Review Article

Adult T-cell leukemia/lymphoma—pathobiology and implications for modern clinical management

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Abstract: Adult T-cell leukemia/lymphoma (ATL) is a highly aggressive malignancy that arises in 2-5% of carriers of human T-cell lymphotropic virus type 1 (HTLV-1). The median overall survival of acute and lymphoma subtypes remains approximately 9–13 months and depressingly, with chemotherapy based approaches survival is largely unchanged in the ~40 years since it was first described. There is a clear and urgent need to conduct clinical trials of novel therapies in this disease. A high proviral load (PVL) (>4%, percentage of HTLV-1 infected mononuclear cells), male gender and smoking were previously the only major known risk factors for developing ATL, and so it has been difficult to advise patients about their individual risk of future ATL. Here, we describe the recent evidence that malignant disease does not occur randomly amongst all asymptomatic carriers but is more likely to arise in a subset of high PVL individuals with abnormally abundant clonal expansions of circulating HTLV-1 infected T-cells which typically express CD3dim+ CD4+ CD5-CD7- CD25+ CCR4+ with monoclonal TCRVβ. These clones also typically harbour known ATL driver mutations such as *PLCG1*, *PRKCB*, *CARD11*, *STAT3*, *VAV1*, *NOTCH1*, *IRF4*, *CCR4*, *CCR7*, *TP53* and *CDKN2*, and may be detectable 10 years prior to disease presentation providing an opportunity to identify at risk individuals prior to clinical ATL. We describe the current classification and clinical features of ATL, and the exciting work of the last few years that underpins our new understanding of the genetic and epigenetic landscape with implications for future therapy. Whilst current therapy for aggressive ATL remain largely ineffective, recent advances may allow for early identification of at-risk individuals, and for pre-emptive therapies, and hope for a new era of effective targeted biological agents.

Keywords: Human T-cell lymphotropic virus type 1 (HTLV-1); adult T-cell leukemia/lymphoma (ATL); clonality; provirus

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Introduction

Adult T-cell leukemia/lymphoma (ATL) is an aggressive CD4+ T-cell malignancy that arises in 2–5% of individuals chronically infected with human T-cell lymphotropic virus type 1 (HTLV-1). ATL presents with diverse clinical features, including circulating leukemic cells, generalized lymph node swelling, hepatosplenomegaly, skin involvement, opportunistic infections, and hypercalcemia and has a poor prognosis, with shorter overall survival relative to other peripheral T-cell lymphomas. Although progress has been made in understanding the biology that underpins ATL, treatment remains unsatisfactory, particularly for those with primary refractory or relapsed

refractory disease.

Which HTLV-1 carriers develop ATL?

Chronic infection with the deltaretrovirus HTLV-1 is the only cause of ATL, which arises decades after infection, arising most commonly in carriers infected during infancy through breastfeeding. The lifetime risk of ATL among HTLV-1 carriers has been estimated to be ~2.5–6% in several endemic areas of Japan (1-3). Globally, there are an estimated 5–10 million people infected with HTLV-1, although this is likely to be a conservative estimate since it is based on epidemiological studies in countries that screen blood donors, which are often low prevalence nations (4). Although it is a blood borne virus, in the UK there is no systematic screening for HTLV-1 infection in antenatal or genitourinary clinics, but testing is undertaken in first-time blood donors, and donors and recipients of stem cell or solid organ transplants.

HTLV-1 is endemic in Japan, the Caribbean, Central and South America, parts of sub-Saharan Africa, Middle East, Melanesia, central Australia and Romania. In the USA and Europe, most prevalent in immigrants from endemic regions and their descendants. The geographic presentation of ATL corresponds with the known epidemiology of HTLV-1. For example, ATL accounts for approximately 25% of peripheral T-cell lymphomas in Asia (primarily Japan), compared with 2% in North America and 1% in Europe (5). The age at onset varies by region. The median age at presentation in Caribbean and South America is 40–50 years. By contrast, in Japan the median age at presentation has been recently reported at 67.5 years which has risen from 56.9 years in 1984–1985, and 58.9 years in 1992–1993 (6). This progressive rise in the age at presentation suggests a cohort effect, i.e., a cohort of the population in Japan that developed a high prevalence of HTLV-1 infection in the 1920s and 1930s. In Japan ATL occurs more frequently in men, although the sex ratio is falling (6), and this male predominance is not observed in Jamaica (7). By contrast a study from Brooklyn, USA suggested a clear female predominance (8).

