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PREVALENCE OF EXPOSURE TO FELINE IMMUNODEFICIENCY VIRUS IN EXOTIC FELID SPECIES

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Abstract: Feline immunodeficiency virus (FIV) is a novel lentivirus that causes T-cell deficiency in the domestic cat (*Felis catus*). Recent studies have revealed the existence of antigenically similar lentiviruses in a large number of nondomestic felid species. We summarize here a comprehensive serological survey for FIV cross-reactive antibodies in free-ranging and captive felid populations. Serum or plasma samples from 1,645 animals representing 20 felid species were screened by western blot analysis for exposure to one or more lentiviral proteins. Feline lentiviruses were confirmed to be endemic in several East and South African populations of lion (*Panthera leo*). Exposure was also detected in nearly all of the natural North American puma (*Felis concolor*) populations surveyed. Antibodies to FIV were also found in a free-ranging population of cheetah (*Acinonyx jubatus*). Lentivirus presence among captive exotic cats in the United States and abroad appears to be sporadic and infrequent. Because FIV is endemic in certain natural populations and absent in others, these data suggest that lentivirus infection postdated the geographic separation of felid populations; and therefore, spread of the virus into other seronegative populations may now be restricted by natural geographical barriers.

Key words: Feline immunodeficiency virus, seroprevalence, epidemiology, Felidae.

INTRODUCTION

Feline immunodeficiency virus (FIV) is a recently discovered lentivirus that has been shown to induce immunologic abnormalities in the domestic cat.[23] Feline immunodeficiency virus shares significant genomic sequence similarity with HIV, the human immunodeficiency virus,[17,18] and like HIV, the virus is T-cell trophic in domestic cats and eventually causes a depletion of the CD4 T lymphocytes within individuals.[1,23–25] Feline immunodeficiency virus is antigenically related to the ungulate lentiviruses, showing serologic cross-reactivity and sequence homology with the capsid proteins of caprine arthritis encephalitis virus (CAEV) and VISNA, a neurologic debilitating lentivirus of sheep.[9,17] Feline immunodeficiency virus has been shown to exist at high titers in the saliva of infected domestic cats, and although other routes of transmission have not yet been carefully explored, horizontal infection has been demonstrated through biting.[25,26] Feline immunodeficiency virus exposure within the domestic cat appears to be low within the United States with an estimated prevalence of 1.5%.[25]

Previous serological studies have revealed the existence of cross-reactive antibodies to FIV in several nondomestic felid species.[2,7] A high prevalence of serum antibodies to FIV has been shown in several free-ranging populations of lion, cheetah, and puma, and evidence for FIV exposure was detected in several captive felid species.[3,18] Feline lentiviral exposure is relatively infrequent in captive species with the exception of the pedigree of Asiatic lions managed together by the Species Survival Plan of the American Association of Zoological Parks and Aquariums.[7] We have speculated that the high FIV incidence in this group may trace to their wild origins. An inadvertent inclusion of African founders in this pedigree may explain the high FIV prevalence because several African lion populations are endemic with FIV.[3,12,18]

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The overall consequences of infectious disease outbreaks in felid species are not fully understood. Modern cheetahs (*Acinonyx jubatus*) are thought to have descended from a population bottleneck that severely reduced genomic heterozygosity relative to other cat species.[13–15] This genetic reduction provides a genetically monolithic host to feline pathogens and may explain severe epizootics that have been observed in the species. For example, feline infectious peritonitis virus (FIPV), an RNA-containing coronavirus, only rarely causes mortality in the domestic cat (*Felis catus*) with less than 5% of infected individuals dying.[22,23] However, in the cheetah, feline coronavirus has been documented to produce up to 60% mortality in captive cheetahs.[5] In the present study, we extend and summarize FIV seroprevalence of feline lentivirus infection in 1,645 serum samples collected from 20 feline species. This report updates previous findings for FIV and related lentiviruses in the wild and in captivity.[2,3,7,18]

MATERIALS AND METHODS

Propagation of FIV in cell culture

The Petaluma isolate of FIV was propagated in a chronically infected Crandall feline kidney cell line.[23] Cells were cultured in Dulbecco's modified essential medium with 10% fetal bovine serum and 1% penicillin/streptomycin. Cultures were split twice weekly 1:3 in a T-150 flask; culture fluids were collected and purified by low-speed centrifugation at 2,000 rpm for 15 min, and then filtered through a 0.45-μm membrane. Virus was concentrated by passing the viral supernatants through 5 ml of a 20% sucrose gradient via ultracentrifugation at 27,000 rpm for 3 hr. Viral pellets were air dried and resuspended in 100 μl of physiological saline (with Mg^{2+}) and stored at −70°C. Lentivirus yields were monitored during this time by Mg^{2+}-dependent reverse transcriptase assays that were performed biweekly on infectious FIV culture fluids.

