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# Genetic analyses of feline foamy virus isolates from domestic and wild feline species in geographically distinct areas

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**Abstract**

To know the genetic diversities and phylogenetic relationship among feline foamy virus (FeFV) isolates from domestic cats (*Felis catus*) and FeFV-related viruses from the Iriomote cats (*Felis iriomotensis*) and leopard cats (*Felis bengalensis*) in geographically distinct areas, we sequenced a partial *gag–pol* region of 17 strains and a partial *env* region of nine strains, and the U3 region of long terminal repeat of three strains of the viruses. FeFV-related viruses from the feral cats were quite similar to the FeFV from domestic cats in the sequenced regions. In the partial *gag* region, the identities of nucleotide sequences among the isolates were from 94 to 99%. In the partial *env* gene, the isolates were divided into two distinct genotypes (F17- and FUV-types) as reported by Winkler et al. (Virology 247 (1999) 144–151). More than 94% nucleotide identities were observed in the *env* region within a particular *env* genotype and about 75% nucleotide identities were noted between the two genotypes. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Feline foamy virus; Phylogenetic analysis; Iriomote cats; Leopard cats; Vietnam; Japan

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## 1. Introduction

Foamy viruses are classified into the genus *Spumavirus* of the family *Retroviridae* and have been isolated from many mammalian species including cats, cattle, a variety of non-human primates and humans (Mergia and Luciw, 1991). Recent findings including the existence of an internal promoter (Löchelt et al., 1993), translation of Pol protein from a splicing transcript (Yu et al., 1996) and the existence of a *cis*-acting element within the *pol* region (Wu et al., 1998) set foamy viruses apart from the other known retroviruses.

Feline foamy virus (FeFV) was first isolated in 1969 from a cat in the USA (Riggs et al., 1969) and FeFV infection was recognized in both healthy and diseased cats worldwide (Jarrett et al., 1974; Mochizuki and Konishi, 1979). Since experimental infection of FeFV caused no clinical signs in domestic cats (Kasza et al., 1969; McKissick and Lamont, 1970), FeFV has been considered to be apathogenic. Recent molecular studies of spumaviruses make it possible to develop spumavirus-based retroviral vectors, which have several potential advantages over currently available vectors (Bieniasz et al., 1997). Therefore, FeFV is now regarded as a promising candidate for a useful retroviral vector for cats.

In primate foamy viruses, more than 10 serotypes have been reported (Bieniasz et al., 1995). Sequencing analysis showed the genetic relatedness apparently coinciding with host species (Broussard et al., 1997). On the other hand, in FeFV, two serotypes have been recognized among isolates from Australian domestic cats (Flower et al., 1985). Winkler et al. (1998) clearly demonstrated that Australian and American isolates could be divided into two distinct sequence groups (FUV7-like and 951-like) in the Env surface (SU) protein and that each group belonged to a single neutralization group (serotype). Previously we reported the biological diversities including growth properties among Japanese and American isolates (Ikeda et al., 1997), however, it remains unknown whether certain Japanese domestic isolates belong to an unrecognized genotype. Moreover, although the isolation of FeFV-related viruses from Asian wild felids has been reported (Mochizuki et al., 1990; Miyazawa et al., 1998), genetic diversity between FeFV and FeFV-related viruses has not been investigated. In the study presented here, we examined the genetic diversities and phylogenetic relationship among 13 FeFV isolates from domestic cats and four FeFV-related viruses from wild felids in geographically distinct areas.

## 2. Materials and methods

### 2.1. Viruses and cells

Three Taiwanese FeFV strains TW1A, TW6 and TW15, and five Vietnamese FeFV strains VN114, VN115, VN119, VN124 and VN150, were isolated from the peripheral blood mononuclear cells (PBMCs) of free-roaming domestic cats in Taipei and Hanoi, respectively, as described previously (Ikeda et al., 1997; Miyazawa et al., 1998). An American isolate, strain Coleman, was kindly supplied by Dr J.M. Gaskin (University of Florida, USA). Japanese isolates, strains S7801 and Sammy-1, were reported previously (Mochizuki and Konishi, 1979; Ikeda et al., 1997; Hatama et al., 2001). Two Argentine strains Ar1 and Ar20 were isolated from PBMCs together with feline immunodeficiency virus (FIV) strains LP1 and LP20, respectively (Pecoraro et al., 1996). Two FeFV-related viruses from the Iriomote cats (*Felis iriomotensis*) in Iriomote island which is located off the south-coast of Japan, designated as Iriomote cat foamy virus (ICFV) strains W-15 and W-13, were reported elsewhere (Mochizuki et al., 1990). Two FeFV-related viruses from leopard cats (*Felis bengalensis*) in Vietnam, designated as FBSV strains NV138 and SV201, were reported previously (Miyazawa et al., 1998). Crandell feline kidney (CRFK) cells (ATCC CCL 94) were grown in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated fetal calf serum and antibiotics.