HTLV-1 infection alone is not sufficient to drive the development of ATL, and the majority of carriers will remain asymptomatic for life. Reported risk factors include ageing (9), a family history of ATL or HTLV-1 associated myelopathy (HAM) (9), an immunocompromised clinical status, and a proviral load (PVL) >4% [PVL, proportion of infected peripheral blood mononuclear cells (PBMCs)]. A higher PVL is an independent risk factor for ATL, even after adjusting for sex, age, and family history (10), and the risk of ATL is carried amongst high load carriers whose individual lifetime risk is >20% (11,12).

Diagnosis & prognosis

Diagnosis of ATL is determined by the combination of clinical presentation (typically leukocytosis, lymphadenopathy, hypercalcaemia, lytic bone lesions, skin lesions, raised LDH, often with opportunistic infections), a characteristic blood film morphology, and immunophenotyping of blood or tissue biopsy. The malignant T-cells typically demonstrate polylobated nuclei ("flower cells") with condensed chromatin, and agranular cytoplasm and express CD3dim+ CD4+ CD5- CD7- CD25+ CCR4+ and a monoclonal TCRVβ. Some cases may be CD8+ CD4-, CD4+CD8+, or CD8- CD4-. The criteria for ATL diagnosis and subtype classification remain as defined by Shimoyama *et al.* (13,14) (summarised in *Table 1*). Several factors that predict poor prognosis include a poor performance status, elevated LDH level, hypercalcaemia, nodal sites >4, age >40 years, thrombocytopenia, eosinophilia, bone marrow involvement, high serum level of interleukin 5, C-C chemokine receptor 4 expression (CCR4), lung resistance-related protein, p53 mutation, and p16 deletion (14), and there is evidence of a higher frequency of these poor prognostic risk factors among Caribbean patients than in those from Japan (15). Depressingly, the median overall survival of ATL in Japanese patients treated with chemotherapy has been largely unchanged in the nearly 40 years since the syndrome was first described (13,16). Risk models that have incorporated combinations of these prognostic risk factors have been developed, and these models may in future guide chemotherapy or targeted agent treatment selection (17,18). Currently the median survival of those with acute or lymphoma ATL remains 9–13 months, and those with chronic or smouldering ATL 2–4 years (16). Death frequently occurs from treatment-refractory disease, transformation from indolent to aggressive subtypes, or opportunistic infection.

Treatment strategies for ATL are based primarily on the disease subtype. Current frontline treatment options for ATL vary by geographic location and include active monitoring (in Japan for indolent subtypes), zidovudine plus interferon-alfa (ZDV/IFN) where available, multiagent chemotherapy, and for a subset of suitable patients

Table 1 Diagnosis of ATL subtypes (Shimoyama)

Subtype	Asymptomatic HTLV- 1 carrier	Smouldering	Chronic	Acute	Lymphoma
HTLV-1 serology	+	+	+	+	+
Monoclonal integration of provirus	–	+	+	+	+ (lymph node)
Lymphocyte count	Normal	Normal	Elevated	Elevated	Normal
Percentage circulating abnormal lymphocytes	<5%	≥5% Or <5% if ATL skin & lung lesions present	≥5%	≥5%	≤1%
Hypercalcaemia	–	–	–	Normal or high	Normal or high
LDH	Normal	Normal or ≤1.5 ULN	Normal or <2 ULN	Normal or high	Normal or high
Lymphadenopathy	–	–	+/–	+/–	+
Skin or lung involvement	–	+/–	+/–	+/–	+/–
Bone marrow or splenic involvement	–	–	+/–	+/–	+/–
Bone, gastrointestinal or central nervous system involvement	–	–	–	+/–	+/–

ATL, adult T-cell leukemia/lymphoma; ULN, upper limit of normal.

allogeneic hematopoietic stem cell transplantation. Novel agents with approvals in Japan include mogamulizumab (a monoclonal antibody against the chemokine receptor CCR4) and lenalidomide. Current treatment strategies are reviewed elsewhere (19,20).

