

# NOVEL FELINE VIRUSES

## Emerging significance of gammaherpesvirus and morbillivirus infections



**Practical relevance:** New technologies capable of sequencing the genetic material in any given biological sample, combined with computer-based algorithms for sequence assembly and analysis, have revolutionised infectious disease research. The rate at which novel viruses are being discovered now exceeds our understanding of their clinical relevance. Novel viruses may contribute to diseases that are major causes of feline morbidity and mortality, including cancer and chronic kidney disease. The identification of new viral pathogens raises the prospect of not only improved patient outcomes through specific treatment but even disease prevention through viral control measures.

**Clinical challenges:** It can be difficult to determine the role of a novel virus in disease development. Disease may be an occasional outcome, often years after infection. A high prevalence of infection in the general population can make disease associations harder to identify and almost impossible to rule out. Host cofactors such as immune dysfunction, genetic background or coinfections may be required for manifestation of disease, and one virus species may be linked to a range of pathological sequelae. Establishing causality relies on evaluating accumulating evidence from multiple investigations, which is often hard to access by practitioners.

**Global importance:** The worldwide distribution of gammaherpesvirus and morbillivirus infections in domestic cats underlines the potential of these viruses to negatively impact feline health and welfare globally.

**Evidence base:** This review relies on grade Ia–III evidence.

**Keywords:** Virus; morbillivirus; gammaherpesvirus; herpes

### Gammaherpesviruses – current understanding and pathogenic potential

The herpesvirus family (*Herpesviridae*) is a large group of double-stranded DNA viruses comprising three subfamilies, the *Alpha-*, *Beta-* and *Gammaherpesvirinae*. Gammaherpesviruses (GHVs) have co-evolved with a diverse range of mammals including humans and other primates, ruminants, horses, sun bears and sea lions.

Until recently, domestic cats were identified as the natural host for a single herpesvirus, the alphaherpesvirus feline herpesvirus 1 (FHV1), a common cause of feline ocular and upper respiratory tract disease.<sup>1</sup> While a bovine GHV,

bovine herpesvirus 4 (BHV4), has been suggested to cause disease in cats, substantiating evidence is not yet available. Experimental infection of cats with BHV4 did not result in disease<sup>2</sup> and molecular epidemiological studies reported divergent results: 26.9% of 104 blood samples from Michigan were found to be BHV4 positive in one study,<sup>3</sup> whereas none of 101 cats from California, Colorado and Florida tested PCR positive in a more recent study.<sup>4</sup>

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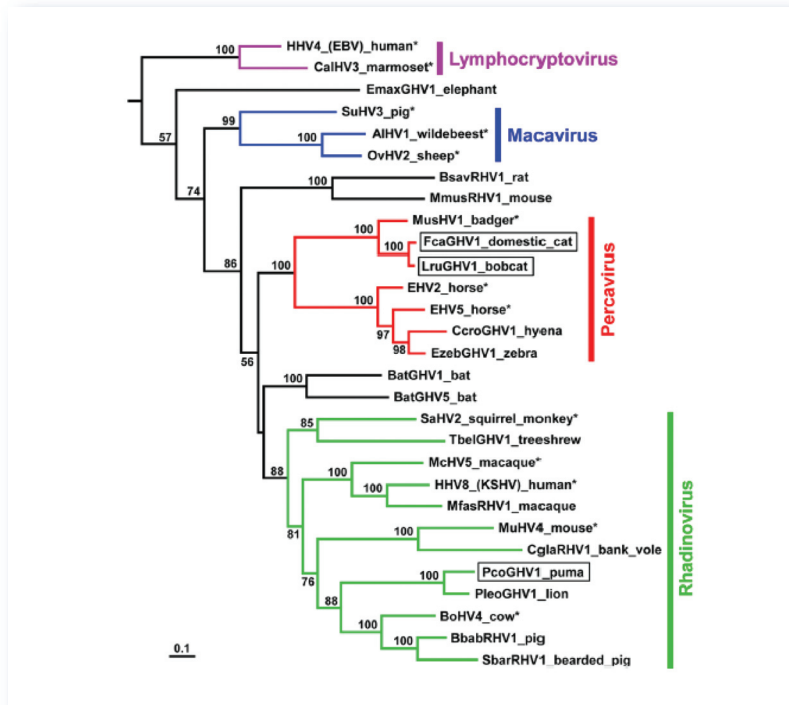
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**Figure 1** Maximum-likelihood phylogenetic analysis of gammaherpesviruses using concatenated DNApol and gB amino alignments. From Troyer et al.<sup>6</sup> © American Society for Microbiology, *Journal of Virology* 2014, 88: 3914–3924. DOI: 10.1128/JVI.03405-13

