

# Leukaemia Section

## Review

### T-lineage acute lymphoblastic leukemia (T-ALL)

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## Identity

**Note:** Most of the recurrent abnormalities in T-ALL are different from those associated with B-lineage ALL. Clinical aspects of the main chromosomal abnormalities observed by conventional cytogenetics are herein described. The numerous oncogenes involved in T-ALL were first characterized by cloning of recurrent chromosomal abnormalities. Subsequently, distinct oncogenic T-ALL subgroups were defined by modern molecular methods. A brief description of the novel cryptic genetic lesions that are intertwined with the molecular cytogenetics of T-cell disease is presented here.

**Other names:** T-cell ALL

## Clinics and pathology

### Etiology

Immunophenotypic and gene expression analyses of T-ALL cells have revealed heterogeneity that is partially related to arrest at distinct stages of development. Initial cytogenetics studies of T-ALL cases showed nonrandom breakpoints within the following three T-cell receptor (TCR) gene clusters: TRA@(TCRA), TRD@(TCRD) locus (14q11.2), or TRB@(TCRB) locus (7q34). The TCR breakpoints were present in about 30% to 35% of T-ALL cases. The TRG@(TCRG) locus (7p14) may be restricted to T-cell ALL in patients with ataxia telangiectasia. During T-cell differentiation, these four loci undergo structural rearrangement that is analogous to the rearrangement of immunoglobulin genes during B-cell development.

The TCR promoter and enhancer elements are juxtaposed to a relatively small number of developmentally important genes that encode transcription factors leading to T-cell malignancies. The chromosomal aberrations that affect the TCR loci

were among the first to be reported in T-ALL. Subsequently, these and other rarer translocations facilitated the identification of genes that are altered in T-ALL, many of which are also transcriptionally activated without evidence of any detectable chromosomal rearrangement affecting these loci. In summary, the ectopic expression of TAL1(SCL), LYL1, LMO1, LMO2, TLX1(HOX11), and TLX3(HOX11L2), NOTCH1-activating mutations, and CDKN2-inactivating deletions are among the most prevalent causes of human T-ALL.

### Epidemiology

Among acute leukemia, T-ALL accounts for about 15% of pediatric cases and 20% of adults cases. As detected by conventional cytogenetic methods, patients with T-ALL have a smaller percentage of abnormal clones (60%-70%) than do patients with B-lineage ALL (80%-90%). Tetraploidy is observed in about 3% of patients with T-ALL, but it has no known prognostic significance. Cytogenetic abnormalities that are common in B-cell ALL (e.g., high-hyperdiploidy) are uncommon in T-cell ALL. Many of the translocations seen in T-ALL are recurrent but with a low frequency. A high number of T-ALL cases have cryptic abnormalities, as shown by fluorescent in situ hybridization (FISH) or other molecular methods. In some instances, this occurs because some of the loci involved in oncogenic rearrangements of T-ALL have a near-telomeric location that generates subtle exchanges in DNA material, and these changes subsequently cause the cryptic translocations. As many as 80% of patients with T-ALL have cryptic deletions of the putative tumor suppressor gene CDKN2A(INK4A) (9p21), and as many as 60% have cryptic deletions of TAL1 (1p32). Other genes such as TLX1(HOX11) (10q24) and NOTCH1 (9q34) are activated at a much higher frequency than expected from cytogenetic studies alone; thus, simultaneous dysregulation of different

signaling pathways may contribute to the multistep pathogenesis of T-ALL subgroups.

### Clinics

The incidence of T-ALL increases with age, i.e., at 1 to 10 years of age, the incidence is about 7%; at 10 to 15 years, about 14%; and at 15 to 18 years, about 29%. T-ALL is more common in boys and is characterized by hyperleukocytosis, enlarged mediastinal lymph nodes, and the scarcity of hyperdiploid (>50 chromosomes) leukemic cells. T-ALL also often involves the central nervous system (CNS). Children and adolescents with T-ALL are much more likely than children with B-lineage ALL to meet 'high-risk' age and white blood cell count criteria (75% for T-ALL versus 32% for B-precursor ALL). However, unlike that in B-precursor ALL, high leukocyte count does not identify high-risk T-ALL in children or adults.

### Prognosis

The historically unfavorable outcome of patients with T-ALL has recently improved through the use of highly effective treatment protocols. T-ALL is now treated the same way as high-risk B-progenitor ALL. With appropriately intensive therapy, children with T-ALL have an outcome similar to that of children with B-precursor ALL, i.e., the estimated 5-year event-free survival (EFS) is 75% to 80%. Nevertheless, patients with T-ALL remain at increased risk for remission induction failure, early relapse, and isolated CNS relapse. In a recent study of adolescents with ALL, no significant difference in outcome of T-ALL was found on the basis of age; older patients did as well as younger ones.

