of novel transcripts from 3′ RACE analysis. Agarose gel electrophoresis of transcripts from W12 cell eluted RNA. The results of the experiment indicate that the transcript originating at nt 1330 to 1322 could correspond to a newly identified viral antisense noncoding RNA without poly(A). Further, we could encode a newly identified transcript of nt 2017 to 2024 starting in the middle of E1 coding gene. ddC, dideoxycytosine; rApp, adenylation-5′; RT, reverse transcriptase.

iments were as follows: for the first RACE experiment, 35 cycles at 94°C for 30 s, 57°C for 30 s, and 72°C for 30 s; for second RACE experiment, 35 cycles at 94°C for 30 s, 57°C for 30 s, and 72°C for 30 s. The results are shown in Fig. 3. PCR products were extracted (Qiagen) and sequenced by Applied Biosystems 3130xl (Fasmac). Importantly, we identified, for the first time, the full coordinates of a novel antisense transcript starting from nt 1330 as a noncoding RNA (ncRNA) without poly(A) and also a novel transcript, nt 2017 to 2024, starting in the middle of the E1 gene. Although most viral RNAs are considered to be polyadenylated at the 3′ end, our finding confirms that the noncoding viral RNA starting from nt 1330 lacks poly(A) signals.

In this study, we performed CAGE analysis and investigated TSSs from the perspective of both the HPV16 and human genomes, using cell lines containing episomal and integrated HPV sequences. All the TSSs used in the HPV16 transcriptome, in the HPV16-containing cervical keratinocyte W12E cell line, and in the cervical cancer-derived SiHa and CaSki cell lines were investigated. Intriguingly, we also show that a diversity of viral transcripts, seen in W12E cells, shared some identity with the CIN1 biopsy specimen subjected to a precise colposcopic examination. Recently, as shown previously in the mammalian transcriptome (29), abundant virally encoded noncoding RNAs (ncRNAs) were identified (30), but this is the first full confirmation of a preliminary observation of antisense transcripts in HPV.

Using the CAGE method, we have successfully established unbiased analyses of reproducible transcriptional start sites across the HPV16 genome, potentially identifying novel transcripts, including ncRNAs, for future RNA therapies (31). Further comprehensive studies will aim to identify possible markers to predict the outcome of infections with HPV.

**Nucleotide sequence accession number.** The sequence data reported are available in the DDBJ BioProject under the accession number PRJDB3385.

## ACKNOWLEDGMENTS

We are grateful to Ri-ichiroh Manabe and Michihira Tagami (Division of Genomic Technologies, RIKEN) for the excellent advice and technical guidance on the preparation of CAGE analysis. All sequencing was performed by the Genome Analysis Support Facility (Division of Genomic Technologies, RIKEN). We are also very grateful to Paul Lambert (University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin) for his kind gift of W12E (20863) cell lines.

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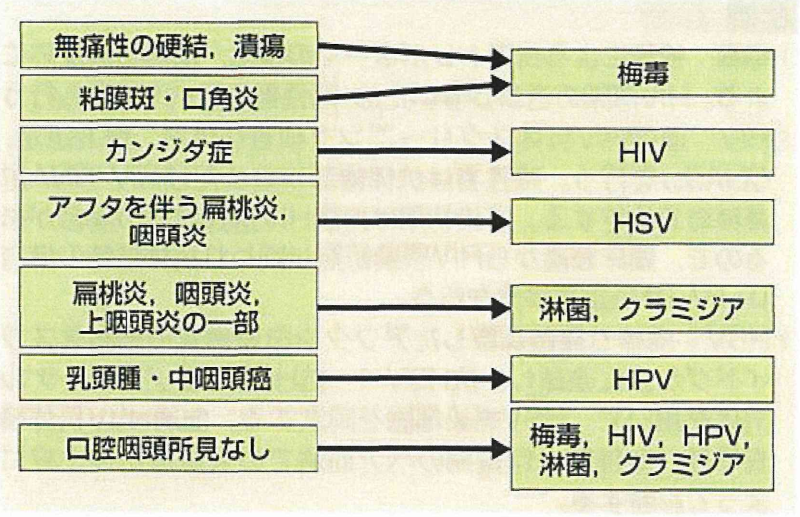
# 55. 口腔・咽頭の性感染症

