

Leukaemia Section

Mini Review

t(7;14)(q35;q32.1) TRB@/TCL1A, inv(14)(q11q32.1) TRA@-TRD@/TCL1A, t(14;14)(q11;q32.1) TRA@-TRD@/TCL1A

Jacques Boyer

Laboratoire d'Hématologie, CH du MANS, France (JB)

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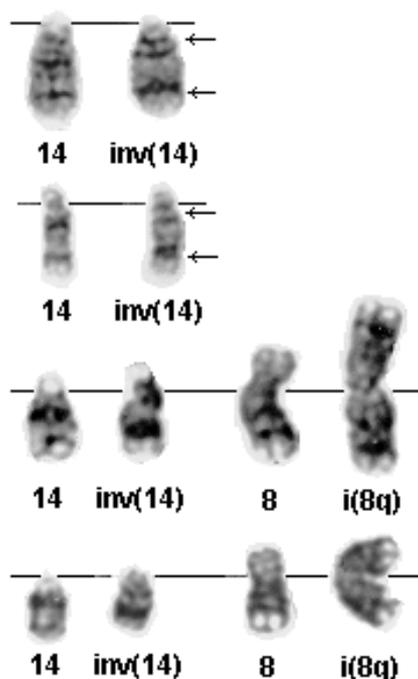
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Identity



inv(14)(q11q32) and accompanying i(8q), G-banding -
Courtesy Jean Luc Lai

Clinics and pathology

Note

These chromosome rearrangements can be found in:
Prolymphocytic leukemia (T- PLL);

Ataxia Teliangectasia;

Adult T-cell leukemia/lymphoma;

Rarely: acute lymphoblastic leukemia of T-lineage or B-lineage, acute myeloid leukemia expressing lymphoid-associated antigens (see references).

Disease

T Prolymphocytic leukemia (T-PLL).

Phenotype/cell stem origin

Mature post-thymic T-cell malignancy.

CD4+CD8- (70%) CD4+CD8+ (25%) or CD4-CD8+ (<10%). CD7+ bright and surface CD3 negative in 20% of cases.

Clinics

T-PLL is rare and affects adults, occurs slightly more often in men at advanced age.

T-PLL main disease features at presentation are splenomegaly (79%), lymphadenopathy (46%), hepatomegaly (39%), skin lesion (23%), pleural effusion (15%) and marked lymphocytosis (> 100 X 10⁹/L) (72%).

Cytology

In 70% of cases proliferation of medium-sized lymphocytes with either a regular or an irregular nuclear outline and one single nucleolus (or absent). The cytoplasm is scanty, agranular, deeply basophilic and often with protrusions (blebs).

In 20% of cases there are no obvious differences between B and T prolymphocytes with prominent nucleolus.

In rare cases T prolymphocytes show a polylobated nucleus or a cerebriform configuration (as Sezary cell).

Cytogenetics

Chromosomal abnormalities are detected in most T-PLL after culture with mitogens like PHA. Karyotype is often complex with high degree of instability.

inv(14)(q11;q32) is the most frequent chromosomal abnormality and occurs in more than two thirds of cases. Few patients may have t(14;14)(q11;q32), the variant t(X;14)(q28;q11) may be found.

Additional anomalies

55 to 80 % of cases have additional abnormality affecting the chromosome 8: i(8)(q10) (43%), t(8;8)(p12;q11) (14%), +8 (14%) and abnormality of the short arm of chromosome 8 (14%)

Anomalies of 11q23, where the ataxia telangiectasia mutated gene is located, have also been reported in T-PLL. Anomalies of the short arm of chromosome 12 seem to be observed with a high frequency so as 13q14.3 deletions.

Prognosis

T-PLL has an aggressive clinical course, although, in a small proportion on cases, disease evolves with a slowly progressive lymphocytosis (phenotype CD45RO-CD45RA-).

Disease

Ataxia telangiectasia (AT).

Clinics

AT is a chromosome instability syndrome with an increased risk of cancer: T-cell malignancies or carcinomas.

Cytogenetics

Spontaneous chromatid/chromosome breaks are found in this disease with a high frequency.

The best diagnosis test is on the highly elevated level (10% of mitoses) of inv(7), t(14;14).

Clonal rearrangement further occurs in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14) or t(X;14).

Clonal rearrangements in T-cell ALL and T-PLL in AT patients are complex with the frequent involvement of t(14;14) or t(X;14) as is found in T-PLL in non AT patients.

Disease

Adult T-cell leukemia/lymphoma.

Cytogenetics

The karyotype is often complex.

The translocation t(14;14)(q11;q32.1) and inv(14)(q11;q32.1) have been reported by a number of investigators.

Additional anomalies: trisomy 3, trisomy 7 or partial trisomy of the long arm of chromosome 7 are frequently found.

Disease

Acute lymphoblastic leukemia (ALL) of T lineage.

Cytogenetics

Inv(14) is exceedingly rare in T cell acute lymphoblastic leukemia. In two cases reported, inv(14) coexists with other cytogenetic aberrations well described in T-ALL, like t(11;14)(p13;q11) and rearrangement at chromosome 7q34.