### 2.2. Polymerase chain reaction (PCR) and genetic analyses

The sequences of synthetic oligonucleotide primers used in this study are as follows (strain FUV nucleotide numbers are given within parentheses). LTR-f1, 5′-TGTCATGGGCCAAAGAGAATTCTC-3′ (9276–9299); LTR-f2, 5′-GTGCCATATAAATCAGTGTC-3′ (9373–9392); LTR-f3, 5′-ACAGCAATGTATTATGATGAAA-3′ (9121–9142); LTR-f4, 5′-ATGTATTCATATCGAAACTATG-3′ (9863–9884); LTR-r1, 5′-CCCACGTTGGGCGCCAACTGT-3′ (281–301); LTR-r3, 5′-TAATAGCAGAAACATGCAACTA-3′ (10 290–10 311); bel-1f, 5′-ACCAGCAGCTGGGAAACTATAA-3′ (7877–7898); bel-2r, 5′-CCAGGTAAATTCAGGCTTTCTA-3′ (9629–9608); gag-f2, 5′-AGACGGCGGTAATCCTCAACA-3′ (1697–1717); pro-r1, 5′-ATACATCTCCTTCCTGCGTTCC-3′ (2035–2014); env-f1, 5′-AAATTCGTGAATCTTTACAACACCCT-3′ (5012–5037); env-f2, 5′-GCTACTTCTACTAGAATAATGTTTTGGATA-3′ (5429–5458); env-f3, 5′-GCTTTCAAAAATATGGACATTGTTATGTTA-3′ (5919–5948); env-f4, 5′-CTCACTATGGGAAGGAGATTGTGGATATTACC-3′ (6436–6467); env-r1, 5′-TTGCAGGACGAGTAGGATCCGTCTT-3′ (8587–8563); env-r2, 5′-AGCCACAGTAGTAATTGCATTGGCCAGGCC-3′ (7012–6983); env-r3, 5′-GTTTCTCCAAAATCTGCAAGCATATGGATG-3′ (6553–6524); and env-r4, 5′-AGGTAATGGACATTGATCTTGTATTAAATC-3′ (6013–5984).

For detection of the proviral DNA, total cellular DNA was extracted from the CRFK cells infected with each of the isolates by QIAamp blood kit (QIAGEN, Hilden, Germany). To amplify FeFV-specific DNAs by PCR, primer pairs gag-f2 and pro-r1, env-f1 and env-r1, LTR-f1 and LTR-r1, LTR-f3 and LTR-r1, and bel1-f and bel2-r were used. The fragments amplified by primer pairs, gag-f2 and pro-r1, LTR-f3 and LTR-r1, and env-f1 and env-r1, were directly subjected to the sequencing analyses. Sequencing reactions for *env* gene and the U3 region of the LTR were performed using 13 primers, env-f1, env-f2, env-f3, env-f4, env-r1, env-r2, env-r3 and env-r4, and LTR-f2, LTR-f3, LTR-f4, LTR-r1 and LTR-r3, respectively as described previously (Uema et al., 1999). To rule out the possibility of contamination by PCR products, we carried out three independent PCR amplification for each of the DNA templates and obtained almost the same results. Control PCR amplification without template DNA did not generate any amplified product.

The GenBank accession numbers for the full sequences of FeFV strains FUV and F17, and for the LTR sequences of FUV strains S7801 and Sammy-1, were AJ223851 and U85043, and AB042567 and AB042568, respectively. Genetic analyses were conducted by a software GENETYX-MAC Ver. 9.0 (SOFTWARE DEVELOPMENT CO., LTD., Tokyo, Japan).

