The First Feline Immunodeficiency Virus in Siberian Tigers (*Panthera Tigris Altaica*) from China

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Abstract

Research on feline immunodeficiency virus (FIV) from tigers is scant throughout the world. In this study, 320 captive Siberian tigers were tested for FIV by nested PCR, and three Siberian tigers were FIV-positive. This is the first time FIV has been detected in Siberian tigers in China. The phylogenetic analysis of three FIV genes, gag-p26, pol-RT, and pol-RNAse, revealed that the Siberian tiger FIV had the minimum genetic divergence, the closest genetic relationship and the highest amino acid similarity with subtype A FIV strains from domestic cats, suggesting that the Siberian tiger FIV may have been transmitted by stray cats.

Introduction

Feline immunodeficiency virus (FIV), like human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV), destroys the immune system of its hosts, which leads to secondary infection with other bacteria and viruses, and eventually causes the death of the host. It was initially isolated from stray cats in California, USA in 1986 [1]. Since then, many studies on FIV infection in felines have been reported successively, and a number of studies have shown that FIV-specific antibodies have been detected in nearly 30 feline species, accounting for about two-thirds of the existing feline species in the world, and species-specific strains of FIV have even been isolated from certain species [2–7]. To date, research on FIV has mainly focused on domestic cats (*Felis catus*), followed by lions (*Panthera leo*), pumas (*Puma concolor*), bobcats (*Lynx rufus*), Pallas's cats (*Otocolobus manul*) and other non-domestic felines, and research on tigers is very scarce. Thus, the only two FIV sequences from tigers in the world are a 450 bp gag gene fragment (Pti-104 strain) [7] and a 505 bp pol gene fragment (FIVfca 13D strain; GenBank accession number EF667041). Currently, there are only four studies on FIV in China, all of which are serological or molecular epidemiological investigations of domestic cats [8–11].

Samples

A total of 320 whole blood samples were collected from captive Siberian tigers in Siberian Tiger Parks in Harbin, Hailin and Shenyang from January 2019 to March 2021, including 225 samples from Harbin, 55 samples from Hailin and 40 samples from Shenyang. The blood sample collection protocol was performed as in a previous study [12], and all samples were stored at -80°C for later use.

Pcr Amplification Of Proviral Dna

Genomic DNA was extracted from whole blood samples with the Baypure™ Universal Magnetic Bead Method Viral DNA/RNA Rapid Extraction Kit (Baybio Co.,Ltd., Guangzhou, China) according to the protocol of the manufacturer. With reference to Troyer et al. [7], degenerate primers for the p26 region of the gag gene, the reverse transcriptase (RT) region, and the RNAse region of the pol gene were designed to perform nested PCR amplification of FIV sequences (Supplementary Table S1). The reaction system of the first-round PCRs was 25 μL, including 1 μL of genomic DNA, 1 μL of each outer-primer (G1F-G2R, P1F-

P2R, P3F-P5R), 12.5 μL of 2× PCR Master mix (Lablead Co., Ltd., Beijing, China) and 9.5 μL of sterilized double distilled water. The cycling conditions were as follows: 3 min at 94°C; followed by 35 cycles of 30 s at 94°C, 30 s at 57°C, 30 s at 72°C; and a final extension of 10 min at 72°C. The second-round PCR used 1 μL of products from the first-round reaction as the template and used internal primers (G2F-G1R, P2F-P1R, P4F-P4R) to amplify under the same conditions. In addition, samples were also run with a touchdown protocol with temperatures from 65°C to 45°C in this round. All other cycling conditions were the same as those described above. These amplifications reactions were performed in a SEDI thermal cycler (Wealtec Corp., USA) and the second-round PCR products were verified by electrophoresis in 1% agarose gels. When bands amplified under the conditions described above were not obvious, the internal primers were used to amplify another round. The positive PCR products were sequenced with internal primers using the Sanger method (Comate Bioscience Co., Ltd., Jilin, China).

