

## ARTICLE



# Association of HPV42 with digital papillary adenocarcinoma and the use of in situ hybridization for its distinction from acral hidradenoma and diagnosis at non-acral sites

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Digital papillary adenocarcinoma (DPAC) is a rare tumor of sweat gland origin that preferentially affects the digits and has the potential to metastasize. Its tumor diagnosis can be difficult. Well-differentiated variants of DPAC can be confused with a benign sweat gland tumor, in particular nodular hidradenoma. With the recent detection of HPV42 DNA in DPAC by next-generation sequence analysis, we reasoned that this association could be used for diagnostic purposes. To this end, we performed in situ hybridization for HPV42 on 10 tumors diagnosed as DPAC as well as 30 sweat gland tumors of various histology types, including 8 acral hidradenomas. All DPAC were positive for HPV42. Positive hybridization signals for HPV42 were seen in both primary and metastatic DPACs. All other tumors and normal tissues were negative. This study confirms the association of HPV42 with the tumor cells of DPAC through in situ hybridization. The positive test result in all lesions of DPAC and lack of detection of HPV42 in any of the acral hidradenomas or other sweat gland tumors examined in this series is encouraging for the potential diagnostic utility of the assay. As documented by two scrotal tumors of DPAC, the in situ hybridization test for HPV42 can also help support the rare occurrence of this tumor at a non-acral site.

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## INTRODUCTION

Digital papillary adenocarcinoma (DPAC) is a cancer of sweat gland origin<sup>1–6</sup>. It is a rare skin cancer with an annual incidence of ~0.08 cases per 1,000,000<sup>6</sup>. There is a wide age range, with a peak between the ages of 50–70 years<sup>1–10</sup>. The male to female ratio is approximately 4:1<sup>6</sup>. The tumor most often occurs on the fingers and toes, but has also been said to occur on the palm of the hand and sole of the foot<sup>9,10</sup>. Rare cases have been reported on non-acral sites<sup>6,11</sup>.

Most tumors present as slow-growing nodule with or without pain. While some tumors are amenable to conservative surgery<sup>12</sup>, most DPACs require amputation for definitive surgical treatment<sup>13,14</sup>. Metastases have been reported in 14–41%, depending on the series<sup>1–10</sup>. They typically involve regional lymph nodes and/or the lung. Sentinel lymph node (SLN) biopsy has been found to be of prognostic value as the status of the node is associated with distant recurrences<sup>13,14</sup>. In a recent series of 18 patients who underwent SLN biopsy, three (17%) had a positive SLN, and two of them subsequently developed distant metastases<sup>14</sup>.

Some DPACs are readily recognized as carcinoma by microscopic examination, because of the presence of infiltrative growth, atypia, mitoses, and/or necrosis<sup>1–3</sup>. However, other tumors can be diagnostically challenging displaying adenoma-like features<sup>1–3</sup>.

They may be confused with various benign sweat gland neoplasms, such as nodular hidradenoma<sup>15</sup>, apocrine hidrocystoma, or cystadenoma<sup>16</sup>. The diagnostic challenge is reflected in the changes of the tumor terminology over time. In the first presentation of the tumor type by Helwig in 1979 (American Academy of Dermatology Clinical Pathology Conference, Chicago, December 1979, unpublished data), it was introduced as “aggressive digital papillary adenoma”. A description of the cases under the same term was published in the differential diagnosis of another article<sup>17</sup>. In a subsequent series from the Armed Forces Institute of Pathology (AFIP) of the United States in 1998, Kao et al. classified the digital tumors from 57 patients as either “aggressive papillary digital adenoma” or “aggressive papillary digital adenocarcinoma”<sup>1</sup>. Requena et al. proposed in 1998 that the neoplasms labeled as adenoma or adenocarcinoma represented variations of the same entity and are carcinomas<sup>18</sup>. In 2000, Duke et al. retrospectively analyzed cases from the AFIP and found that 9 of the 30 cases initially diagnosed as “adenoma” recurred and 3 metastasized<sup>2</sup>. These observations led to the proposal that all digital papillary sweat gland tumors, even if their circumscribed growth and low-grade cytology may suggest an adenoma, should be regarded and treated as adenocarcinoma. Arguments were then put forward that the term aggressive digital papillary adenoma be abandoned<sup>19</sup>.

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**Table 1.** Digital papillary adenocarcinoma—clinical and pathologic findings.

