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## Papillomaviridae

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This family of double-stranded DNA viruses was once included with polyomaviruses in the discontinued family Papovaviridae. The myriad papilloma viruses cause papillomas (warts) of the skin and mucous membranes of most domestic animals and a wide variety of other mammals and birds.

### **Viral Characteristics**

- These viruses are nonenveloped, circular dsDNA viruses with icosahedral symmetry (see Fig. 12-1).
- The genome consists of a single, circular molecule of double stranded DNA. The complete genome is ~8,000-nucleotide base pairs in length and encodes 12 genes, two of which are associated with the capsid. Only one strand of the dsDNA encodes the genes.
- The dsDNA serves as a template for transcription of mRNAs and progeny genomes by host enzymes. Replication and virion assembly occur in the nucleus and virions are released by destruction of the nuclear and cell membranes.
- Papillomaviruses replicate in the nucleus and new virions are released with the lysis of the cell.
- Because papillomaviruses grow poorly if at all in cell culture, it has taken significantly longer to understand how they replicate. Much has been learned recently by the study of bovine papillomavirus-1 (BPV-1). However, the scope and detail of the studies go beyond the scope of this book.
- Papillomaviruses produce diagnostically significant koilocytotic (vaculated) cells while replicating.
- The viruses are resistant and remain viable for long periods of time on contaminated premises.
- Transmission is mainly by direct contact and fomites.
- These viruses are host species-specific.
- Papillomaviruses target squamous epithelial cells of the skin and mucous membrane.
- The many papillomatoses are common and occur worldwide.
- The immune response to papillomaviruses associated with the spontaneous regression of warts and is mediated by both cellular and humoral immune responses.
- Some papillomaviruses cause neoplastic transformation of cells and have been implicated in the cause of bovine and human cancers.



Figure 12-1. Papillomaviridae (~55 nm). Illustration of the icosahedral capsid. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

## **Classification**

This family has a single genus, Papillomavirus.

The papillomaviruses, which are species-specific, infect many animals including humans, chimpanzee, monkeys, cattle, deer, dog, horse, sheep, elephant, elk, opossum, rabbit and birds.

The genus consists of a number of antigenically distinct papillomaviruses:

- six types occur in cattle,
- three types in dogs,
- two in rabbits and more than 100 in humans.

Types are largely distinguished by the characteristic restriction endonuclease cleavage of their genome.

## **Bovine Papillomatosis**

(Common warts of cattle)

### Cause

Six types of papillomavirus cause bovine papillomatosis.

### Occurrence

Bovine papillomatosis occurs frequently worldwide, mainly affecting young cattle. They occur with greater frequency in stabled cattle.

### Clinical & Pathologic Features

Papillomas develop as small nodular growths of the skin or mucous membrane. They initially grow slowly, but then more rapidly and eventually become larger, horny, pendulant and sometimes cauliflower in shape. They ultimately necrose and fall off. The most common sites affected are the head (particularly around the eyes), neck, and shoulders. They may occur on the penis of the bull and in the vaginal mucosa of the female, resulting in breeding difficulty. After about a year there is usually spontaneous recovery.

The recognized six types of bovine papillomaviruses are associated with particular sites as follows:

- Types 1 and 2: head, neck and shoulders; penis and vaginal mucosa.
- Type 3: persistent papillomas of the skin.
- Type 4: papillomas in the alimentary tract; malignant transformation associated with concomitant bracken fern ingestion has been reported.
- Type 5: "rice-grain type" papillomas of the teat.
- Type 6: flattened (frond-like) papillomas of the teat.

### Diagnosis

- This is usually based on characteristic gross appearance. Laboratory diagnosis is not usually sought.
- Definitive diagnosis requires histological examination for the presence of koilocytes.
- Although not employed for diagnosis, types 1 and 2 bovine papillomaviruses can be cultivated in cell cultures and on the chorioallantoic membrane of chicken embryo.

### Prevention

- Commercial wart vaccines and autogenous wart vaccines, both consisting of finely ground warts, are used. Formalin is often used to kill the virus and a preservative is added. Their value is questionable.
- To prevent spread, affected animals should be isolated.

The BPV-1 is currently being investigated as a potential shuttle vector for moving genes into animals. In addition to BPV-1, human papillomavirus (HPV)-6b, -11, -16, -18, and -31 are also being investigated for use in this manner.