Phylogenetic Analysis

The sequences of gag-p26, pol-RT and pol-RNAse were subjected to Basic Local Alignment Search Tool (BLAST) analysis to confirm the sequencing result. Genetic divergence analysis of nucleotides and amino acids, phylogenetic analysis and alignment of the predicted amino acid sequences were performed using MEGA 7.0 software. After compilation and alignment of FIV strains from different species using the Clustal W program, the Kimura 2-parameter model and the Dayhoff matrix based model were selected to analyze the genetic divergence of nucleotides and amino acids, respectively. The optimal model for nucleotide sequence evolution (for gag-p26 and pol-RT the Tamura 3-parameter model, and for pol-RNAse the general time-reversible model) was estimated by the Models program, the maximum likelihood method was selected to construct the nucleotide phylogenetic tree, and a bootstrap analysis using 1,000 iterations was performed.

Nucleotide Sequence Accession Numbers

The nucleotide sequences of pol-RNAse, gag-p26 and pol-RT obtained in this study were submitted to the GenBank database under the accession numbers MW809410, MW809411 to MW809412, and MZ189264. The accession numbers of other nucleotide sequences used in the phylogenetic analyses were obtained from the GenBank database and are shown in Supplementary Table S2.

Nested Pcr

In this study, whole blood samples from 320 captive Siberian tigers were tested by nested PCR technology, and three Siberian tigers (HD094, HD1786 and HD631) from Hailin were FIV-positive, with a positive rate of about 0.09% (3/320). The result was significantly different from previous studies. We did not amplify more FIV genes, although attempts were made with different primers, amplification procedures, amplification times, and nucleic acid concentrations. Given that captive Siberian tigers are all kept in the same area, and FIV can be transmitted horizontally through direct contact and vertically from mothers to kittens, theoretically the positive rate should be higher [4, 13–14]. The main reason for this

difference may be that FIV is a highly unstable RNA virus, which is prone to mutation, the nucleotide genetic divergence of FIV between different species is generally greater than 20%, and the FIV sequence of tigers has only two gene fragments, so it is impossible to design specific primers [7, 15–16].

Phylogenetic Analysis Of Gag-p26 Gene

According to the correlation analysis results for the gag-p26 gene (Supplementary Table S3, Fig. 1A, Fig. 2A), the nucleotide and amino acid genetic divergences between the two tiger FIV strains HD094 and HD1786 identified in this study and the subtype A FIV strains from domestic cats were minimal among different species, which was supported by the phylogenetic tree and alignments of the predicted amino acid translation products, especially for the CHN17 strain. In addition to being on the same internal evolutionary branch with HD094 and HD1786 strains in the phylogenetic tree, its amino acid changes were basically consistent with those in these two strains. However, the Pti-104 strain, of which the host was also a tiger, had the minimum genetic divergence, the closest genetic relationship and basically the same amino acid changes as the lion FIV strains, especially the 1027 strain of subtype E. According to the report by Troyer et al. [7], both the tiger and snow leopard were captive animals kept in Asian zoos, and both were FIV-positive. This was the result of cross-species transmission of lion FIV, which could explain the close relationship between the Pti-104 strain and lion FIV strains. Similarly, it was possible that the FIV infection of the two Siberian tigers HD094 and HD1786 was a cross-species transmission of domestic cat FIV.

Phylogenetic Analysis Of Pol-rt And Pol-rnase Genes

According to the correlation analysis results for the pol-RT and pol-RNAse genes (Supplementary Table S4-S5, Fig. 1B-1C, Fig. 2B-2C), the tiger FIV strain HD631 identified in this study had the minimum genetic divergence of nucleotides and amino acids, the closest genetic relationship and the highest amino acid similarity with subtype A FIV strains from domestic cats, among the different species, especially the CHN17 strain. Both of these sequences indicated that the FIV from the Siberian tiger HD631 might have originated from a cross-species transmission of domestic cat FIV. In the analysis of the pol-RT gene, the FIVfca 13D strain was similar in genetic divergence, genetic relationships and amino acid similarity to the HD631 strain and FIV subtype A strains from domestic cats. According to the information provided by Adams et al. in the GenBank database, the host of this strain was an Asian tiger living in South Africa. Based on the species name of the strain, we speculate that this tiger was also infected by domestic cat FIV cross-species transmission, like HD631.

