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Decreased Expression of *RNase L* and *ABCE1* in Adult T-Cell Leukemia/Lymphoma (ATLL) Patients

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Abstract

Background: Human T-cell lymphotropic virus type 1 (HTLV-1) is the etiological agent of adult T-cell leukemia/lymphoma (ATLL). The endoribonuclease L (RNase L) is a critical component of the immune response, degrading viral and host RNA and inhibiting protein synthesis, while ATP-binding cassette E1 (ABCE1) regulates its activity. Although the expression of the RNase L and ABCE1 genes has been studied in various cancers and viral infections, their role in HTLV-1, particularly in ATLL, remains unexplored. This study aims to determine the expression of RNase L and ABCE1 in ATLL patients, HTLV-1 asymptomatic carriers (ACs), and healthy controls (HCs).

Methods: This study included 20 ATLL patients, 20 HTLV-1 asymptomatic carriers (ACs), and healthy controls (HCs). DNA and mRNA were extracted from peripheral blood mononuclear cells (PBMCs) to assess HTLV-1 proviral load (PVL) and the expression of ABCE1 and RNase L genes using real-time PCR. Statistical analyses were performed with SPSS version 18 and GraphPad Prism 10.3.1.

Results: ABCE1 and RNase L expression were significantly lower in ATLL patients compared to ACs and HCs ($p < 0.001$). A significant positive correlation was found between RNase L and ABCE1 expression in ATLL patients ($r = 0.725$, $p < 0.001$). There was no significant relationship between HTLV-1 PVL and gene expression levels ($p > 0.05$). However, the PVL was significantly higher in ATLL patients compared to ACs ($p<0.001$).

Conclusion: The observed downregulation of ABCE1 and RNase L expression in ATLL suggests a profound dysregulation of this innate immune pathway, contributing to ATLL pathogenesis.

Keywords: *ABCE1*, ATLL, HTLV-1, *RNase L*.

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) infects an estimated 10 to 20 million individuals worldwide, with endemic regions found in Japan, the Caribbean, South America, Africa, and northeastern Iran, especially the cities of Mashhad and Neyshabour (1-2). While the majority of carriers remain asymptomatic, a subset of individuals develops adult T-cell leukemia/lymphoma (ATLL), a highly aggressive hematologic malignancy with a generally poor prognosis (3). Despite notable

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advances in genomic research, the precise mechanisms driving ATLL pathogenesis remain poorly understood, and current therapeutic approaches provide limited survival benefits (4). Thus, identifying the genetic and molecular factors underlying HTLV-1-induced leukemogenesis is crucial for developing more effective and targeted treatments.

RNase L is an essential endoribonuclease involved in antiviral defense, immune regulation, and tumor suppression (5,6). As a central effector of the (IFN)-induced 2-5A pathway, RNase L is activated by 2′-5′ oligoadenylates (2–5A) and selectively degrades single-stranded RNAs (ssRNA). This process results in the degradation of both viral and host cellular RNAs, the inhibition of protein synthesis, and amplification of IFN-driven immune responses (7,8). RNase L has also been shown to play a role in apoptosis, autophagy, cellular proliferation, and differentiation (9). Dysregulation of RNase L has been previously implicated in viral diseases, notably in HIV patients and various cancers (10), including prostate (11), and lung (12).

ABCE1, also recognized as the RNase L inhibitor (RLI), is a key regulatory factor of the 2-5A/RNase L pathway (13). It forms a heterodimer complex with RNase L, thereby preventing 2-5A binding and inhibiting RNase L activation. Through this mechanism, ABCE1 modulates the extent of RNase L–mediated RNA degradation and antiviral and immune responses (14). Beyond its antiviral activity, ABCE1 is involved in multiple cellular processes, including tumor cell proliferation and anti-apoptotic mechanisms (15). Overexpression of ABCE1 has been shown in several types of human cancers (16,17). Moreover, the gene encoding ABCE1 is located on chromosome 4q31, a fragile site frequently associated with structural rearrangements in leukemia and other cancers, suggesting ABCE1 as a potential tumorigenic factor (18,19). However, its precise role in oncogenesis and metastasis remains to be further investigated.

