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# CLASSIFICATION AND CLINICAL SIGNIFICANCE OF PAPILLOMAVIRUS INFECTION IN DOMESTIC CATS

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**Abstract**

During the last decades, the infection with papillomavirus in domestic cats gained interest from the veterinary community due to its significant impact on the companion's animal's health. Therefore, in this review, we aim to present a concise classification of feline papillomaviruses and their clinical relevance in domestic felines. Initially, the different types of papillomaviruses affecting domestic cats are described. Here, we emphasize the molecular diversity and transmission ways to better understand each virus type and its clinical implications. Furthermore, we explore the clinical importance of papillomavirus infections, analyzing their various manifestations such as skin or oral lesions. We outline the signs and symptoms of these infections, shedding light on the oncogenic mechanisms used by the virus. The knowledge gained from this analysis holds the potential to refine veterinary medical practices, enabling the effective management of this condition and ultimately enhancing the overall quality of life for our feline companions.

**Key words**: Feline papillomavirus, molecular biology, skin and oral lessions, classification

## INTRODUCTION

Papillomaviruses (PVs) are a group of circular DNA viruses with a double-stranded structure. Their genetic structure includes five or six early (E) genes and two late (L) genes. Typically, PVs are specific to certain species and exhibit a preference for specific types of epithelial tissues and even specific areas of the body (Doorbar et al., 2012). PVs are categorized based on the highly conserved L1 gene. If two PVs share 60–90% similarity in the L1 open reading frame (ORF), they are considered different types. PVs with less than 60% similarity are likely to belong to different genera (Bernard et al., 2010). Within a genus, these viruses often infect closely related host species, leading to similar lesions in those hosts (Bernard et al.,2010). Papillomaviruses have been discovered in a wide range of species, including mammals, birds and reptiles (Rector & Van Ranst, 2013). Most species are infected by multiple PV types, often from different genera (Bernard et al., 2010).

The papillomavirus life cycle is synchronized with cells' regular division and differentiation processes in the mucocutaneous stratified epithelium. Initial microtrauma provides the entry point for PV into basal cells. The expression of PV E1 and E2 genes enables the virus to generate a limited number of copies, which then infect neighbouring basal cells. Infection of these basal cells enables the persistence of PV, although viral replication only occurs when a basal cell differentiates terminally and transitions to the suprabasal layer of the epithelium. At this stage, the PV interferes with cell regulation through the action of E6 and E7 proteins, preventing terminal differentiation, retaining the nucleus, and compelling epithelial cells to divide and replicate the virus. As infected cells approach the epithelium's surface, the expression of L1 and L2 proteins facilitates virion assembly. Eventually, cells shed from the epithelial surface, and the natural degeneration of epithelial cells releases viral particles into the environment (Graham, 2017).

While it is well established that PVs are linked to various cancers, the progression from a PV infection to an associated cancer is a rare occurrence (Stanley, 2010). In terms of viral replication, the shift to cancer is typically a non-productive or 'dead-end' event for the virus. Persistent infection, which can last for several years in basal and stem epithelial cells, especially

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in the presence of at least one high-risk PV (HR-PV), seems to be the primary factor leading to cancer progression (Moody & Laimins, 2010). However, mere infection, even though necessary, is not adequate to fully trigger tumorigenesis. Regardless of the infected anatomical site, the crucial alteration required for advancing to malignancy involves heightened expression of the viral oncoproteins E6 and E7 in dividing infected cells. This increased activity of E6 and E7 can promote cell growth, impede differentiation, and induce chromosomal instability, ultimately leading to tumorigenesis. In the majority of cases, approximately 70% to 85%, alterations in oncoprotein expression occur due to the integration of the HR-PV genome into the host genome (Pett & Coleman, 2007).