**Virus discovery**

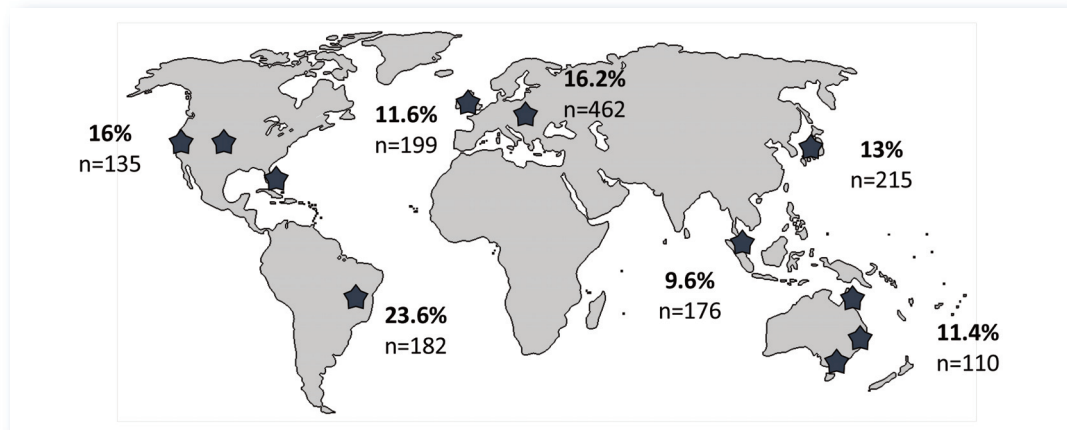
In 2014, an international collaboration identified the first GHV known to infect domestic cats, *Felis catus* gammaherpesvirus 1 (FcaGHV1; proposed species *Felid gammaherpesvirus 1*).<sup>5,6</sup> The impetus for this targeted virus discovery programme was the clinical observation that cats develop the types of cancer that, in humans, are caused by GHVs. Specifically, many lymphomas arising in immunodeficient patients are causally linked to one or both of the GHVs that infect humans, namely Epstein-Barr virus (EBV) and Kaposi’s sarcoma-

associated herpesvirus.<sup>7</sup> Given that feline immunodeficiency virus (FIV)-infected cats have an increased risk of developing similar lymphomas, and that FIV infection alone is rarely directly lymphomagenic, the existence of a feline GHV with oncogenic potential was proposed.<sup>8–10</sup> PCR assays that detect broadly conserved herpesvirus sequences were used to probe DNA extracted from domestic cats and two other felids, resulting in the discovery of three novel viruses: FcaGHV1 in domestic cats, *Lynx rufus* GHV1 (LruGHV1) in bobcats and *Puma concolor* GHV1 (PcoGHV1) in pumas (Figure 1).<sup>6</sup>