At present, there are no genetic markers in T-ALL that reliably predict treatment response or outcome. Gene expression analysis has revealed the prognostic significance of T-ALL oncogenes and the stage of thymocyte differentiation in which they are expressed. Some genetic markers have been shown to be of clinical relevance in a small series of pediatric patients with T-ALL: TLX1(HOX11)+ was associated with favorable outcome, and TAL1+ and LYL1+ were associated with unfavorable outcome. A favorable prognosis was also found with TLX1(HOX11)+ in adult T-ALL, possibly due to downregulation of antiapoptotic genes. The poor prognosis associated with T-ALL subtypes expressing TAL1 or LYL1 is thought to be caused by the concomitant upregulation of antiapoptotic genes that confer resistance to chemotherapy.

In early studies, the overexpression of TLX3(HOX11L2) was associated with poor prognosis; however, similar, more recent studies have not confirmed such findings. This difference is probably a reflection of the current aggressive treatments that have improved the therapeutic response in this subgroup of T-ALL. Therefore, the clinical significance of genetic

lesions in T-ALL remains largely unknown. The prognostic significance of T-ALL subtypes most likely depends on the type and intensity of the treatment administered. The development of targeted therapy for T-ALL might be contentious, given the simultaneous presence and the high prevalence of some genetic lesions affecting T-ALL.

## Cytogenetics

**Note:** Conventional molecular cytogenetic analyses of genetic lesions in T-ALL are summarized below. The following section presents prominent, recurring chromosomal abnormalities that affect either TCR or genes other than TCR (non-TCR genes) in T-ALL (Table 1). The breakpoints of some chromosomal rearrangements and gene names may have been modified from the original report for consistency and according to current HUGO gene nomenclature.

### Cytogenetics morphological

#### TCR GENETIC LESIONS IN T-ALL

##### TRB@ (7q34)

Conventional cytogenetic analysis revealed that chromosomal abnormalities affecting 7q34 (TRB@) occur in 5% to 8% of T-ALL cases with an abnormal karyotype. Recent molecular cytogenetics studies have revealed a higher incidence of TRB@ locus rearrangements (about 20% of all T-ALL cases). This finding demonstrates that the frequency of TRB@ rearrangements is similar to that of TRA@ (14q11.2) (about 24% of all T-ALL cases). Simultaneous rearrangements targeting both the TRB@ and TRA@ loci were observed in five of 126 (4%) patients with T-ALL, possibly reflecting the higher susceptibility for errors in VDJ recombination.

**t(1;7)(p32;q34).** The variant t(1;7)(p32;q34) disrupts TAL1 (TCL5/SCL) by juxtaposing to the TRB@ locus.

**t(1;7)(p34;q34).** This rare t(1;7)(p34;q34) is present in less than 1% of T-ALL cases and results in the fusion of LCK and TRB@ loci, thereby activating LCK.

**t(7;9)(q34;q34.3).** The t(7;9)(q34;q34.3) occurs in about 2% of T-ALL, resulting in the fusion of TRB@ and NOTCH1 loci. NOTCH1 is an early transcription factor that commits lymphoid progenitor cells toward T-cell development. NOTCH1-activating mutations have been shown in more than 50% of T-ALL cases. This finding suggests that NOTCH1 helps transform T-lineage cells. One study demonstrated that NOTCH1-activating mutations predict a more rapid, early treatment response and significantly better 4-year EFS than those without mutations (90% vs. 71%). NOTCH1 mutations are associated with the expression of TAL1, LYL1, TLX1, TLX3, MLL-MLLT1, and PICALM-MLLT10, all of which define the major subtypes of T-ALL.

**Table 1. Immunophenotype-specific rearrangements generated by T-cell receptor (TRC) and non-TCR genes in T-lineage acute lymphoblastic leukemia (T-ALL)**