## 3. Results

### 3.1. Amplification of proviral FeFV by PCR

By the PCR using the primer pair of gag-f2 and pro-r1 (Fig. 1a), the proviral DNAs of isolates from 13 domestic and four feral cats were all

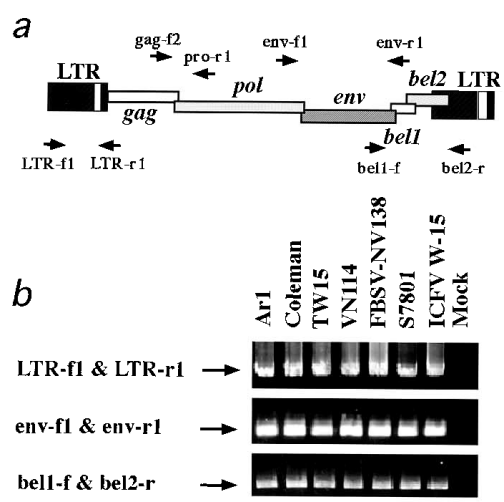
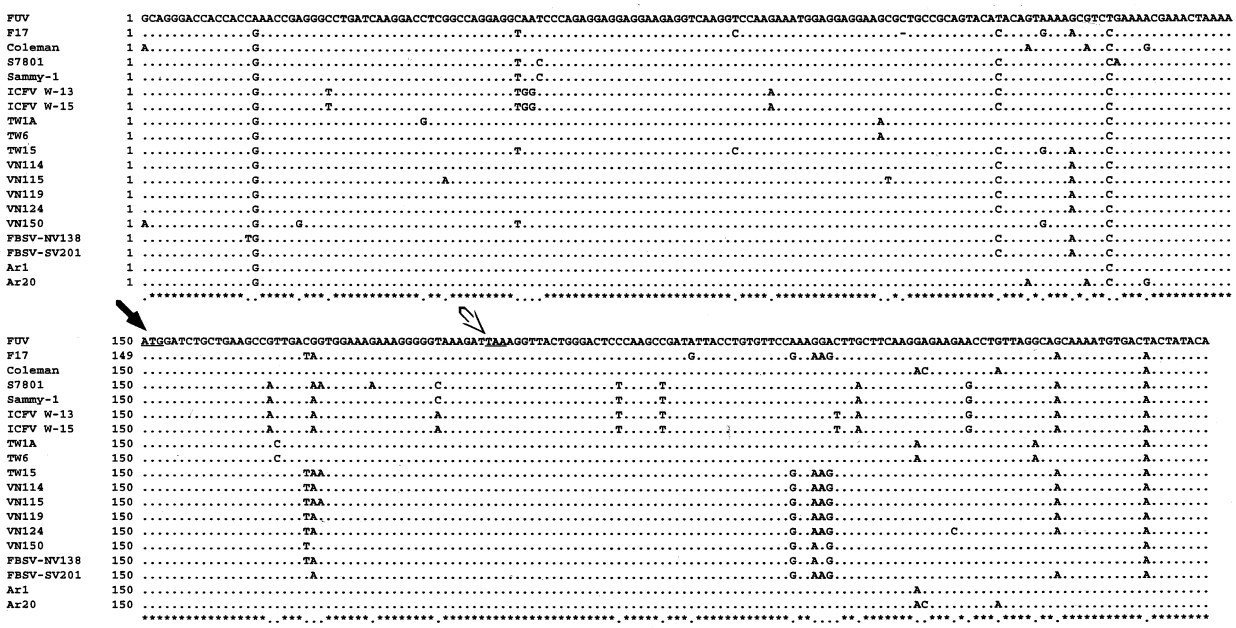



Fig. 1. Genomic construction of FeFV and amplification by PCR. (a) A schematic representation of FeFV genome. Short arrows indicate oligonucleotide primers; (b) Comparison of the sizes of the *env*, *bel1* and *bel2* and LTR regions of seven isolates.



(a)

Fig. 2. (a) Alignment of the nucleotide sequences of the amplified *gag–pol* region of 13 FeFV and four FeFV-like virus isolates. A closed arrow indicates the start codon of the *pol* gene. An open short arrow indicates the stop codon of the *gag* gene; (b) Alignment of the amino acid sequences of partial Env proteins of 10 FeFV isolates and one ICFV isolate; (c) Alignment of the nucleotide sequence of the U3 region of seven FeFV isolates. Asterisks and dots indicate the conserved and non-conserved sequences, respectively.