Viral determinants in the development ATL

HTLV-1-infected T-cell clones appear to persist indefinitely during chronic infection. The clones replicate more frequently than uninfected T-cells (21) and as a consequence replicative errors are likely to make a significant contribution to genomic instability and cellular transformation. Like other retroviruses the integrated HTLV-1 proviral genome consists of two long terminal repeats, structural and regulatory genes and an additional sequence designated pX, which encodes proteins including two crucial proteins that regulate the persistence, expression and pathogenesis of HTLV-1: Tax and HBZ (HTLV-1 B-zip protein). Tax is a transcriptional transactivator protein which, in addition to driving replication of HTLV-1, strongly activates cellular gene expression in pathways involved in the proliferation of T-lymphocytes, mainly via the activation of NF-κB and AP-1 pathways. Tax-expressing cells may bypass normal cell-cycle checkpoints and affect DNA damage and apoptosis pathways, resulting in the accumulation of genetic, epigenetic and RNA modifications. Tax-transgenic mice develop tumours including T-cell lymphoma, and so Tax has been considered to be a critical viral factor involved in the immortalization and transformation of infected cells. HBZ messenger RNA was also shown to also promote proliferation of ATL cells and has a variety of functions, including modulation of Tax expression. HBZ also drives cell proliferation, increases hTERT transcription, inhibits apoptosis and interferes with micro RNAs and HBZ transgenic mice also develop T-cell lymphomas as well as systemic inflammation (reviewed (22-24). However, neither *tax* nor *HBZ* should be considered as oncogenes, such as those of acutely transforming retroviruses e.g., Rous sarcoma virus containing viral-*src*, but that oncogenesis is an indirect, and fortunately, uncommon consequence of the persistent replication of HTLV-1 infected cells, which in turn depend upon the cooperative expression and actions of these two genes.

Expression of the HTLV-1 proteins in turn exposes infected cells to virus-specific cytotoxic T-lymphocytes (CTL), and the efficiency or 'quality' of the CTL response is a key determinant in the host PVL, and the likely clinical outcome of infection (25). The key factor that determines a high quality anti-HTLV-1 CTL response are the host genotype in the HLA Class 1 and killer immunoglobulin-like receptor (KIR) loci, and the

ability to present epitopes from the HBZ antigen to CTLs (22,25). Thus, virus-infected CD4+ T cell clones continue to proliferate over decades of infection, with selection of clones carrying mutations that promote T-lymphocyte proliferation and survival, and those whose pattern of intermittent HTLV-1 reactivation minimizes their exposure to the CTL response. CTL escape is evident in ATL: immunodominant viral epitopes and host genes (e.g., *HLA-A* and *HLA-B*) involved in antigen presentation are frequently silenced and/or deleted, and genes implicated in reduced immune surveillance (PD-L1) are overexpressed (26-28).

The role of the stromal microenvironment—particularly fibroblasts—on immortalisation, tumour induction and propagation has been extensively reported in epithelial cancers, but is less well understood in HTLV-1 infection and ATL. There are three main reasons for this. First, *ex vivo* culture rapidly alters HTLV-1 expression, stimulating a burst of transcription of the proviral plus strand. Second, there is a lack of robust animal models of HTLV-1 transformation. Third, HTLV-1 infection typically remains clinically latent for decades before the presentation of ATL. There have been reports that co-culture of murine marrow stromal cells with either *ex vivo* ATL cells, HTLV-1-infected cells or ATL cell lines, can support the growth of primary cells and cell lines (29); however, HTLV-1 does not infect mouse cells, and the physiological significance of these findings is unclear. ATL cell lines and primary cells, co-cultured with epithelial like cells were found to be protected from apoptosis, became quiescent and acquired a cancer stem cell-like phenotype (30). Finally, stromal cells may suppress viral expression via type 1 interferons (31).

