Preferential Host Switching by Primate Lentiviruses Can Account for Phylogenetic Similarity with the Primate Phylogeny

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Abstract.— Primate lentiviruses (PLV) from closely related primate species have been observed to be more closely related to each other than to PLV from more distantly related primate species. The current explanation for this observation is the codivergence hypothesis; that is, the divergence of a virus lineage results from the divergence of the host lineage. We show that, alternatively, frequent cross-species transmission of PLV, coupled with a tendency for more closely related primate species to exchange viruses "successfully," can result in apparent codivergence. This host-switching hypothesis reconciles several puzzling observations related to the evolution of PLV. [Cophylogeny; host switch; lentivirus; phylogenetic similarity.]

More and more cases in the literature of coevolution are being characterized at a phylogenetic level (Page, 2002). One of these is of particular interest to the scientific community involved with the study of the HIV/AIDS pandemic—the relationship between the primate lentiviruses (PLV) and their host phylogenies. Most importantly, the phylogenetic proximity of HIV to viruses infecting nonhuman primates (the SIVs) indicates that the emergence of HIV is the result of zoonotic events involving African primates (Hahn et al., 2000).

Here we are interested in the phylogenetic relationships between the SIV lineages. In particular, specific matches between the primate phylogeny and that of the primate lentiviruses have been cited as evidence for "host-dependent evolution," or codivergence, the divergence of a virus lineage being the result of the divergence of its host lineage (Muller et al., 1993; Jin et al., 1994; Beer et al., 1999b; Gao et al., 1999). However, this codivergence hypothesis implies that SIV has been infecting these primate species or subspecies for a considerable time, that is, since the time of the primates' common ancestor, estimated at hundreds of thousands to millions of years ago, whereas the best attempts to date PLV divergences with molecular sequence analysis techniques have yielded timings involving only hundreds to thousands of years in the past (discussed in Sharp et al., 2000). This discrepancy in timings could be the result of the current dating

techniques being grossly inaccurate, though it seems highly unlikely that using more sophisticated models of sequence evolution could reconcile the timing of virus and host divergences to such an extent.

If codivergence is insufficient to explain the similarity between the virus and host phylogenies, could any other process generate such coincidental results? We present here an alternative hypothesis of preferential host switching among primate host lineages, with host switching more likely to be successful between more closely related hosts than between more distantly related hosts. This hypothesis is used in a simulation study in which an artificial virus phylogeny is "grown" on the primate host phylogeny by a process of divergence (not *co*divergence) and host switching. We demonstrate how this simple principle can lead to artificially similar looking host and virus phylogenies, which can erroneously suggest codivergence where none occurred.

THE HOST-SWITCHING HYPOTHESIS

Successful host switching clearly has occurred frequently, given our current estimates of the primate and lentivirus phylogenies (Hahn et al., 2000). The two such events that are most supported are the transmission of HIV-1 from chimpanzees to humans (Gao et al., 1999) and of HIV-2 from sooty mangabeys to humans (Chen et al., 1997). Thus, assuming that host switching

occurs frequently between different primate species and subspecies, we postulate that much of the apparent phylogenetic agreement between primate and virus phylogenies can be accounted for by differentially successful host switching as a result of the host switching being more likely to occur between more closely related hosts than between more distant ones. We assume the latter because more closely related primate species (particularly subspecies) are more likely to share a similar niche and behavior patterns and so will come into contact if their ranges meet or overlap. In addition, for a host switch to occur, not only must interactions between primates take place that facilitate transmission, but also the lentivirus must be able to establish an infection and persist sufficiently to permit infection of other members of that newly infected population. The latter is more likely in a new host that is genetically more similar to the "usual" host. Thus, although relatively unrelated primate species may sometimes interact and transmit their PLV, "successful" host-species switching will have a tendency to occur more often between closely related primate species. We emphasize that we are not postulating that host-lineage switching between more distantly related primate species does not occur; rather, it will occur less frequently than between a closely related PLV host and potential host.