**Epidemiology**

FcaGHV1 infection is widely endemic (Figure 2). A virus-specific qPCR targeting the glycoprotein B gene of FcaGHV1 DNA in blood has been used for most epidemiological studies to date.<sup>5</sup> Because the detection of viral DNA does not differentiate between virus-infected cells, virions or free DNA in plasma, the term DNAemia, rather than viraemia, is used. The prevalence of FcaGHV1 DNAemia is 9.6–23.6% in cats from Australia, the USA, Europe, Singapore, Japan and Brazil.<sup>5,6,11–14</sup> Molecular studies do not detect all FcaGHV1 infections. A recent serological study suggests that the true FcaGHV1 infection rate could be at least double that indicated by molecular studies.<sup>15</sup> Age, sex, neuter status, health status and infectious cofactors have been identified as risk factors for FcaGHV1 DNAemia, with some regional variations.<sup>5,6,11–14</sup> Adult male cats are most likely to be infected, and FcaGHV1 DNAemia is rare in cats under 2 years of age. Among coinfections, FIV infection increases

**Comparative evidence suggests that while gammaherpesvirus (GHV) infections typically remain subclinical, in certain circumstances, often after many years of infection, GHVs can cause severe disease that is frequently fatal.**



**Figure 2** FcaGHV1 molecular epidemiology. Stars indicate regions from which published studies of molecular prevalence in feline whole blood are available. The percentages of samples positive for FcaGHV1 DNA using virus-specific PCRs are indicated along with the number of cats tested<sup>5,6,11–14</sup>

**If FcaGHV1 infection is pathogenic, it is likely that disease would be only a rare outcome of chronic infection, with most infected animals remaining asymptomatic.**



the chance of FcaGHV1 DNA detection by five to six times, whereas detection of haemoplasma DNA (*Mycoplasma haemofelis*, 'Candidatus Mycoplasma haemominutum') is associated with a 19-fold increased risk of FcaGHV1 DNA detection compared with age- and sex-matched controls.<sup>5,12</sup> This epidemiological picture supports horizontal transmission during territorial aggression as one possible route of FcaGHV1 infection. Recent data from a study of oronasal swabs and tissues from shelter-housed and client-owned cats demonstrate that cats can be infected with FcaGHV1 from 2 months of age and suggest that most adult cats are persistently infected with FcaGHV1.<sup>16</sup> The potential for FcaGHV1 to be transmitted between cats via oronasal secretions is also demonstrated in this study.

### Pathogenesis

It is not yet known whether FcaGHV1 has any pathogenic role in cats. Persistent infection is a common feature of herpesviruses and, in other species, most GHV infections quickly become latent in their natural host. However, comparative evidence suggests that while GHV infections typically remain subclinical, in certain circumstances, often after many years of infection, GHVs can cause severe diseases that are frequently fatal. For example, EBV infects over 90% of adult humans and is usually innocuous. Occasionally, however, EBV causes lymphomas, carcinomas and other cancers. Because EBV infection is common, these cancers together comprise 2% of the global cancer burden.<sup>17</sup> Risk factors including loss of T cell immunity and genetic predisposition are defined for some, but not all, EBV-associated malignancies. EBV infection is also linked to several respiratory, neurological, dermatological and other conditions, where the role of the virus, if any, remains to be defined.<sup>18</sup>

Among veterinary species, malignant catarrhal fever is recognised as an acute fatal lymphoproliferative disease where one of several ruminant GHVs infects a non-adapted, but susceptible host. As with EBV, most cattle that are infected by GHVs do not develop clinical disease and the factors that result in the development of disease are poorly understood. Horses harbour two endemic GHVs, equine herpesvirus (EHV)2 and EHV5.



**Figure 3** A significant proportion (40–55%) of FIV-infected cats are FcaGHV1 DNAemic.<sup>5,11,13</sup> Big Kev, an adult male entire domestic shorthair rescued from a shelter in Sydney, Australia was found to be coinfecting with FIV and FcaGHV1. After neutering and rehoming he remained disease-free for 3.5 years. Sadly, he went on to develop high grade B cell lymphoma presenting as a large transmural jejunal mass with splenic, renal and lymph node (cervical, thoracic, mesenteric) involvement. While lymphoma is a common presentation in cats, the cause of most lymphomas is unknown. The role of FcaGHV1 as a potential copathogen in FIV infection requires further investigation. Courtesy of Dr Jelena Vukcevic