T-ALL gene or cluster (chromosome location)	Abnormality	Partner gene
TRB@ (7q34)	t(1;7)(p32;q34)	TAL1(TCL5/SCL)
	t(1;7)(p34;q34)	LCK
	inv(7)(p15.3q34) or t(7;7)(p15.3;q34)	HOXA@
	t(7;9)(q34;q32)	TAL2
	t(7;9)(q34;q34.3)	NOTCH1(TAN1)
	t(7;10)(q34;q24)	TLX1(HOX11)
	t(7;11)(q34;p13)	LMO2(RBTN2)
	t(7;11)(q34;q24)	UNKNOWN
	t(7;12)(q34;p13.3)	CCND2
	t(7;14)(q34;q32.1)	TCL1
	t(7;19)(q34;p13.2)	LYL1
	TRA@ or TRD@ (14q11.2)	t(1;14)(p32;q11.2)
t(1;14)(p34;q11.2)		LCK
t(5;14)(q35.1;q11.2)*		TLX3(HOX11L2)
t(7;14)(p15.1;q11.2)		HOXA@
t(8;14)(q24.1;q11.2)		MYC(CMYC)
t(9;14)(p21;q11.2)		CDKN2A(INK4A/P16/MTS1/P19/ARF)
t(10;14)(q24;q11.2)		TLX1(HOX11)
t(11;14)(p13;q11.2)		LMO2(RBTN2)
t(11;14)(p15;q11.2)		LMO1(RBTN1)
t(12;14)(p13.3;q11.2)		CCND2
t(14;14)(q11.2;q32.1) or inv(14)(q11.2q32.3)		TCL1A, TCL1b(TML1), TCL6, BCL11B(CTIP2)
t(14;21)(q11.2;q22.1)		OLIG2(BHLHB1)
t(14;14)(q28;q11.2)	MTCP1	
Non-TCR Genes	del(1)(p32)*	TAL1(STIL/SCL)
	t(1;3)(p32;p21)	TAL1-TCTA
	t(1;5)(p32;q31)	TAL1-UNKNOWN
	t(4;11)(q21;p15.5)	NUP98-RAP1GDS1
	t(4;21)(q31;q22)	RUNX1(AML1/CBFA2)-UNKNOWN
	t(5;7)(q35.1;q21)	CDK6-TLX3(HOX11L2)
	t(5;14)(q35.1;q32.2)*	BCL11B(CTIP2)/NKX2-5(CSX)-TLX3(HOX11L2)
	dup6q23*	MYB
	del(9)(p21)	CDKN2A(INK4A/P16/MTS1/P19/ARF) and/or CDKN2B(INK4B/P15/MTS2)
	t(9;12)(p24;p13)	ETV6(TEL)-JAK2
	t(9;12)(q34;p13)	ETV6(TEL)-ABL1(ABL)
	t(9;14)(q34;q32)*	EML1-ABL1(ABL)
	t(9;22)(q34;q11.2)	BCR-ABL1
	amp9q34*	NUP214(CAN)-ABL1(ABL)
	dup9q34*	UNKNOWN
	t(10;11)(p12;q14)	PICALM(CALM)-MLLT10(AF10)
	t(10;11)(q25;p15.5)	NUP98-ADD3
	del(11)(p12p13)	LMO2(RBTN2)
	t(11;18)(p15.5;q12)	NUP98-SETBP1
	t(11;19)(q23;p13.3)	MLL-MLLT1(ENL)
t(11;19)(q13.1;q23)	MLLT7(AFX1)-MLL	

\*Submicroscopic

This review has adopted the new ISCN 2005 nomenclature.

Standardization of the probe nomenclature is a requirement, as per GDB or HUGO: <http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl>

Table 1. Immunophenotype-specific rearrangements generated by T-cell receptor (TRC) and non-TCR genes in T-lineage acute lymphoblastic leukemia (T-ALL).

These findings highlight the importance of the multiple pathways regulated by NOTCH1 signaling in the process of leukemogenesis. Targeted therapies directed toward the NOTCH1 pathway may be of potential clinical relevance for patients with T-ALL who carry such activating mutations. Furthermore, gamma-secretase inhibitors (GSI) induce cell cycle arrest in vitro in T-

ALL cell lines harboring NOTCH1 mutations. Therefore, GSIs are a potential therapeutic strategy for the treatment of T-ALL. However, the integration of such targeted therapy should be implemented with caution because of the recently reported excellent treatment outcome for patients with NOTCH1-activating mutations.

**t(7;9)(q34;q32).** The infrequent t(7;9)(q34;q32) results in the altered expression of TAL2.

**t(7;10)(q34;q24).** A variant of the more common t(10;14)(q24;q11.2), t(7;10)(q34;q24) activates the expression of the DNA-binding transcription factor gene TLX1 (HOX11).

**t(7;11)(q34;p13).** A variant of the more common t(11;14)(p13;q11.2), t(7;11)(q34;p13) activates the expression of the DNA-binding transcription factor gene LMO2.

**t(7;12)(q34;p13.3).** The rare t(7;12)(q34;p13.3) deregulates CCND2 by chromosomal translocations to the TRB@ locus in T-ALL. This translocation and its variant, t(12;14)(p13;q11.2), are also associated with other genetic lesions observed in T-ALLs, a finding that suggests that CCND2 dysregulation contributes to multievent oncogenesis in various subtypes of T-ALL.

**t(7;14)(q34;q32.1)/TCL1.** The variant t(7;14)(q34;q32.1) is also seen in T-cell leukemias, juxtaposing TRB@ with TCL1A.

**t(7;19)(q34;p13.2).** In the t(7;19)(q34;p13.2), the LYL1 gene is juxtaposed to the TRB@ locus, resulting in the constitutive expression of LYL1, which is not expressed in normal T cells. Patients whose leukemic blast cells ectopically express LYL1 have an unfavorable outcome, which is thought to be due to the upregulation of antiapoptotic proteins.