The resulting association of the virus and host phylogeny then comes about as a result of standard population genetics. For example, after a successful cross-species transmission, the transmitted virus will eventually form a monophyletic group in the new host population, whereas the original virus population will continue to gain and lose lineages according to standard processes, until all the lineages in the original host population will be descendent from just one lineage. This will be the case as long as between-species transmissions occur much less frequently than within-species transmissions. Thus, the clades of viruses in the original and new host populations will appear to be sister clades and will match the host phylogeny if the original and new host species themselves form sister clades. This outcome for the virus lineages is conceptually similar to the fate of lineages in gene genealogies when populations speciate and the gene tree reflects the species tree; it can also be thought of in terms of the fixation and loss of alleles by genetic drift, or selection, under a migration model with restricted gene flow, leading to each isolated population comprising descendants of a single ancestral lineage.

METHODS

The primate phylogeny used is shown in Figure 1 (left) along with the lentivirus phylogeny (right). Also shown in that figure are the associations of each virus strain with its host. For convenience we refer to the former phylogeny as H (host) and the latter as V_i (virus), where $i = 1 \ldots 15$ for each of the alternative virus phylogenies tested. The primate
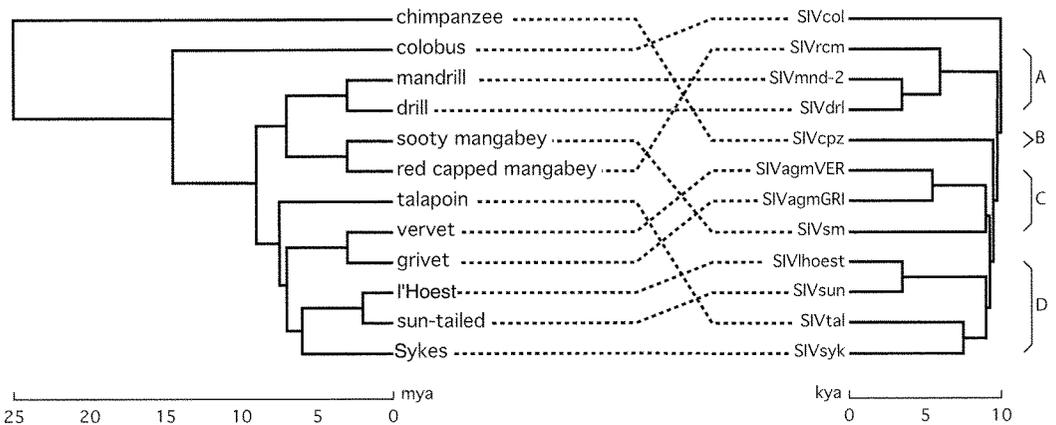

FIGURE 1. Primate/lentivirus tanglegram. Tanglegram showing the estimated primate and PLV phylogenies, and the associations between the virus and host lineages. Horizontal branch lengths correspond to time. The scale and direction of evolution is indicated by the scale bars (mya = millions of years ago, kya = thousands of years ago). Vertical branch lengths are for clarity only.

phylogeny and dates were derived from van der Kuyl et al. (1995); Disotell (1996); Goodman et al. (1998); Stewart and Disotell (1998); and Page et al. (1999). The lentivirus phylogeny was derived from Osterhaus et al. (1999); Beer et al. (2001); Courngaud et al. (2001); and Souquiere et al. (2001). Where differences in the relationships of SIVs in phylogenies have been inferred from different genomic regions (presumed to be the result of recombination between divergent SIVs), the associations postulated to correspond to codivergence events are shown. The oldest estimate to date for the most recent common ancestor of PLV is 2,500 years, based on an estimate of the date of split of HIV-1 and HIV-2 (Sharp et al., 2000). We use a value of 10,000 years as a conservative upper limit.