Cross-species Transmission Of Fiv

The analysis of different gene fragments demonstrated that three Siberian tigers, HD094, HD1786 and HD631, were all infected with domestic cat FIV strains, and they all came from Hailin, so it is reasonable for them to have been infected with the same species' strain. In addition to the case of cross-species transmission of FIV reported above by Troyer et al. [7], Carpenter et al. [4] also reported a captive puma in an Argentinian zoo that was infected with a domestic cat FIV strain. Moreover, wild felines infected by

domestic cat FIV, wild felines infected by wild feline FIV, and experimental cross-species transmission have also been reported [17–21]. Initially, we had speculated that Siberian tigers were likely to be infected by lion FIV because tigers in the Siberian Tiger Park were once kept in the same area as lions, and these lions were imported from Africa without being tested for FIV; most lions in Africa are infected with FIV, and some are even infected with multiple subtypes of the FIV strains [15, 22]. In the long-term breeding strategy, lions and Siberian tigers often have contact during behaviors such as competing for food and territory, which greatly increases the possibility of FIV infection. However, according to the results obtained, these three Siberian tigers were infected with domestic cat FIV rather than lion FIV. Combined with the hypothesis that puma infection with bobcat FIV may be caused by predation [20–21], we speculated that the cross-species transmission of FIV was caused by Siberian tigers having direct or indirect contact with domestic cats (most likely during predation).

The FIV strains from the three Siberian tigers were all most closely related to the CHN17 strain, which was carried by a stray cat living near Shanghai Zoo in China. Owing to the numerous visitors and abundant food in zoos there are a large number of stray animals around zoos. Two studies estimated the number of stray cats in two regions at different times: 64 stray cats per km^2 in Yangfangdian, Beijing and 1.2 stray cats per km^2 in Hefei [23–24]. According to incomplete statistics, the number of stray cats in Beijing reached more than 5 million at the end of 2019, with some of them living around zoos. Given the harsh living conditions, stray animals can easily become vectors of various diseases, including rabies, toxoplasmosis, bartonellosis, salmonellosis, etc., which poses a threat to the health of humans and other animals [25–26]. In addition, the Siberian tigers (except for those with clinical signs) in these three places are all kept in outdoor areas surrounded by thick wire mesh. Although the mesh prevents the huge Siberian tigers from escaping, stray cats, which are much smaller than the Siberian tiger, can enter and leave freely. This makes it possible for the Siberian tigers to make contact with stray cats. Once the stray cats enter the park, the Siberian tiger, as one of the top predators on land, is likely to prey on it, leading to the cross-species transmission of FIV. Although there are no reports about the Siberian tiger preying on domestic cats, studies have shown that Siberian tigers prey on a wide range of animals, such as bears, bobcats, leopard cats, deer, wild boar, livestock, etc., and even their own kind, which demonstrates that Siberian tigers are very likely to prey on domestic cats [27, 28–30]. It is therefore important to manage the stray cats around the Siberian Tiger Park strictly. In addition, in order to protect the diversity of wildlife species, it is necessary to control the threat to wildlife of diseases carried by related domestic species.

In this study, the analysis of tiger FIV was mainly based on the subtype A domestic cat FIV strains with the closest genetic relationship. However, due to the limited number of samples it is impossible to know whether tiger FIV is species-specific. What happens to the amino acids? What is the exact route of infection? Will tigers show relevant clinical signs or pathological changes after infection? A large amount of data and in-depth research is required before any relevant conclusions can be drawn. This is the first time that FIV from Siberian tigers has been detected in China, and four tiger FIV gene fragments have been obtained. The findings not only enriched the epidemiological data on FIV worldwide, but also further

illustrated the necessity and urgency for surveillance of FIV in non-domestic felines in China, and provided a theoretical foundation for follow-up studies of FIV.

Declarations

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Author contributions

Conceptualization: Yajun Wang, Methodology: Yajun Wang, Enqi Liu, Liying Ma, Formal analysis and investigation: Enqi Liu, Liying Ma, Shuping Huang, Writing-original draft preparation: Enqi Liu, Writing-review and editing: Yajun Wang, Enqi Liu, Funding acquisition: Yajun Wang, Hongliang Chai, Resources: Dan You, Lijun Guo, Haitao Xu, Dan Liu, Supervision:Yajun Wang, Hongliang Chai.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Availability of data and material

Nucleotide sequence data reported are available in the GenBank databases under the accession numbers MW809410 to MW809412, and MZ189264.

Ethics Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the Laboratory Animal Management and Ethics Committee of Northeast Forestry University approval has been received.