Acral Digital Tumors							
Case	Age (yrs)	Gender	Anatomic site	Size (mm)	Growth	ISH HPV42	Metastasis
1	68	M	rt 3rd finger	17	nodular	POSITIVE	
2	36	M	rt 2nd finger	8	nodular	POSITIVE	LN, ST
3	60	M	rt 2nd finger	30	infiltrative	POSITIVE	
4	68	M	rt 3rd finger	5	nodular	POSITIVE	
5	31	M	rt 4th toe	13	nodular	POSITIVE	LN (4/10)
6	21	M	rt great toe	20	nodular	POSITIVE	
7	37	M	rt 5th finger	18	nodular	POSITIVE	
8	65	M	lt thumb	16	nodular	POSITIVE	LN
Non-Acral Tumors							
9	80	M	scrotum	20	nodular	POSITIVE	
10	77	M	scrotum	8	nodular	POSITIVE	

M male, rt right, lt left, mm millimeter, yrs years, ISH in situ hybridization, LN lymph node, ST soft tissue.

In light of those proposals pathologists have hesitated to render a diagnosis of sweat gland adenoma affecting the digits. However, benign tumors, such as poroma or hidradenoma can occur in the skin of the fingers and toes, and criteria exist for their correct diagnosis. As documented by Wiedemeyer et al., a combination of microscopic parameters, such as the lack of papillary structures, and immunohistochemical findings (e.g., in the case of hidradenoma, diffuse positivity for p40 and absence of S100 and SMA expression) can help support the diagnosis<sup>19</sup>. However, due to limitations in sensitivity and specificity of antigen expression and morphologic overlap in microscopic features, especially on a partial biopsy, it can on occasion be difficult to render a precise diagnosis.

Since a recent study analyzing DNA extracted from tumors for viral sequences found a unique association of HPV42 with DPAC<sup>20</sup>, we decided to expand on those observations with an in situ hybridization assay for HPV42 and to explore the possibility of using it for the diagnosis of DPAC its distinction from other sweat gland tumors, in particular acral hidradenomas.

## MATERIALS AND METHODS

### Tissue material and in situ hybridization

The study was conducted under the institutional review board protocols 16–1613, 12–245, and 18–128. Cases with a diagnosis of DPAC and acral hidradenoma as well as a set of 22 miscellaneous sweat gland neoplasms were retrieved from the institutional archive and personal consultation files of the authors. Eight DPACs with available tissue material were found as well as two scrotal adenocarcinomas, which had been diagnosed as non-acral DPAC. They looked similar to acral DPAC and, and like their digital counterparts, contained both epithelial and myoepithelial cells, and were immunoreactive for both cytokeratins and S100 protein. In situ hybridization was performed on archival formalin-fixed and paraffin-embedded tissue using the Leica Bond III platform for processing. Commercially available kits were used, (Leica, catalog # 407528 [<https://acdbio.com/search/site/%252A407528%252A/cms/probes>] and 548288 [<https://acdbio.com/search/site/%252A548288%252A/cms/probes>]) with ready to use probe dilutions for a short and long probe, respectively. Pretreatment of the tissue sections including enzymatic treatment (ACD RNAscope Protease 15' [AR9773]) and HEIR (ER2 for 20 min at 95 °C. Hybridization times with either short or long probe was 2 h. The hybridization temperature was 42 °C. RNAscope (DS9790) was used for detection.

### Detection of DNA viruses

The detection of viruses was completed utilizing data generated for the MSK-IMPACT clinical assay with threshold for optimal performance characteristics for detection of human papilloma viruses, as was previously reported<sup>20</sup>. In short, all sequenced reads are aligned to the human genome (hg19). The reads that do not align to the human genome were processed