The HIV-1, HIV-2, SIVmac, and SIVmnd-1 strains were omitted from our analysis because they are almost certainly the result of cross-species transmission. Their inclusion would add nothing to our study because we are interested in finding out whether preferential host switching accounts for the similarity of the other PLVs with their primate hosts, excluding humans. For simplicity, only two African green monkey primate and virus lineages are included.

First we had to establish that there is indeed a significant cophylogenetic match between primate and virus phylogenies, which we achieved by using the program TREE-MAP[TM] by Charleston and Page (Page and Charleston, 2002). TREEMAP first constructs the "jungle" (Charleston, 1998; Page and Charleston, 1998) for a given tanglegram (host and associate phylogeny with known current associations). The jungle is a graph containing all the maps of the associate (here, PLV) phylogeny V_i into the host (primate) phylogeny H that may be optimal under some scheme of assigning costs to the four event types—codivergence, duplication, loss, and host switching. Codivergence occurs when both host and associate diverge into new lineages at the same time; duplication is a divergence of an associate lineage into new lineages without the host diverging; loss includes extinction, failure to codiverge ("missing the boat" [Paterson et al., 1993]), and sampling error; host switching is the successful migration of a new associate lineage onto another host lineage. The jungle may then be searched to find those maps having the least total cost, or the set of only those maps that might be optimal under some cost scheme. This is generally substantially fewer than the number of possible maps, which grows exponentially. These solutions to the phylogeny reconciliation problem can then be considered on their own merit. Perhaps the most intuitive measure of the degree of fit between host and associated phylogenies is the maximum number of codivergences that can be inferred from the trees to explain their similarity (in combination which losses, duplications, and host switches to explain their differences). This is the standard method in TREEMAP program and is the one used here.

The two optimal maps of V_1 into H had as many as 8 of a possible 11 codivergences. These two solutions are shown in Figure 2.

Significance Testing

The maximum number of codivergence events for the true phylogenies is compared with the distribution of the maximum numbers r_i of codivergence events for randomized associate phylogenies with the same associations as for the original. As the program TREEMAP is currently implemented, the significance testing is faster the more restrictive are the constraints on the maps, because the jungle is constructed only as far as is required to answer the question as to whether a solution exists within those constraints. For this reason, the significance testing related herein is more precise near the tail of the distribution: 1,000 randomized phylogenies were used to determine the proportion that would allow maps with at least eight codivergence events, but only 500 randomizations were possible in a reasonable amount of time if as few as five codivergence events were admissible.

The distribution is shown in Figure 3, with error bars of the estimated P values.

The artificial virus phylogenies were much more similar to the primate phylogeny than random trees would be. Two of them had as good a fit as the real virus phylogeny, the significance for which was itself estimated as $P = 0.002$ through randomization tests, and 23 of them were borderline at significance level $P = 0.06$.

