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Molecular epidemiology of feline immunodeficiency virus in the domestic cat (*Felis catus*)

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Abstract

Studying the evolutionary mechanisms of feline immunodeficiency virus in the domestic cat (*Felis catus*), FIV_{Fca}, provides a good comparison to other lentiviruses, such as HIV and FIV_{Pco} in the cougar (*Puma concolor*). We review the current epidemiological and evolutionary findings of FIV_{Fca},. In addition to the five accepted FIV_{Fca}, subtypes, several recent phylogenetic studies have found strains that form separate clades, indicative of novel subtypes. In New Zealand cats, these strains of unknown subtype have been found to be involved in complex patterns of intergenic recombination, and whole genome sequences are required to resolve these. Evidence of recombination events has been documented with the highest levels in the *env* gene, the region involved in host cell receptor recognition. Several cases of FIV_{Fca}, multiple infection, both inter- and intra-subtype, have been reported. The findings of both unknown subtypes and relatively high levels of recombination suggest the need for further testing of the current vaccine. Limited studies on the evolutionary rate of FIV_{Fca}, document a value twice to three times that of FIV in the cougar, a result suggesting the different levels of co-adaptation between the viruses and their respective hosts. We studied the tissue distribution of FIV_{Fca}, in feral domestic cats, finding the first case of FIV compartmentalisation, a phenomenon well-documented in HIV-1 patients.

Keywords

Feline Immunodeficiency Virus; domestic cat; *Felis catus*; subtype; evolution; recombination

Introduction

Feline Immunodeficiency Virus (FIV) is a lentivirus that infects members of the Felidae and Hyaenidae (Troyer et al., 2005), and each host species usually has its own FIV strain (Brown et al., 1994; Carpenter et al., 1996; Carpenter et al., 1998; Troyer et al., 2005; Franklin et al., 2007; Pecon-Slattery et al., 2008). The strain that circulates in populations of the domestic cat (*Felis catus*), FIV_{Fca},, is pathogenic and can lead to feline AIDS, with symptoms similar to

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Conflict of interest
The authors have no financial or personal relationships with other people or organisations that could inappropriately influence or bias this paper.

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that produced by Human Immunodeficiency Virus (HIV) in humans (Pedersen et al., 1989; Bendinelli et al., 1995; VandeWoude and Apetrei, 2006). Furthermore, shared characteristics of HIV-1 and FIV$_{Fca}$,, such as the worldwide distribution, the occurrence of recombinants, and high viral RNA loads in plasma suggest that FIV$_{Fca}$, is a good model for HIV-1 (Carpenter et al., 1998; Yamamoto et al., 2002; Yamamoto et al., 2007).

In other host species, such as the African lion (*Panthero leo*) and the North American cougar (*Puma concolor*), FIV is apparently less pathogenic than in the domestic cat (Carpenter and O'Brien, 1995; Carpenter et al., 1996; Bull et al., 2003; Brennan et al., 2006; Roelke et al., 2006). The difference in the disease status of these hosts suggests that FIV has persisted in the lion and cougar much longer than FIV in the domestic cat, such that a period of host adaptation has occurred (Carpenter et al., 1996). This hypothesis is also supported by a higher prevalence and greater genetic variation of FIV in lion and cougar populations compared to the domestic cat (Brown et al., 1994; Carpenter and O'Brien, 1995; Biek et al., 2003). The similarity between FIV$_{Fca}$, and HIV-1, and the difference between FIV$_{Fca}$, and, for example, FIV$_{Pco}$ in the cougar, provide two important reasons for studying FIV$_{Fca}$,.

Here we provide a general overview of the prevalence, subtypes and recombination of FIV$_{Fca}$, and include some recent findings on the evolutionary rate and tissue distribution of FIV in the domestic cat. For this review, we define three categories of domestic cat populations: companion, feral, and stray. Companion cats are pets; owned by and reliant on humans. Feral cats are free-ranging, inhabit rural areas like forest and scrubland, and have minimal or no human contact. Stray cats are also free-ranging but inhabit urban areas and have some human contact.