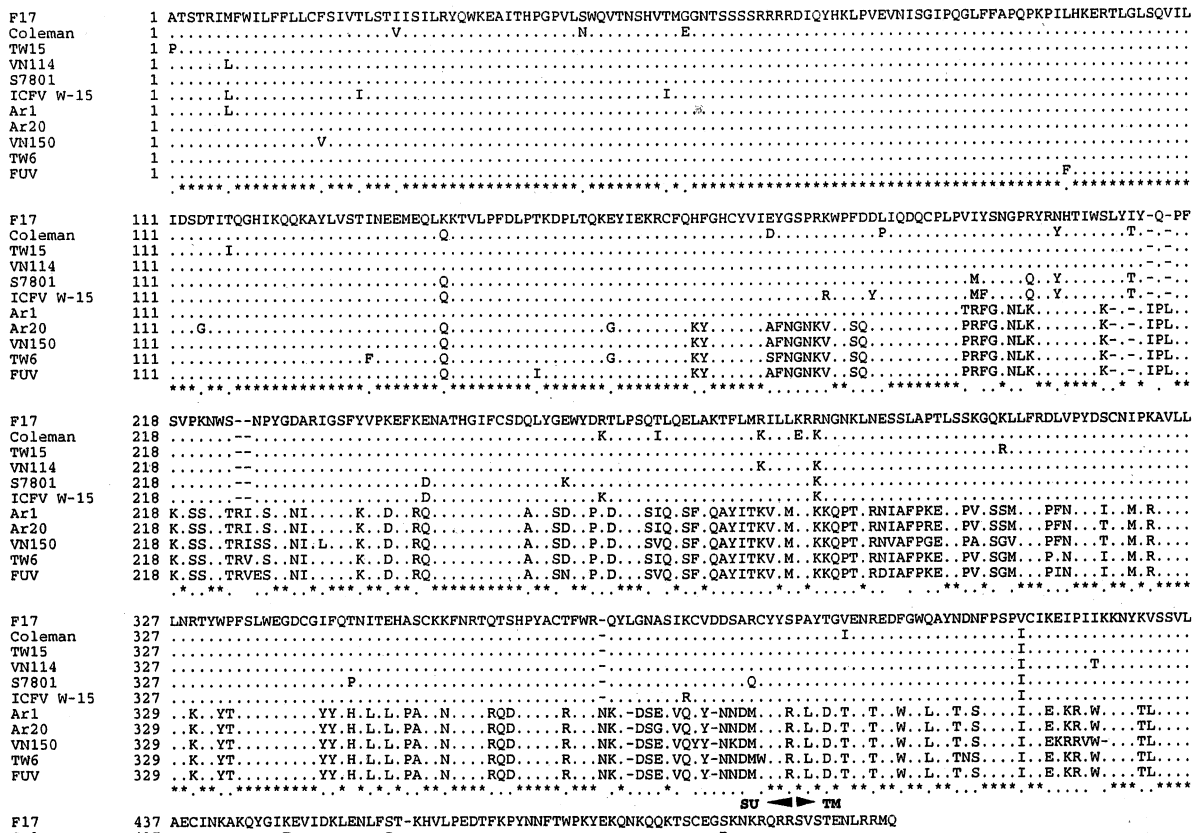
amplified. The sizes of the amplified fragments were almost the same among the isolates (data not shown). Moreover, when the lengths of *bel*, *env* and LTR regions of several FeFV isolates were compared by the PCR using the primer pairs of LTR-f1 and LTR-r2, env-f1 and env-r1, and bel1-f and bel2-r (Fig. 1a), the sizes of the amplified fragments were shown to be almost the same among the isolates (representative PCR results are shown in Fig. 1b). These data indicate no obvious variations of lengths in the regions. In addition, any primer pairs did not amplify specific fragments from DNA of uninfected CRFK cells by PCR (data not shown).

### *3.2. Sequence and phylogenetical analyses of a partial gag–pol region*

There might be a risk that the passage of FeFV isolates in CRFK cells in vitro causes homogenization of the viruses through selective pressures imposed by the culture conditions. To know the risk, we compared the partial *gag–pol* sequence of a primary FeFV isolate (strain Sammy-1) with the corresponding stock virus (two passage history in CRFK cells). The partial *gag–pol* sequence of the primary isolate (which was directly amplified from CRFK cells cocultured with PBMCs of a cat infected with the strain) was identical with that amplified from CRFK cells infected with the stock virus (data not shown). These data indicate that such risk is considered to be very low, if any. However, to minimize the possible risk, we used viruses at a low passage history. Except FeFV strain Coleman with unknown passage history, all the FeFV, ICFV and FBSV strains isolated in our laboratories were at a low passage history in CRFK cells (two or three passage history).

