

## Cytogenetic Implication in Adult T-Cell Leukemia A Hypothesis of Leukemogenesis

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**ABSTRACT:** The close association between adult T-cell leukemia (ATL) and human T-cell leukemia virus type I (HTLV-I) has been established. Nevertheless, the mechanism of progression of ATL by HTLV-I infection is still uncertain, because the virus contains no typical oncogene and no significant expression of the viral RNA has been generally found. I propose a model of leukemogenic process in ATL based on our cytogenetic data and molecular results in the literature. It seems that the rearrangement of some proto-oncogene and alpha-chain gene of the T-cell antigen receptor (TCR- $\alpha$ ) is necessary for the development to overt ATL. A deficiency in the rearrangement of proto-oncogene to TCR- $\alpha$  may result in only a minor proliferation of abnormal lymphocytes and remain in the preleukemic state of ATL or in the HTLV-I carrier state.

### HTLV-I CONTAINS NO TYPICAL ONCOGENES

Because of close association between HTLV-I [1-3] and ATL [4, 5], the analysis of leukemogenesis in ATL was done mainly by studying the HTLV-I gene. It was made clear that HTLV-I contained no typical oncogene [6] and that its integration sites were different from one patient to another [7]. As a result, the theory of a transacting viral function, that is, a pX protein of HTLV-I acting in not only viral genes but also some cellular genes such as interleukin-2 (IL-2) and IL-2 receptor gene, was proposed to explain leukemogenesis in ATL [8]. However, no significant expression of viral RNA was generally found in fresh tumor cells of ATL patients [9], and the mechanism of progression of ATL by HTLV-I is still uncertain.

Shimoyama et al. [10] reported five ATL patients with neither integration of HTLV-I in their leukemia cells nor anti-HTLV-I antibody in their sera. These findings indicate that HTLV-I may be merely one of the factors in leukemogenesis of ATL.

### SPECIFIC CHROMOSOME IN ATL

A review of the numerous data on specific chromosome changes in various hematologic disorders showed that cytogenetic studies on ATL are scarce. Various chromosome abnormalities such as trisomy 3, partial deletion of the long arm of chromosome

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6 (i.e., 6q-) and trisomy 7, and elongation of the long arm of chromosome 14 with a break at band 14q32, have been reported [11-18]. These observations suggest that there were no specific chromosome abnormalities in ATL associated with specific B-cell neoplasms predominantly involving the immunoglobulin heavy-chain region other than t(8;14)(q24;q32), t(11;14)(q13;q32) and t(14;18)(q32;q21) [19].

In 1984, we first reported the chromosome 14 anomaly at band 14q11 was specific to the acute type of ATL with positive CD4 antigen and anti-HTLV antibody [20]. In six out of eight patients, the presence of 14q11 anomaly was confirmed at the ATL Karyotype Workshop 1985 in Japan (organized by the ATL Karyotype Review Committee 1985, supported by a grant from the Japanese Welfare Ministry, and arranged by Drs. Kei-ichi Suemasu and Masanori Shimoyama of the National Cancer Center) [21]. In 1987, Miyamoto et al. [22] also reported the 14q11 anomaly in six out of eight ATL patients, which supported our finding that this is the specific chromosome for ATL.

In 1984, when we first found 14q11 anomaly in ATL [20], Ueshima et al. [23] described that most of the reported patients with T-cell malignancies, such as Sézary syndrome, mycosis fungoides, cutaneous T-cell lymphoma, and T-cell chronic lymphocytic leukemia (T-CLL), had 14q11 anomaly. On the basis of these facts, they stated that 14q11 anomaly probably constitutes the most common nonrandom abnormality in the various T-cell malignancies.

#### RECENT ADVANCES IN MOLECULAR BIOLOGY

In 1985, Croce et al. [24] reported that the locus of TCR- $\alpha$  is at band q11.2 of chromosome 14. Erikson et al. [25] proved that TCR- $\alpha$  was split from the sample of T-cell acute lymphoblastic leukemia by translocation, t(11;14)(p13;q11). Russo et al. [26] reported that the molecular rearrangement between TCR- $\alpha$  on 14q11 and *tcl-1* proto-oncogene on 14q32.1 was caused by translocations t(14;14)(q11;q32) or inv(14)(q11q32). Furthermore, Mathieu-Mahul et al. [27] and McKeithan et al. [28] described molecular cloning of the breakpoint junction t(8;14)(q24;q11) involving the TCR- $\alpha$  and sequences on the 3' side of *c-myc* gene. These results indicate that the proto-oncogene of *c-myc* may be activated by chromosomal translocation to TCR- $\alpha$  region. The mechanism for this activation might be similar to that involving transcriptional deregulation of the *c-myc* gene in Burkitt's lymphoma [29].