1. Prevalence of FIV$_{Fca}$, in *F. catus* populations

Companion cat prevalence—Generally, the prevalence of FIV$_{Fca}$, in companion cat populations worldwide is about 4–12 % (Courchamp and Pontier, 1994). Companion cats in the USA and Canada have FIV prevalence at the lower end of the range, between 1 % and 7 % in low-risk and high-risk cats respectively (Shelton et al., 1989; Yamamoto et al., 1989; O'Connor et al., 1991). In contrast, companion cats in Japan have a higher prevalence value, of up to 44 % in clinically ill cats, which is suggested to be the result of relatively higher cat density (Ishida et al., 1989). The worldwide distribution of FIV$_{Fca}$, in domestic cats is thought to be a result of low virulence levels and low rates of transmission of the virus (Fromont et al., 1997).

Feral cat prevalence—Worldwide studies of feral and free-ranging cats have found FIV$_{Fca}$, prevalence of about 8–19 % (Baneth et al., 1999; Winkler et al., 1999; Ostrowski et al., 2003; Danner et al., 2007; Hayward, 2009) but see Carpenter et al. (1998) and Yamaguchi et al. (1996). The higher FIV$_{Fca}$, prevalence observed in feral cats compared to companion cats may be explained by differences in behavioural patterns and the main route of FIV transmission. Feral cats tend to be free-ranging and more aggressive in their interactions with other cats, and as such, have a higher frequency of biting encounters (Courchamp et al., 1998). For this same reason, male, sexually mature cats are at the highest risk of FIV$_{Fca}$, infection (Hosie et al., 1989; Courchamp et al., 1998; Levy et al., 2006).

2. FIV-Fca subtypes

Five FIV$_{Fca}$, subtypes, A to E, (Fig. 1) have been established based on phylogenetic analyses of sequences from the *env* V3-V5 region (Sodora et al., 1994;Kakinuma et al., 1995;Pecoraro et al., 1996). Recent papers have also used the *gag* gene to confirm the *env* clades (Kakinuma et al., 1995;Duarte et al., 2002;Steinrigl and Klein, 2003;Reggeti and Bienzle, 2004;Weaver et al., 2004;Hayward and Rodrigo, 2008). Subtypes A, B and C are most widespread

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worldwide, with subtype D only found in Japan and Vietnam (Kakinuma et al., 1995;Nakamura et al., 2003) and subtype E only found in Argentina (Pecoraro et al., 1996). The four subtypes A to D are found in cat populations from Japan (Kakinuma et al., 1995;Nishimura et al., 1998) but see Yamamoto et al. (2007) for worldwide FIV prevalence and subtype distribution details. There appears to be subtype-specific differences in disease, for example, subtype A infection has been reported to be associated with neurological disease (Nishimura et al., 1996;de Rozieres et al., 2008) while subtype B is less likely to be symptomatic (Bachmann et al., 1997).

In addition, sequences of unknown subtype have been documented. Eleven FIV_{Fca}, isolates from Texas were tentatively designated subtype F (Weaver et al., 2004). More recently, these Texas sequences were assigned as a subclade within subtype B and the Portuguese sequences were proposed as subtype F (Fig. 1) (Duarte and Tavares, 2006). Furthermore, eighteen *env* sequences from New Zealand (NZ) cats have been identified as distinct from any previously-described subtype, designated U-NZenv (Fig. 1) (Hayward et al., 2007; Hayward and Rodrigo, 2008). Phylogenetic analyses of *gag* and *pol* sequences from NZ cats also showed evidence of one and two unknown subtypes respectively, although the samples included in these unknown clades were not identical across the three genes (Hayward and Rodrigo, 2008). The finding that the NZ *env* unknown subtype group is not monophyletic across the three main genes leads us to question the suitability of FIV_{Fca}, subtyping using the *env* V3-V5 region only. In light of recent sequencing technologies and the HIV-1 nomenclature recommendations that at least two full-length genomes from epidemiologically-unrelated hosts are required to name a new subtype (Robertson et al., 1999), a precautionary approach in designating new subtypes is suggested.

The Fel-O-Vax vaccine (Fort Dodge), which is commercially available in a number of countries including USA, Australia, Japan and NZ, confers protection against subtypes A, B and D but has not yet been tested on subtype C, despite the wide distribution of this subtype (Yamamoto et al., 2002; Kusuhara et al., 2005). Furthermore, the findings of FIV strains of unknown subtypes suggest further testing of the vaccine in cat populations is warranted.