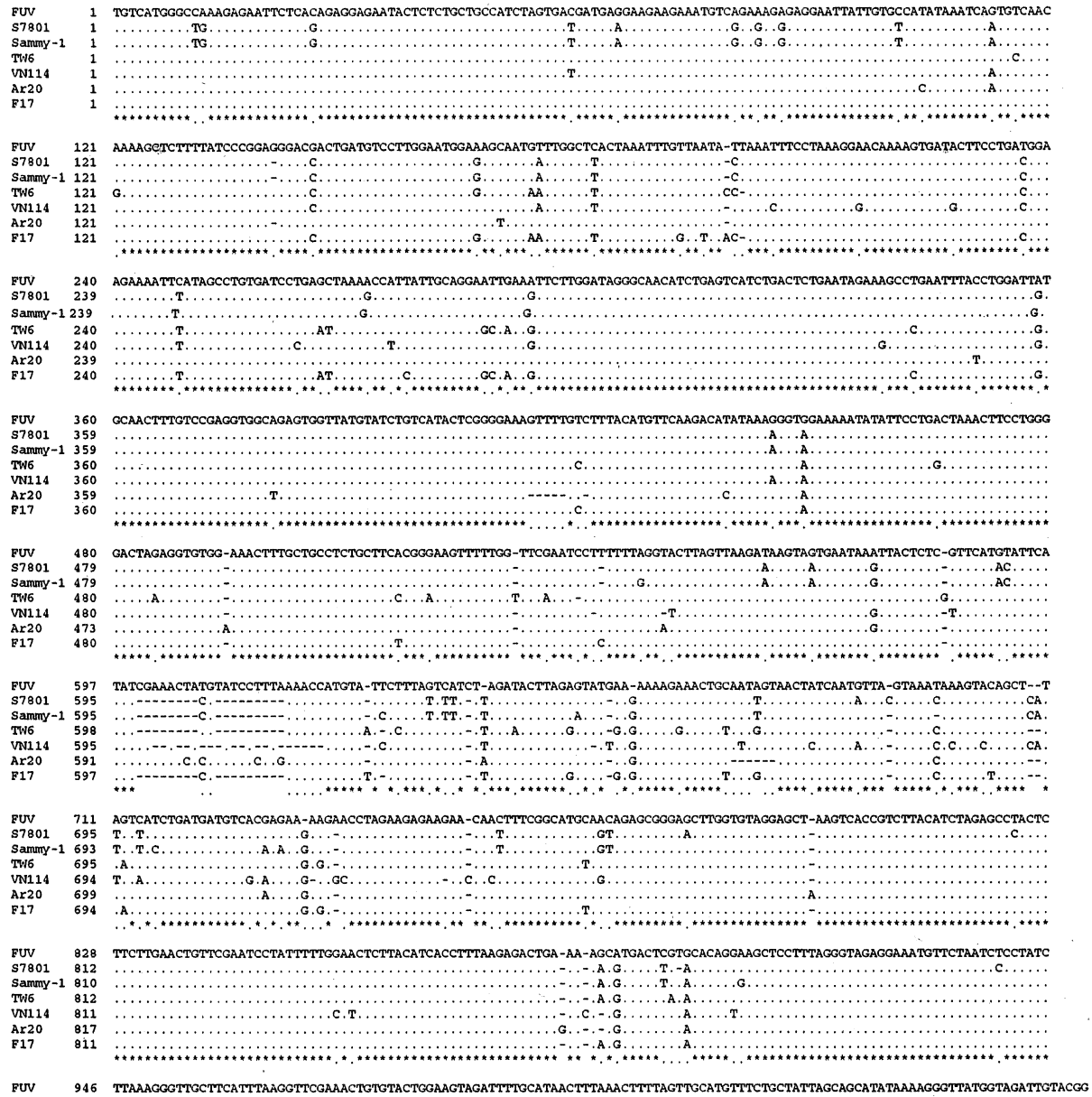
Fig. 2a shows the nucleotide sequences of the partial *gag–pol* region (amplified by the primer pair of gag-f2 and pro-r1) of the 17 isolates along with Australian strain FUV and USA strain F17.

The length of the amplified region was 295 base pairs in all the strains and no deletion and insertion were found. The first ATG codon of the *pol* gene was conserved among the isolates, which may confirm the previous report that the translation of Pol protein occurs from a spliced transcript (Bodem et al., 1996). Phylogenetic analysis of the partial *gag–pol* sequences revealed that FeFV isolates formed two distinct clusters consisting of Japanese and non-Japanese isolates (Fig. 3a). In the cluster of Japanese isolates, the isolates further formed two sub-clusters; one consisted of FeFV isolates from Japanese domestic cats and the other consisted of ICFV isolates from the Iriomote cats. The cluster of non-Japanese isolates consisted of FeFV isolates from several distant countries and FBSV isolates. Surprisingly, a Taiwanese isolate (strain TW15) and a USA isolate (strain F17), and an Argentine isolate (strain Ar20) and a USA isolate (strain Coleman) were closely related with each other, although they were isolated from different countries. We carefully repeated the sequencing analyses of the FeFV strains TW15, Coleman, and Ar20 and