Previous studies have documented altered expression of RNase L and ABCE1 in various human cancers and viral infections (19,20). Given that RNase L mediates antiviral RNA degradation and ABCE1 regulates its activity, dysregulation of this pathway could influence viral persistence and malignant transformation. Despite this, no studies have yet explored the relationship between RNase L and ABCE1 expression in the context of HTLV-1 infection and its associated malignancy, ATLL. Investigating their expression in newly diagnosed ATLL patients may reveal links between innate immune dysregulation and disease development and identify potential biomarkers or therapeutic targets. This study aims to address this gap by evaluating the expression levels of RNase L and ABCE1 in patients with ATLL.

Materials and Methods

Ethics approval

This study received approval from the Ethics Committee of Mashhad University of Medical Sciences (MUMS), and informed consent was obtained from all participants (Ethics code: IR.MUMS.fm.REC.1394.612).

Patients and sample preparation

This cross-sectional study was conducted at the Hematology Department of Mashhad University of Medical Sciences, Mashhad, Iran, and included 20 patients with newly diagnosed adult T-cell leukemia/lymphoma (ATLL), 20 asymptomatic HTLV-1 carriers (ACs), and 10 healthy controls (HCs). Inclusion was based on the latest World Health Organization (WHO) criteria for ATLL or HTLV-1 infection. ATLL diagnosis was confirmed through evaluation of the clinical presentation, examination of blood or bone marrow smears, and flow cytometry analysis of CD2, CD3, CD4, CD5, CD7, CD8 and CD25 T-cell markers (21,22). HTLV-1 infection in patients and ACs was verified by ELISA and confirmed by Western blot or PCR, while HCs had no history of HTLV-1 infection or hematologic disease. Participants were excluded if they had received prior

ATLL treatment, had other chronic illnesses, or were taking medications affecting immune function or gene expression. Demographic and clinical data were obtained from medical records, and peripheral blood mononuclear cells (PBMCs) were isolated from EDTA blood samples using Ficoll-Paque (Sigma-Aldrich) for molecular analyses.

RNA isolation and cDNA synthesis

Total RNA was extracted from peripheral blood (PB) samples using the TriPure Isolation Reagent Kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions. RNA quality and quantity were assessed using a NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA) at an absorbance ratio of 260/280 nm. cDNA synthesis was performed with the RevertAid™ H Minus First Strand cDNA Synthesis Kit (Thermo Fisher, St. Leon-Rot, Germany), according to the following protocol: 9 µl of RNA was combined with 2 µl of nuclease-free water and then 1 µl of random hexamers, incubated at 70 °C for 5 minutes. Subsequently, 4 µl of RT buffer, 2 µl of dNTP mix, 1 µl of reverse transcriptase, and 1 µl of RiboLock were added, followed by incubation at 25 °C for 5 minutes, 42 °C for 60 minutes, and 70 °C for 5 minutes.

Quantitative reverse transcription–polymerase chain reaction (qRT-PCR)

TaqMan-based quantitative reverse transcription PCR (qRT-PCR) was performed to assess the expression levels of RNASE L (NCBI accession number: NM_021133.4) and ABCE1 (NCBI accession number: NM_002940.3) in ATLL patients, HTLV-1 asymptomatic carriers (ACs), and healthy controls. The reactions were carried out using Premix ExTaq™ DNA Polymerase (Perfect Real Time, Cat. No. RR039A) in a Rotor-Gene 6000 Real-Time PCR Thermocycler. The amplification conditions were as follows: an initial denaturation at 95 °C for 2 minutes, followed by 45 cycles of 94 °C for 15 seconds and 60 °C for 30 seconds. The primer sequences for RNASE L, ABCE1, and β2-microglobulin (used as a housekeeping gene) are provided in Table 1. This study utilized the expression of a housekeeping gene, β2-microglobulin**,** to normalize target gene expression.