In 1988, Isobe et al. [30] reported that the locus of TCR- $\delta$  is at band q11 of chromosome 14. Using a set of TCR- $\delta$  probes, we found the deletion of the TCR- $\delta$  locus in all five ATL patients [31]. Kimura et al. [32] also reported that all 27 ATL patients had a deleted TCR- $\delta$  locus. These findings suggest that the rearrangement of TCR- $\delta$  is not necessarily related to the leukemogenesis of mature type of T-cell malignancies such as ATL.

#### A RULE OF BREAKPOINTS OF DONOR CHROMOSOME INVOLVING 14q11 ANOMALY IN ATL

Karyotypes of eight ATL patients with translocation or inversions associated with 14q11 anomaly in the literature [21, 22] are summarized in Table 1. The inv(14)(q11q32) was reported in four patients, and t(11;14)(p13;q11), t(14;14)(q11;q32), t(7;14)(p11;q11), and t(X;14)(q11;q11) in one patient each. The t(7;14)(p11;q11) seems to be t(7;14)(p12;q32) from the picture reported by Miyamoto et al. [22]. These findings indicate that the major chromosome abnormality is inv(14)(q11q32) in ATL as well as in T-CLL [33] and T-cell prolymphocytic leukemia [34]. The remaining two karyotypes of t(11;14)(p13;q11) and t(14;14)(q11;q32) in reported ATL patients were also described in other types of T-cell malignancy [23]. As shown in Table 1, there was a

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**Table 1** Cytogenetic findings of ATL, pre-ATL and HTLV-I carriers in the literature

| Disease         | Karyotype with 14q11 anomaly | Proto-oncogene on breakpoints of donor chromosome | Ref. |
|-----------------|------------------------------|---|------|
| ATL             | t(11;14)(p13;q11)            | <i>tlc-2</i>                                      | 21   |
|                 | t(14;14)(q11;q32)            | <i>tcl-1</i>                                      | 21   |
|                 | inv(14)(q11q32)              | <i>tcl-1</i>                                      | 21   |
|                 | inv(14)(q11q32)              | <i>tcl-1</i>                                      | 21   |
|                 | inv(14)(q11q32)              | <i>tcl-1</i>                                      | 22   |
|                 | inv(14)(q11q32)              | <i>tcl-1</i>                                      | 22   |
|                 | t(7;14)(p11-12;q11)          | <i>erb B</i>                                      | 22   |
|                 | t(X;14)(q11;q11)             | H-ras (?)   | 22   |
| Pre-ATL         | t(14;15)(q11;q15)            | None  | 33   |
|                 | t(1;14)(q42;q11)             | None  | 33   |
|                 | t(14;18)(q11;p11)            | None  | 33   |
|                 | t(7;14)(q32;q11)             | None  | 33   |
| HTLV-I carriers | t(14;22)(q11;p11)            | None  | 35   |
|                 | t(14;22)(q11;p11)            | None  | 35   |
|                 | t(14;15)(q11;p11)            | None  | 35   |

variation in the breakpoints of donor chromosomes involved in the translocation of 14q11 anomaly. Interestingly, on all breakpoints the proto-oncogenes have been assigned *tcl-2* on 11p13, *tcl-1* on 14q32.1, *erbB* on 7p13, and H-ras probably on Xq11. These findings indicate that the breakpoints in most patients lie near the proto-oncogenes and TCR-α, which suggests that some proto-oncogenes may be activated by translocation to the TCR-α gene. It should be emphasized here that no chromosome breaks on 7q32-36 or 7p15 with assigned locus TCR-β or CTR-τ, respectively, were detected in the reported ATL patients [21, 22].