Epigenetic modifications in ATL cells may promote both cell survival and chemotherapy resistance. The genome of the ATL clone frequently has extensive CpG island DNA hypermethylation with associated transcriptional silencing. Approximately 40% of ATL samples were associated with a CpG island methylator phenotype (CIMP) and the CIMP status was associated with aggressive clinical ATL phenotypes. However, ATL was not associated with mutations in known epigenetic regulators in other cancers (*TET2*, *IDH2* and *DNMT3A*). HLA class 1 genes were also either silenced by hypermethylation or lost in many cases of ATL, contributing to immune evasion by ATL cells (26,32). Although abnormalities in histone acetylation have not been well described in ATL, histone deacetylase inhibitors can induce apoptosis and inhibit NF-κB expression in HTLV-1 and ATL cell-lines (33,34). Clinical trials of HDAC inhibitors in T-cell malignancies are ongoing, but future studies to understand the mechanism and efficacy in HTLV-1 and ATL are required. A recent comprehensive study of the polycomb-dependent epigenetic and transcriptomic landscape of ATL cells revealed genome-wide deposition of H3K27me3, the characteristic mark of polycomb repressive complex 2 (PRC2) (35). H3K27me3 was abnormally increased in over half the genes (53.8%) with consequent downregulation of key gene expression (*miR-31*, *BCL2*, *EVC1/2*, *CDKN1A* and *NDRG2*) associated with disease progression from indolent to aggressive ATL. An international clinical trial of an oral dual inhibitor of EZH1/2 is underway (clinical trials ID NCT04102150).

Clonality in HTLV-1

A typical healthy carrier with HTLV-1 infection carries tens of thousands of infected T-cell clones, usually with one copy of HTLV-1 integrated in each genome, which can be distinguished by a unique viral integration site (36). Integration occurs throughout the human genome: it is not random but is biased toward transcriptionally active regions and near certain transcription factor binding sites, including those for STAT1, TP53 and HDAC6 (37). Using high throughput sequencing, within an individual, ATL cells are typically characterised by a single dominant integration site (91% cases), and in ~10% of ATL cases, the malignant clone contains two or more copies (38), which is consistent with earlier reports using Southern blot methods (39,40). Integration sites were originally mapped and enumerated by Southern blot analysis, but more recently high-throughput sequencing methods have led to significantly increased estimates of clone frequency and abundance of non-malignant clones (41-43). In ATL cells, there are no hot-spots of integration in the host genome. Integration within 10 kb of a known oncogene confers a survival advantage in vivo, but this does not appear to contribute directly to leukaemogenesis (38). However, integration within 15 kb upstream of host genes that are frequently dysregulated in other leukemias occurs more frequently than expected by chance (accounting for ~6% cases of ATL) (38) and that integration in the vicinity of cancer drivers may be affected either by provirus-dependent transcription termination or as a result of viral antisense RNA-dependent cis-pertubation (44). More recently it was shown that the HTLV-1 provirus has the ability to alter the host chromatin structure and disrupt host gene regulation: CTCF, a master regulator of chromatin structure and gene expression,

binds to HTLV-1, forms loops between the provirus and host genome, and alters the expression of proviral and host genes (45).

During chronic infection, low-abundance HTLV-1 infected clones make up most of the HTLV-1 PVL. The PVL determines both the risk of ATL and the risk of associated inflammatory diseases, and the PVL correlates with the total number of clones within in an individual and not the degree of oligoclonal proliferation (42). However, when one or more clones have started to undergo malignant transformation, they constitute a disproportionately high fraction of the PVL, even before clinical presentation. In an observational follow up study of HTLV-1 carriers with 'monoclonal' populations of HTLV-1 infected cells in the peripheral blood (detected by low resolution, semi quantitative Southern blot), 42% developed ATL in a 20-year period (48 cases/1,000 carrier years). This disproportionate clonal proliferation can now be rigorously quantified by the oligoclonality index (OCI); *Figure 1*]. The OCI score, derived from the Gini index, was initially applied to precise integration site mapping and clonal abundance following linker mediated PCR and high throughput sequencing. However since this method is technically and bioinfomatically demanding, we developed a flow cytometric assay to estimate the OCI—the 'OCI-flow'—by quantifying TCRVβ usage in the HTLV-1-infected CADM1+CCR4+CD26- T cells; this method can more easily be applied in diagnostic laboratories (46). An OCI-flow of zero indicates that all TCRVβ subunits have the same frequency in the studied cellular population (i.e., polyclonality), and an OCI-flow of one indicates that only a single clonal population is present (monoclonal), with all cells expressing one TCRVβ subunit. We have recently reported that 19 % of high PVL carriers (>4 copies of the HTLV-1 provirus per 100 PBMCs) have PBMCs with oligoclonality scores in the ATL range (OCI-flow >0.770) (47). In samples from these carriers, ATL-like clonal expansions comprised >2% of $CD3^+$ T cells. Two of the asymptomatic carriers with ATL-like clones have since transformed to aggressive ATL, and others had a first-degree relative with ATL (a known risk factor for ATL). These data strongly suggest that these 'ATL-like' clones represent premalignant lesions, although full transformation of expanded clones likely requires additional genetic events.