Table. 1. The primer sequences of RNase L, ABCE1 and β2 Microglobulin genes.

Primer		Sequence (5 to 3)
RNase L	Forward	5-GGAGAGCAGGGATCATAACAACC-3
	Reverse	5-CTGGACCAGGTCAACATCTTCG -3
ABCE1	Forward	5-GACCTAAAAGCCATCATCAAACCTC-3
	Reverse	5-GCCTGTGTCTTTGTTTCATCTTTTC-3
β2 Microglobulin	Forward	5-CCACTGAAAAAGATGAGTATGCCT-3
	Reverse	5-CCAATCCAAATGCGGCATCTTCA-3

Measurement of HTLV-1 proviral load

HTLV-I proviral load was quantified by isolating PBMCs from EDTA-treated blood samples. A validated commercial kit, utilizing specific primers and probes, was employed for quantification (Novin Gene, Iran) in a real-Time PCR Thermocycler (Rotor Gene 6000). Proviral load was normalized to the albumin gene as an internal reference. Absolute quantification was achieved using standard curves generated from five known

concentrations. The HTLV-I proviral load was expressed as the ratio of HTLV-I DNA copies to albumin DNA copies per 10^4 PBMCs.

Statistical analyses

For each quantitative variable, we calculated the mean, median, and standard deviation. The Kolmogorov-Smirnov test was used to evaluate the data distribution of the data. To compare a quantitative variable between two groups, we employed the unpaired t-test; for comparisons among three groups, we used one-way ANOVA. When ANOVA results were significant, Tukey's honestly significant difference (HSD) test was conducted for pairwise comparisons. The Chi-square test was used to compare nominal categorical variables between groups. A p-value of ≤ 0.05 was considered statistically significant.

Results

Patients' characteristics

A total of 50 participants were enrolled, including 20 ATLL patients (13 females, 7 males), 20 HTLV-1 asymptomatic carriers (ACs) (18 females, 2 males), and 10 healthy controls (HCs) (8 females, 2 males). The mean ages were 53.17 ± 9.79 years for ATLL patients, 46.25 ± 11.11 years for ACs, and 49.0 ± 8.1 years for HCs. Statistical analysis showed no significant differences in age or gender distribution among the groups ($p > 0.05$) (Table 2).

Table.2. Characteristics and clinical features of study participants.

Characteristics	New-case ATLL patients (N=20)	Asymptomatic carriers (N=20)	Healthy controls (N=10)	Statistical significance (p-value)
Demographic				
Age (years ±SD)	53.17±9.79	46.25±11.11	49±8.1	p>0.05
Sex (Female/Male)	13/7	18/2	8/2	p>0.05
HTLV-1 marker				
Proviral load (Median)	3,568 copies	488.19 copies	N/A	p<0.001
Clinical Features				
Lymphadenopathy	61%	N/A	N/A	N/A
Immuno-related deficiency syndrome	21 %	N/A	N/A	N/A
Skin lesions	18 %	N/A	N/A	N/A

*N/A: Not Applicable.

Regarding clinical features, the most prominent signs were lymphadenopathy (61%), skin lesions (18%), and immunodeficiency-related symptoms (21%). Notably, no individual patient exhibited all symptoms simultaneously. Statistical analysis revealed no significant differences in age or gender among the ATLL patients, and HTLV-1 asymptomatic carrier with healthy control group ($P > 0.05$).

Proviral load levels

Patients with ATLL exhibited a substantially higher proviral load, with a median of 3,568 copies per 10^4 PBMCs, compared to a median of 488.19 copies in HTLV-1 asymptomatic carriers (ACs). This difference was significant ($p < 0.001$) (Table 2).