#### CHARACTERISTICS OF CHROMOSOME ABNORMALITIES IN PRE-ATL AND HTLV-I CARRIERS

Kinoshita et al. [35] described pre-ATL, which is a subclinical T-cell abnormality differing from ATL. It is characterized by an insidious onset and appearance of abnormal T-lymphocytes (10%–40%) in the peripheral blood without any clinical symptoms. Nishino [36] reported 14q11 anomaly in four out of nine pre-ATL patients showing a low percentage of lymphocytes stimulated with phytohemagglutinin (PHA). As shown in Table 1 a total of 4 cells with 14q11 anomaly, i.e., t(14;15)(q11;q15), t(1;14)(q42;q11), t(14;18)(q11;p11), and t(7;14)(q32;q11) were found. There was variation in the breakpoints of donor chromosomes associated with 14q11 anomaly, such as 15q15, 1q42, 18p11, and 7q32. No proto-oncogene was assigned until recently on these breakpoints. This may indicate that pre-ATL cells without rearrangements of proto-oncogene and TCR-α did not develop into overt ATL.

Recently, we had an opportunity to conduct chromosome examinations in both the pre-ATL and overt ATL stages in one patient. Although no specific chromosomes with 14q11 could be found from the lymphocytes stimulated with PHA in pre-ATL, a major clone with inv(14)(q11q32) was detected from the peripheral leukemic cells in the early stage of overt ATL [37].

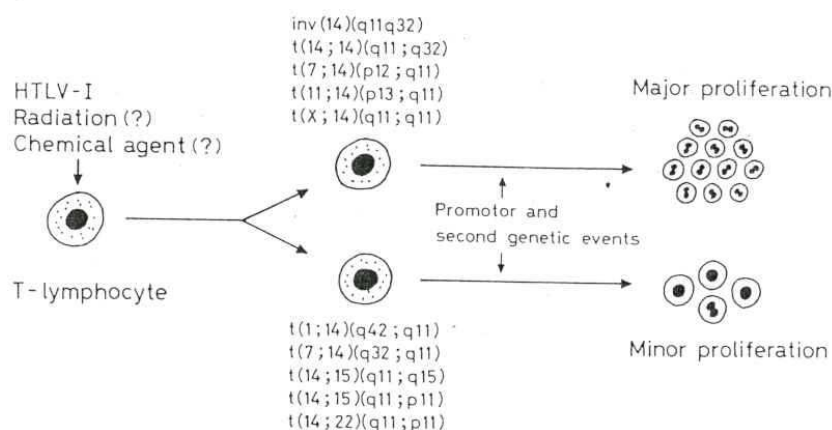


Figure 1 Model of leukemogenic process in adult T-cell leukemia.

#### CHARACTERISTICS OF 14q11 ANOMALY IN HTLV-I CARRIERS

We performed cytogenetic studies of lymphocytes stimulated with PHA in three HTLV-I carriers and three non-HTLV-I carriers in an ATL family [38]. As a result, in the HTLV-I carriers, 4 of the 311 cells examined (1.3%) had 14q11 anomaly, while in the non-HTLV-I carriers, none of the 260 cells examined had 14q11 anomaly. As shown in Table 1, the three cells with translocations involved in 14q11 anomaly showed karyotypes of t(14;22)(q11;p11) in two cells and t(14;15)(q11;p11) in one cell. Proto-oncogenes have not yet been assigned on these breakpoints (22p11 and 15p11) of donor chromosomes associated with 14q11 anomaly. Our data also indicate that 14q11 anomaly is already present at the stage of HTLV-I carrier.

#### A MODEL OF LEUKEMOGENIC PROCESS OF ATL

As shown in Figure 1, some DNA damage might be induced in CD4 positive lymphocytes mainly by HTLV-I, and occasionally by irradiation or chemical agents, probably in infancy. It has been clarified that HTLV-I infection occurs by milk-borne transmission from carrier mothers to their children [39]. A few cells with 14q11 anomaly produced by a mistake in the repair of DNA damage may be potential ATL cells. However, most cells with 14q11 anomaly are probably killed by immune homeostasis. The cells without rearrangement of proto-oncogene to TCR- $\alpha$  may result in only a minor proliferation of abnormal lymphocytes and remain in a pre-ATL stage or HTLV-I carrier state. If cells with rearrangement between some proto-oncogene and TCR- $\alpha$  appear by chance, the qualified leukemia cell as ATL will increase in number as a clone over a long period of time, generally more than 40 years. It will be accompanied by clonal evolution, escape immune homeostasis, and finally lead to the patient's death. In the process of ATL, HTLV-I might act as a promotor agent on ATL cells in the same manner as the Epstein-Barr virus in Burkitt lymphoma [29].

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