Simulation

The basis of our simulation trial was to generate artificial virus phylogenies to undergo host switching among the tips of H.
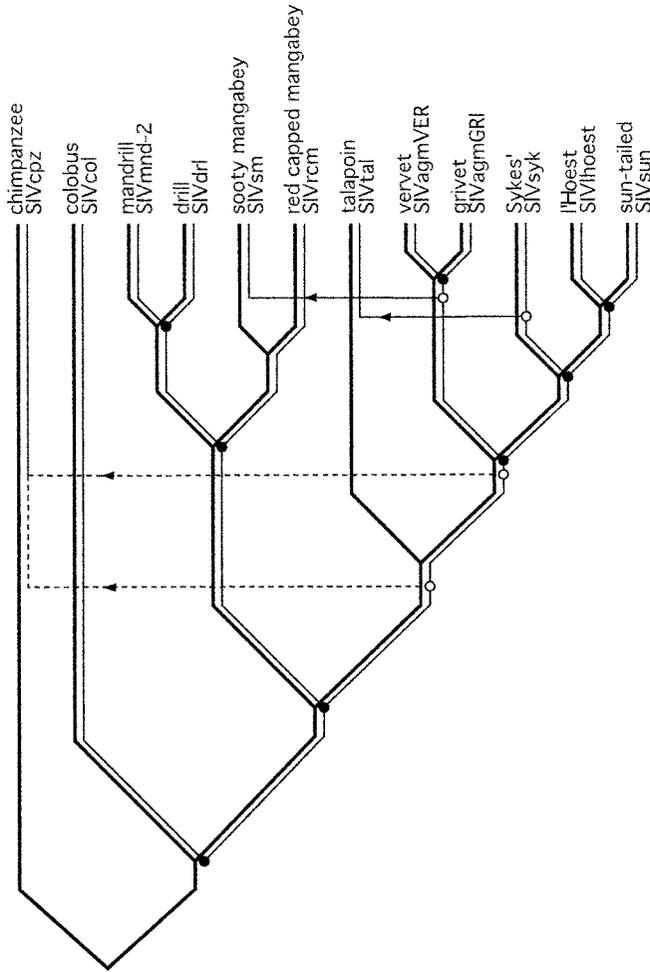
FIGURE 2.   The two codivergence-optimal maps of the lentivirus phylogeny into the primate phylogeny. The dotted lines show the two alternative locations for the earliest host switch on to the chimpanzee lineage.

The idea of the host-switching hypothesis is simply that host switching is more likely to be successful between more closely related hosts; for a simulation, however, we must choose an appropriate function for this success rate. We incorporated this hypothesis into a preferential host-switching model, which could generate artificial virus phylogenies in which only host switching and no codivergence took place. This enabled us to assess the effect of host switching only; clearly a more realistic model would have a mixture of host switching and codivergence, but that was not the aim here.

We chose an exponential function $f(d) = \exp(-3d^2)$, where d is evolutionary time (in millions of years) on V_i between take-off and landing of the virus lineage undergoing the switch. This function had the desired properties of decreasing fast enough to give a notable difference in success rates between different pairs of lineages in H, but the success rates were never so low as to be unlikely to occur at all. We could have chosen some other decreasing function, but we decided this one was the most appropriate for our purposes because it permitted enough successful host-switching events to allow the sampling strategy to yield statistically meaningful results. Moreover, in each simulation, all host switches occurred at least five times, even between the most distantly related hosts.

At the beginning of each simulation, a random leaf of the primate phylogeny was chosen as the host of the original virus
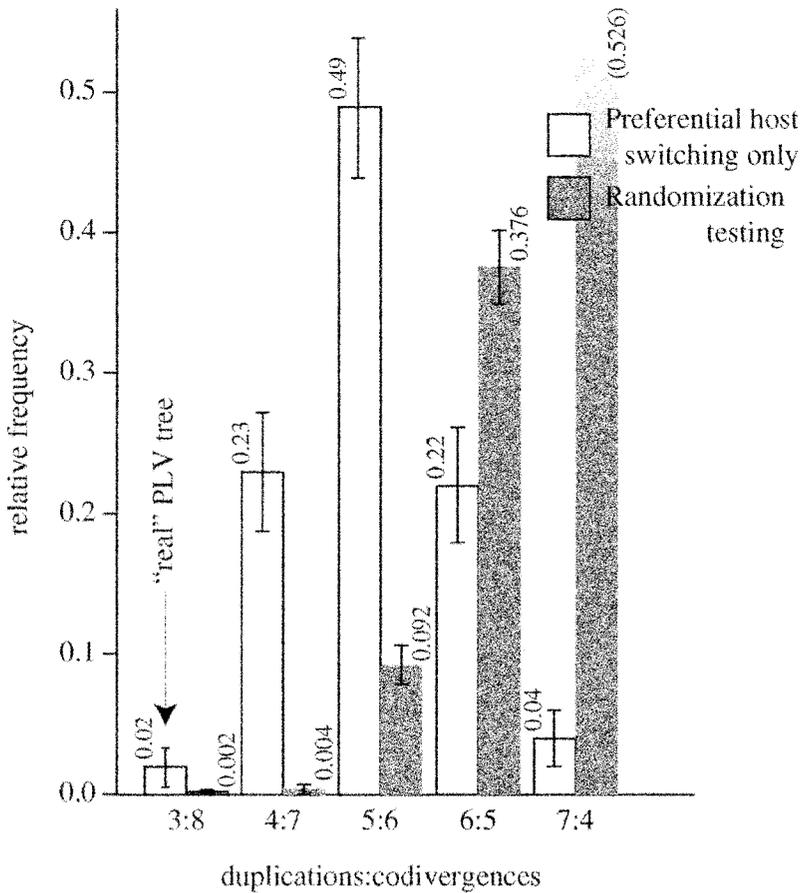
FIGURE 3.   The distribution of the maximum number of apparent codivergences that can be placed on the primate host tree for randomized parasite phylogenies (gray) and for phylogenies generated under the host-switching model (white). Error bars are calculated as ± 1 SD, based on sample size.