RNASE L and ABCE1 gene expression levels in ATLL patients, HTLV-1 asymptomatic carriers (ACs), and healthy controls

The gene expression levels of RNase L and ABCE1 were markedly reduced in ATLL patients compared with both asymptomatic HTLV-1 carriers (ACs) and healthy controls (Fig. 1). In ATLL patients, the mean logarithmic expression levels of RNASE L and ABCE1 were 4.45 ± 2.36 and 5.69 ± 1.78, respectively. In contrast, HTLV-1 asymptomatic carriers (ACs) exhibited mean values of 7.61 ± 1.29 and 9.66 ± 1.72, while healthy controls demonstrated 8.86 ± 0.71 and 8.81 ± 0.98, respectively. Statistical analysis revealed a significant downregulation of both genes in ATLL patients relative to the other groups ($p < 0.001$). No significant difference was observed between HTLV-1 asymptomatic carriers (ACs) and healthy controls ($p = 0.375$), suggesting that the reduced expression of RNASE L and ABCE1 is specifically associated with ATLL development and may contribute to disease progression.

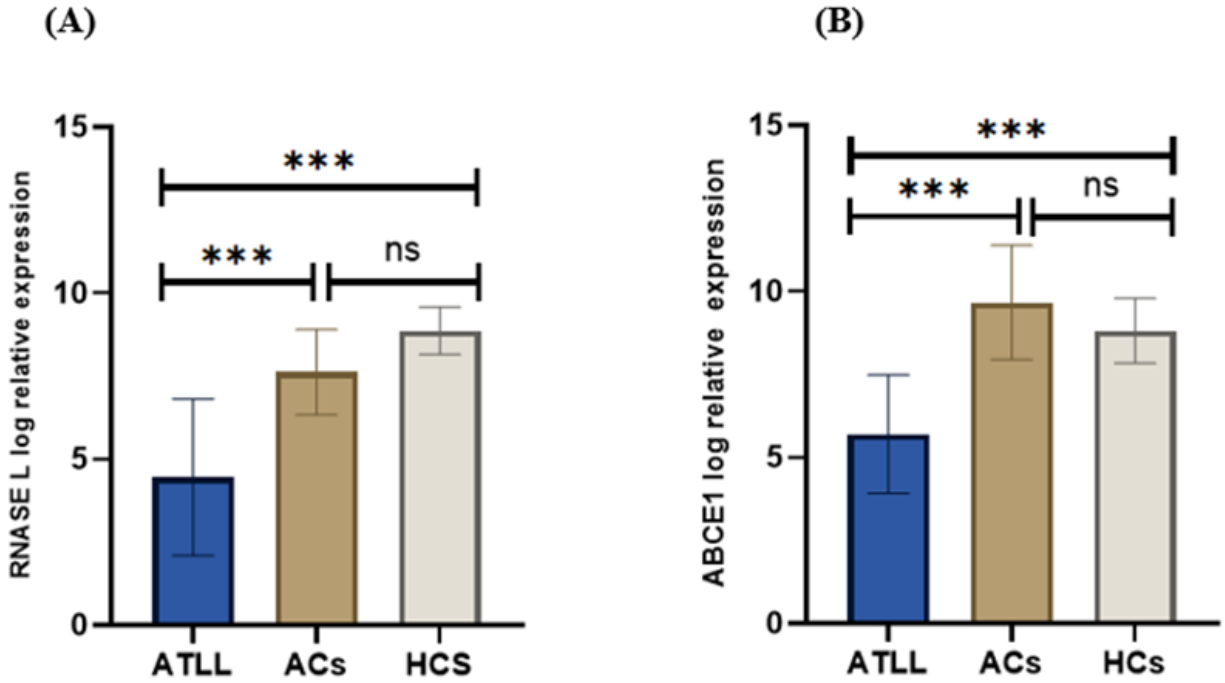

Fig. 1. Relative logarithmic gene expression of RNase L (A), and ABCE1 (B) in ATLL patients, HTLV-1 asymptomatic carriers (ACs), and Healthy controls (HCs). β2-microglobulin was used as the reference gene. Both RNase L and ABCE1 expression levels are significantly lower in ATLL patients than in both ACs and HCs (p-value < 0.001). No significant relationship was found between the AC and HC groups (p-value> 0.05). Error bars show standard deviation. *** denotes p-values < 0.001, and NS denotes non-significant.