**inv(7)(p15.3;q34)/t(7;7)(p15.3;q34).** As a result of a cryptic inv(7)(p15q34) and t(7;7)(p15;q34), the TRB@ locus is juxtaposed to the HOXA@ at 7p15 in about 3.3% of T-ALL cases. This rearrangement leads to transcriptional activation of several HOXA genes, including HOXA10 and HOXA11. One case was identified carrying a triplication of the TRB@-HOXA fusion on a ring chromosome 7; this finding suggested an additional mechanism of transcriptional activation of HOXA@. Furthermore, HOXA@ expression is increased in the absence of these chromosomal rearrangements in 25% of T-ALL cases. The upregulation of HOXA gene expression was also found in MLL-MLLT1(ENL)+ and PICALM(CALM)-MLLT10(AF10)+ T-ALLs, a NOTCH1-activating mutation, and a deletion of 9p21. These findings indicated a more general role of HOXA@ genes in T-cell oncogenesis. The outcome of 14 patients with the TRB@-HOXA@ in a larger study was similar to that of other patients with T-ALL who did not carry the fusion transcript.

**Other cryptic breakpoints.** Evaluations of cryptic 7q34/TRB@ with FISH probes include new putative transcription factor genes at 11q24, 20p12, and 6q22. The subtle rearrangements at 7q34 can be explained by distant chromosomal location of the TRB@ (7q34) and the partner gene(s). For example, the t(7;7)(p15.3;q34), inv(7)(p15.3q34), t(7;11)(q34;q24), and t(7;10)(q34;q24) all have distal breakpoints.

#### **TRG@ (7p14)**

The TRG@(TCRG) locus (7p14) may be restricted to T-cell tumors in patients with ataxia telangiectasia. The TRG@ locus is not involved in translocations in T-ALL. Historically, it was thought that the inv(7)(p15;q34) or t(7;7)(p15;q34) juxtaposed TRB@ to TRG@, but recently it was shown that the TRB@-HOXA fusion is generated by such rearrangements. One exception was a t(1;7)(p31-32;p13) in a 16 year-old male patient who had precursor T-cell lymphoblastic leukemia/lymphoma. This rearrangement was identified during the evaluation of FISH probes to detect TCR breakpoints. It was speculated that the breakpoint at 1p may have involved the TAL1 or LCK oncogenes.

#### **TRA@ or TRD@ (14q11.2)**

Among the most common chromosomal abnormalities observed by conventional cytogenetics, those associated with T-ALL are chromosome 14 alterations in which the breakpoint is located at 14q11.2. By conventional cytogenetics, this abnormality represents about 17% of all T-ALL cases (Table 1). By molecular cytogenetics studies, the incidence of TRA@/TRD@ rearrangements is about 24% of all T-ALL cases.

**t(1;14)(p32;q11.2).** This translocation is observed in about 3% of T-ALL. The TAL1(TCL5/SCL) gene, which is located on 1p32, is juxtaposed with the TRD@ locus. As a result of t(1;14)(p32;q11.2), TAL1 is controlled by the regulatory elements of the TRD@, which results in disruption of TAL1 and its ectopic expression (see 1p32/TAL1(SCL) deletion below).

**t(5;14)(q35.1;q11.2).** The t(5;14)(q35.1;q11.2) disrupts the TLX3(HOX11L2) by translocating to TRD@.

**t(7;14)(p15.1;q11.2).** The cloning of T-ALL from one patient who carried a t(7;14)(p15.1;q11.2) showed the juxtaposition of HOXA@ with the TRD@ overexpressing HOXA genes. The leukemic cells of this patient also had a t(10;11)(p12;q14) /PICALM-MLLT10.

**t(8;14)(q24.1;q11.2).** This translocation is seen in approximately 2% of patients with T-ALL, but it is not restricted to the T-lineage. The t(8;14)(q24.1;q11.2) results in the rearrangement of the TRA@ locus with the MYC(CMYC) oncogene, which in turn dysregulates MYC transcription. The disease in these cases is aggressive, and the response to conventional therapy is poor.

**t(10;14)(q24;q11.2).** The t(10;14)(q24;q11.2) and its variant t(7;10)(q34;q24) is seen in 5% to 10% of patients with T-ALL or T-cell lymphomas. These rearrangements are more frequent in adults than in children. The t(10;14) results in the translocation of TLX1(HOX11) (10q24) to TRA@/TRD@ (14q11.2) and the overexpression of TLX1. The t(10;14) can be detected by PCR, and a dual-color FISH probe is often used to detect HOX11 translocations on 10q24.

However, TLX1 overexpression in leukemic blasts has been observed in the absence of 10q24 rearrangement in as many as 50% of T-ALL cases. Therefore, other trans-acting mechanisms, e.g., disruption of gene silencing, may cause aberrant expression of the gene. The gene expression pattern of TLX1-expressing lymphoblasts is similar to that of early cortical thymocytes. Therefore, the lack of expression of antiapoptotic genes during this stage of thymocyte development (and in TLX1-expressing lymphoblasts) may explain why pediatric and adult patients with this type of lymphoblast have a highly favorable outcome. Other studies have not demonstrated significant improvement in outcome. Furthermore, activation of other mutant genes, including NOTCH1, is found in most TLX1+ T-ALL. This finding suggests that multiple cooperating changes lead to T-cell differentiation arrest.