Separation of viral proteins by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)

Fifty μl of viral stock suspension were added to 150 μl of RIPA buffer (5 M NaCl, 0.5 M EDTA, 0.5% deoxycholate, 1% nonidet-P-40), 1 M Tris-HCl, pH 7.5) and 200 μl and 2× Laemmli sample buffer (0.2 M Tris, pH 6.8, 10% β-mercaptoethanol, 20% glycerol, 0.4% bromophenol blue, 4% SDS). The suspension was boiled for 5 min followed by a 5-min incubation period on wet ice. The mixture was then loaded into a preparatory well in a stacked 10–20% SDS-polyacrylamide graded gel, and the viral proteins were resolved at 35 mA of current. A protein molecular weight standard (Rainbow markers, Amersham Life Sciences, Arlington Heights, Illinois 60005, USA) was included on each gel to determine the sizes of the various viral antigens.

Western blots (immunoblots) for antibodies against FIV

The western blot (immunoblot) technique used was a modification of that described.[3,17] Viral proteins were transferred from the SDS-PAGE gel onto an Immobilion-P membrane (Millipore Corp., Bedford, Massachusetts 01730, USA) using a voltage-blotting apparatus (Electro-blot, Bio-Rad Laboratories, Richmond, California 94804, USA). Membranes were then blocked in 3% bovine serum albumin (BSA) (in phosphate-buffered saline [PBS]) for 2 hr, dried between 3MM filter paper, and cut into individual strips. The strips were then incubated for 1 hr in a 1:100 dilution of serum samples suspended in a 0.2% Tween-20, 1% BSA diluent. The strips were rinsed three times in PBS with 0.2% Tween-20 and incubated for another hour with a biotinylated goat anti-cat conjugate at 37°C (Kirkegaard and Perry Laboratories, Inc., Gaithersburg, Maryland 20879, USA). The wash cycle was repeated as above, and the strips were incubated with streptavidin alkaline phosphatase, which adheres to all

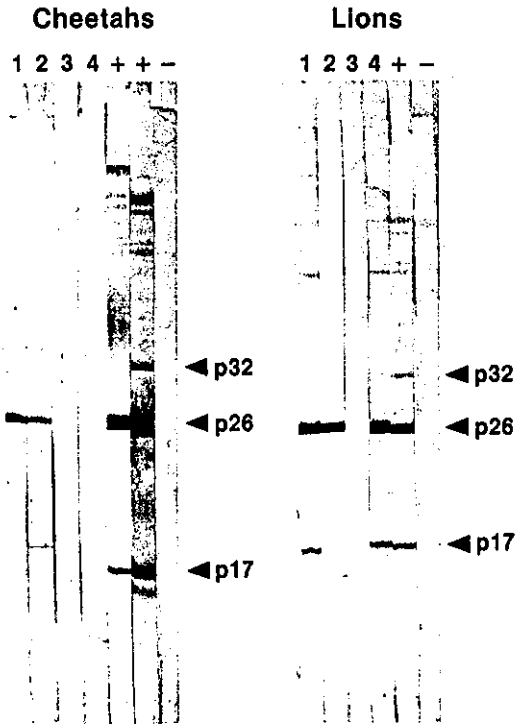

Figure 1. Western blot analysis of plasma samples from free-ranging lions and cheetahs. The lion samples in lanes 1–4 are from East Africa, Serengeti National Park, Tanzania. All but lane 3 are seropositive. The cheetahs are also from East Africa. Lanes 1 and 2 are positive, while 3 and 4 are negative. Lanes + and − indicate control sera from FIV-positive and FIV-negative domestic cats, respectively. The numbered arrows indicate the position and size (in kilodaltons) of the FIV viral protein (p) cross-reacting with the serum sample.

bound biotin. The membranes were then exposed to a BCIP/NBT color development system (Kirkegaard & Perry Laboratories, Inc.) and examined for protein-specific serum antibodies.

Serum samples from free-ranging and captive felids

Seven hundred and twenty-seven plasma or serum specimens were collected from free-ranging populations and wildlife reserves. Nine hundred and eighteen of the samples were from captive animals held in United States and foreign zoos. The samples were collected between 1978 and 1991 with the earliest free-ranging specimens being drawn in 1983. Positive control serum was obtained from naturally and experimentally FIV-infected domestic cats, while negative serum came from seronegative animals.