The correlation between RNase L and ABCE1 in ATLL patients, HTLV-1 asymptomatic carriers (ACs), and healthy controls

A strong positive correlation was observed between RNASE L and ABCE1 gene expression in both ATLL patients ($r = 0.725$, $p < 0.001$) and healthy controls ($r = 0.671$, $p = 0.034$). However, no significant correlation was found between these two gene expressions in HTLV-1 asymptomatic carriers (ACs) ($p > 0.05$) (Fig. 2).

The Association between proviral load and RNASE L and ABCE1 gene expression

Despite the elevated proviral load observed in ATLL patients, no significant correlations were identified between HTLV-1 proviral load and the RNASE L or ABCE1 transcript levels across the patient cohort ($p > 0.05$), indicating that the expression of these genes may be regulated independently of viral burden.

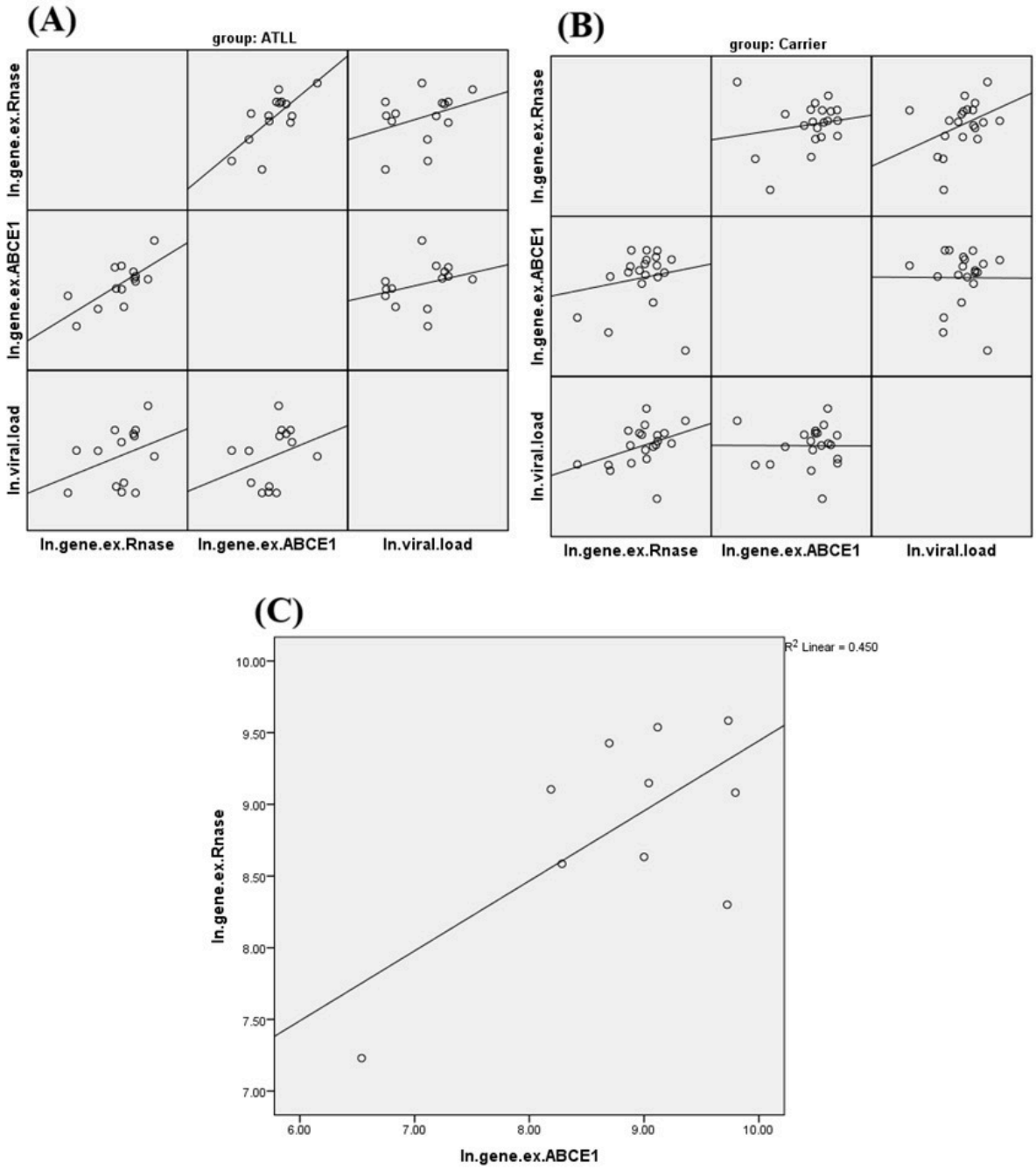

Fig. 2. Pearson's correlation analysis between RNase L, ABCE1, and HTLV-1 proviral load in (A) ATLL patients, (B) HTLV-1 asymptomatic carriers (ACs), and (C) healthy controls. A strong positive correlation was observed between RNASE L and ABCE1 gene expression in both ATLL patients (r = 0.72, p = 0.001) and healthy control individuals (r = 0.671, p = 0.034). However, no correlation was found in HTLV-1 asymptomatic carriers (ACs) (r=0.176**,** *p-value* =0.458). No significant correlation was found between HTLV-1 proviral load and the expression of either gene in ATLL patients or asymptomatic carriers (p-value > 0.05)

Discussion

In this study, we demonstrated that RNase L and ABCE1 expression are significantly downregulated in patients with newly diagnosed ATLL compared with HTLV-1 asymptomatic carriers (ACs) and healthy controls (HCs). This dual downregulation suggests a disrupted antiviral defense that underlies the mechanisms driving the aggressive nature of ATLL. RNase L and ABCE1 are critical components of the 2-5A antiviral pathway and RNA metabolism (23).