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Figures

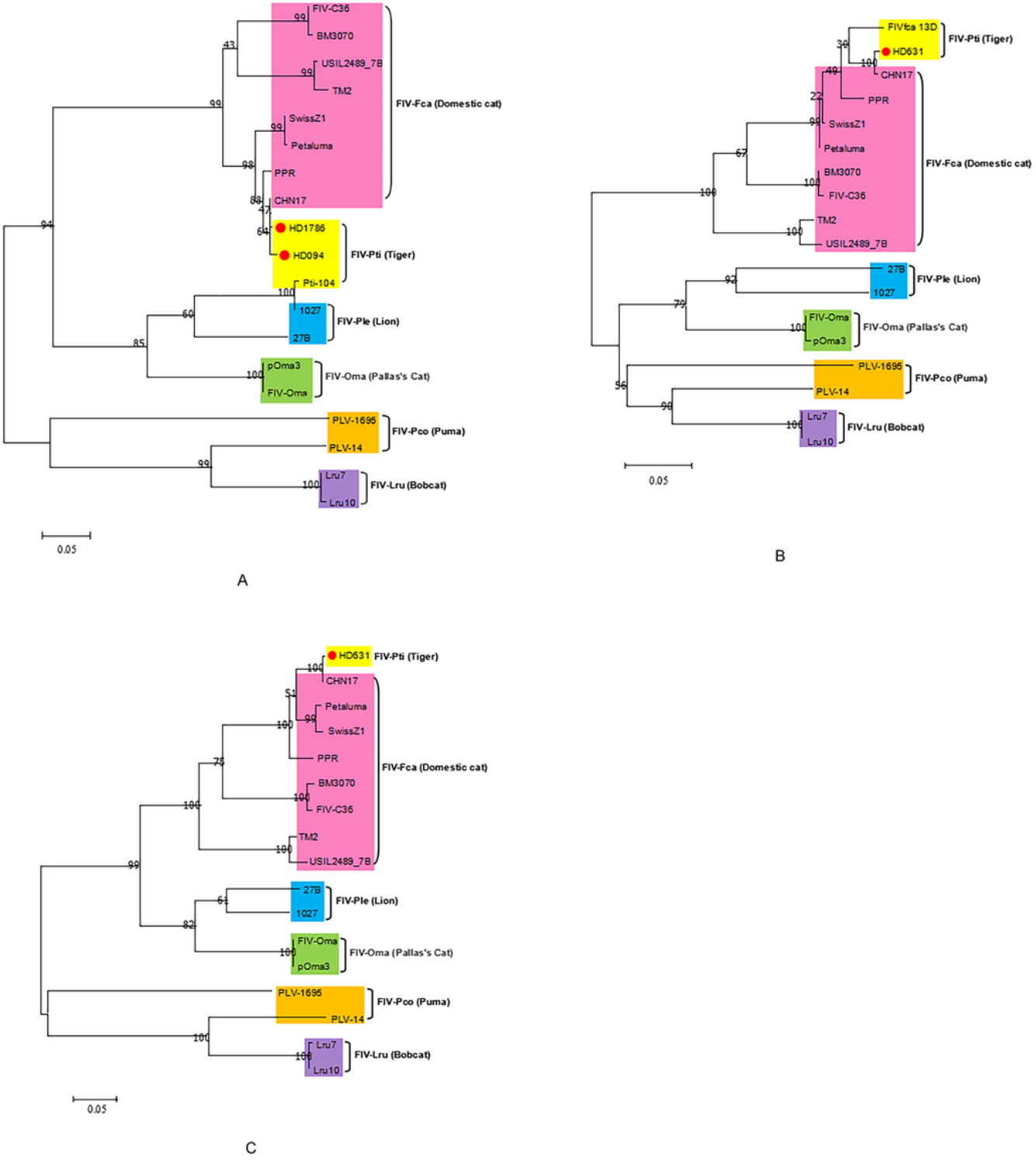

Figure 1

Phylogenetic tree for FIV nucleotide sequences constructed by the maximum likelihood method based on 1,000 bootstrap replicates. The red circle represents the FIV strains identified in this study. A. gag-p26, 417 sites included in analysis. B. pol-RT, 552 sites included in analysis. C. pol-RNAse, 715 sites included in analysis.