Since PV infection does not lead to cell necrosis and its effects are primarily confined to the superficial layers of the epithelium, PVs typically trigger a mild inflammatory response. This phenomenon is particularly observed in slow-replicating and asymptomatic PVs (Doorbar, 2006). When the body mounts a response, it identifies and eliminates infected cells through a cell-mediated immune response (Egawa & Doorbar, 2017). This immune reaction can stop PV replication, and because PV proteins affecting cell growth are lost, any hyperplastic lesion induced by the infection tends to resolve. The onset of the cell-mediated immune response varies, explaining why some oral papillomas in dogs spontaneously vanish within three months while others persist for up to a year (Sancak et al., 2015). Despite lesion resolution caused by the immune response, PVs can persist in basal cells and likely continue replicating at a low rate. The immune system's role in controlling PV replication is evident in the lack of visible lesions resulting from the skin's ubiquitous infection with human betapapillomaviruses in immunocompetent individuals (Forslund et al., 1999).

In addition to causing the formation of hyperplastic papillomas, PVs have the capacity to disrupt normal cell regulation, potentially contributing to the development of cancer (Graham, 2017). In humans, PVs are the most common viral agents linked to cancer, particularly the high-risk alphapapillomaviruses, responsible for about 5% of all human cancers, including a significant portion of cervical squamous cell carcinomas (SCCs) and oral SCCs (Plummer et al., 2016). Similarly, in various domestic species such as horses, dogs, cattle, pigs, and sheep, PVs have been associated with neoplastic conditions (Borzacchiello & Roperto, 2008; Munday et al., 2020; Munday, Dunowska, et al., 2016; Sykora et al., 2017; Vitiello et al., 2017). However, it's crucial to note that the majority of PV infections in both humans and animals do not culminate in neoplasia. Other factors like the speed of the immune response or the presence of additional neoplasia-promoting factors play a pivotal role in determining whether a PV infection progresses to cancer (Doorbar, 2006; Munday, 2014).

## MATERIAL AND METHOD

A comprehensive literature research was conducted using electronic databases such as PubMed, Scopus, and Web of Science. The search terms included "papillomavirus infections in cats," "feline papillomavirus classification," "types of lesions," and "neoplastic transformation in feline PV infections." Articles and studies published up to the date of the search were retrieved for analysis.

The retrieved literature was reviewed to understand the classification systems used for feline papillomaviruses. This involved analyzing molecular characteristics, genomic structures, and phylogenetic analyses of feline papillomaviruses. Special attention was given to the criteria and methods employed by various researchers and organizations in classifying these viruses into different types and genotypes.

Studies reporting clinical cases and pathological findings related to feline papillomavirus infections were reviewed. The focus was on identifying and categorizing the types of lesions associated with these infections. Lesions were classified based on their location, morphology, and severity. Detailed information on cutaneous, mucosal, and oral lesions was extracted and analyzed.

Special emphasis was placed on studies investigating the potential of feline papillomaviruses to induce neoplastic transformation. Cases reporting papillomavirus-associated cancers in cats were identified and thoroughly examined. Data on histopathological features, tumor types, and molecular markers indicating neoplastic transformation were collected and analyzed to understand the underlying mechanisms of papillomavirus-induced carcinogenesis.

## CLASSIFICATION OF FELINE PAPILLOMAVIRUS

### 1. *Felis catus Papillomavirus* Type 1

The complete sequence of the first papillomavirus (PV) in domestic cats was published in 2002 (Tachezy et al., 2002). Initially named *Felis domesticus PV* (FdPV) 1, PVs identified in this species were later renamed *Felis catus PVs* (FcaPVs) to align with the correct taxonomic name for domestic cats, which is *Felis*

*catus*. Among FcaPVs, Felis catus PV type 1 (FcaPV1) is the sole known *lambdapapillomavirus* that infects domestic cats. Interestingly, FcaPV1 is closely related to *lambdapapillomaviruses* found in exotic felids (Rector & Van Ranst, 2013). Despite the discovery, there are limited reports of FcaPV1, leaving the age at which cats become infected and the proportion of infected cats unknown. Although FcaPV1 was first identified in a skin lesion, subsequent findings have confined its detection solely to the oral cavity (Munday et al., 2015; Munday & French, 2015).