Pharyngitis, lymphadenopathy and lymphocytosis in foals have been associated with EHV2 infection and are suggested to have an immune-mediated pathogenesis. EHV5 has been linked to equine multinodular pulmonary fibrosis and a role for GHVs in some cases of idiopathic pulmonary fibrosis in humans is postulated.<sup>19</sup>

If FcaGHV1 infection is pathogenic, it is likely that disease would be only a rare outcome of chronic infection, with most infected animals remaining asymptomatic. On the other hand, given how widely distributed FcaGHV1 is, the total number of potential disease-affected animals could be sizeable. Deciphering the impact of FcaGHV1 in cats will require multiple lines of investigation. In a retrospective study of over 200 cats from Australia and Singapore, animals infected with FcaGHV1 were 2.8 times more likely to be classified as sick than healthy on physical examination by a veterinarian blinded to the cat's infection status, lending indirect support for a pathological role for FcaGHV1.<sup>5</sup> The relationship between FIV and FcaGHV1 is particularly interesting; independent studies report significantly higher FcaGHV1 DNAemia in FIV-infected cats compared with matched controls (Figure 3).<sup>5,11</sup> However, neither ciclosporin treatment nor progressive feline leukaemia virus infection had an effect on FcaGHV1 DNAemia, suggesting that the relationship between FIV and FcaGHV1 may not be solely a consequence of immunodeficiency.<sup>20</sup>

A recent study found no association between the detection of FcaGHV1 and the development of high grade or other clinically aggressive lymphomas.<sup>21</sup> However, survival time from diagnosis was significantly shorter in cats with FcaGHV1 DNAemia compared with FcaGHV1-negative cats.<sup>21</sup> A large prospective investigation would assist in understanding whether FcaGHV1 DNAemia could be a clinically useful negative prognostic indicator for cats with lymphoma.

### Diagnosis, prevention and zoonotic potential

Currently, diagnosis of FcaGHV1 infection is limited to a small number of research laboratories. Should the diagnosis of FcaGHV1 be found to have prognostic significance then it is likely that commercial tests would become available. FcaGHV1 is not known or suspected to infect humans. Most GHVs are highly host-specific. However, limited transmission of GHVs between felids is possible; infection of critically endangered Tsushima leopard cats with FcaGHV1 has recently been identified in Japan<sup>14</sup> and LruGHV1 infects bobcats and pumas.<sup>6</sup>

## Morbilliviruses – current understanding and pathogenic potential

Feline morbillivirus (FeMV) was named the seventh species in the genus *Morbillivirus*, family *Paramyxoviridae*, by the International Committee on the Taxonomy of Viruses in 2016.<sup>22</sup> Members of the *Morbillivirus* genus are important pathogens of humans and animals, causing significant morbidity and mortality. The other recognised morbilliviruses are measles virus, canine distemper virus, the now eradicated rinderpest virus, peste des petits ruminants virus, phocine distemper virus and cetacean morbillivirus.<sup>23</sup> Morbilliviruses are negative-sense, single-stranded, non-segmented RNA viruses.<sup>23</sup>

### Virus discovery

FeMV was first reported in domestic cats in Hong Kong and China in 2012.<sup>24</sup> In the 7 years since its discovery, FeMV has been detected in Japan,<sup>25</sup> Europe (Germany,<sup>26</sup> Italy,<sup>27</sup> Turkey,<sup>28</sup> UK<sup>29</sup>) and the Americas (USA,<sup>30</sup> Brazil<sup>31</sup>). Despite the apparent widespread distribution of this virus, whether

## The mode of feline morbillivirus (FeMV)

transmission is currently unknown; however, findings suggest that close contact between cats may be necessary.



Naturally acquired FeMV may be an asymptomatic and self-limiting viral infection, or it may result in disease in cats that has previously been attributed to other causes or considered to be idiopathic.

or not FeMV causes disease in cats remains unclear.