**t(11;14)(p13;q11.2).** The t(11;14)(p13;q11.2) is among the most common nonrandom abnormalities detected by conventional cytogenetic methods in T-ALL blast cells. This rearrangement is found in less than 10% of children with T-ALL. The t(11;14)(p13;q11.2) TRA@ or TRD@ dysregulates LMO2. A rare variant, t(7;11)(q34;p13), may also be found with an LMO2-TRB@ fusion that constitutively activates the LMO2 gene. However, high levels of LMO2 expression have also been reported in the absence of translocations in as many as 30% of T-ALL cases. This finding suggests that alternative mechanisms in T-ALL cells activate LMO2.

**t(11;14)(p15;q11.2).** The t(11;14)(p15;q11.2) occurs in 1% of patients with T-ALL. The breakpoint on chromosome 11 is found in one of the rhombotin-2-related, stage-specific differentiation genes (e.g., LMO1). LMO1 and LMO2 are expressed in patients whose leukemic cells also have deregulated expression of TAL1 or LYL1.

**t(12;14)(p13.3;q11.2).** The t(12;14)(p13.3;q11.2) dysregulates CCND2 by translocating it to the TRA@/TRD@ loci.

**t(14;14)(q11.2;q32.1) or inv(14)(q11.2q32.1).** These chromosomal abnormalities have been detected with high frequency in patients with ataxia telangiectasia and mature T-cell leukemias but less frequently in patients with acute T-cell leukemias. Most cases with a t(14;14)(q11.2;q32.1) or inv(14)(q11.2q32.1) result in the rearrangement of the TRA@ or TRD@ loci with the TCL1A oncogene on 14q32.1 centromeric to the IGH@ locus (14q32.3). The variant t(7;14)(q34;q32.1) was also seen in T-ALL, juxtaposing TRB@ with TCL1A. A study to evaluate the detection of TCR breakpoints by FISH showed that most, but not all, cases with 14q11.2 breaks involve TRA@/TRD@; likewise, not all 14q32 breaks involve TCL1A. In that series, one adult T-cell leukemia/lymphoma case with a t(14;14)(q11.2;q32) indicated a breakpoint in BCL11B, which is the gene involved in the t(5;14)(q35;q32),

generating the BCL11B-TLX3 fusion. In another study, the leukemic blasts of a patient with T-ALL had other complex chromosomal aberrations and an inv(14)(q11.2q32) that juxtaposed the disrupted BCL11B gene with TRD@. Other genes located to the same 14q32.1 region, centromeric to TCL1A (e.g., TCL1b(TML1) and TCL6), are activated in T-cell malignancies. Of note, a few cases with t(14;14)(q11.2;q32) and B-lineage ALL were reported with IGH involvement.

**t(14;21)(q11.2;q22.1).** The t(14;21)(q11.2;q22.1) translocates OLIG2(BHLHB1) to the TRA@ locus.

t(X;14)(q28;q11.2). The t(X;14)(q28;q11.2) is mostly observed in mature T-cell leukemias and dysregulates the MTCPI gene.

#### NON-TCR GENETIC LESIONS IN T-ALL

**del(1)(p32)/TAL1(SCL).** A cryptic interstitial deletion of TAL1 in the chromosome region 1p32 is observed in as many as 30% of patients with T-ALL. The deletion (about 90 kb) is in the coding region of the STIL(SIL) gene, which is also located on 1p32, and in the untranslated region of the TAL1 gene, thereby placing the TAL1-coding region under the control of the STIL(SIL) promoter region and generating STIL-TAL1 fusion transcripts. The common site-specific deletion in TAL1 results in its ectopic expression via illegitimate recombinase activity. Also, misexpression of TAL1 has been observed in approximately 30% of patients who have T-ALL but no detectable TAL1 abnormality. Therefore, TAL1 protein is ectopically expressed in leukemic blast cells in as many as 60% of patients with T-ALL. The 90-kb deletion in the TAL1-coding region can be detected by FISH, Southern blot analysis, genomic PCR, or RT-PCR for identification of the various types of fusion genes generated. It is not detected by conventional cytogenetics. TAL1 is essential for primitive hematopoiesis and adult erythropoiesis and megakaryopoiesis. In one study, patients with T-ALL whose leukemic blast cells ectopically expressed TAL1 had an unfavorable outcome, which was thought to be due to the upregulation of antiapoptotic proteins. However, the clinical relevance of TAL1 rearrangements remains unclear.

**t(1;3)(p32;p21).** The t(1;3)(p32;p21) disrupts TAL1(SCL/TCL5) by juxtaposing with the TCTA gene.

**t(1;5)(p32;q31).** The t(1;5)(p32;q31) dysregulates the expression of TAL1 by an unknown gene.

t(4;11)(q21;p15.5). The t(4;11)(q21;p15.5) was observed in a subgroup of T-ALL whose leukemic cells coexpressed myeloid markers. The t(4;11) results in the NUP98 - RAPIGDS1 fusion.