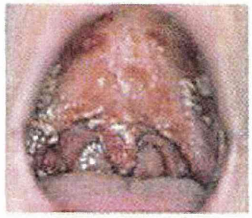


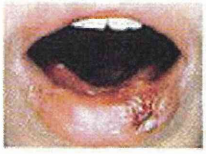

## 1 概念

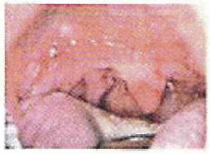
①**定義・分類**：性感染症は性行為によって伝搬する感染症の総称である。口腔・咽頭の性感染症は，口腔・咽頭に病変を生じるものと，口腔・咽頭に病変がない無症候性感染でありながら口腔・咽頭が感染源となるものに分類される。

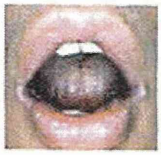
②**病因・病態**：口腔・咽頭の性感染症の主な原因として，梅毒，HIV，HSV，淋菌，クラミジア，HPVがある。これらはすべて，病変を生じる場合と，無症候性感染の場合がある。

③**症状・所見**：梅毒第1期の初期硬結・硬性下疳は無痛であるが，第2期の粘膜斑・口角炎は咽頭痛や違和感を生じ，特徴的な所見から診断の契機になる。HIVではカンジダ症，再発性アフタ性口内炎，多形性紅斑，苔癬，非特異的口腔潰瘍，カポジ肉腫が，HSVでは歯肉口内炎，咽頭・扁桃炎が，淋菌では咽頭炎，扁桃炎が，クラミジアでは上咽頭炎が，HPVでは乳頭腫，中咽頭癌が生じる。

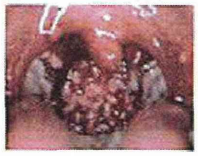

HIV感染者における口腔・咽頭カンジダ症


硬性下疳
梅毒第1期


粘膜斑


口角炎

梅毒第2期


HSV
咽頭・扁桃炎

④**合併症**：淋菌，クラミジアは性器感染の合併が多く，性器感染が放置されると不妊の原因になり得る。

## 2 診断

①**梅毒**：検鏡による梅毒トレポネーマの検出，梅毒血清反応による。HIV感染の合併が多いため，陽性者にはHIV検査も行う。

②**HIV**：血清HIV抗体スクリーニング検査(PA法，ELISA法，CLIA法)を行う。陽性者は抗体確認検査またはHIV-RNA定量検査で確定する。感染初期は血清HIV抗体陰性の場合があるので，臨床経過からHIV感染初期が疑われ抗体陰性の場合はHIV-RNA定量検査を行う。

③**HSV**：綿棒で擦過採取したアフタや白苔病変の細胞をスライドグラスに塗抹し，抗HSV-1・抗HSV-2モノクローナル抗体を用いて，HSV感染細胞を同定する。血清HSV抗体検査では，急性期と回復期のペア血清での有意な抗体上昇によって診断する。

④**淋菌，クラミジア**：核酸増幅法のSDA，TMA，PCRのいずれかを用いる。臨床的に淋菌とクラミジアの判別が難しく，同時感染もあるため，淋菌とクラミジアを両方検査する。

⑤**HPV**：腫瘍組織の病理学的所見，*in situ* hybridizationによるHPV-DNAの証明，PCR法・LAMP法で遺伝子型を確定する。

## 3 治療

①**梅毒**：ベンジルペニシリンベンザチン１回40万単位(ない場合は代用としてアモキシシリンまたはアンピシリン１回500mg)を１日３回，第１期では２～４週間，第２期では４～８週間，投薬を継続する。感染後，１年以上経過している例や感染時期が不明な場合には８～12週間投与する。

②**HIV**：抗HIV薬の多剤併用療法ART(antiretroviral therapy)を行う。

③**HSV**：経口でバラシクロビル１回500mg，１日２回５日間，またはアシクロビル１回200mg，１日５回５日間，経口摂取困難例ではアシクロビル注５mg/kg/回，１日３回８時間毎７日間投与する。

④**淋菌**：セフトリアキソン２g １回/日を１～３日間点滴投与する。治療後３日以上あけて核酸増幅法で陰性化を確認する。

⑤**クラミジア**：アジスロマイシン1,000mgの単回投与，またはクラリスロマイシン200mgを１日２回14日間投与する。投薬終了２週間後に，核酸増幅法で陰性化を確認する。

⑥**HPV**：HPV感染そのものへの治療法は確立していない。

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# 性感染症に関する特定感染症予防指針に基づく対策の推進に関する研究

（H24－新興－一般－004）

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