Based on our findings, we suggest that their coordinated downregulation may contribute to viral persistence, T cell proliferation, and tumor progression in the setting of HTLV-1 infection. To our knowledge, this is the first study to report simultaneous downregulation of RNase L and ABCE1 in ATLL, highlighting their potential as novel biomarkers and therapeutic targets in this disease.

Our findings of RNase L downregulation in ATLL are supported by previous research highlighting its involvement in other malignancies. Notably, a study by Casey G. et al. demonstrated that the Arg462Gln polymorphism in the RNase L gene impairs protein dimerization and enzymatic activity, reducing its ability to induce apoptosis. Their large-scale analysis identified significant associations between Arg462Gln and Asp541Glu polymorphisms and increased prostate cancer risk, suggesting a role for RNase L dysfunction in tumor development (24). In line with our results, other studies have shown that RNase L expression is diminished in rapidly proliferating cells, reflecting its antiproliferative and tumor-suppressive functions (19,25). For instance, Liang SL. et al. reported that mice lacking RNase L exhibited markedly increased bone marrow cell proliferation in response to GM-CSF (19), a pattern that parallels the enhanced T-cell proliferation observed in ATLL patients. These findings provide a context for our observation that RNase L downregulation may contribute to uncontrolled cellular proliferation in ATLL.

Further reinforcing our findings, previous studies have shown a broader pattern of RNase L impairment in various cancers. Tnani et al. reported a complete absence of RNase L expression in the human hepatoma cell line HepG2 (26), while Yin H et al. demonstrated a significant reduction in RNase L function in both the nucleus and cytoplasm of lung cancer cells, but not in normal lung tissue. Notably, their study showed that treatment with interferon-γ (IFN-γ) restored RNase L activity, prompting them to propose interferon-based immunotherapy as a potential cancer treatment strategy (13). Collectively, these studies support a broader role for RNase L dysfunction across malignancies and reinforce its potential as a biomarker and therapeutic target in cancers such as ATLL.