**t(4;21)(q31;q22).** A t(4;21)(q31;q22) was seen in a 12-year-old boy with T-ALL. FISH analysis showed that the RUNX1(AML1/CBFA2) (21q22) gene was rearranged by the translocation.

+4. Trisomy 4 as the sole chromosomal abnormality in ALL has been reported in T-ALL, but it is not limited to this lineage of disease. The clinical implications of +4 remain unknown.

**t(5;14)(q35.1;q32.2).** The t(5;14)(q35.1;q32.2), a recurrent cryptic translocation specific to T cells, has been observed in as many as 20% of pediatric patients and 13% of adults patients with T-ALL. The t(5;14) is not observed by conventional cytogenetics, but FISH probes are available for its detection. In most instances, the t(5;14) results in the activation of the TLX3(HOX11L2) homeobox gene at 5q35.1. This gene is activated by T-cell regulatory elements downstream of BCL11B(CTIP2) gene, which is located at 14q32.2 and is highly expressed during T-cell differentiation. A neighboring, related homeobox gene at 5q35.1, NKX2-5(CSX), is similarly activated in T-ALL by a rarer variant t(5;14)(q35.1;q32.2) or by t(5;14)(q35.1;q11.2) involving TRD@ locus. Ectopic expression of TLX3 has also been identified in cases of childhood T-ALL without evidence of the t(5;14). A few case with t(5;14)/BCL11B-TLX3 fusion have also shown the 9q34amp/NUP214-ABL1 fusion. Some studies reported that TLX3 overexpression was associated with poor prognosis, whereas other studies did not confirm these findings.

**t(5;7)(q35.1;q21).** A variant t(5;7)(q35.1;q21) involving the CDK6 gene on 7q21, TLX3, and other cryptic rearrangements affecting TLX3 have been reported.

**del(6q).** Cytogenetic analyses revealed that deletion of the q arm of chromosome 6 occurs in about 15% of T-ALL cases. Molecular analyses revealed that this rearrangement occurs in 15% to 32% of cases. Furthermore, del(6q) is more frequent in T-ALL than in precursor B-lineage ALL. The crucial regions of loss of heterozygosity in the q arm of 6q are between 6q15 and 6q21, but no tumor suppressor gene has yet been identified. Earlier studies reported that del(6q) is associated with an inferior early response to treatment and poor outcome, but no prognostic significance has been noted in subsequent studies. This most likely reflects the fact that T-ALL cases are now stratified into the high-risk arm of treatment protocols; thus, the prognostic value of del(6q) depends on the treatment.

**t(6;7)(q23;q32-36).** The t(6;7)(q23;q32-36) is an infrequent but recurrent translocation in T-ALL. The 6q breakpoints established in two cases were only 150 kb apart. In one case, the breakpoint potentially disrupted or deregulated the MYB gene, and in the other case, it potentially disrupted the AH11 gene.

**dup6q23/MYB.** Recently, a duplication of 6q23 region was identified in 9 of 107 (8.4%) patients with T-ALL by the array comparative genome hybridization (array-CGH) method. The commonly duplicated region covered the MYB gene

**del(9)(p21).** Deletion or inactivation of genes located in close proximity on 9p21 is one of the most common

genetic defects in T-ALL. By conventional cytogenetics, translocations involving 9p have been seen in 9% to 12% of children with ALL. However, FISH and other molecular methods have shown that homozygous deletions of CDKN2A(INK4A) [encoding p16(INK4a) and p14(ARF) proteins] occur in 60% to 80% of children with T-ALL; homozygous deletions of CDKN2B(INK4B) (encoding p15 protein) occur in approximately 20% of children with T-ALL. Hemizygous deletion of INK4A occurs in about 10% of pediatric T-ALL cases, and that of INK4B occurs in about 15%. One study has reported inactivation of INK4A in 93% of T-ALL cell samples tested and that of INK4B in 99%. Other contiguous genes such as IFN1@ and MTAP can be included in the deletions; thus, ALL with 9p21 is a rather heterogeneous group. Because proteins encoded by these genes might influence the response to treatment, the prognosis of patients with 9p21-deleted T-ALL could vary according to the extent of the deletion. The prognostic significance of loss of heterozygosity of CDKN2A in childhood ALL remains controversial.

**9p13/PAX5.** The gene involved in 9p13 abnormalities is PAX5; its role is unclear in leukemogenesis in T-cells.

**t(9;12)(p24;p13).** JAK2 was fused to ETV6(TEL) as a result of the t(9;12)(p24;p13) in a child with T-ALL. The role of the ETV6-JAK2 fusion gene in T-ALL pathogenesis was confirmed by the finding that fatal leukemia accompanied by preferential expansion of CD8+ T cells developed in mice whose lymphoid cells contained an ETV6-JAK2 transgene.