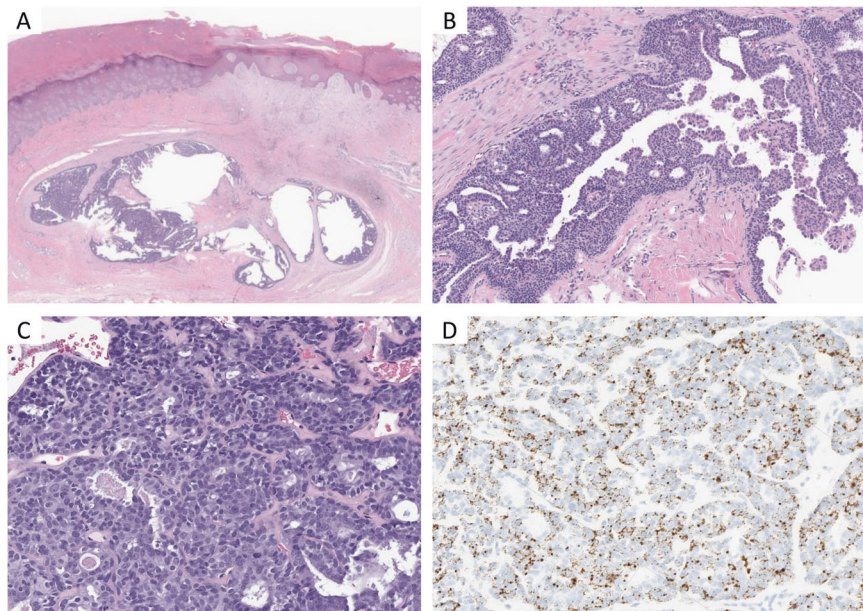
with blastn program and mapped to the genomes of DNA viruses known to infect humans. Each paired read that aligned with >90% identity was quantified as a read for the specific virus. Samples with >2 paired reads for a specific virus were considered positive for the virus. A total of 48,148 solid tumors was sequenced by MSK-IMPACT from January 2014 to October 2020 and an additional validation cohort 7814 of tumors was sequenced from November 2020 through October 2021.

## RESULTS

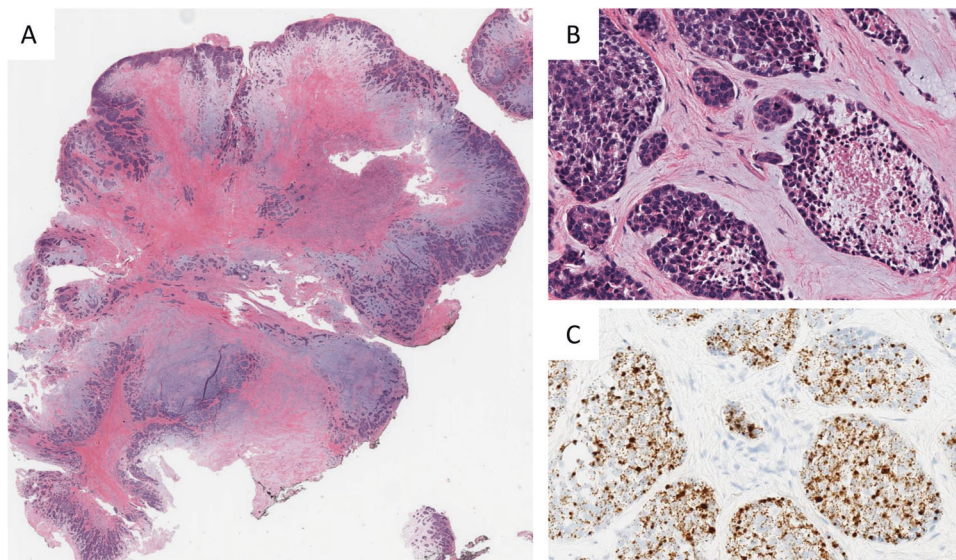
A total of eight tumors of acral DPAC were analyzed by in situ hybridization for HPV42 as well as two scrotal tumors. The clinical and pathologic findings of these cases are summarized in Table 1. All patients were men. Their ages ranged from 21 to 80 years. Six of the acral DPACs affected the fingers. Two tumors involved the toes. Three of the patients of this series are known to have developed metastatic disease. In two patients the lymph node metastasis was detected at the time of initial surgical resection. In one case (Table 1, #5), enlarged lymph nodes were apparent clinically and a lymph node dissection revealed four positive nodes. This patient is currently still alive 9 years after the amputation and lymph node dissection. In the other case (Table 1, #2), the metastasis was clinically occult, but detected by sentinel lymph node biopsy. The patient subsequently developed a soft tissue metastasis 6 years later, but is currently (13 years after the initial resection) free of disease. In the third patient, the lymph node metastasis was detected clinically 12 years after the initial tumor resection (Table 1, #8). Among the patients with no known metastasis, two had follow-up of 12 and 18 months, respectively. No or inadequate follow-up was available in the other cases.