(b)

Fig. 2. (*Continued*)




(c)

Fig. 2. (*Continued*)

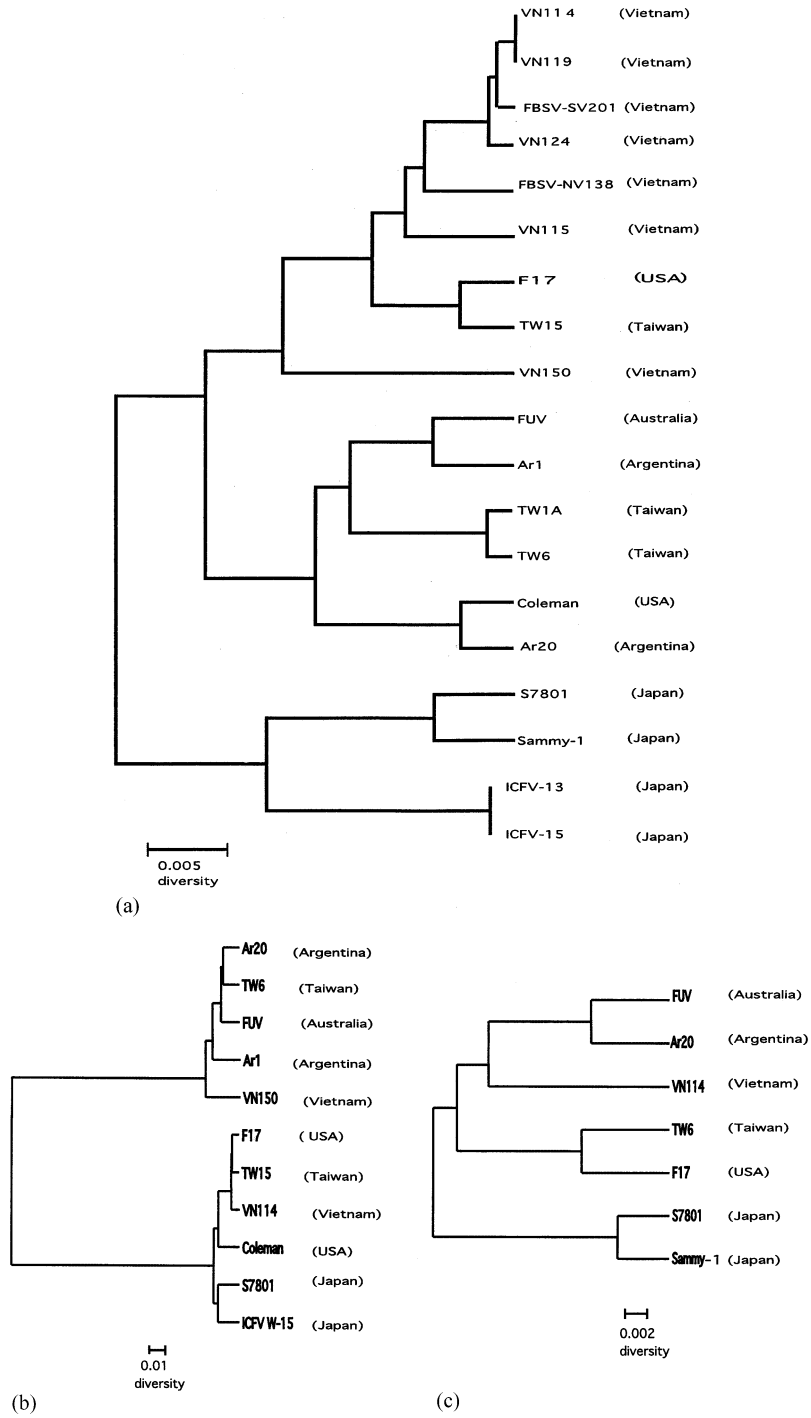



Fig. 3. Phylogenetic tree based on the nucleotide sequences of the partial *gag–pol* region (a), partial *env* region (b), and U3 region of LTR (c). The trees were constructed using UPGMA program of GENETYX-MAC Ver. 9.0 (SOFTWARE DEVELOPMENT CO., LTD., Tokyo, Japan).

obtained the same results. Moreover, we have never dealt with FeFV strain F17 in our laboratories, and the viral stock of FeFV strain Coleman used in this study was stored at −80°C in 1981 before the isolation of FeFV strain Ar20 in 1993. Therefore, we believe that cross-contamination has never occurred in this study.