lineage. We set the time of this initial invasion at 10,000 years ago, to provide a long enough time for the artificial virus phylogeny to invade all the host lineages; this is a conservative upper estimate of the time of the original invasion. For the simulation, each time a new virus lineage invaded an already occupied host lineage, the original virus was ousted automatically, being replaced by the new virus lineage. This is a matter of convenience only; if we incorporated a fixed probability q for each such occurrence that the new virus outcompeted the original one, this would reduce only the success *rates* of all host switching by a constant factor, effectively multiplying our function f by q. At the extreme, where no virus can successfully invade a host that is already occupied, then

there can be only $(n - 1)$ successful duplication and host-switching events for n virus lineages, which leads to the same overall outcome.

By the end of each replicate, each host lineage was occupied by one virus lineage. The pattern of host switches completely determines the final virus tree, and it was this tree we compared with the original primate phylogeny. Those cophylogeny maps were found for these artificial virus phylogenies into the original primate phylogeny, which maximized the number of codivergence events possible. One hundred artificial virus trees were generated and analyzed in this way.

Little uncertainty characterizes the primate phylogeny, but the PLV phylogeny remains doubtful because of a lack of resolution between virus lineages near the root.

One simple way of investigating the effect of this uncertainty is to repeat our tests of the significance of fit of the phylogenies by using different PLV trees. We can accommodate some of the uncertainty in the PLV phylogeny by testing several alternative PLV trees, according to the arrangement of the four clades labeled A–D in Figure 1, while retaining the position of the outgroup SIVcol. This allows 15 alternative PLV phylogenies ($V_1 \ldots V_{15}$), each of which we tested to find a map that maximized the number of codivergence events.

RESULTS

Our results come in two parts. The first pertains to the assessment of whether the primate and lentivirus trees are significantly similar, that is, whether they do indeed appear to be coevolving at the phylogenetic level. The second then addresses whether virus trees simulated under a model of preferential host switching have a greater degree of similarity than do completely random trees, and whether such a process could account for some of the observed similarity in real life.

The jungles for the primate and alternative lentivirus phylogenies yielded various sets of potentially optimal solutions of the phylogeny reconciliation problem, which had as many as 8 codivergences events of a possible 11 events for perfectly matched trees (Figure 2). Of the 15 resolutions, 10 permitted 8 codivergences, and 5 permitted 7 codivergences when mapping them into the primate tree. These are significant at $P = 0.015$ (± 0.004) and $P = 0.104$ (± 0.010), respectively, under the standard randomization test in which the associate tree is randomized and using 1,000 replicates for each estimate.

The phylogenies generated under the preferential host-switching model show a much greater degree of similarity with the primate phylogeny than would be expected by chance: 2 of the 100 permitted at least 8 codivergence events, a further 23 permitted at least 7, and a further 49 permitted at least 6 codivergences. These are shown in Figure 3.