2. *Felis catus Papillomavirus* Type 2

Among the papillomaviruses (PVs) that infect domestic cats, FcaPV2 seems to be the primary type behind diseases, garnering significant attention in feline PV research. Its full sequence was unveiled in 2009, classifying it as the sole member of the *dyothetapapillomavirus* genus (Lange et al., 2009). Cats typically contract FcaPV2 within the initial days of life, possibly during birth from the queen or through close contact while suckling and grooming (Thomson et al., 2015). FcaPV2 infection is widespread, with viral DNA detectable in skin swabs from nearly all clinically normal cats (Geisseler et al., 2016; Munday & Witham, 2010; Thomson et al., 2019). Furthermore, approximately a quarter of cats exhibit detectable serum antibodies against FcaPV2 (Geisseler et al., 2016). Intriguingly, FcaPV2 DNA and gene expression have been identified in blood samples from healthy cats, indicating viral replication in non-epithelial cells and the potential for viral transmission through blood or placenta (Altamura et al., 2018).

Studies have shown that *Felis catus* PV type 2 can disrupt normal cell regulation through various pathways. In human cancers, PVs contribute to cancer development by degrading the retinoblastoma protein (pRb), a crucial regulator in the cell replication pathway, thereby promoting cell division. Correspondingly, FcaPV2-infected lesions in cats exhibited intense p16 immunostaining, indicative of elevated p16 levels within cells (Munday et al., 2013; Munday et al., 2011a; Munday & Aberdein, 2012). Subsequent research confirmed that the FcaPV2 E7 protein binds to pRb, suggesting that FcaPV2 promotes cell division by E7-mediated degradation of pRb within cells (Altamura et al., 2016).

Additionally, 'high-risk' PVs in humans promote cancer by degrading the p53 protein. Although initial immunohistochemical (IHC) studies did not reveal a clear link between the presence of FcaPV2 DNA in lesions and the absence or presence of p53 protein (Munday et al.,2019), recent molecular studies demonstrated that the FcaPV2 E6 protein can promote p53 degradation within the cell, suggesting that this PV might interfere with normal p53 function (Altamura et al., 2016). Furthermore, FcaPV2 may enhance cell replication by upregulating mitogen-activated protein kinases and inhibit cell apoptosis by increasing protein kinase B expression (Altamura et al., 2016).

3. *Felis catus Papillomavirus* Type 3

The comprehensive genetic sequence of this specific papillomavirus type was initially documented in 2013 (Dunowska et al., 2014). FcaPV3's L1 open reading frame (ORF) sequence exhibits less than 60% similarity with both FcaPV1 and FcaPV2, but interestingly, it shows the highest resemblance to canine PVs in the *Taupapillomavirus* genus. This genetic and behavioral affinity led to the classification of this PV as the inaugural member of the species 3 *Taupapillomaviruses* (Van Doorslaer et al., 2018). Subsequent findings have identified FcaPV3 in hyperplastic and neoplastic skin as well as oral lesions in cats, indicating its capacity to influence cell regulation (Chu et al., 2020; Munday et al., 2018; Yamashita-Kawanishi et al., 2018). Moreover, lesions containing FcaPV3 DNA displayed prominent p16 immunostaining, suggesting the virus's ability to degrade pRb (Munday et al., 2018). The prevalence of asymptomatic FcaPV3 infections in cats and the precise timing of initial infections by this specific PV type remain unknown.

4. *Felis catus Papillomavirus* Type 4

The full genetic sequence of this particular papillomavirus (PV) was documented in 2014, following its discovery in a sample from a cat's mouth (Dunowska et al., 2014). Interestingly, the L1 open reading frame (ORF) of this virus exhibits the highest similarity to FcaPV3, leading to its classification as a species 3 *Taupapillomavirus* (Van Doorslaer et al., 2018). Rarely, this virus has also been found in cutaneous lesions in cats (Vascellari et al., 2019; Yamashita-Kawanishi et al., 2018; Yamashita-Kawanishi, Gushino, et al., 2021). Notably, in some cases where FcaPV4 was the sole PV type detected, it suggests that this PV has the potential to induce diseases in cats. Furthermore, the presence of FcaPV4 DNA has been linked to intense p16 immunostaining, indicating that this PV type might enhance cell replication by disrupting normal pRb function

(Munday, Gibson, et al., 2011). The prevalence of FcaPV4 infections in cats and the age at which cats are typically infected by this specific PV type remain unknown.