Disease

Leukemias of B lineage.

Cytogenetics

Inv(14) is a exceedingly rare phenomenon in lymphoid malignancy of B lineage. It has been reported in a patient with B-cell chronic lymphocytic leukemia but only in a PHA stimulated bone marrow. Only two cases of lymphoblastic leukemia of B-lineage with inv(14) have been reported. These two cases are pre-B2 ALL (CD10+ and cytoplasmic μ chain negative).

Disease

Acute myeloid leukemia with lymphoid associated antigens.

Genes involved and proteins**TCL1****Location**

The TCL1 (or TCL1A) oncogene is located on chromosome 14q32.1. It belongs to the TCL1 family. TCL1A gene is 6.5 Kb in size and contains four exons.

Note

TCL1B is located on 14q32.1 16 Kb centromeric of TCL1A and shows 60% similarity to TCL1; TCL1A and TCL1B are located in the about 160 kb region of breakpoints observed in T cell leukemia cases with translocations at 14q32.1.

Semi quantitative RT-PCR analysis revealed that both TCL1A and TCL1b genes are expressed in spleen, tonsil, fetal liver, fetal kidney and fetal thymus. However the TCL1B gene is expressed in a wide variety of tissues. Normally, TCL1A expression is observed in early T cell progenitors (CD4- CD8- CD3-) and lymphoid cell of the B lineage: pre B cells and immature IgM expressing B cells.

TCL1A, TCL1B encode for protein of about 14 kDa. TCL1A 14 kDa protein consists of an eight-stranded antiparallel beta barrel with a hydrophobic core and are predicted to bind small hydrophobic ligands such as retinoids, nucleosides or fatty acids.

In addition to TCL1 and TCL1b the locus contains two additional genes TCL1- neighboring gene (TNG1 and TNG2) encoding proteins of 141 and 110 amino acids. Recently two novel genes have been identified in this region: TML1 and TCL6. Since the TCL1, TCL1b, TML1, TCL6 genes are expressed in T-cell leukemias carrying a t(14;14) translocation, they are four candidate genes potentially involved in leukemogenesis.

MTCP1**DNA/RNA**

The MTCP1 is located at Xq28 and activated in rare cases of T-PLL with a t(X;14)(q28;q11) translocation.

Protein

MTCP1 encodes for two proteins p8MTCP1 and p13MTCP1.

TCR alpha TCR delta

Location: 14q11.2

DNA/RNA

The size of TCR alpha/delta locus is about 1 Mb. The TCR delta variable (V) diversity (D) joining (J) and constant region genes are situated within the TCR alpha locus between the TCR alpha V and the TCR alpha J segments.

The TCR delta locus contains three D segments and four J segments, whereas the TCR alpha J regions spans approximately 80 Kb and contains at least 61 segments.

The TCR alpha/delta locus is transcribed in a centromer to telomer direction.

Protein

T-cell receptor.

Result of the chromosomal anomaly**Hybrid gene****Description**

TCL1A and TCL1B are expressed at very low level in normal bone marrow and peripheral lymphocytes but are activated in the T-PLL by juxtaposition to the T cell receptor alpha/delta locus at 14q11.

The another gene of TCL1 family, MTCP1 is activated in rare cases of T-PLL with a t(X;14) translocation and is also homologous to TCL1A gene.

Breakpoints at 14q32.1 involve a chromosomal segment of about 160 Kb and cluster in two regions. The centromeric region is mainly involved in inversions, whereas the telomeric region is involved in simple translocations.

Fusion protein**Oncogenesis**

The protein kinase AKT, the homologue of v-akt isolated from the retrovirus AKT8, which causes T-cell lymphomas in mice, is a key player in transduction of antiapoptotic and proliferative signals in T-cell. The TCL1 protein, encoded by the TCL1A oncogene, interacts with the AKT, this interaction results in the enhancement of the AKT kinase activity and promotes its nuclear transport. In contrast, AKT kinase does not interact with the TCL1B protein. The biological outcome of the TCL1A-induced enhancement of AKT activity is expected to occur through the

phosphorylation of AKT specific targets. Because the TCL1A activated AKT translocates into the nucleus, the most likely targets are nuclear.

To be noted**Note**

A sporadic form of inv(14)(q11;q32) is found occasionally in cultured normal lymphocytes (at the level of about 1/500). It involves a site specific recombination between the immunoglobulin heavy chain (IgH) variable region on 14q32.3 with TCR J alpha on 14q11 and probably arises from illegitimate recombinase joining of the rearranged genes TCR J alpha and IgH in lymphoid progenitors.

The TCL1 is also activated in the majority of the cases of B cell lymphoma.

Although rearrangement of c-myc has not been demonstrated, cell from T-PLL with trisomy 8 or iso(8)(q10) overexpress the c-myc protein. It is then possible that a high expression of c-myc plays a role in disease progression as a secondary event.

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