DISCUSSION

The PLV and primate phylogenies do indeed show a very high degree of cophylogenetic match, which could be accounted for by a significantly high number of codivergence events between the two groups. However, the difference in best estimates of the evolutionary rates between them is so large (Sharp et al., 2000) that other explanations as to the cause of this similarity must be sought. Thus, we simulated virus trees to determine whether preferential host switching could account for at least some of the similarity between the primate and virus phylogenies. Because of the uncertainty in the PLV tree, we tested 15 resolutions of it, all of which showed significant similarity with the primate tree under the normal randomization test. This adds support to the ability of our preferential host-switching hypothesis to account for at least a large portion of the similarity between the primate and PLV trees, because all the apparent codivergences occur near the tips of the primate tree, that is, in the more recent past. If the arrangement of the clades A–D (Fig. 1) made a great difference in the maximum permitted number of codivergences, then we would have to infer some apparent codivergence events further back in the primate tree, which have not been observed.

The simulation tests show that a large number of the artificial virus phylogenies—which were generated with no codivergence at all—showed a significant apparent cophylogenetic match, which could give the impression of significantly high rates of codivergence between primates and lentiviruses. Thus, the preferential host-switching hypothesis provides a plausible explanation for the similarity without needing to stretch to the breaking point any estimates of evolutionary rate.

A potential counter for an exclusive host-switching scenario for all currently postulated instances of codivergence is the geographic isolation of host species, which physically prevents cross-species transmission. Specifically, l'Hoest and solatus monkey populations are separated geographically, making it plausible that codivergence rather than host switching is the best explanation for the match between these virus and host lineages (Beer et al., 1999a). However, SIVlhoest and SIVsun together form a sister clade to SIVmnd-1 from the mandrill, a more distantly related primate species, raising the possibility that cross-species transmission of SIV from a third unknown monkey species has occurred in this case.

Also, several well-documented examples support cross-species transmission involving distantly related primate species: (1) SIV of the type infecting vervet monkeys (SIVagmVER) has been found both in yellow (Jin et al., 1994) and in chacma (van Rensburg et al., 1998) baboons, and (2) SIVsm, a virus infecting sooty mangabeys, a distantly related monkey species to humans, infects humans in West Africa (Hirsch et al., 1989; Gao et al., 1992). Such transmissions between quite distantly related primates may seem to violate our assumption that more closely related species tend to transmit viruses to each other. However, we reiterate that the host-switching hypothesis does not preclude the occurrence of virus transmission between distantly related hosts; rather, it assumes that such cross-species transmission events will be successful less frequently. One should also remember that baboons and humans hunt other primates, thereby increasing their chances of coming into direct contact with blood infected with SIV. Importantly, there is no evidence that these transmissions to baboons are anything other than incidental infections; that is, the baboon SIVs do not appear to be circulating in their respective populations. Other examples of transmission between distantly related primate species have occurred in captivity; for example, a white-crowned mangabey was found to be infected with SIVagmVER-like virus (Tomonaga et al., 1993). Such transmissions are presumably a direct result of their close proximity in captivity, which permits more frequent opportunities for virus transmission.

In conclusion, given the host-switching model, the apparent codivergence of certain PLV and their host lineages can be explained by cross-species transmission between closely related primates, rather than codivergence. The preferential host-switching hypothesis is a general trend rather than an absolute principle; thus, by predicting that successful host switching is more likely to occur between more closely related hosts, we expect in general that the virus phylogeny will tend to appear more like the host phylogeny than we would expect by chance. This does not, however, preclude the occurrence of genuine codivergence. Codivergence may indeed be occurring, but its imprint on the virus phylogeny has been lost because of subsequent host-switching.

There may well be other cases of host/parasite coevolution in which this phenomenon occurs. We are not suggesting that preferential host switching accounts for all instances of observed similarity, but it could account for many cases where otherwise codivergence might be inferred. This kind of effect, therefore, must be incorporated into realistic models used in reconstructing ancient associations of host and parasite.

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