### 3.3. Sequence and phylogenetical analyses of a partial env gene

For analysis of the genetic diversities in *env* gene among FeFV isolates, the nucleotide sequences of partial *env* gene (mainly the external SU region) were determined. We selected eight FeFV strains from different areas (strains Coleman, TW6, TW15, VN114, VN150, S7801, Ar1 and Ar20) and one ICFV strain (strain W-15). Fig. 2b shows the deduced amino acid sequences of the partial *env* region of the nine determined isolates comparing with those of previously reported strains F17 and FUV. Phylogenetic analysis (Fig. 3b) clearly demonstrated that FeFV strains Coleman, TW15, VN114, and S7801, and ICFV strain W-15 belonged to F17-type and that FeFV strains Ar1, Ar20, VN150 and TW6 belonged to FUV-type. To determine the types of the other two FeFV strains TW1A and TW11, ICFV strain W-13, and FBSV strain NV138, additional sequencing analyses of a short Env SU region were performed. Consequently, we found that FeFV strain TW1A belonged to FUV-type while ICFV W-13, TW11 and FBSV NV138 belonged to F17-type (data not shown). There was no relationship between the *env* genotype and phylogenetic clustering based on the *gag–pol* region (Fig. 3a).

### 3.4. Sequence and phylogenetical analyses of U3 region of LTR

For analysis of the genetic diversities in LTR of FeFV isolates, nucleotide sequences of the U3 region of LTR were determined. We sequenced three FeFV strains from different areas (strains Ar20, VN114 and TW6). Fig. 2c shows the determined nucleotide sequences of the U3 region comparing with those of previously reported strains FUV, F17, Sammy-1, and S7801. Phylogenetic analysis (Fig. 3c) revealed that FeFV isolates formed two distinct branches consisting of Japanese and non-Japanese isolates. This branching pattern was similar to that based on the partial *gag–pol* region (Fig. 3a).

### 3.5. Homologies of the partial gag and env regions in FeFV isolates

Based on the sequence results (Fig. 2a–b) obtained in this study, we calculated nucleotide and predicted amino acid identities of C-terminal *gag* region and the partial *env* region. Table 1 shows the results of the C-terminal *gag* region of eight strains (seven FeFV strains and one ICFV strain) and Table 2 shows the results of the partial *env* sequences of 11 strains (10 FeFV strains and one ICFV strain). The identities of nucleotide and amino acid sequences of the C-terminal *gag* re-

Table 1
Nucleotide and predicted amino acid identities (%) between the partial *gag* genes of FeFV and ICFV isolates

| Isolates | F17 | Coleman | TW15 | VN114 | S7801 | ICFV W-15 | Ar1 | FUV |
|---|---|---|---|---|---|---|---|---|
| F17 | – | 93.9 | 98.5 | 100.0 | 93.9 | 90.8 | 96.9 | 96.9 |
| Coleman | 94.4 | – | 93.9 | 93.9 | 92.3 | 89.2 | 96.9 | 96.9 |
| TW15 | 99.0 | 94.4 | – | 98.5 | 95.4 | 90.8 | 96.9 | 96.9 |
| VN114 | 98.0 | 96.5 | 98.0 | – | 93.9 | 92.3 | 96.9 | 96.9 |
| S7801 | 94.4 | 93.9 | 95.5 | 95.5 | – | 90.8 | 95.4 | 95.4 |
| ICFV W-15 | 94.4 | 93.9 | 94.4 | 95.5 | 95.5 | – | 92.3 | 90.8 |
| Ar1 | 96.0 | 98.5 | 96.0 | 98.0 | 95.5 | 95.5 | – | 100.0 |
| FUV | 95.0 | 97.5 | 95.0 | 97.0 | 94.4 | 94.4 | 99.0 | – |

Nucleotide identities are presented in the lower half of the matrix and amino acid identities in the upper half.

Table 2
Nucleotide and predicted amino acid identities (%) between the partial *env* genes of FeFV and isolates

