Poster presentation

Open Access Do humans have replication-competent endogenous retroviruses? Robert Belshaw^{*1} and Michael Tristem²

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Endogenous retroviruses (ERVs) are typically defined as retroviruses that have integrated into the germline of their vertebrate hosts and are then passed vertically from parent to offspring. The human genome sequence contains approximately 100,000 ERV loci, but none are active (replication-competent), typically as the result of mutations introduced during replication of the host genome.

The only ERV lineage that has been replicating in humans since the human-chimp divergence is the HERV-K(HML2) family. Some of its loci are unfixed in the human population, have intact ORFs, and little or no sequence divergence between their flanking LTRs (which are identical at integration) [1]. This family also has the strongest link to disease, including having an accessory gene which causes cancers when injected into immunocompromised mice [2]. Two groups have used 'fossil' HERV-K(HML2) sequences to reconstruct active viruses [3,4], and we believe that the likelihood that the family causes disease depends on whether or not it is still active today.

No active HERV-K(HML2) loci have been found, but this does not mean that the family has itself ceased replicating. The human genome sequence contains only ERV loci which have drifted to, or near, fixation, and such loci will by definition be old and thus likely to have accrued inactivating mutations. By contrast, active ERVs, if they exist, will be at low allele frequencies (Figure 1).

We have already shown that the proportion of unfixed loci in a small sample of human individuals is consistent with the family being active today [5], and - thanks to a recent Wellcome Trust grant - are currently investigating a much larger sample size, which should give us the statistical power to determine whether or not this family is still replicationally active today. We also hope to find intact loci, which we will investigate experimentally for infectivity.

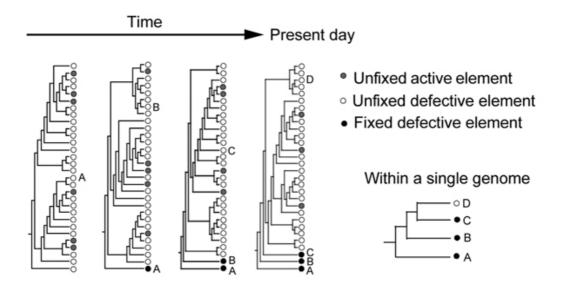


Figure I

Conceptual model of ERV evolution. Circles represent individual ERV loci and the tree their genealogical relationships. Newly integrated, active loci will be present initially only in single host individuals and must eventually be inactivated (and rendered neutral if originally harmful) by mutations acquired during host replication. A small proportion of these loci (= $1/2N_e$ where N_e is the long-term effective population size) will eventually drift to fixation in the host population and thus appear in any published genome sequence. If active ERV loci are harmful, they will be found at even lower frequencies (until inactivated or lost due to negative selection).

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