3. Recombination in FIV

$_{Fca}$, Retroviruses have been documented to have relatively rapid rates of recombination due to the presence of a diploid genome (that is, two identical copies of ssRNA) and the occurrence of multiple infection (Hu and Temin, 1990). Naturally-occurring multiple FIV_{Fca}, infection, either as a result of co-infection or superinfection, has been identified in cats from Australia, USA and NZ (Kyaw-Tanner and Robinson, 1996; Bachmann et al., 1997; Kann et al., 2007; Hayward and Rodrigo, 2008). Several of these cases involve two strains of the same subtype (Kyaw-Tanner and Robinson, 1996; Hayward and Rodrigo, 2008). Given that multiple infection is a prerequisite for recombination, it is expected that the level of multiple infection would be similar to the level of unique recombinants circulating in cat populations. However, intra-subtype recombination is difficult to document, because of the similarity of the parent strains involved (Hayward and Rodrigo, 2008). It is important to note that recombination is only detected when the two parent strains are different but recombination does also occur in cells infected with virus whose genome is homodimeric, that is, when the two copies of the viral RNA are identical.

For clarity, here we distinguish between two types of recombinant sequences. Intragenic recombinant sequences include a crossover event within a single gene region while intergenic recombinants include a crossover between two gene regions. Intragenic recombinant FIV_{Fca}, sequences from the *env* region have been isolated from cats in Canada (A/B), Japan (A/B, B/D), NZ (A/C) and USA (A/B, A/C, A/B/C) (Bachmann et al., 1997; Carpenter et al., 1998; Reggeti and Bienzle, 2004; Hayward and Rodrigo, 2008). *Gag* intragenic recombinant

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sequences have been found in samples from Canada (A/B, A/C) and NZ (A/C) (Reggeti and Bienzle, 2004; Hayward and Rodrigo, 2008).

Across all studies, the *env* gene has the highest detected level of recombination. Indeed, about 6 % (n = 156) of NZ *env* sequences were found to be putative recombinants compared to 2 % (n = 48) of the *gag* sequences (Hayward and Rodrigo, 2008). Immunologically, this is an expected result because *env* encodes the surface proteins, which are important in recognition of viruses by the host immune system, and therefore subject to positive selection (Flynn et al., 1995; Seibert et al., 1995). High levels of variation, caused by a high evolutionary rate, are observed in this gene allowing the virus to escape the immune response. Recombination is one factor that aids in increasing the evolutionary rate of a virus (Coffin et al., 1997). However, it is also possible that the reason for the greater number of recombination events observed in *env* is simply a consequence of our ability to better detect recombination in highly diverse regions.

Complex intergenic recombination patterns, between subtypes A and undefined parent strains, have been identified from FIV_{Fca}, sequences isolated from NZ cats (Fig. 2) (Hayward and Rodrigo, 2008). For example, one cat was found with subtype A FIV in the *env* region, “unknown” subtype (most closely related to subtype C) FIV in the *pol* region, and subtype A FIV in the *gag* region. Sequences encompassing the whole FIV genome are needed to obtain a complete picture of the recombination events that have occurred between the different gene regions.

4. Evolutionary rate of FIV_{Fca}

Only one published study has reported an evolutionary rate for FIV-Fca, of 3.4×10^{-3} substitutions per site per year from the V1-V2 *env* region (Greene et al., 1993). and was calculated from a single sequence from each of three serial samples taken one year apart from a naturally-infected cat. Recently, we estimated the evolutionary rate of the *env* V3-V6 region using a Bayesian coalescent method as implemented in the program BEAST (Drummond and Rambaut, 2007). We used endpoint sequences generated from serial blood samples taken six to eleven months apart, from three FIV-infected NZ companion cats. A strict molecular clock model was used and the MCMC chain was run for 50,000,000 iterations. We used a prior to constrain the root of each tree and this was set to the age of each cat. Our estimates range from 3.1×10^{-3} to 6.6×10^{-3} substitutions per site per year (Hayward, 2009), thus confirming Greene et al.’s earlier estimate (Table 1).