Somatic evolution in ATL

A landmark report from Japan in 2015 described the genomic landscape of ATL and showed a high frequency of specific gain-of-function mutations in ATL, particularly in genes involved in the T-cell receptor and NF-κB signalling pathways, T cell trafficking and immunosurveillance. Frequently mutated genes include *PLCG1*, *PRKCB*, *CARD11*, *STAT3*, *VAV1*, *NOTCH1*, *IRF4*, *CCR4*, *CCR7*, *TP53* and *CDKN2A* (26). These variants were designated potential ATL driver mutations and have since also been observed in an independent cohort of patients with ATL of Afro-Caribbean descent (48).

We hypothesised that ATL-driver mutations are acquired in a stepwise process, and some will be present in the circulation before the diagnosis of ATL. In a cohort of asymptomatic carriers who later developed ATL, we recently reported that mutations accumulate in the ATL-like CADM1+CCR4+CD26- T cells in the circulation in a stepwise manner during the premalignant stage, before the development of aggressive ATL (27). Cells carrying known ATL-driver mutations circulate at high frequencies in the blood (>5% of mononuclear cells) up to 10 years before the diagnosis of ATL, but were not observed in high-PVL asymptomatic HTLV-1 carriers (AC) followed up for a median of 10 years who did not develop ATL (*Figure 2*). Subclonal evolution was observed within the malignant clone: new clusters of somatic mutations appeared in blood samples from later timepoints. In the six-month window before diagnosis of ATL, the frequency of cells bearing mutations increased in the blood (*Figure 2*). These data support the multi-hit model of ATL oncogenesis, in which a clone of HTLV-1-infected cells containing known oncogenic driver mutations can persist stably for many years, progressively accumulating additional mutations that culminate in causing an aggressive malignancy. Similarly, in indolent ATL, emergence of subclonal ATL-driver mutations predicts progression to aggressive subtypes (48), and malignant transformation in HAM/TSP patients. Early detection of such mutations by targeted capture sequencing may enable more effective prevention of ATL by intervening at a time when the disease may be susceptible to therapies.

These mutational profiles may also have a future role as disease biomarkers that can be used for diagnosis, prognosis or for tailoring personalised treatment decisions. We have preliminary evidence that lymphoma type ATL-derived cell-free DNA (cfDNA) is released into the plasma and can be used for non-invasive genomic profiling. In normal physiology, short fragments (~145 bp) of degraded genomic DNA are constantly released into extracellular fluids by dying cells. Turnover of HTLV-1-infected cells