### Epidemiology

The majority of the FeMV literature focuses on its prevalence in domestic cat populations around the world. Most investigators have used RT-PCR to detect FeMV in urine samples, using primers targeting the FeMV *L* gene or consensus pan-paramyxovirus primers.<sup>24–37</sup> A small number of investigators have performed RT-PCR for FeMV on kidney tissue, among other samples and tissues.<sup>28,35</sup> Of note, few investigators have successfully isolated the virus from clinical samples, and thus the significance of a positive RT-PCR result has been debated. False-positive RT-PCR results are possible, and there is the additional possi-

## Morbilliviruses and CKD

An association between FeMV and tubulointerstitial nephritis (TIN), the pathological manifestation of chronic kidney disease (CKD), has been suggested in several reports including the first report of FeMV, where TIN was identified in two FeMV RT-PCR-positive cats at necropsy.<sup>24</sup> Not surprisingly, this has resulted in significant interest among the veterinary community, given the relatively high prevalence of CKD in cats and its associated morbidity and mortality. However, conclusive evidence that FeMV causes TIN or CKD is lacking.

Woo and colleagues investigated an association between FeMV and TIN in 27 pet cats; 12/27 cats were RT-PCR positive for FeMV infection in urine, of which 9/12 (75%) had TIN.<sup>24</sup> Information on the health status of these cats was not reported, nor was routine clinicopathological data. Of the 15/27 cats that were FeMV RT-PCR negative, only two cats had evidence of TIN at necropsy.<sup>24</sup> The difference in proportions of cats with TIN between the FeMV RT-PCR-positive and negative groups was statistically significant.<sup>24</sup> However, it is noteworthy that there were cats in the FeMV RT-PCR-positive group that did not have TIN, suggesting that infection does not inevitably cause this disease. Additionally, there were cats in the FeMV RT-PCR-negative group that did have TIN, suggesting that TIN can be caused by factors other than FeMV infection.

A number of research groups have reported the presence of FeMV in renal tubular cells using immunohistochemistry.<sup>24,28</sup> Woo et al raised antiserum for anti-FeMV nucleocapsid (N)

protein in guinea pigs and used it to stain feline renal tubules.<sup>24</sup> Yilmaz et al, using the same polyclonal serum, reported intracytoplasmic immunostaining in renal tubular parenchymal cells, although no association between FeMV RT-PCR-positive status

in urine and the presence of TIN was identified.<sup>28</sup> A study by Sieg et al suggested an association between CKD and FeMV infection, although scrutiny of the data casts doubt on this conclusion.<sup>26</sup> Among urine samples from 120 diseased cats, five were FeMV RT-PCR positive, whereas 0/80 samples from healthy cats were positive.<sup>26</sup> Of the five FeMV RT-PCR-positive diseased cats, three had lower urinary tract disease, and two had kidney disease. However, the latter were poorly characterised, with a description of 'renal cyst' in one and 'chronic renal failure' in the other.<sup>26</sup> The authors also identified a novel paramyxovirus that is genetically distinct from FeMV and, at this stage, remains an unclassified paramyxovirus.<sup>26</sup> In contrast to the above-mentioned study, a recent clinical epidemiological investigation of FeMV did not identify an association between either FeMV RT-PCR positivity in urine or seropositivity and azotaemic CKD in cats in the UK.<sup>29</sup> This group of researchers also identified an unclassified paramyxovirus in 3/24 non-azotaemic cats.<sup>29</sup>

Although the link between FeMV infection and TIN is tantalising, caution must be exercised until definitive pathogenesis studies have been performed to assess causation.

Although the link between FeMV infection and tubulointerstitial nephritis is tantalising, definitive pathogenesis studies are required to assess causation.

bility of amplifying non-viable nucleic acid. Nonetheless, current evidence suggests that FeMV has a global distribution, and that the presence of FeMV RNA in urine is not uncommon in domestic cats.