## **Bovine Papilloma Virus 2 and 4**

The combined action of bracken fern and BPV 2 or 4 are thought to produce tumors in the upper digestive track of cattle. Enzootic hematuria due to ingestion of bracken fern occurs in cattle worldwide. The hematuria results from hemorrhages caused by tumors in the bladder wall. Studies suggest that the oncogenesis is due to the combined action of bracken compounds and BPV 2.

## **Equine Papillomatosis**

(Common warts of horses)

### Cause

A papillomavirus.

### Occurrence

Worldwide in horses, mules and donkeys usually up to three years of age. Warts in older horses persist longer.

### Clinical Features

Warts generally occur on the nose and lips, vary in size and number and usually disappear within three months. Congenital papillomatosis has been reported but occurs rarely.

A different papillomavirus is associated with genital lesions in both male and female horses.

### Diagnosis

- This is usually based on the characteristic gross lesions.
- Histologic examination of affected tissue provides confirmation.

### Prevention

- Autogenous formalin-inactivated wart vaccines are sometimes administered but their value is questionable; repeated doses are recommended.
- Surgical removal of warts may be helpful.
- Equine warts, like the warts of other species, will frequently disappear spontaneously.

## **Equine Sarcoids**

### Cause

There is some evidence that bovine papillomavirus types 1 and 2 may be involved in the etiology of sarcoid. This is mainly based on the demonstration of viral DNA sequences in sarcoid tissue, and the fact that experimental infection with these viruses in horses results in sarcoid-like lesions.

### Occurrence

Sarcoid, a fibroblastic tumor that occurs frequently worldwide, is the most common neoplasm of horses, mules and donkeys less than four years of age.

### Transmission

Evidence suggests that sarcoids are transmitted by direct contact fomites and probably by arthropod vectors.

### Clinical & Pathologic Features

These cutaneous tumors, which occur most commonly on the head and neck regions, ventral abdomen and limbs, are relatively benign. Most animals will have multiple lesions. They vary in size from 1 - 20 cm and are flat, raised, pedunculated or verrucous, firm and adherent to the underlying connective tissue.

They do not metastasize, but as high as 50% may recur after surgical removal.

### Diagnosis

- Diagnosis is usually based on the characteristic appearance.
- Definitive diagnosis requires histologic examination.

### Treatment

- Cryosurgery is the preferred treatment; two freeze-thaw cycles are used.
- Immunotherapy using BCG vaccine or an extract of *Mycobacterium bovis* (commercial preparations are available); the control rate is about 50%.
- Radiation and chemotherapy are also used with varying success.
- Some untreated lesions regress spontaneously.

### Prevention

Vaccines are not available.

## **Canine Oral Papillomatosis**

(Common warts of dogs)

### Cause

Three types of papillomavirus cause canine warts, a common worldwide disease of young dogs.

### Clinical & Pathologic Features

Numerous papillomas may occur on the mucous membrane of the mouth, lips, tongue, and pharynx of young dogs.

Infections begin as small, white elevated areas that enlarge to form small cauliflower-like lesions. Warts may occasionally involve the eyelid.

Skin warts are seen in older dogs and may be caused by a particular type of papillomavirus.

Warts usually regress spontaneously in several months. Recovered dogs are immune, and dogs older than two years are

usually immune.

#### Diagnosis

- The disease is clinically characteristic.
- Histologic examination of warts or biopsies is confirmatory.

#### Treatment

- Surgical excision may be employed.
- Autogenous wart vaccines are considered of questionable value in treatment.

#### Prevention

Vaccination for prevention is not generally practiced.

### **Papillomaviruses and Human Cancer**

Although not of direct veterinary significance, it is of interest that some papillomaviruses are implicated in the cause of human cancers. There are at least 30 human types of papilloma viruses that infect the genital tract. Human papillomavirus 16 and 18 (HPV-16 and HPV-18) has been implicated as a cause of cervical cancer. Two papillomavirus genes (E6 and E7) are involved in carcinogenesis. These genes encode proteins responsible for inactivating proteins encoded by the tumor suppressor gene p53 and the retinoblastoma (RB) gene.

Human genital warts are usually caused by types HPV-1 and HPV-6.

### **Glossary**

BCG vaccine: BCG stands for Bacille Calmette-Guérin. It is a vaccine to prevent tuberculosis prepared from an attenuated strain of *Mycobacterium bovis*.

koilocytes: These are epidermal cells in the superficial layers of the epidermis that have a swollen, glassy, highly eosinophilic cytoplasm. They contain papillomavirus.

shuttle vector: Any DNA molecule capable of autonomous replication within a host cell and into which other DNA sequences can be inserted. They are used for transporting foreign genes into recipient cells.

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