The FIV_{Fca}, evolutionary rate estimates are twice to three times higher than that found for the *env* region in the cougar FIV_{Pco} strain using similar methods (Table 1) (Biek et al., 2003). A higher rate for domestic cat FIV is expected because FIV_{Fca}, is postulated to have a more recent origin than FIV_{Pco} (Carpenter et al., 1996). More recently-emerged viruses can be expected to have higher evolutionary rates than their ancestors because there has been no co-adaptation between the virus and new host species (Nelson and Holmes, 2007). Likewise, HIV-1 in humans is considered a younger virus than FIV_{Fca},, and the HIV-1 rate estimates are generally higher than that documented for FIV_{Fca}, (Table 1). However, multiple factors can affect evolutionary rate estimation, such as the evolutionary model, the gene region and the infection stage of the host (McGrath et al., 2001).

Moreover, we found evidence of positive selection in the FIV_{Fca}, *env* sequences from two of the three NZ companion cats (Hayward, 2009). These two cats suffered numerous conditions typical of FIV infection and had relatively high proviral loads. We suggest that the high level of virus circulating in these two cats caused responses by the host’s immune systems, which in turn resulted in genetic changes by the virus to evade the host immune response (Yamaguchi and Gojobori, 1997). The positively-selected sites were generally identified in variable regions

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(Hayward, 2009), possibly indicating the importance of variation in viral escape from the immune system. The third cat, with no evidence of positive selection, was the healthiest cat with the lowest proviral load and lowest average viral diversity (Hayward, 2009). This result highlights the virus-host relationship in the early stages of infection. The lack of positive selection suggests that the immune system from this third cat is not eliciting a strong response to the presence of the virus.

5. FIV$_{Fca}$, distribution in tissue compartments

Compartmentalisation is the restriction of virus movement between different tissues or cell types (Nickle et al., 2003). In HIV-1 infected individuals, it is suggested that compartmentalisation is a result of differential immune system pressures in the different tissue environments (Zhang et al., 2002; Kemal et al., 2003). The genitourinary tract, CNS, lymph node and lung have all been documented as HIV-1 compartments when compared to peripheral blood in the same individuals (Ball et al., 1994; Itescu et al., 1994; Korber et al., 1994; Byrn et al., 1997; Coombs et al., 1998). To date, an equivalent restriction of movement of FIV has not been published. Recently, we investigated the distribution of FIV$_{Fca}$, *env* sequences in multiple tissues of sixteen feral cats (Hayward and Rodrigo, in prep). In general, low intrahost diversity was found e.g. the FIV$_{Fca}$, sequences isolated from the different tissues were very similar (Hayward and Rodrigo, in prep).

This result could be due to recent infection events in the hosts, as it has been shown that HIV-1 populations are homogeneous in the initial stages of infection (Wolfs et al., 1992; Zhang et al., 1993; Zhu et al., 1993; Delwart et al., 2002). Several cats had some diversity, however, with one cat providing the first known evidence of FIV compartmentalisation, that is, the sequences grouped in their tissue types more often than expected by chance alone (Hayward and Rodrigo, in prep).

Finally, two cases of dual infection in different tissue types were identified (Hayward and Rodrigo, in prep). One cat had same-subtype dual infection in lung, liver and lymph node tissue samples (Hayward and Rodrigo, in prep). The second cat was identified with subtypes C and “unknown” FIV in the popliteal lymph node (Hayward and Rodrigo, 2008) and lung tissue samples (Hayward and Rodrigo, in prep). These findings emphasise the freedom of virus movement between the tissue types and suggest recent infection events.

Summary

Although FIV in the domestic cat was first isolated more than twenty years ago, research is still ongoing to learn more about this lentiviral relative of HIV. Comparisons to FIV in larger cats, such as the North American cougar and the African lion, help to explain disease differences from an evolutionary perspective. One of the more significant opportunities for research involves the notion that FIV has adapted to its host in those species where it persists endemically. The biological and evolutionary mechanics of host adaptation is still an open question and FIV may be an appropriate model system to study this.

As this review highlights, further research is still required, in particular, to resolve recombination patterns and novel unknown subtypes, with further testing of the currently available vaccine.