Strain	1	2	6	9	10	12	13	14	16	17	19	20	21	25	34	39	42	47	48	50	52	54	56	57	60	61	64	66	67	68	69	73	74	78	80
HD094	V	S	E	D	I	E	N	L	Q	L	L	V	I	Q	S	M	I	F	A	V	L	N	T	V	A	A	E	M	Y	T	Q	D	T	T	E
HD1786	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	T	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CHN17	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Petaluma	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	V	.	.	A	.	.	.	.	.	.	.	.	.	S	.	.	.	M	.
PPR	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
SwissZ1	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	V	.	.	A	.	.	.	.	.	.	.	.	.	S	.	.	.	M	.
TM2	.	T	.	.	.	.	T	.	.	.	S	I	.	.	.	.	T	.	.	A	I	.	.	.	.	T	.	.	.	A	.	.	.	V	.
USIL2489_7B	.	T	.	.	.	.	T	.	.	.	S	I	.	.	.	.	T	.	.	A	I	.	.	.	.	T	.	.	.	A	.	.	.	I	.
BM3070	.	T	.	.	.	.	T	.	.	.	.	I	.	.	.	.	V	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	S	.	.
FIV-C36	.	T	.	.	.	.	T	.	.	.	.	I	.	.	.	.	V	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Pls104	.	.	.	.	.	.	.	.	.	.	.	L	V	E	N	A	A	L	G	.	V	Y	R	A	T	E	C	L	W	N	V	N	S	E	G
27B	.	T	D	E	L	V	.	I	S	I	T	L	V	E	N	A	A	L	G	.	I	Y	K	A	T	E	C	L	W	K	I	N	S	E	G
1027	.	T	D	E	M	V	.	I	N	I	T	L	V	E	N	A	A	L	G	.	V	Y	R	A	T	E	C	L	W	N	V	N	S	E	G
FIV-Oma	.	T	D	K	L	.	.	I	.	V	N	L	V	M	N	A	K	L	G	.	I	F	K	A	T	D	V	L	W	E	I	N	S	E	G
pOma3	.	T	D	K	L	.	.	I	.	V	N	L	V	M	N	A	K	L	G	.	I	F	K	A	T	D	V	L	W	E	I	N	S	E	G
PLV-14	A	C	D	.	V	.	T	.	E	I	N	F	.	.	.	N	K	L	T	A	V	K	P	C	T	E	I	L	.	E	T	L	G	D	K
PLV-1695	.	A	D	A	P	T	S	V	D	.	D	L	.	S	.	C	K	L	V	A	C	.	K	C	T	D	I	L	F	K	I	E	A	N	I
Lru7	A	C	D	E	V	.	T	.	E	I	N	F	.	.	.	N	K	L	T	A	V	K	P	C	T	E	I	L	.	E	T	K	G	D	Q
Lrul0	A	C	D	E	V	.	T	.	E	I	N	F	.	.	.	N	K	L	T	A	V	K	P	C	T	E	I	L	.	E	T	K	G	D	Q

Strain	83	84	85	87	90	91	92	93	94	95	96	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	120	124	129	131	133	136	148	152	161
HD094	G	K	E	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	A	T	A	A	D	K	S	G	Q	N
HD1786	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CHN17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Petaluma	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.
PPR	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
SwissZ1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.
TM2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
USIL2489_7B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
BM3070	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.
FIV-C36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.	.	.	.	.	.	.	.	.	.	.
Pls104	T	?	I	E	S	A	W	Q	V	K	T	K	G	A	V	G	L	R	E	P	Q	E	I	V	K	E	V	V	P	N	R	A	.	.
27B	S	D	V	E	N	A	W	Q	A	K	V	R	E	G	L	G	L	R	E	P	Q	E	L	V	K	E	V	V	P	N	R	A	T	L	D
1027	T	N	V	E	S	A	W	Q	V	K	T	K	G	A	V	G	L	R	E	P	Q	E	I	V	K	E	V	V	P	N	R	A	T	L	D
FIV-Oma	.	E	.	A	S	A	F	Q	A	K	E	Q	K	G	V	G	L	R	D	P	Q	D	I	A	K	E	V	Q	P	N	R	A	T	L	D
pOma3	.	E	.	A	S	A	F	Q	A	K	E	Q	K	G	V	G	L	R	D	P	Q	D	I	A	K	E	V	Q	P	N	R	A	T	L	D
PLV-14	E	N	L	E	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	V	V	S	N	R	A	S	V	D
PLV-1695	E	.	.	E	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	A	G	.	N	R	A	S	I	D
Lru7	K	S	.	E	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	V	V	S	N	R	A	S	V	D
Lrul0	K	S	.	E	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	V	V	S	N	R	A	S	V	D