RESULTS

By western blot analysis (Fig. 1), we have confirmed and extended our previous findings of widespread seroprevalence of serum antibodies to FIV in captive and exotic populations of felid species.[3,18] Seroprevalence within cheetahs is presented in Table 1. Forty-one samples were screened from the Serengeti National Park and Ngorongoro Crater in Tanzania. Nineteen other free-ranging cheetah samples were tested including animals from Kenya (Nairobi Animal Orphanage), South Africa (Kruger Park), and Namibia (Etosha Pan). Samples from 237 captive-held cheetahs were also screened with the majority originating from zoos in the United States, Europe, South Africa, and Australia. Within the free-ranging cheetah samples, seroprevalence was evident only in the Serengeti ecosystem with 29% seropositive. No other infected individuals were found in any of the other populations. Overall, 20% of the free-ranging cheetahs were positive, whereas only 1.3% of the captive population showed antibodies.

We have tested 306 East African lions for lentivirus exposure (Table 2). Three hundred of these samples came from the Serengeti ecosystem (including 50 from the Ngorongoro Crater), while five originated from Lake Manyara in Tanzania and one from the Masai Mara, Kenya. Fifty-five lions from Kruger Park, South Africa were tested along with 44 southwestern African (Namibia) lions and 4 Asiatic lions (Gir Forest, India). The highest levels of exposure were found in Kruger Park with an infection rate of 91%, whereas 84% of the Serengeti lion population also had reactive antibodies to the major core proteins of FIV. Exposure rates were also found to be elevated in the Ngorongoro Crater and Lake Manyara with seroprevalence of 70% and

Table 1. Seroprevalence of feline lentivirus exposure in cheetahs (*Acinonyx jubatus*).[a]

Living status/location	No. positive	No. tested	% positive
Free-ranging			
East Africa			
Tanzania (Serengeti/NGC[b])	12[c]	41	29
Kenya (Nairobi Animal Orphanage)	0	9[d]	0
South Africa			
Kruger Park	0	1	0
West Africa			
Namibia	0	9	0
Total	12	60	20
Captive			
DeWildt Breeding Center (South Africa)	1	56	1.8
Zoos (U.S. and abroad)	2[e]	181	1.1
Total	3	237	1.3

[a] All serum samples (1:100 dilution) were tested by western blot assay.
[b] NGC = Ngorongoro Crater Wildlife Preserve in Tanzania.
[c] Two of the 12 positive animals originated from the Ngorongoro Crater.
[d] One animal was from the Masai Mara reserve; the rest are from the Nairobi animal orphanage, and all were wild born.
[e] One animal was from the Toledo Zoo; the other was from the St. Louis Zoological Park.

Table 2. Seroprevalence of lentivirus exposure in lions (*Panthera leo*).[a]

Living status/location	No. positive	No. tested	% positive
Free-ranging			
East Africa[b]			
Serengeti	209	250	84
Ngorongoro Crater	35	50	70
Masai Mara	1	1	100
Lake Manyara	4	5	80
South Africa			
Kruger Park	50	55	91
West Africa			
Namibia (Etosha Pan)	0	44	0
India			
Gir Forest	0	4	0
Total	299	409	73
Captive			
Unknown subspecies			
U.S. zoos	5[c]	43	12
Circus lions	2	3	67
Johannesburg Zoo (South Africa)	6	9[d]	67
Asiatic subspecies			
U.S. zoos	23	35	66
Sakkarbaug Zoo (India)	0	51[e]	0
Negara Zoo (Malaysia)	0	8	0
Total	36	149	24

[a] All serum samples (1:100 dilution) were tested by western blot assay.
[b] The Masai Mara is in Kenya; all other locations are in Tanzania.
[c] Three of these lions were from the National Zoological Park, and two were from Kings Dominion Safari.
[d] All were probably wild born.
[e] Fifteen were wild born and had been captive for up to 12 yr before sampling.

80%, respectively. All samples from Etosha Pan, Namibia, and the Gir Forest Sanctuary, India were seronegative. Exposure within captive (non-Asian) lions in the United States was shown to be 12%, whereas exposure in the Johannesburg Zoo, South Africa was 67%. With the exception of individual lions held in the United States zoos known to be African/Asian hybrids,[18] Asiatic lions appear to be free of infection. The overall exposure rate within free-ranging lions was 73%, while the captive lion population had a seroprevalence of 24%.