The sizes of the tumors ranged from 5 mm to 3 cm (Table 1). All but two tumors displayed a circumscribed nodular or nodulocystic silhouette; two were infiltrative. All tumors contained both duct epithelial and surrounding myoepithelial cells, which was supported by immunohistochemistry (available in seven of the ten cases) for cytokeratins, p63, SMA calponin, and/or S100 protein. Typically, there was a mixture of tubular, cribriform, solid and papillary growth patterns in proportions that varied from tumor to tumor. Well-formed papillary structures constituted only a minor element (<5%) in most tumors, except for two neoplasms, in which the papillary growth amounted to ~25–30% of the tumor. Two tumors lacked a papillary growth component and contained only ductal tubular structures in midst solid tumor cell aggregates. The myoepithelial cell population displayed focal clear cell features in all tumors. None of the tumors had perineural invasion.

To evaluate the potential utility of the in situ hybridization test for HPV42 for the distinction of DPACs from other tumors, we also



**Fig. 1** Digital papillary adenocarcinoma from the right 5th finger of a 37-year-old man (Table 1, case 7). **A** Nodulocystic tumor in dermis. **B** The tumor displays papillary and cribriform growth. **C** The tumor also contains solid areas with ducts surrounded by myoepithelial cells. **D** The tumor is diffusely positive for HPV42 by in situ hybridization.



**Fig. 2** Digital papillary adenocarcinoma from the right 2nd finger of a 60-year-old man (Table 1, case 3). **A, B** There is a poorly differentiated epithelial tumor with necrosis. **C** The tumor cells are diffusely positive for HPV42.

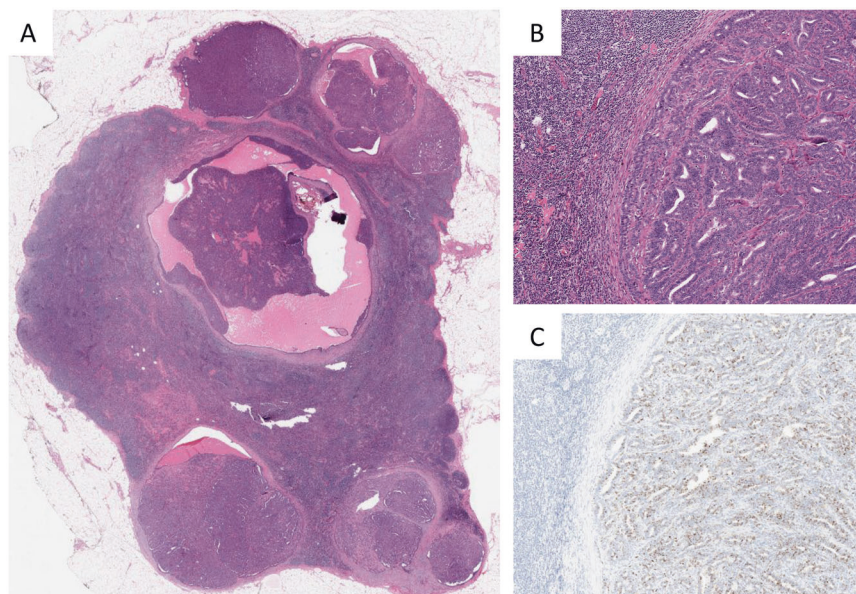
examined eight cases of acral hidradenomas. Seven of them occurred on the hand, one on the foot. Two of the patients were women, six were men. Their ages ranged from 20 to 76 years, with a mean age of 47 years and median of 45 years.

All ten DPACs, including primary and metastatic tumors, and both scrotal adenocarcinomas were positive for HPV42 by in situ hybridization. A case of well-differentiated primary DPAC is illustrated in Fig. 1. A poorly differentiated DPAC is shown in Fig. 2. A lymph node metastasis from DPAC is illustrated in Fig. 3. The scrotal tumor is shown in Fig. 4. As apparent in all of these figures, labeling for HPV42 was restricted to tumor cells. It was not seen in the overlying epidermis, surrounding stroma, lymph node or any inflammatory cells. There was no difference in the test result between the short and long hybridization probe.

Four tumors were also analyzed by MSK-IMPACT next generation sequence (NGS) analysis with reads for HPV42 that were above the threshold for positivity. These four tumors showed widely divergent genomic profiles. The only recurrent mutation was in *TP53*, which was detected in three of the four tumors with NGS data. No copy number alterations, including chromosome arm level gains and losses, were present in more than one tumor. No structural variants were observed in the cohort. One tumor showed no genomic alterations. None of the tumors had a *BRAFV600E* mutation.