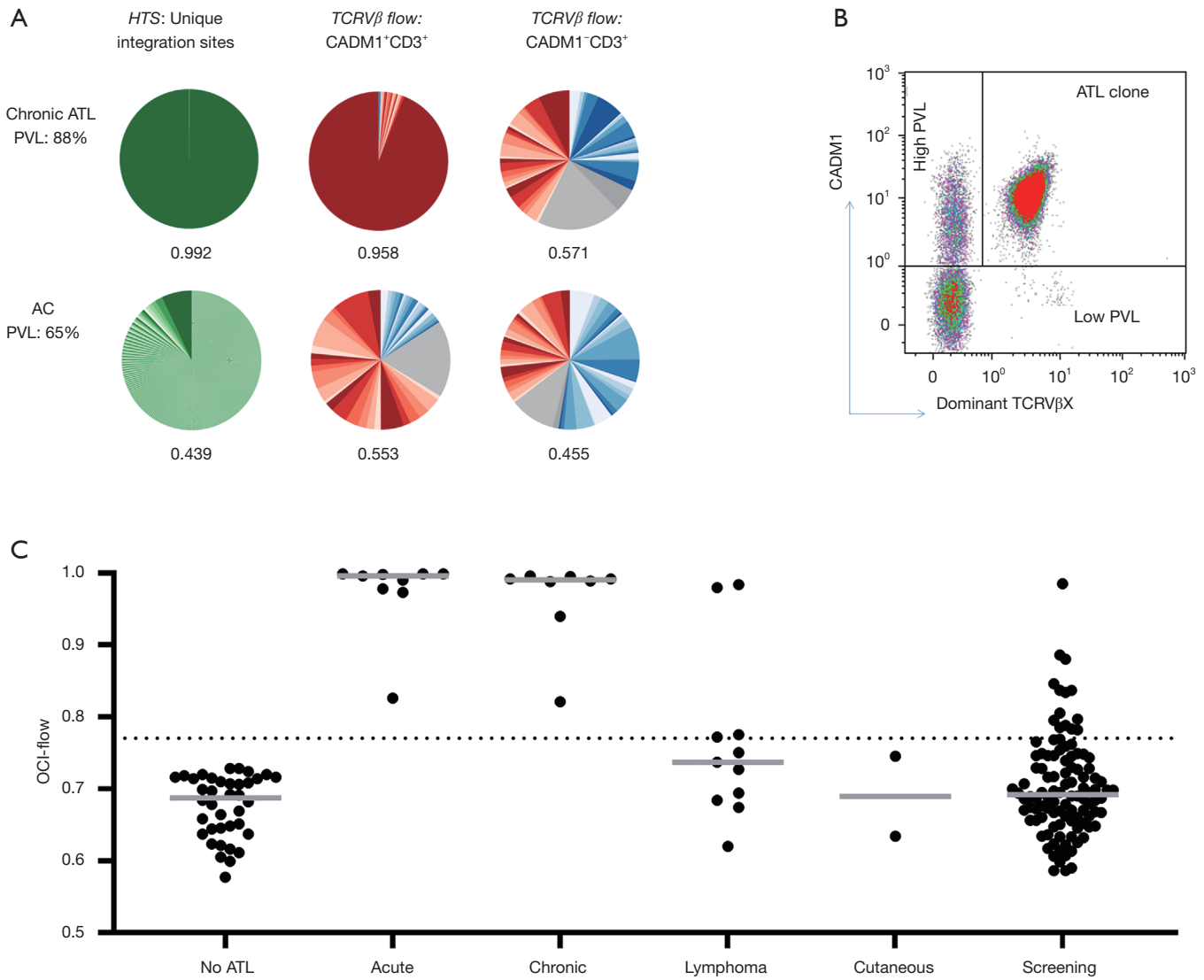

Figure 1 Detecting oligoclonal expansions in HTLV-1 carriers in health and disease. (A) Relative abundance of proviral integration sites (green pie charts) and TCRVβ subunits of CADM1+ and CADM1- CD3+ T cells (red and blue pie charts) typical of a patient with chronic ATL and an asymptomatic carrier. Each slice of the pie represents a unique integration site or unique population of T cells as defined by expression of CD4 (red) CD8 (blue) and 25 groups of TCRVβ subunits. In the ATL case, a single dominant integration site, and a dominant population of CD4+ T cells which share expression of one TCRVβ subunit are observed. Numbers underneath are the OCI, a metric of the clonality of each sample, which is calculated using the Gini index. (B) Representative image of CADM-1 and TCRVβ subunit expression on CD4+ T cells of a chronic ATL patient. CADM1+ is expressed on the majority of HTLV-1 infected cells, including malignant ATL cells. ATL cells are derived from a single infected T cell, which inherit that T cells rearranged T cell receptor genes, and thus all express T cells receptors which utilise the same T cell receptor Vβ subunit. Expression of the dominant TCRVβ subunit is shown here. (C) OCI-flow scores of PBMC from high load HTLV-1 carriers (PVL >4%) who did not develop ATL in a median of 10 years clinical follow up (n=38); patients with acute (n=10), chronic (n=9), lymphoma (n=11) or cutaneous subtype ATL; and a cross sectional screen of HTLV-1 carriers (n=106) showing a subset of carriers who have ATL-like OCI-flow scores. *Panel A & B adapted from Rowan et al., PLoS Pathog 2016;12:e1006030. Panel C adapted from Wolf et al., Blood Cancer J 2021;11:66*. HTLV-1, human T-cell lymphotropic virus type 1; ATL, adult T-cell leukemia/lymphoma; OCI, oligoclonality index; PBMC, peripheral blood mononuclear cell.