The prevalence of FeMV, as determined by RT-PCR in cat urine and kidney tissues, is summarised in Table 1. Although these studies vary considerably in size and the demographic of the cats enrolled, they document that FeMV sequences can be found in both healthy and sick cats, with a prevalence ranging from 3%<sup>30</sup> to 52.9%.<sup>31</sup> Interestingly, studies that included multi-cat environments had the highest rate of positive RT-PCR tests from urine: 22/72 (30.6%) cats in a colony in Italy,<sup>36</sup> and 9/17 (52.9%) cats that had contact with a colony of 23 stray cats in Brazil.<sup>31</sup> These findings suggest that close contact may be necessary for FeMV to be transmitted between cats. However, the mode of FeMV transmission is currently unknown.

Studies evaluating FeMV seroprevalence are summarised in Table 2. Published seroprevalence varies widely depending on the population tested and the assay used. Various serological methods have been used, but virus neutralisation assays, the gold standard for diagnostic serology, have not been developed. Therefore, it is important to view percentage seropositivity data with caution, particularly since the range is wide (Table 2). Combining the results of urine RT-PCR and serology identifies four groups of cats: those that are RT-PCR negative and seronegative, RT-PCR negative but seropositive, RT-PCR positive and seronegative, and both RT-PCR positive and seropositive (see box below).

Persistence of FeMV RT-PCR positivity for up to 15 months has been documented in a healthy pet cat.<sup>30</sup> Chronic infection is a feature of FeMV that warrants further investigation. Persistent morbillivirus infection is recognised in other species; for example,

**Table 1** Molecular prevalence of FeMV sequences in cat urine or kidney tissues in published studies

Region/country	Prevalence (by RT-PCR)
<b>Asia</b>	
Hong Kong/China <sup>24</sup>	53/427 = 12.4%
Japan <sup>25,32-35</sup>	53/383 = 13.8%
<b>Europe</b>	
Germany <sup>26</sup>	0/86 = 0%, healthy control cats 5/120 = 4.2%, diseased cats
Turkey <sup>28</sup>	6/110 = 5.5% overall 3/15 kidney samples of deceased cats 3/68 unhealthy cat urine samples
Italy <sup>36</sup>	16/156 = 10.3%, stray cats 22/72 = 30.6%, colony cats
UK <sup>29</sup>	1/16 = 6.3%, azotaemic CKD cats 4/24 = 16.7%, non-azotaemic cats
<b>Americas</b>	
USA <sup>30</sup>	10/327 = 3%
Brazil <sup>31</sup>	9/17 = 52.9%, healthy cats in a multi-cat household 3/35 = 8.6%, 'diseased' cats
FeMV = feline morbillivirus, CKD = chronic kidney disease	

**Table 2** Seroprevalence of anti-FeMV antibodies in cats in published studies

Country	Seropositivity in RT-PCR-positive cats	Seropositivity in RT-PCR-negative cats	Overall seroprevalence
Hong Kong/China <sup>24</sup>	54/56 = 96.4%	78/401 = 19.5%	132/457 = 28.9%
Japan <sup>31,34</sup>	15/25 = 60%	9/88 = 10.2%	24/113 = 21.2%
Italy <sup>36</sup>	18/24 = 75%	16/38 = 42.1%	34/62 = 54.8%
UK <sup>29*</sup>	5/5 = 100% <sup>†</sup>	12/26 = 46.2% <sup>‡</sup>	46/69 = 66.7% <sup>‡</sup>

FeMV = feline morbillivirus

\*Not all cats had both urine RT-PCR and serology performed. Seropositive includes all results reported as positive (strong positive, positive, weak positive) in this study. Serology results reported as 'high background' are excluded