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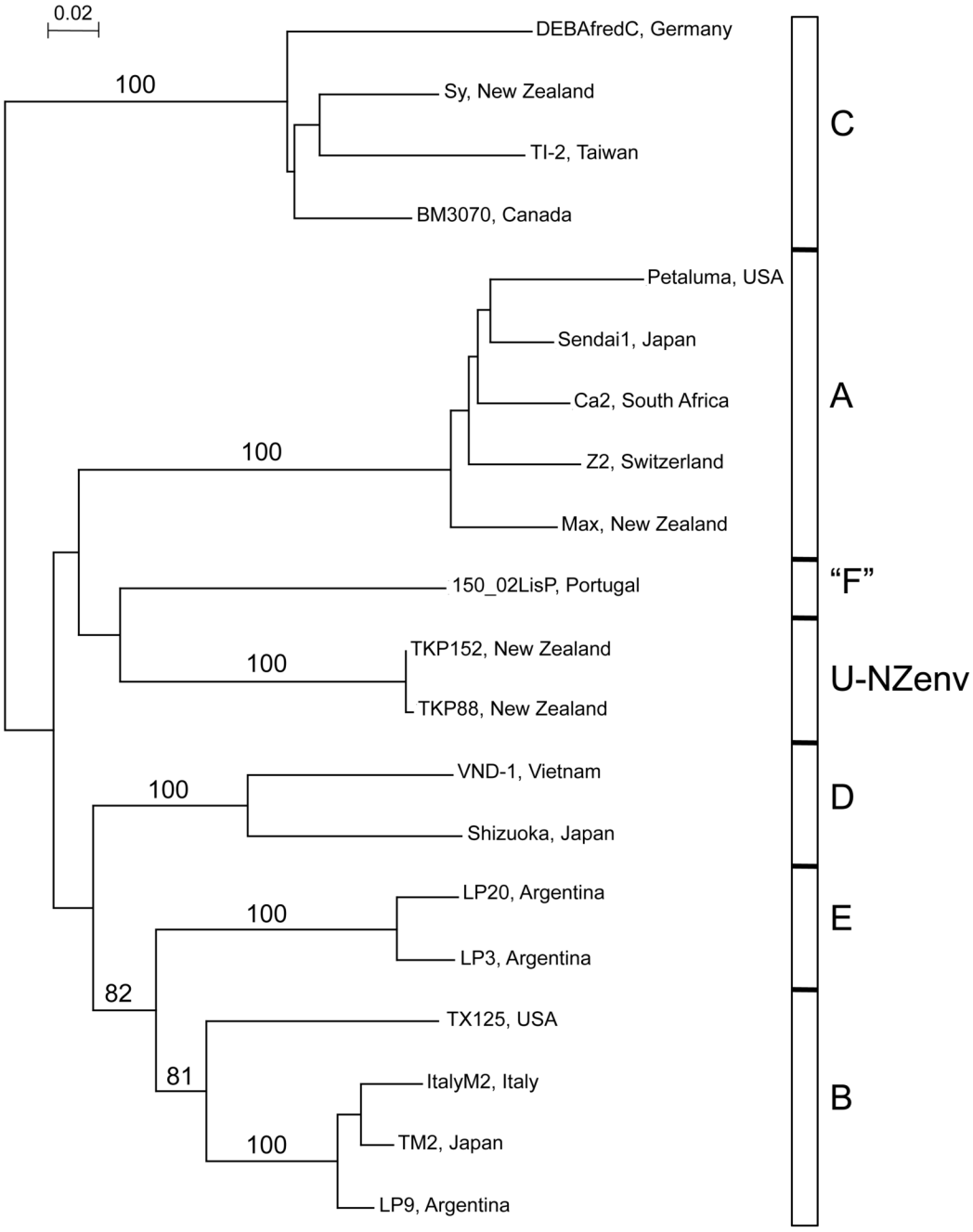

Figure 1.

Neighbour Joining phylogenetic tree of *env* V3-V5 sequences. Tree was constructed using a general time reversible model incorporating invariant sites (0.4086) and a gamma distribution of mutation rates (shape = 1.6859), as determined by Modeltest3.7 (Posada and Crandall, 1998). Numbers shown are bootstrap values, based on 1000 iterations. Subtypes A to E, "F" (Duarte and Tavares, 2006), and U-NZenv (Hayward et al., 2007; Hayward and Rodrigo 2008) are shown along the right side of the tree. Strains are DEBAfredC (U57020), Sy (GQ357641), TI-2 (AB016026), BM3070 (AF474246), Petaluma (M25381), Sendai1 (D37813), Ca2 (DQ873714), Z2 (X57001), Max (GQ357642), 150_02LisP (DQ072566), TKP152

(GQ357640), TKP88 (EF153977), VND-1 (AB083502), Shizuoka (D37811), LP20 (D84498), LP3 (D84496), TX125 (AY139094), ItalyM2 (X69501), TM2 (M59418), LP9 (D84497).