The current study also revealed a decrease in ABCE1 expression in ATLL patients compared to HTLV-1 asymptomatic carriers (ACs) and healthy controls (HCs), which is notably different from findings in other cancers and viral infections. Previous studies have consistently reported ABCE1's significant role in various malignancies, including lung carcinoma (27), colorectal cancer (28), metastatic melanoma (29), human esophageal cancer (30), retinoblastoma (31), and breast cancer (32) cell lines, suggesting a potential role in tumor progression and invasion. Moreover, in HIV infection, elevated ABCE1 expression has been shown to suppress RNase L activity, thereby enhancing viral replication and facilitating immune evasion (33). These findings point to a functional role for ABCE1 in supporting viral survival and tumorigenesis by modulating the 2-5A/RNase L pathway.

In contrast, our observation of reduced ABCE1 expression in ATLL patients, but not in asymptomatic HTLV-1 carriers (ACs), suggests that HTLV-1 may employ a distinct mechanism in ATLL to suppress RNase L activity and evade host immunity. This is consistent with evidence that viruses utilize diverse strategies to circumvent the 2–5A/RNase L antiviral pathway (34). For example, the vaccinia virus expresses the E3L protein, which binds double-stranded RNA, inhibits 2–5A synthetase, and prevents RNase L-mediated apoptosis (35). These examples of viral adaptability support the notion that, unlike HIV, which may rely on ABCE1 upregulation, HTLV-1 in ATLL patients may simultaneously downregulate both RNase L and ABCE1 to more effectively disrupt the pathway, thereby enhancing viral persistence and promoting leukemogenesis.

Importantly, HTLV-1 encoded oncoproteins such as Tax and HBZ are known to interfere with host gene regulation and

immune recognition. While Tax is highly immunogenic and activates viral transcription, HBZ suppresses Tax expression, helping the virus evade immune surveillance while maintaining its oncogenic potential. Both proteins are highly expressed in infected cells (36-39). The decreased ABCE1 expression observed in our study suggests that RNase L suppression in ATLL is likely mediated by viral oncoproteins such as Tax and/or HBZ rather than ABCE1 itself. This highlights a distinct viral strategy by HTLV-1 to evade host immunity and warrants evaluation in future studies. All ATLL patients in this study were newly diagnosed, and both RNase L and ABCE1 expression were significantly altered compared with asymptomatic carriers (ACs) and healthy controls (HCs). While disease severity was not formally quantified, the main clinical features included lymphadenopathy, immunodeficiency, and skin lesions. These findings indicate that dysregulation of RNase L and ABCE1 may contribute to immune evasion and early disease progression. Future studies should investigate whether RNase L and ABCE1 expression correlates with disease severity, prognosis, or therapeutic response, which could suggest their utility as biomarkers or targets for intervention.

This study identified a direct correlation between ABCE1 and RNase L gene expression, both of which were significantly reduced in ATLL patients compared to HTLV-1 asymptomatic carriers (ACs) and healthy controls. No significant association was found between gene expression levels and proviral load. These results suggest that altered RNase L and ABCE1 regulation play a role in ATLL pathogenesis. Nevertheless, the interpretation of these findings should be made with caution, as the relatively small sample size, particularly in the healthy control group, may have reduced the statistical power of the analyses. Overall, our results highlight the importance of the RNase L-ABCE1 axis in HTLV-1-related leukemogenesis and provide a foundation for future research. Further studies with larger cohorts are required to validate these results and to better clarify the role of the ABCE1-RNase L pathway in ATLL pathogenesis.

Authors' contribution

Samaneh Houshmand: Methodology, Investigation, Data Curation, Visualization, Writing – Original Draft; Houshang Rafat-Panah: Conceptualization, Supervision, Methodology, Study Design; Mohammad Mehdi Akbarin and Mohammad Reza Keramati: Supervision, Study Design, Project Administration; Arefeh Mazhari and Tayebeh Sohrabi: Investigation, Methodology, Resources; Shahla Rahmani and Payam Siyadat: Investigation, Writing- Original Draft, Writing – Review & Editing. All authors have read and approved the final manuscript.

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Conflict of Interest

None declared.

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