<sup>†</sup>Includes 1/1 azotaemic and 4/4 non-azotaemic cats

<sup>‡</sup>Includes cats that did not have RT-PCR performed

**Chronic infection is a feature of FeMV that warrants further investigation.**



#### Interpretation of combined FeMV urine RT-PCR and serology results

- ❖ **RT-PCR negative and seronegative** Cats have probably never been exposed to FeMV.
- ❖ **RT-PCR negative and seropositive** Cats have presumably been infected by the virus at some time in their life, developed an antibody response, and either eliminated the virus, or at least stopped shedding virus in their urine.
- ❖ **RT-PCR positive and seronegative** Cats may be in the acute phase of infection, prior to seroconversion; convalescent serology of this population, to assess for evidence of seroconversion, would be ideal but no data have yet been published.
- ❖ **RT-PCR positive and seropositive** Cats may still be early in infection, prior to elimination of the virus, or may be chronically infected.

measles virus causing subacute sclerosing panencephalitis and measles inclusion body encephalitis in humans.<sup>37</sup>

#### Pathogenesis

Morbilliviruses are highly lymphotropic and immunosuppressive, with infection of epithelial cells occurring in the later stages of disease.<sup>38-42</sup> The other recognised morbilliviruses spread systemically and clinical signs can manifest in the skin, respiratory and gastrointestinal tracts and nervous system.<sup>38-42</sup> Whether or not FeMV results in a similar spectrum of disease remains to be determined.



## Despite the apparent widespread distribution of this virus, whether or not FeMV causes disease in cats remains unclear.

A single study evaluating FeMV cell tropism in vitro documented viral replication in cat fibroblasts, lymphoid cells and glial cells.<sup>43</sup> No other morbilliviruses have been linked to kidney disease (see box on page 8), although they can infect epithelial cells of the urogenital tract. In addition to the hypothesis that FeMV may cause kidney disease, one study has suggested a potential association with liver disease,<sup>28</sup> although strong evidence is lacking. It would be surprising if FeMV caused significant acute mortality in domestic cats, since it appears to be a prevalent infection, yet few cat deaths go unexplained.

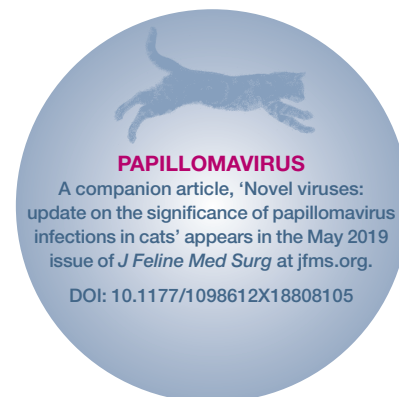
### Diagnosis, prevention and zoonotic potential

Until there is more definitive evidence of a link between FeMV and feline disease, the development of diagnostic tools beyond the research setting may be premature. There is a need to unite molecular virology and veterinary medicine to attain a comprehensive understanding of the basic biology of the virus, the lack of which represents a major deficit in the field. Future studies focusing on acute and chronic pathogenesis in a natural animal model of disease will help elucidate the route of infection, assess modes of transmission and characterise the immune responses to FeMV.

Evidence from other animal species suggests that FeMV is extremely unlikely to infect humans. The potential for infection of other felids is yet to be determined.

### Role of practising veterinarians

The range of feline diseases that are linked to known or novel infectious agents is expanding and, with increased availability of advanced molecular techniques, more novel infectious agents of cats will be identified. The role of practising veterinarians in progressing clinical research, as experts at diagnosing disease and collecting appropriate samples, should not be underestimated – veterinary clinicians together with pathologists are as important a part of the research team as laboratory-based investigators. While the pathogenic potential of novel viruses can be difficult to determine, recognition of these agents may offer the opportunity to improve the diagnosis, treatment and prevention of significant causes of suffering in cats.



### KEY POINTS

- ❖ FcaGHV1 was first reported in 2014 and FeMV in 2012. Evidence to date suggests that both viruses commonly infect domestic cats worldwide.
- ❖ An understanding of the pathogenic potential of FcaGHV1 and FeMV is important for feline health and welfare globally.
- ❖ Disease prevention through vaccination and improved patient outcomes from treatments targeting any new viruses are key goals of novel pathogen discovery.



### Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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