In contrast to the DPACs, all acral hidradenomas were negative for HPV42. Furthermore, an additional set of 22 sweat gland tumors was also negative for HPV42. The lesions included 12 benign tumors (4 poromas, 2 tubular and papillary eccrine





**Fig. 3 Metastatic digital papillary adenocarcinoma in lymph node.** The corresponding primary tumor was from the right 4th toe of a 31-year-old man (Table 1, case 5). **A** Nodulocystic tumor deposits in soft tissue with solid, tubular, and papillary growth patterns. **B** Most tumor cells display a ductal growth pattern. **C** The tumor cells are positive for HPV42.

adenomas, 2 cylindromas, 2 spiradenomas and 2 apocrine mixed tumors) and 10 carcinomas of different histologic types (2 cribriform carcinomas, 2 adenoid cystic carcinomas, 2 porocarcinomas, 1 sclerosing sweat duct carcinoma, 1 spiradenocarcinoma and 2 apocrine duct carcinomas not otherwise specified).

## DISCUSSION

We recently explored the use of NGS to identify viral sequencing in tumor samples<sup>20</sup>. In a set of 55,962 tumor samples, HPV42 was detected in four cases of DPAC. Since HPV42 was not found in any other tumor type in the large sample cohort, we reasoned that this is likely a biologically relevant association, which could be used for diagnostic purposes to distinguish DPAC from other tumors.

The findings reported herein confirm that HPV42 is strongly associated with DPAC and that an in situ hybridization assay documenting the presence or absence of HPV42 has potential diagnostic value. All cases with histopathologically confirmed DPAC were positive for HPV42. With regard to the utility of two different commercially available probes, there was no difference in the intensity or distribution pattern.

Of note, a positive hybridization signal was only seen in the tumor cells. No positive staining was seen in the overlying epidermis or any adjacent normal skin structure. Furthermore, positive signals were seen in both primary as well as metastatic tumors. These observations suggest that the association of papillary digital adenocarcinoma with HPV42 is not due to an incidental contamination of HPV42 in the skin where the tumor is located. HPV42 is likely an oncogenic driver for DPAC, but further studies are needed to determine its role in tumor formation.

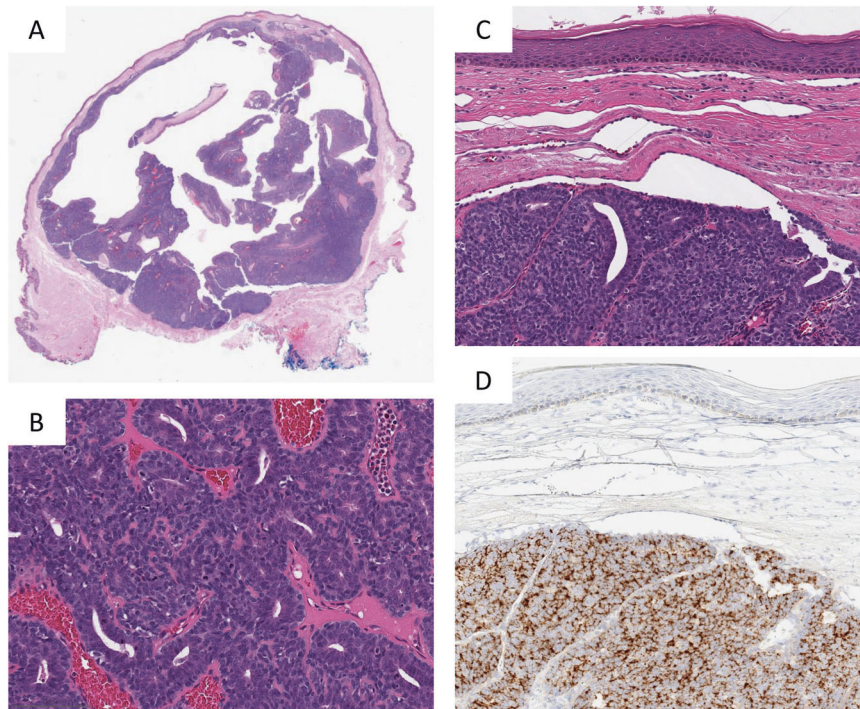
There is limited information on molecular aberrations in DPACs. One study of eight tumors using gene expression profiling found a tendency for FGFR2 overexpression<sup>21</sup>. A small series found one of nine tumors positive for BRAFV600E, and a separate single case study reported a tumor with a BRAFV600E mutation<sup>22,23</sup>. However, it is of interest that in both publications the case said to be positive for BRAFV600E was clinically not typical: it affected a woman and occurred at a non-digital site. Since both BRAFV600E-positive tumors had well-differentiated adenomatous features and it is known that tubular and papillary sweat gland adenomas commonly carry BRAFV600E mutations<sup>24</sup>, it is difficult to be certain whether they

