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Leukaemia Section
Short Communication

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

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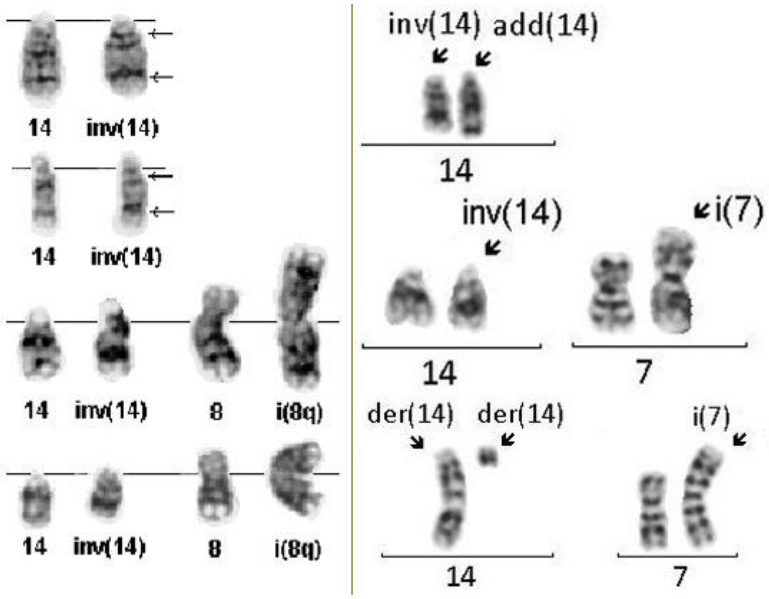
Abstract

Review on t(7;14)(q35;q32), inv(14)(q11q32) and t(14;14)(q11;q32), with data on clinics, and the genes involved.

Keywords

Chromosome 7; Chromosome 14; TCL1A; TRA; TRD; B lymphoblastic leukaemia/lymphoma; T lymphoblastic leukaemia/lymphoma; Adult T-cell leukemia/lymphoma; T-cell prolymphocytic leukemia; Angioimmunoblastic T-cell lymphoma; Chronic lymphocytic leukemia; syndrome; Mycosis fungoides; Hepatosplenic T-cell lymphoma; Acute myeloid leukaemia; Ataxia telangiectasia.



Left: inv(14)(q11q32)and i(8q), G- banding - Courtesy Jean Luc Lai; right: inv(14)(q11q32) and t(14)(14) with i(7q), G- banding - Courtesy Tatiana Gindina.

Clinics and pathology

Disease

Ataxia telangiectasia (AT)

Clinics

AT is a rare multisystem disease characterized by cerebellar ataxia, immunodeficiency, sensitivity to ionizing radiation, chromosome instability and predisposition to lymphoid malignancies, including T-PLL.

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

T Prolymphocytic leukemia (T-PLL)

An inv(14)(q11q32.1) was found in about 80% cases of T-PLL. In 10%, there is t(14;14)(q11;q32.1) (Brito-Babapulle et al., 1991; Maljaei et al, 1998).

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 10^9/L) (72%)

Cytology

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

In 20% of cases there are no obvious differencies between B and T prolymphocytes with proeminent 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)(q11q32) 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:

Anomalies of 11q23, where the ataxia teliangectasia 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.

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%). Deletions at 12p13 and 22q and amplification of 5p are on FISH and/or SNP array (Hetet et al., 2000; Bug et al., 2009; Nowak et al., 2009). Abnormalities of chromosomes 6 (33%) and 17 (26%) have also been identified by karyotyping and CGH (Brito-Babapulle et al., 1991, Costa et al., 2003). The TP53 gene is deleted, with overexpression of p53, in some cases (Brito-Babapulle et al., 2000).

Prognosis

T-PLL has an aggressive clinical course in most patients with median survival times ranging from 7 to 30 months. Cases with a more chronic course have also been reported, but such cases may progress after 2-3 years (Durig qt al., 2007).

Disease

Adult T-cell leukemia/lymphoma.

Inversion inv(14)(q11q32.1) and translocation t(14;14)(q11;q32.1) were reported in 10 and 2 cases, respectively (Miyamoto et al., 1984; Fujita et al., 1986; Sadamori et al., 1986; Sanada et al., 1987; Isobe et al., 1990; Sadamori et al., 1991; Kamada et al., 1992; Itoyama et al., 2001).

Cytogenetics

The karyotype is often complex. Deletion of 6q, 13q, 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 cytoplamic μ chain negative).

Disease

Angioimmunoblastic T-cell lymphoma.
The translocations (7;14)(q35;q32.1), t(14;14)(q11;q32.1) and inversion inv(14)(q11q32.1) were found in 2 cases for each anomaly (Cosimi et al., 1990; Schlegelberger et al., 1990; Leich et al., 2007).

Cytogenetics

Additional aberrations were trisomy 3, trisomy 7, i(7q), dup(7q).

Disease

Hepatosplenic T-cell lymphoma.
Only 2 cases with translocation t(7;14)(q35;q32.1) (Yabe et al., 2016; Yabe et al., 2016).

Cytogenetics

The translocation was as a sole aberration.

Disease

Mycosis fungoides/ Sezary syndrome.
The inversion inv(14)(q11q32.1) were observed in 2 cases (Brito-Babapulle et al., 1997).

Cytogenetics

Complex karyotype in both cases.

Disease

Acute myeloid leukemia with lymphoid associated antigens.

Genes involved and proteins

TCL1A (T-cell leukemia/lymphoma 1A).

Location
14q32.13.

Note
The 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.
TCL1B is located on 14q32.1 16 Kb centromeric of TCL1A and shows 60% similarity to TCL1A; 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 TCL1A and TCL1B the locus contains an additional TCL1- neighboring gene (TCL6) encoding proteins of 141 and 110 amino acids (Saitou et al., 2000).

MTCP1 (Mature T Cell Proliferation 1)

Location
Xq28

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

TRA (T cell Receptor Alpha)

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

TRD (T cell Receptor 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

TCL1A has been shown to promote cell proliferation and survival by acting as a coactivator of the protein kinase B (AKT), a key intracellular survival regulator. 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. Recent work revealed that the TCL1A oncoprotein also inhibits activation-induced cell death and growth arrest by inhibiting the proapoptotic PRKCG and ERK pathways (Despouy et al., 2007; Hsi et al., 2014).

To be noted

A sporadic form of inv(14)(q11q32) 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 MYC has not been demonstrated, cell from T-PLL with trisomy 8 or iso(8)(q10) overexpress the 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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