a

Strain	4	6	7	11	32	69	101	105	109	111	121	178	179
HD631	D	V	E	K	R	M	R	A	R	Y	I	L	W
FIV fca 13D	-	-	-	R	K	.	K	K	I	.	V	-	-
CHN17	E	.	.	.	.	.	.	.	.	.	.	.	.
Petaluma	E	.	.	R	K	I	.	.	.	F	.	.	.
PPR	E	.	.	R	K	.	.	.	.	F	.	.	.
SwissZ1	E	.	.	R	K	I	.	.	.	F	.	.	.
TM2	.	.	.	S	K	.	.	.	.	.	V	.	.
USIL2489_7B	.	.	.	S	K	.	.	.	.	.	V	.	.
BM3070	E	.	.	.	K	L	.	.	.	.	V	.	.
FIV-C36	E	.	.	.	K	L	.	.	.	.	V	.	.
27B	E	.	Y	S	K	D	K	Q	E	F	V	.	.
1027	E	.	Y	.	K	E	K	Q	E	F	V	.	.
FIV-Oma	E	.	Y	.	K	E	K	S	E	F	V	.	.
pOma3	E	.	Y	.	K	E	K	S	E	F	V	.	.
PLV-14	E	.	.	T	K	.	N	Q	.	.	V	I	F
PLV-1695	E	.	.	.	K	R	S	Q	.	.	V	.	.
Lru7	E	.	.	.	K	Q	N	Q	.	.	V	.	F
Lrul0	E	?	.	.	K	Q	N	Q	.	.	V	.	F

B

Strain	27	33	38	43	45	78	80	91	95	102	109	110	126	128	129	134	155	203	215
HD631	I	C	I	V	C	L	Q	N	A	T	D	K	I	K	V	I	V	A	V
CHN17	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	.	.
Petaluma	L	Y	.	I	S	M	R	C	V	V	.	N	V	R	I	.	M	G	I
PPR	L	H	M	I	S	.	.	H	.	V	E	.	V	R	I	T	M	.	I
SwissZ1	L	H	.	I	S	M	R	C	V	V	.	N	V	R	I	L	M	G	I
TM2	.	H	M	I	S	.	K	C	G	Q	E	.	V	R	I	L	I	.	I
USIL2489_7B	.	H	M	I	S	.	K	C	S	Q	E	.	V	R	I	L	I	.	I
BM3070	L	H	L	M	S	Q	K	C	N	I	E	.	V	R	I	.	M	.	I
FIV-C36	L	H	L	M	S	Q	K	C	N	I	E	.	V	R	I	.	M	.	I
27B	L	H	.	I	K	K	K	C	S	K	E	G	.	.	I	.	Q	.	I
1027	L	H	V	I	K	K	K	C	E	I	E	G	.	.	I	L	Q	.	I
FIV-Oma	L	H	V	I	K	K	K	C	E	E	E	.	M	N	I	.	Q	.	I
pOma3	L	H	V	I	K	K	K	C	E	E	E	.	M	N	I	.	Q	.	I
PLV-14	.	T	.	I	K	S	G	Y	S	I	E	G	M	N	I	D	Q	C	N
PLV-1695	L	T	L	I	S	E	G	V	L	S	E	Q	M	N	I	M	.	.	I
Lru7	.	T	.	I	K	M	G	Y	S	I	E	Q	.	N	I	E	M	C	N
Lrul0	.	T	.	I	K	M	G	Y	S	I	E	Q	.	N	I	E	M	C	N

C

Figure 2

Alignments of the predicted amino acid translation products of FIV sequences. Single-letter amino acid code was used. Only amino acids differing from the top sequence are shown. A dot designates identity with the top sequence. Dashes indicate missing data or a gap introduced to optimize the alignment. Question marks indicate that proviral DNA contains degenerate bases that cannot be translated. Yellow for tiger, pink for domestic cat, blue for lion, green for pallas's cat, orange for puma, purple for bobcat. A. gag-p26 translation products, 163 sites included in analysis. B. pol-RT translation products, 184 sites included in analysis. C. pol-RNAse translation products, 246 sites included in analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.xlsx
- TableS2.xlsx
- TableS3S5.xlsx