were indeed DPACs. While we acknowledge the possibility of genetic heterogeneity among DPAC, including rare BRAF mutations, none of the four tumors of our series that had sufficient tissue for NGS analysis carried a BRAF mutation. No recurrent genomic events were observed but the sample size is too small for firm conclusions.

The main goal of our study was to explore the potential diagnostic utility of in situ hybridization for HPV42 for the diagnosis of DPAC and its distinction from other sweat gland neoplasms, in particular acral hidradenomas. The distinction of DPAC from acral hidradenoma can usually be accomplished with a combination of microscopic criteria and be supported by immunohistochemical studies. In difficult cases, one may also consider ancillary studies to document the presence of a gene fusion associated with hidradenomas, such as by performing fluorescence in situ hybridization analysis for MAML2 to help establish a precise diagnosis<sup>24–26</sup>. However, the sensitivity and specificity of those methods are limited, and they take longer and cost more than an in situ hybridization assay.

Since none of the cases of acral hidradenomas were positive for HPV42 and none of the other types of sweat gland neoplasms that were examined, our results suggest that in situ hybridization for HPV42 could be used as an efficient ancillary method for diagnostically challenging cases to distinguish DPAC from other sweat gland neoplasms affecting acral skin. A single positive in situ hybridization test result confirming the presence of HPV42 would support a diagnosis of DPAC. The observation that no HPV42 DNA sequence was found in a large number of carcinomas<sup>20</sup> suggests that in situ hybridization for HPV42 may also be used for the distinction of DPAC for miscellaneous non-cutaneous adenocarcinomas.

Our study also confirms that tumors with the phenotype of a DPAC are not limited to the hands or feet. While such cases have previously been reported, the evidence presented that the tumors were bonafide DPAC and not a different type of adenocarcinoma with papillary features was not convincing<sup>5,11</sup>. One report, for example, classified a tumor on the face as DPAC in spite of the fact that no tumor cells were positive for p63<sup>11</sup>, which is not what one would expect for a DPAC, which typically contains both epithelial and myoepithelial elements. In the current series, we present two tumors from the skin of the scrotum with microscopic and immunohistochemical findings typical of a DPAC. Both were



**Fig. 4** Scrotal adenocarcinoma from an 80-year-old man (Table 1, case 9). **A** Silhouette of a large nodulocystic tumor. **B** The tumor contains tubular structures surrounded by myoepithelial cells. **C** The tumor shows a lobular peripheral growth and does not involve the epidermis. **D** The tumor cells are positive for HPV42. The overlying epidermis is not.

positive for HPV42 by in situ hybridization. Thus, the availability of an in situ hybridization assay for HPV 42 can also help diagnose HPV42-associated DPAC at non-acral sites.

In conclusion, while we acknowledge that larger studies are needed for independent confirmation, we document herein that an in situ hybridization assay for HPV42 consistently labels DPAC in a small set of tumors. Our observations suggest that testing for HPV42 can be used to support the diagnosis of DPAC and help distinguish it from other histologic simulants, in particular acral hidradenomas. In situ hybridization can also help identify tumors of similar phenotype at non-acral sites. Since the digital location is not unique, papillary growth is often not pronounced, but the presence of HPV42 seems to be a consistent and distinctive finding, consideration may be given to re-classify DPACs as HPV42-associated sweat gland carcinoma.

#### DATA AVAILABILITY

Data generated or analyzed during this study are included in this published article.

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## AUTHOR CONTRIBUTIONS

K.J.B. performed the study concept and design. K.J.B., C.V., and T.B. performed writing, review, and revision. T.B., G.H., and A.M. contributed pathology material. C.A. and E.A. provided clinical data. All authors read and approved the final paper.

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## COMPETING INTERESTS

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

## ETHICS APPROVAL

The study was conducted under the institutional review board protocols 16-1613, 12-245, and 18-128.

## ADDITIONAL INFORMATION

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