Twelve separate North American puma populations were typed for antibodies to FIV (Table 3). Ten of the puma populations were from the western United States and Canada, while two of the populations were from South Florida in the Big Cypress Swamp ecosystem and Everglades National Park. Two free-ranging pumas from Chile were also included.[18] A total of 206 free-ranging pumas were screened, and all 12 North American populations showed lentivirus exposure. Another 141 captive-held pumas were tested with 6% showing seropositivity. Ten percent of South American wild-born captive pumas were FIV positive.

Seventeen other species of Felidae were screened for cross-reactive antibodies to FIV (Table 4). Exposure was observed in free-ranging bobcats (*Lynx rufus*) from South

Table 3. Seroprevalence of feline lentivirus exposure in pumas (*Felis concolor*).[a]

Living status/location	No. positive	No. tested	% positive
Free-ranging			
Florida (Big Cypress)	10	48	21
(Everglades National Park)	4	10	40
Arizona	9	13	69
California (Santa Ana Mtns.)	10	24	42
Colorado	6	9	67
New Mexico (San Andreas Mtns.)	1	3	33
Oregon	1	11	9
Texas	6	22	27
Utah	1	2	50
Wyoming (Yellowstone)	7	41	17
Idaho	2	15	13
Canada/Alaska	3	7	43
South America (Chile)	0	2	0
Total	60	207	29
Captive			
Canada	3[b]	9	33
U.S. zoos	2[c]	102	2
Central/South America	3[d]	30[e]	10
Total	8	141	6

[a] All serum samples (1:100 dilution) were tested by western blot assay.

[b] All three were wild born.

[c] One of these pumas was from the National Zoological Park; the other was from the Waldo Animal Retirement home in South Florida.

[d] All three were probably wild born, one in Brazil, one in Venezuela, and one in Peru.

[e] These pumas were from Belize, Chile, Brazil, Venezuela, Peru, and Guatemala.

Florida and leopards (*Panthera pardus*) from Kruger Park, South Africa. Although sample size was limited, we failed to detect antibodies to FIV in free-ranging tigers (*Panthera tigris*). Among the 391 other captive samples screened, exposure was found in snow leopards (*P. uncia*), jaguars (*P. onca*), leopards (*P. pardus*), flat-headed cats (*Ictailurus planiceps*), and leopard cats (*Prionailurus bengalensis*). Seroprevalence among captive felids was low at 2.3%, whereas exposure in the domestic cat was determined to be minimal at 3.5%.

DISCUSSION

We have presented a serological survey of the prevalence and incidence of feline lentiviruses in free-ranging and captive felids. Exposure rates have been summarized between species (Table 5). Feline lentivirus appears to be endemic in certain east African lion populations in Serengeti National Park, Ngorongoro Crater, and Lake Manyara, Tanzania. Although two seronegative populations of lions were observed, exposure rates in the lion surpass the other species of free-ranging Felidae sampled for serum antibodies. Significant exposure in free-ranging pumas and cheetahs was also observed, while most of their captive counterparts remained seronegative. These observations that FIV infection in captive felids is rare suggest that exposure to the virus in captivity is infrequent. This conclusion contrasts the epidemiology of other feline RNA viruses. Feline infectious peritonitis, an infectious coronavirus, has been documented to spread rapidly among captive cheetahs and to have caused severe pathological epizootics in captive populations resulting in high mortality among individuals.[3,5]

The failure to detect FIV cross-reactive antibodies in some but not all free-ranging felid species' populations suggests that introduction of the virus into the cat followed the geographic separation of the species isolates. Lentivirus exposure probably did not occur until after geographic division of the cat species, and now the virus spread may be restricted by physical barriers that could slow or prevent its dissemination.[18] In eastern and southeastern Africa, the virus appears to be endemic in the Serengeti ecosystem and Kruger Park, while both lion and cheetah populations in southwestern Africa (Namibia) appear free of exposure. The Namibian cats are separated from the East African species by the Kalahari desert, which spans south-central Africa and may act as a faunal barrier to prevent FIV infection. Exposure was also not detected in

Table 4. Seroprevalence of feline lentivirus exposure in other nondomestic and domestic felids.[a]

