# The HTLV-1c genomic graveyard reveals host-virus interactions

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**Abstract**

Retroviruses infect a range of vertebrate hosts. Upon infection, the viral genome is reverse transcribed and integrated into the host genome. The integrated provirus and host genome are enmeshed and have an ongoing reciprocal influence on one another, impacting both host and viral fitness. The integrated provirus thus has the potential to archive host-virus interactions.

Human T-cell leukemia virus 1 (HTLV-1) is a pathogenic retrovirus, which upon infection integrates its 9kb genome into the human genome. ~10-20 million people carry HTLV-1 worldwide. Central Australia has the highest rate of HTLV-1 infection globally, with a prevalence of ~40% reported in some remote Communities. HTLV-1c is the highly divergent molecular variant of HTLV-1 found in Australia.

HTLV-1 integration into the human genome has profound consequences on its target cell. However, the consequence of integration on HTLV-1 fitness is poorly understood. To characterise the genomic interface of human-HTLV-1c interactions, we have performed end-to-end sequencing of $> 400$ individual HTLV-1c genomes using the Oxford Nanopore platform. Samples were obtained from patients with bronchiectasis (n=3), asymptomatic carriers (n=3), and humanised mice in the late stage of HTLV-1c infection (n=2).

The HTLV-1c landscape is overwhelmingly dominated by defective clones. HTLV-1c provirus is highly enriched in CCR4+ cells, which contain $> 90\%$ defective provirus. Most defects disrupt the canonical retroviral genes, consistent with clonal expansion seen in disease. Unexpectedly, a large subset of proviral integrants contain internal human genomic sequences, including exons and repetitive elements, potentially placing these sequences under the control of strong LTR promoters. Breakpoint analyses revealed that in-del junctions have homology to the HTLV-1c LTR, suggesting a recombination-based mechanism of deletion. CCR4+CD4+ T-cells are thought to drive HTLV-1 associated disease. We found CCR4-CD4+ T-cells enriched for full-length HTLV-1c provirus, raising the possibility that CCR4-CD4+ T-cells could provide a reservoir of full-length, replication-competent provirus.

**Keywords:** bronchiectasis, infectious mobile DNA, retrovirus

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