5. *Felis catus Papillomavirus* Type 5

This specific papillomavirus type was identified in 2017 from a skin lesion (Munday, Dittmer, et al., 2017). Although it has not been officially assigned to a genus yet, its genetic sequence closely resembles that of FcaPV3 and FcaPV4, indicating a probable classification as a species 3 *Taupapillomavirus*. Since its initial discovery, there have been occasional reports of FcaPV5 found in skin lesions in cats (Kok et al., 2019; Vascellari et al., 2019). The lesions linked to FcaPV5 exhibited p16 immunostaining, indicating that the virus might impact cell growth by disrupting normal pRb function (Munday, Marshall, et al., 2017).

6. Felis catus Papillomavirus Type 6

The latest papillomavirus type identified in domestic cats was fully sequenced from a skin lesion and was documented in 2020 (Carrai et al., 2020). Its L1 open reading frame (ORF) sequence shares the closest resemblance to FcaPV3, hinting at its probable classification as a species 3 *Taupapillomavirus*. Felis catus papillomavirus type 6 has not been reported subsequently, indicating that this specific PV type might be a rare culprit behind skin diseases in domestic cats (Munday et al., 2021).

7. *Bovine Papillomavirus* Type 14

While this specific papillomavirus type is capable of infecting cats, it is cattle that serve as the definitive hosts for BPV14. In cattle, this virus has been identified in papillomas (warts), bladder cancers, and normal skin samples (Da Silva et al., 2012; Munday & Knight, 2010; Roperto et al., 2016). In contrast, BPV14 has only been found in sarcoids, a type of mesenchymal neoplasia, in cats. Notably, this PV does not cause asymptomatic infections in cats, and cats appear to be dead-end hosts for this virus (Munday et al., 2010). Apart from domestic cats, BPV14 has also been detected in sarcoids from African lions and cougars (Munday, French, et al., 2011a).

## FELINE PAPILLOMAVIRUS-ASSOCIATED LESIONS

1. Feline Viral Plaques and Bowenoid In Situ Carcinomas

Originally, feline viral plaques and Bowenoid in situ carcinomas (BISCs) were perceived as separate skin lesions. Nevertheless, given their common origin from PV infection and comparable histological characteristics, it is more accurate to regard them as varying degrees of severity within the same disease. To streamline discussions, this text will henceforth refer to all these conditions collectively as BISCs (Munday et al., 2021).

Bowenoid in situ carcinomas are rare skin lesions typically found in middle-aged to older cats. These lesions appear as multiple pigmented or non-pigmented, non-painful, non-pruritic, slightly raised growths, often up to 2 cm in diameter, commonly on the face, head, and neck (Wilhelm et al., 2006). Interestingly, these lesions can develop on both haired and non-haired skin, indicating that sunlight exposure might not be the primary cause. The expected behavior of BISCs remains poorly understood. Some smaller BISCs have been reported to regress spontaneously, but others persist and progress to invasive squamous cell carcinoma (SCC). While early reports suggested a link between immunosuppression and BISC development, many cats with BISCs do not have identifiable immunosuppressive diseases. Certain cat breeds, such as Sphinx and Devon Rex, are predisposed to BISCs, and these lesions tend to occur at an earlier age in these breeds. Moreover, in these specific breeds, BISCs progress more rapidly to invasive and metastatic SCC (Munday et al., 2016; Ravens et al., 2013).

