Structural Deletions in HTLV-1 Proviruses Correlate with Disease Severity in Adult T-cell Leukemia

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Mikel Blanco-Otaegui[1], Rafael Muñoz[1], Ariadna Rando[2], Diego Ortega[3], Paloma Liendo[4], Mª José Pena[5], Andrea Huertas[1], Alejandro Muñoz[1], José Manuel Ramos[6], Vicente Soriano[7] & Carmen de Mendoza[1] on behalf of HTLV Spanish Study Group

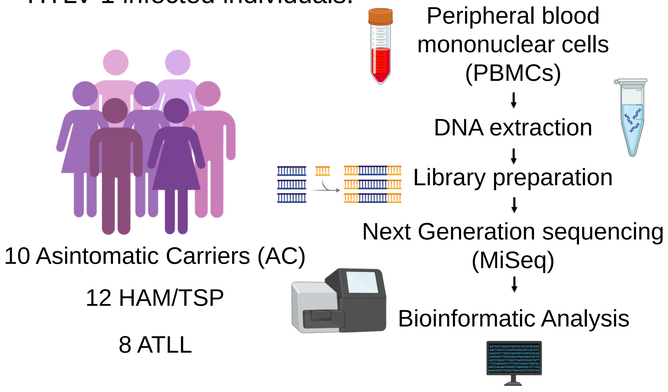
[1]Puerta de Hierro University Hospital & Research Institute, Madrid, Spain, [2]Hospital Universitario Vall d' Hebrón, Barcelona, Spain, [3]Hospital Universitario Miguel Servet, Zaragoza, Spain, [4]Hospital Universitario de Basurto, Bilbao, Spain, [5]Hopital Universitario Dr. Negrín, Gran Canaria, Spain, [6]Hospital Universitario Dr. Blamis, Alicante, Spain, [7]UNIR Health Sciences School, Madrid, Spain.

BACKGROUND

HTLV-1 is a neglected retrovirus associated with severe neurological and lymphoproliferative disorders, including tropical spastic paraparesis/HTLV-1–associated myelopathy (HAM/TSP) and adult T-cell leukemia/lymphoma (ATLL). Although Spain is considered a non-endemic country, more than 550 individuals with HTLV-1 infection have been reported to date. A national HTLV-1 registry has been in place since 1989. Most diagnosed cases correspond to migrants originating from endemic areas in Latin America and Equatorial Africa. Diagnostic delay remains substantial, as reflected by the high proportion of patients (22%) who are already symptomatic at the time of diagnosis. Virological determinants of HTLV-1 disease progression, however, remain poorly understood.

METHODS

Peripheral Blood Mononuclear Cells (PBMCs) from 30 HTLV-1 infected individuals.



Proviral DNA was sequenced using Next Generation Sequencing (NGS) with 149 biotinylated probes and 1 million reads per sample (Katsuya et al., 2019). Demographic and clinical data including disease status, proviral load (measured by ddPCR and reports as "%"), and treatment history were examined along with proviral genomic structure.

Defective HTLV-1 proviruses are significantly **more prevalent in patients with Adult T-cell Leukemia** and may play a role in **oncogenesis** and **immune escape**

RESULTS

HTLV-1 cohort	
No. Individuals	30
Gender	
Male	10 (30%)
Female	22 (70%)
Median age, years (range)	54 (26-80)
Origin	
Latin America	28 (93%)
Spain	1
Africa (Ivory Coast)	1

6 out of 30 patients have large deletions and all of them are ATLL

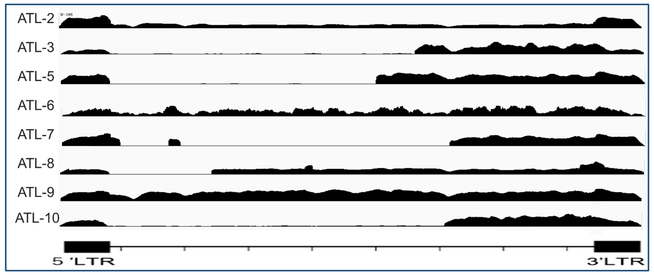


Figure 1: HTLV-1 genome coverage profile of ATLL patients

- Post-treatment analysis of two patients revealed partial restoration of deleted proviral regions from 4.2% to 62.1% in one and from 0.2% to 14.5% in another.

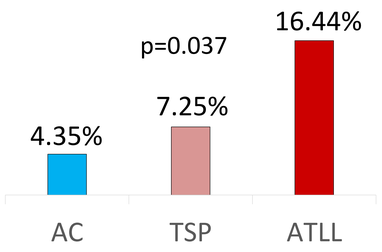


Figure 2: Median HTLV-1 Proviral Load by clinical status

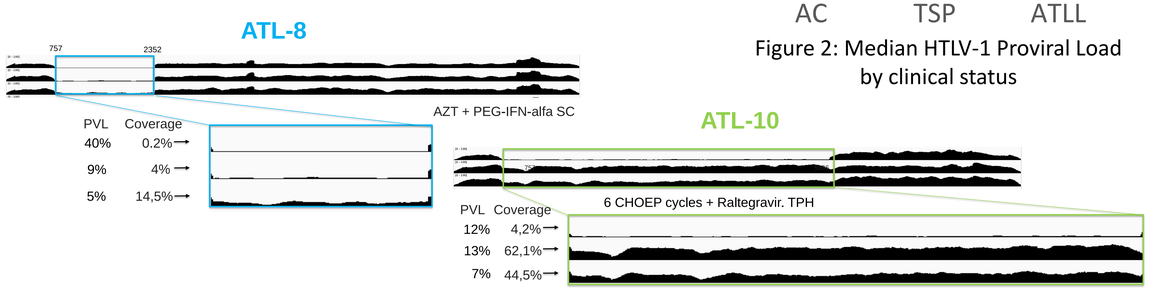


Figure 3: Longitudinal HTLV-1 genome coverage in two ATLL patients across three sequential post-treatment samples

CONCLUSIONS

- Defective proviruses were identified in most patients with ATLL. Five patients showed a Type I deletion (loss of gag, pol, and env) and one Type II.
- The recovery of coverage in two patients with deleted regions after chemotherapy suggests a dynamic proviral landscape, with treatment-driven shifts in dominant cellular clones.
- Type I deletions may contribute to oncogenesis and immune evasion. The dynamic nature of proviral structure following treatment highlights the importance of longitudinal genomic sequence monitoring in HTLV-1-infected individuals.

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Author Contact Information: mbotaegui@idiphim.org

PLAIN LANGUAGE SUMMARY

Our study found that many people with HTLV-1–related leukemia carry damaged or incomplete versions of the virus within their cells. We also observed that these viral fragments can change after treatment. These findings suggest that tracking how the virus evolves over time may be important for improving patient monitoring and care.