Living status/location	No. positive	No. tested	% positive
Free-ranging			
Bobcat (*Lynx rufus*)			
Florida	2	23	9
Tiger (*Panthera tigris*)			
Siberia	0	1	0
India	0	4	0
Leopard (*Panthera pardus*)			
Sri Lanka	0	7	0
Zimbabwe (Chipengali)	0	1	0
India	0	3	0
Kruger Park (South Africa)	5	7	71
Namibia (West Africa)	0	3	0
Total	7	49	14.3
Captive			
United States, European, Central/South American, South African, Asian zoos			
Tiger (*P. tigris*)	0	102	0
Snow leopard (*Panthera uncia*)	2[b]	65	3
Jaguar (*Panthera onca*)	1[c]	16	6
Leopard (*P. pardus*)	1[d]	122	0.8
Clouded leopard (*Neofelis nebulosa*)	0	2	0
Bobcat (*Lynx rufus*)	0	1	0
Leopard cat (*Prionailuras bengalensis*)	1[e]	5	20
Flat-headed cat (*Prionailuras planiceps*)	1[f]	3	33
Marbled cat (*Pardofelis marmorata*)	0	1	0
Serval (*Leptailurus serval*)	0	8	0
Caracal (*Caracal caracal*)	0	1	0
Domestic cat (*Felis catus*)	2[g]	55	3.5
Sand cat (*Felis margarita*)	0	5	0
European wildcat (*Felis sylvestris*)	0	1	0
Ocelot (*Leopardus pardalis*)	0	1	0
Margay (*Leopardus wiedii*)	0	3	0
Total	8	391	2.0

[a] All serum samples (1:100 dilution) were tested by western blot assay.
[b] One was from the Cheyenne Mountain Zoo and the other from the Granby Zoo.
[c] This animal was from the Johannesburg Zoological Garden.
[d] This was a captive animal in Sri Lanka.
[e] This animal was from the National Zoological Park.
[f] This animal was from the Lincoln Park Zoo.
[g] One animal was from a South Florida ranch and one from a National Institutes of Health holding facility.

felids from Asia, notably Asian lions from the Gir Forest and in the Sakkarbaug Zoo,[12] 5 tigers and 10 leopards from India and Sri Lanka.[3,7,10,18] There may also be differential prevalence in pumas, particularly in South America. Of the free-ranging and wild-born pumas sampled, seropositive individuals were found in Brazil, Venezuela, and Peru. The pumas tested from Chile remained free of exposure. The Andes Mountain Range

Table 5. Seroprevalence summaries from free-ranging and captive Felidae.

Species	% FIV positive	
	Free-ranging	Captive
Cheetah	20	13
Lion	73	24
Puma	29	6
Leopard	24	0.8
Others	7.1	26

separates most of Chile from the rest of the continent and may provide an effective faunal barrier for pumas.

The primary mode of FIV transmission is not well understood. The domestic cat FIV isolate has been shown to be transmissible through biting.[26] We have recently documented the seroconversion of two Serengeti lions with feline lentivirus suggesting that the lion virus can be spread horizontally through contact. It is not clear whether the virus can be passed vertically across the placenta from infected mothers to their offspring. Frequent transmission to offspring whether in utero or postnatally could help to account for the endemic rates of infection within the lion. It has been demonstrated that certain East African lion populations have undergone a population bottleneck that has resulted in a marked decrease in genetic variation within the population.[11,21] Because East African lions are organized into physically interactive social groups or prides,[19–21] a founder or survivor population of lentivirus-infected lions would rapidly elevate the prevalence of infection in that species. This may explain in part the high FIV prevalence in lion populations compared to other species like cheetah that lead a more solitary life.[4]

It is not yet clear whether these nondomestic feline lentiviruses cause pathology in the big cats. The widespread prevalence of FIV-related lentivirus throughout the Felidae makes this question particularly intriguing. It may be that FIV causes a gradual immune depletion of CD4 T lymphocytes as in domestic cats [24,25] or has little pathological effect as is observed in SIV-infected species of *Cercopithecus* monkeys.[6,8,16] T-cell subsets, clinical status, and immune function are important areas to emphasize in future studies of these species.

The implications of the present findings for species conservation merit some discussion. Although there is no persuasive evidence for FIV pathology in nondomestic felids, neither are there sufficient data to preclude disease sequelae. Indeed, the fact that close lentivirus relatives do cause immune deficiency in domestic cats, in humans, and certain Asian primate species would suggest that lentivirus infection should be carefully monitored. Even under the more optimistic scenarios whereby the big cat lentivirus may have evolved to a harmless version (or conversely that wild cat species developed genetic resistance to disease induced by lentiviruses they harbor), the apparent symbiosis is likely temporary at best because lentivirus pathogens are well known for both genetic and functional adaptation. Further, genetic homogenization in certain host populations of wild cat species (e.g., cheetah, Florida panther, and Asian lion) would confound the potential emergence of a pathogenic strain because genetically identical species are often uniformly susceptible to the same pathogens.[11–15,18] These considerations add an additional peril that warrants closer monitoring, particularly in free-ranging populations of endangered cat species.

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