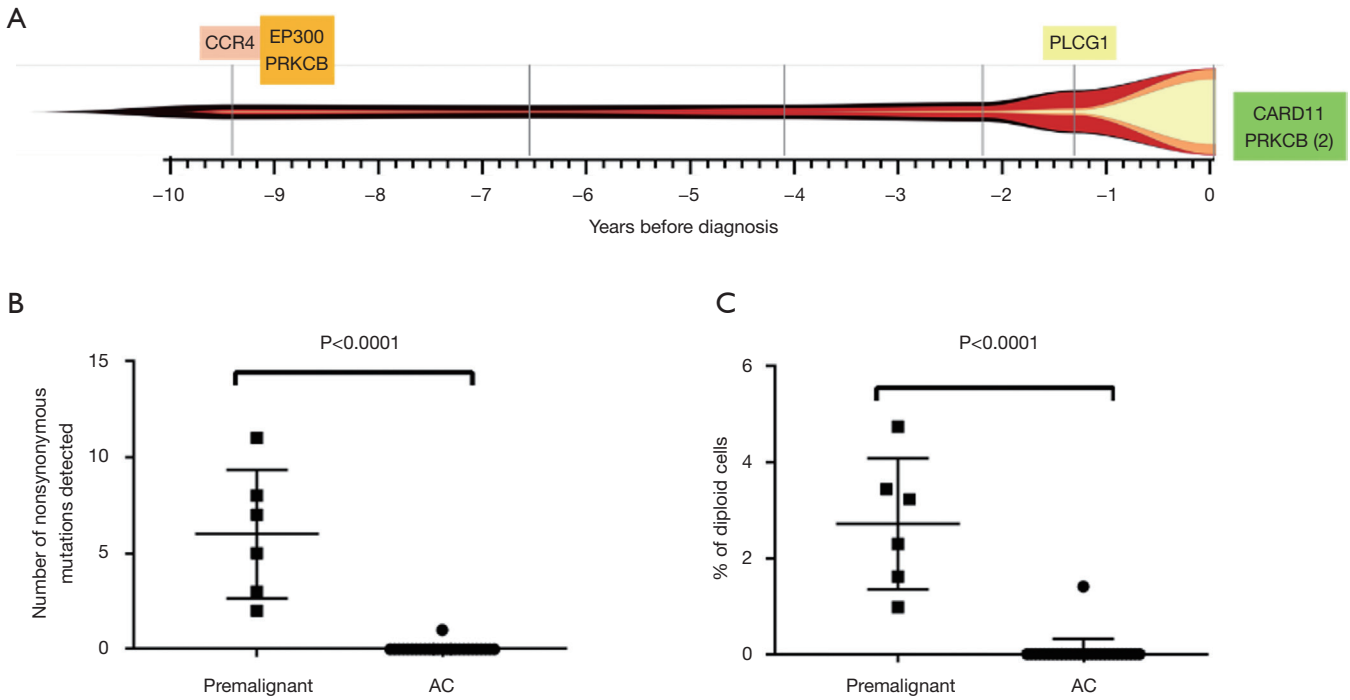

Figure 2 ATL driver mutations are detectable in PBMC DNA before diagnosis of ATL. (A) The timing of ATL driver mutations is indicated. The tumor tissue carried additional *CARD11* and *PRKCB* mutations not detected in the blood. (B) The number of somatic mutations and (C) the frequency of PBMCs carrying somatic mutations in premalignant cases and high PVL asymptomatic carriers who had not been diagnosed with ATL a median 10 years since the sample was taken. PBMC genomic DNA was sequenced using Haloplex technology, and somatic variants were identified using deepSNV. *Adapted from Rowan et al., Blood 2020;135:2023-32*. AC, asymptomatic carrier; PBMC, peripheral blood mononuclear cell; PVL, proviral load.

within tissues releases cfDNA into the plasma. We detected HTLV-1 proviruses in cfDNA extracted from blood plasma from HTLV-1-infected individuals and in patients with lymphoma, the quantity of HTLV-1 proviruses found in cfDNA was several-fold higher than expected. Thus, plasma sampling and genomic analysis of cfDNA may also be used to longitudinally monitor the evolution of lymphoma-type ATL.

Future perspectives

The exciting results from mutational profiling in ATL need to be validated in larger cohorts of patients. But further questions arise: how can we use these tests in practice, at speed and reduced cost? Which mutations are most important? Is the order of acquisition critical to disease development? And, can mutational profiling predict the response to immunotherapy? The combination of PVL measurement, OCI-flow score and targeted sequencing of genomic or cfDNA may make possible a practical prognostic algorithm to identify HTLV-1 carriers at risk of ATL, to select appropriate novel therapies, and to monitor patients with ATL when either on or off therapy.

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Footnote

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