Most BISCs have been linked to FcaPV2 infection. Studies using PCR primers designed to detect FcaPV2 found the virus in a significant number of BISC cases (Munday et al., 2007, 2008; Munday, French, et al., 2011b; Munday & Peters-Kennedy, 2010; Nespeca et al., 2006; Vascellari et al., 2019). In situ hybridization techniques have further localized FcaPV2 within the proliferating cells of BISCs (Demos et al., 2019; Vascellari et al., 2019). Although FcaPV2 appears to be the primary cause of BISCs, FcaPV3, FcaPV4, and FcaPV5 have also been associated with these lesions. Some regional differences in the predominant PV type have been suggested, and subtle differences in histological features caused by different PV types have been reported. For instance, FcaPV3 may cause proliferation of cells deeper within the hair follicle, while FcaPV5

infection might lead to proliferation of follicular structures as well as cells within sebaceous glands (Munday, Marshall et al., 2017). There is a hint, based on limited data, that BISCs caused by FcaPV3 might exhibit less aggressive behavior than those caused by FcaPV2 (Munday et al., 2016).

The mechanisms by which different FcaPV types induce hyperplasia and neoplasia remain unclear. However, intense p16 immunostaining has been observed in lesions containing FcaPV2, FcaPV3, FcaPV4, FcaPV5, and FcaPV6, indicating that all these PV types can disrupt normal pRb function (Carrai et al., 2020).

## 2. Feline Cutaneous Squamous Cell Carcinomas (SCCs)

Cutaneous squamous cell carcinomas (SCCs) are common in cats and are typically highly invasive, leading to significant morbidity and mortality. Similar to humans, most cutaneous SCCs in cats are believed to result primarily from sunlight exposure, occurring in non-haired, non-pigmented areas like the pinna, nasal planum, and eyelids. Although these SCCs often progress from actinic keratosis (a sun-induced intraepithelial neoplastic lesion) in sun-exposed skin, a smaller number develop in UV-protected areas, raising the possibility of progression from a Bowenoid in situ carcinoma (BISC) in these cases, although such progression has been documented in only a few instances (Munday, Benfell, et al., 2016; Ravens et al., 2013).

In 2006, DNA sequences from FcaPV2 were first identified in feline cutaneous SCCs (Nespeca et al., 2006). Subsequent studies showed more frequent detection of FcaPV2 DNA in cutaneous SCCs than in normal cat skin (Munday et al., 2008). Researchers from various parts of the world have also found PV DNA in feline cutaneous SCCs, with additional evidence supporting PVs' role in these cancers. Higher viral loads have been detected in BISCs and a subset of SCCs compared to normal skin (Thomson et al., 2016), and FcaPV2 gene expression has been identified and localized within feline cutaneous SCCs (Altamura et al., 2016; Hoggard et al., 2018; Thomson et al., 2016). Intense p16 immunostaining has been observed in SCCs containing PV DNA, highlighting the potential link between PV infection and cancer development, especially in cases with p16-positive SCCs showing longer survival rates (Munday et al., 2013; Munday, Gibson, et al., 2011).

Current evidence indicates that PVs influence around 30% of SCCs arising from UV-exposed skin and 75% of those from UV-protected skin (Munday et al., 2011). However, the precise impact of PV infection compared to other potential factors remains uncertain. FcaPV2 is the most commonly detected PV type in PV-associated cutaneous SCCs in cats, although a smaller proportion of SCCs contain FcaPV3, FcaPV4, or FcaPV6 DNA sequences (Carrai et al., 2020; Munday et al., 2011; Vascellari et al., 2019; Yamashita-Kawanishi et al., 2018; Yamashita-Kawanishi, et al., 2021). Regional differences have been observed, with FcaPV3 being most frequently detected in SCCs from cats in Japan (Yamashita-Kawanishi et al.,2021). Currently, whether the subsequent behavior of SCCs is influenced by the specific PV type causing the lesion remains unknown.

## 3. Feline Oral Squamous Cell Carcinomas (OSCCs)

Feline oral squamous cell carcinomas (OSCCs) are highly aggressive neoplasms that are almost always fatal. Currently, treatment options are limited, and cats diagnosed with these tumors typically survive for about 5 weeks on average (Klobukowska & Munday, 2016). While the cause of feline oral SCCs remains unknown, it is well established that a portion of human oral squamous cell carcinomas (OSCCs) are caused by papillomavirus (PV) infection (Schwartz et al., 1998). Given the role of PVs in human OSCCs and feline cutaneous SCCs, researchers have explored the possibility that PVs may also contribute to the development of feline OSCCs.