| Isolates | F17 | Coleman | TW15 | VN114 | S7801 | ICFVW-15 | Ar1 | Ar20 | VN150 | TW6 | FUV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| F17 | – | 96.5 | 98.8 | 98.6 | 96.9 | 95.5 | 73.0 | 70.5 | 69.9 | 70.1 | 70.1 |
| Coleman | 95.5 | – | 96.5 | 97.1 | 96.3 | 95.5 | 71.8 | 69.9 | 69.3 | 69.5 | 69.3 |
| TW15 | 98.8 | 95.4 | – | 98.6 | 96.9 | 95.5 | 72.8 | 70.3 | 69.9 | 69.9 | 69.9 |
| VN114 | 97.7 | 96.4 | 97.6 | – | 97.1 | 96.1 | 73.8 | 70.9 | 70.3 | 70.5 | 70.5 |
| S7801 | 97.1 | 95.6 | 97.3 | 96.1 | – | 96.7 | 73.1 | 70.9 | 70.5 | 70.5 | 70.5 |
| ICFV-W-15 | 95.5 | 94.8 | 95.7 | 95.5 | 97.1 | – | 72.2 | 69.9 | 69.3 | 69.5 | 69.7 |
| Ar1 | 77.8 | 76.8 | 77.9 | 78.1 | 76.9 | 76.4 | – | 96.1 | 93.0 | 95.7 | 95.5 |
| Ar20 | 74.9 | 74.8 | 75.0 | 74.8 | 74.6 | 74.2 | 96.4 | – | 95.5 | 97.5 | 97.1 |
| VN150 | 74.6 | 74.4 | 74.7 | 74.6 | 74.6 | 73.8 | 94.0 | 96.0 | – | 94.6 | 94.9 |
| TW6 | 74.1 | 74.3 | 74.2 | 74.3 | 74.1 | 73.5 | 94.9 | 97.5 | 95.2 | – | 97.1 |
| FUV | 74.4 | 74.8 | 74.5 | 74.9 | 74.4 | 73.8 | 95.3 | 97.7 | 95.2 | 97.0 | – |

Nucleotide identities are presented in the lower half of the matrix and amino acid identities in the upper half.

gion were approximately 94–99% and 89–100%, respectively (Table 1). On the contrary, remarkable genetic diversities (approximately 75%) were observed in the partial *env* gene between F17-type and FUV-type viruses (Table 2). However, it is notable that more than 94% identity was observed in the *env* region within a particular *env* genotype even though the viruses were isolated in distinct areas. These results may suggest that the *env* region is as conserved as the *gag* region in FeFV.

## 4. Discussion

A statistical link between FIV and FeFV infection in domestic cats (Yamamoto et al., 1989) and the presence of FIV and FeFV in saliva (Bandecchi et al., 1992) suggest that biting is the predominant means of FeFV transmission as indicated in FIV infection (Yamamoto et al., 1989). FIV, which belongs to the genus *Lentivirus* of the family *Retroviridae*, has been classified into five sub-types, A, B, C, D and E, based on the Env amino acid sequences and the different FIV subtypes are generally localized to particular geographic regions, i.e. subtype A in Europe, the USA and Australia, subtype B in Japan, Europe and the USA, subtype C in Canada and Taiwan, subtype D in Japan and subtype E in Argentina (Sodora et al., 1994; Pecoraro et al., 1996; Uema et al., 1999). In addition, phylogenetic analysis of FIV-related viruses isolated from feral cats revealed that each FIV-related virus has its own species-specificity (Carpenter and O'Brien, 1995). On the other hand, the two genotypes (FUV and F17-types) of FeFV were not reflected by geographic distances and we could not find any relationship between the FeFV Env genotypes and predominant subtypes of FIV in each area where respective FeFVs were isolated. These data might indicate that the ancestors of the domestic cats have harbored the two genotypes of FeFV before they spread worldwide. In addition, no evidence of FIV infection in cats in northern Vietnam (Miyazawa et al., 1998) may support the hypothesis that FeFV spread in cats earlier than FIV.

In this study, we also found that ICFV and FBSV, which were isolated from the Iriomote cats and leopard cats, respectively, were genetically quite similar to the FeFV of domestic cats. ICFV strains used in this study were isolated from the Iriomote cats inhabiting Iriomote island which is located off the south-coast of Japan, and was geographically isolated about 200 000 years ago (Masuda and Yoshida, 1995). Since the Iriomote cats are not infected with devastating domestic feline pathogens such as feline panleukopenia virus, feline herpesvirus type 1 and FIV, it is presumed that they seldom come into contact with domestic cats and that ICFVs have been retained in its population

(Mochizuki et al., 1990). As shown in Fig. 3a, however, ICFV isolates were more genetically close to the FeFV isolated from Japanese domestic cats than the FBSV from the continental leopard cats. These observations may suggest that transmission of FeFV occurred between domestic and the Iriomote cats in the local area in ancient times.

At present, the precise mechanism of the emergence of the two genotypes is still not resolved in detail. Further characterization of FeFV or FeFV-related viruses from domestic and wild felids in the other countries will provide new insight into the evolution and potential origins of the two genotypes of FeFV.

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