**t(8;9)(p22;p24).** This t(8;9) formed a PCM1 -JAK2 fusion in a patient with T-cell lymphoma. Such translocations have been found in other patients with myeloid diseases.

**9q34/ABL1.** The genetic lesions affecting the ABL1 locus generate fusion proteins that are constitutively phosphorylated tyrosine kinases. These kinases, which are described in more detail below, excessively activate pathways that regulate cell survival and proliferation. Gene-targeted therapy aimed to inhibit tyrosine kinases (e.g., imatinib mesylate) could improve the outcome of patients with ABL-fusion+ T-ALL.

**t(9;22)(q34;q11.2)/BCR-ABL1(ABL).**

The t(9;22)(q34;q11.2)/BCR-ABL1(ABL), also known as Philadelphia (Ph)+ ALL, is associated with the worst prognosis in children. It occurs in 3% to 5% of children and in 25% of adults with the disease. Most cases of Ph+ ALL are phenotypically pre-B cell lineage, but an international pediatric study showed that 2% had a T-cell immunophenotype. In that series, there was no significant prognostic difference between Ph+ pre-B ALL and Ph+ T-ALL. Most cases of Ph+ T-ALL have an aggressive course, persistence of the clone, as detected by minimal residual disease (MRD), and a dismal prognosis. Distinguishing Ph+ T-ALL from chronic myelogenous leukemia (CML) with T cell-

derived leukemic blast crisis may be challenging and of clinical relevance in the imatinib era.

**9q34amp/NUP214-ABL1.** The 9q34 amplification (multiple signals of the ABL1 gene per nucleus) is a cryptic abnormality. Although this rearrangement is not detectable by conventional cytogenetics, it occurs in about 3% to 6% of T-ALL cases. It is detected by FISH using ABL1 or BCR-ABL1 probes that show a variable number of extrachromosomal amplified elements of the ABL1 locus independent of BCR in metaphase, and multiple signals in most interphase cells. The episomes contained ABL1, LAMC3, and NUP214 genes localized within a 500-kb region on 9q34. Subsequently, the circular nature of the genomic region from ABL1 to NUP214 was discovered; this formation created an extrachromosomal episomal structure that contains the NUP214-ABL1 fusion genes. The copy number of the episome may vary from cell to cell, increasing due to unequal segregation during cell division. Most karyotypes of cases with 9q34amp are abnormal, including some of the recurrent translocations seen in T-ALL. The 9q34 amp is associated with the deletion of CDKN2A and CDKN2B and ectopic expression of TLX1 or TLX3. A few cases with t(5;14) also had the NUP214-ABL1 extrachromosomal episomal amplification. Of interest, a T-ALL case with t(5;14)/BCL11B-TLX3 fusion also had an amplified NUP214-ABL1 fusion inserted in the 2q21 region. This was in addition to the normal ABL1 signals on both 9q34 copies, without evidence of extrachromosomal episomal amplification. The NUP214-ABL1 fusion appears to be associated with aggressive disease and poor outcome. A recent report of NUP214-ABL1 in adult T-ALL did not find a statistically significant difference in overall survival when compared with that in patients lacking the fusion. Like BCR-ABL1, the NUP214-ABL1 fusion is a constitutively active tyrosine kinase with transforming activity in vitro. However, because of the heterogeneity in the genetic lesions observed in many cases, the response to imatinib in NUP214-ABL1+ cases should be evaluated with caution. Ph+ CML with amplification of BCR-ABL1 is resistant to imatinib.

**9q34dup/amp.** Recently, a duplication of 9q34 region was identified in 33% of pediatric T-ALL cases by array-CGH. The exact size of the amplified region differed slightly among patients, but the crucial region encompassed many genes such as NOTCH1 that were distal from ABL1 and NUP214. The size of the 9q34-amplified region varied among patients, and in some cases, it was observed as only a minor leukemic clone. The duplication appears to be an independent genetic event from both the episomal NUP214-ABL1 amplification and the NOTCH1 mutations but may lead to the activation of other putative regulatory genes in the 9q34 region. Some of the patients with the 9q34dup also had NUP214-ABL1 episomal amplification but in an independent leukemic clone. The subclones with the

9q34dup were also observed in patients with other clonal abnormalities frequently seen in T-ALL cases. At present, the meaning of this finding is unclear.

**t(9;12)(q34;p13).** Another ABL1 fusion seen in a T-cell ALL case is t(9;12)(q34;p13), which generates the ETV6-ABL1 fusion.

**t(9;14)(q34;q32).** A cryptic t(9;14)(q34;q32) was seen in one T-ALL case. This rearrangement resulted in EML1-ABL1 fusion with dysregulated tyrosine kinase activity. The leukemic cells from this patient also showed ectopic expression of TLX1 and hemizygous deletion of the CDKN2A. Subsequently, the patient experienced T-ALL relapse with no evidence of the EML1-ABL1 but newly acquired NUP214-ABL1 positivity.