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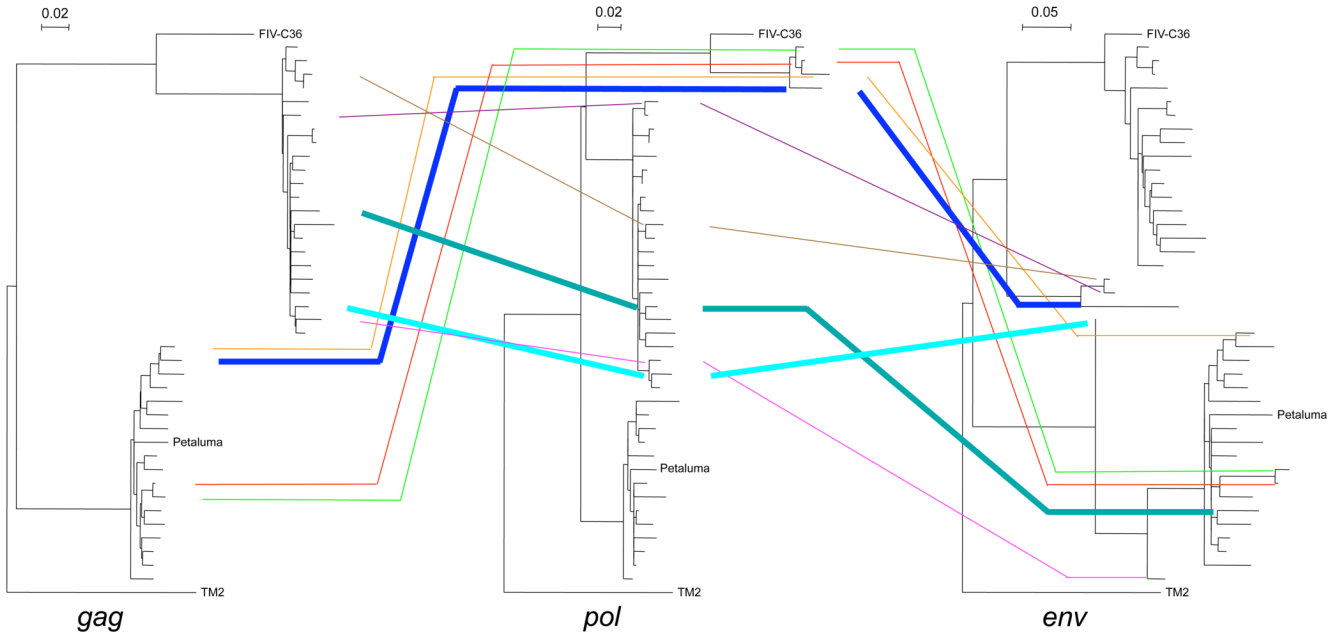

Figure 2.

Complex intergenic recombination patterns between fragments of the *env*, *gag* and *pol* genes (modified from Hayward and Rodrigo, 2008). Lines link sequences isolated from the same host, to highlight incongruities in subtype assignment between the different gene regions. The three thickened lines show the significant intergenic recombinant sequences, as determined by the SH test (Shimodaira and Hasegawa, 1999) (see Hayward and Rodrigo, 2008). Reference sequences are FIV-C36 (subtype C; AY600517), Petaluma (subtype A; M25381), TM2 (subtype B; M59418).

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Table 1

Estimates of evolutionary rates from FIV and HIV-1 studies

Lentivirus and region	Rate estimate ($\times 10^{-3}$ substitutions per site per year)	Reference
FIV-Fca V1-V2 *env*	3.4	(Greene et al., 1993)
FIV-Fca V3-V6 *env*	3.1–6.6[§]	(Hayward, 2009)
FIV-Pco V4-V5 *env*	1–3	(Biek et al., 2003)
HIV-1 gp160 *env*	2.4	(Korber et al., 2000)
HIV-1 C2-V5	10	(Shankarappa et al., 1999)
HIV-1 V3 *env*	6.7	(Leitner and Albert, 1999)
HIV-1 V3 *env*	8.7	(Zhang et al., 1997)

[§]95 % highest posterior density (HPD) for each cat is 2.2–4.1, 5.0–8.4, and 3.3–9.2