In the initial comprehensive study of feline OSCCs, PV sequences were detected in one out of 20 cancers but not in any of the 20 non-cancerous oral samples. Interestingly, the identified PV sequence in the feline OSCC belonged to a human PV type (Munday et al., 2009). In a subsequent study, PV DNA sequences were amplified from two out of 32 feline OSCCs. However, one of the sequences couldn't be sequenced, and the other was from a human PV type, raising concerns about potential sample contamination (O'Neill et al., 2011).

In contrast, no PV DNA was found in a series of 30 feline OSCCs from cats in New Zealand and in another study involving seven feline OSCCs from cats in Japan (Munday et al., 2011; Yamashita-Kawanishi et al., 2018). In a different New Zealand study, FcaPV1 sequences were detected in one out of 36 OSCCs and one out of 16 inflammatory gingival lesions, with no other PV types identified (Munday & French, 2015). A recent study in North America used advanced sequencing techniques to analyze 20 feline OSCCs

and nine samples of normal feline gingiva. Although various virus types were found, only one OSCC was found to contain a PV sequence, specifically from FcaPV3 (Chu et al., 2020). Conversely, an Italian study identified FcaPV2 in 10 out of 32 (31%) feline OSCCs and in four out of 11 (36%) samples of ulcerative gingivitis. The presence of gene expression in many positive samples indicated viral replication in oral tissues. However, efforts to confirm the location of FcaPV2 DNA within the samples through in situ hybridization yielded inconclusive results (Altamura et al., 2020). Additionally, FcaPV2 DNA sequences were found in 11 out of 19 (58%) OSCCs in a recent study of cats from Taiwan, although non-cancerous oral samples were not included in this analysis (Yamashita-Kawanishi, Chang, et al., 2021).

Several studies have reported varying levels of p16 immunostaining in feline oral SCCs. However, this variability has not been linked to the presence of PV DNA in feline OSCCs, suggesting that spontaneous mutations within the neoplasms might be responsible for the inconsistent immunostaining, rather than a PV-related cause (Altamura et al., 2020; Munday et al., 2019; Munday, Knight, et al., 2011; Yamashita-Kawanishi et al., 2018).

4. Feline Basal Cell Carcinomas (BCCs)

Basal cell carcinomas (BCCs) are much rarer in cats compared to squamous cell carcinomas (SCCs). Unlike SCCs, these tumors lack a connection to the overlying epidermis, and keratinization is generally absent. The neoplastic cells in BCCs are small and darkly basophilic, resembling cells found within the basilar layers of the epidermis (Goldschmidt et al., 2018).

The potential association between BCCs and papillomavirus (PV) infection in cats was first noted when it was observed that these lesions often occur alongside adjacent Bowenoid in situ carcinoma (BISC) lesions, and PV cytopathic changes were observed in cells within some BCCs (Gross et al., 2008). Subsequently, a cat with multiple BCCs containing FcaPV3 DNA was reported, indicating a link between PV infection and these tumors (Munday et al., 2018). Furthermore, short sequences from a novel PV type were amplified from a feline cutaneous BCC (Munday, French, et al., 2017). This PV type has not been fully sequenced, suggesting the likelihood of discovering additional PV types associated with cats in the future (Munday, French, et al., 2011a).

## CONCLUSIONS

In conclusion, this article sheds light on the intricate classification and diverse lesions caused by feline papillomaviruses (FcaPVs). Through an exploration of various FcaPV types and their associated lesions, we have deepened our understanding of the complexities within this viral family. The identification and characterization of these lesions are crucial steps toward early detection, accurate diagnosis, and effective management of FcaPV-related diseases in domestic cats.

Furthermore, our analysis underscores the necessity for continuous research in this field. As new FcaPV types and their corresponding lesions emerge, it becomes imperative to stay updated and adapt diagnostic and therapeutic approaches accordingly. Collaborative efforts between researchers, veterinarians, and public health authorities are essential to enhance our knowledge of FcaPVs, leading to improved preventive measures and treatments.

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