**t(10;11)(p12;q14).** The PICALM(CALM)-MLLT10(AF10) fusion gene is created by the t(10;11)(p12;q14), which is a recurrent abnormality in about 4% to 9% of T-ALL cases. However, this rearrangement also has been observed in non-T-cell acute leukemias. The translocation is not always evident by conventional cytogenetic methods, but it can be detected by FISH or RT-PCR. Furthermore, distinction of this chromosomal abnormality from t(10;11)(p12;q23) involving MLL-MLLT10(AF10) can be challenging, often requiring FISH or RT-PCR to make the differential diagnosis. Some T-ALL cases with the PICALM-MLLT10 fusion also demonstrate upregulation of the HOXA@ genes.

**t(10;11)(q25;p15.5).** This t(10;11)(q25;p15.5) was seen in a patient with T-ALL whose leukemic cells expressed myeloid markers. The rearrangement resulted in the NUP98-ADD3 fusion.

**del(11)(p12p13)/LMO2.** A cryptic deletion of 11p was detected recently by array-CGH in about 4% of pediatric patients with T-ALL. The localization of genomic breakpoints in the deletion was heterogeneous. In most del(11p) cases, the oncogene LMO2 was activated independent from other recurrent cytogenetic abnormalities that are frequently present in T-ALL. In one of six patients, the RAG2 promoter controlled the expression of LMO2, thereby generating a RAG2-LMO2 fusion. In other cases, the deletion of negative regulatory sequences upstream of LMO2 was suggested to contribute to its ectopic expression.

**11p13/LMO2 - Insertional Mutagenesis.** T-ALL developed in two of 10 infants enrolled in the retroviral IL2RG gene therapy trial for X-linked severe combined immunodeficiency (X1-SCID). Retroviral insertion in the proximity of the LMO2 gene leads to aberrant transcription and expression of LMO2. In that trial, leukemia was diagnosed 3 years after the gene therapy was completed.

**11q23/MLL.** Abnormalities of 11q23 have been observed in approximately 4% of children with T-ALL and in 6% to 8% of adults with the disease. In an international collaborative study of ALL with 11q23 abnormality and known immunophenotype, T-ALL

was present in 40 of 459 (8.7%) cases. Most patients with T-ALL and 11q23 rearrangements have a t(11;19)(q23;p13.3), though cases with a del(11)(q23) should be further evaluated by FISH using the MLL probe to rule-out a subtle translocation such as t(6;11)(q27;q23). Other translocations seen infrequently in T-ALL include (4;11)(q21;q23), t(9;11)(p22;q23), t(10;11)(p12;q23), and others seen in B-lineage ALL or AML. MLL fusion proteins have increased transcriptional activity; thus, these proteins can also cause increased expression of HOXA9, HOXA10, HOXC6, and the MEIS1 HOX coregulator. T-ALL cells with MLL fusions are characterized by differentiation arrest at an early stage of thymocyte differentiation. Despite the historical, relatively adverse outcome generally associated with T-ALL, those cases with MLL aberrations have a much better prognosis than do their 11q23+ B-lineage counterparts.

**t(11;18)(p15.5;q12).** The t(11;18)(p15.5;q12) was observed in a 9 year-old boy with T-ALL. The t(11;18) results in the NUP98-SETBP1 fusion.

**t(11;19)(q23;p13.3).** T-ALL with t(11;19)(q23;p13.3) results in the MLL-MLLT1(ENL) fusion, which is associated with a good prognosis.

#### Summary:

In addition to conventional cytogenetic studies, molecular techniques that are more reliable, rapid, and sensitive are needed to detect multiple genetic lesions associated with T-ALL. The improved characterization of T-ALL genetic subgroups may facilitate the development of targeted gene therapy for those patients with refractory disease and less toxic therapy for those with responsive disease.

In recent years, the introduction of more intensive therapy has improved the overall outcome of patients with T-ALL, as indicated in the following landmark discoveries: Most of the recurrent abnormalities in T-ALL are different from those associated with B-lineage ALL.

- In B-lineage ALL, certain chromosomal subgroups have strong prognostic association. In contrast and with a few exceptions, cytogenetic features have no predictive value in T-ALL.

- Most cases of Ph+ T-ALL have an aggressive course and poor prognosis, similar to those of Ph+ B-lineage ALL.

- Cases of T-ALL with MLL aberrations have a much better prognosis than do their 11q23+ B-lineage counterparts.

- The t(10;14)(q24;q11.2) or upregulation of TLX1(HOX11) appears to be associated with better prognosis.

- Treatment outcome for patients with a NOTCH1-activating mutation is typically good.

- Tetraploidy is observed in about 3% of T-ALL and has no known prognostic significance.

- Hyperdiploidy (>50 chromosomes), which is seen in 25% to 30% of children with ALL, is rarely observed in T-ALL.

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