

Leukaemia Section

Short Communication

del(9p) in Acute Lymphoblastic Leukemia

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Abstract

Review on del(9p) in acute lymphoblastic leukemia, with data on clinics, and the genes involved.

Keywords

chromosome 9; del(9p); acute lymphoblastic leukemia

Identity

Deletion of 9p is a common recurring chromosomal aberration in acute lymphoblastic leukemia (ALL) of both B- and T-lineages ALL. The 9p region contains numerous cancer-associated genes such as JAK2, CD274 (PDL1)/ PDCD1LG2 (PDL2) at 9p24.1, CDKN2A, CDKN2B, MTAP, IFN, MLLT3, and HACD4 (PTPLAD2) at 9p21.3 as well as PAX5 at 9p13.2. Several of these genes have been implicated in the leukemogenesis of ALL (Mullighan CG 2012, Harrison CJ 2013).

Clinics and pathology

Disease

Acute lymphoblastic leukemia (ALL)

Epidemiology

Visible deletions of 9p by karyotype are seen in approximately 10% of ALL cases of both children (7-11%) and adult (5-15%). The loss of 9p is the second most frequent abnormality after t(9;22)/Ph in adult ALL, and the third after high

hyperdiploidy and t(12;21) in pediatric ALL (Moorman et al 2010). The minimal commonly deleted segment is band 9p21 encompassing the tumor suppressor genes CDKN2A and CDKN2B.

Clinics

At diagnosis patients are likely to have higher WBC counts, older age, male gender, splenomegaly, and hypodiploid karyotype than patients lacking 9p deletions (Heerema et al 1999). In addition, patients with a 9p abnormality have an increasing incidence of both marrow and central nervous system relapses.

Prognosis

The prognostic significance of 9p21/CDKN2A deletion has remained indecisive particularly in pediatric B-ALL. The differences in patient population and study designs among different studies may have had an impact on the overall results.

In Pediatric B-ALL Initial studies on a small number of patients suggested that deletion of 9p/CDKN2A was associated with an increased risk of relapse and death although other report concluded no prognostic effect on the disease outcome (Kees et al 1997, Zhou et al 1997). On a large cohort study, Heerema et al showed a high frequency of 9p abnormalities in ALL patients with high-risk or lymphomatous features, and an overall poorer outcome compared with those lacking this abnormality. Their data also indicated that 9p abnormalities identify a subgroup of NCI standard-risk patients with increased risk of treatment failure.

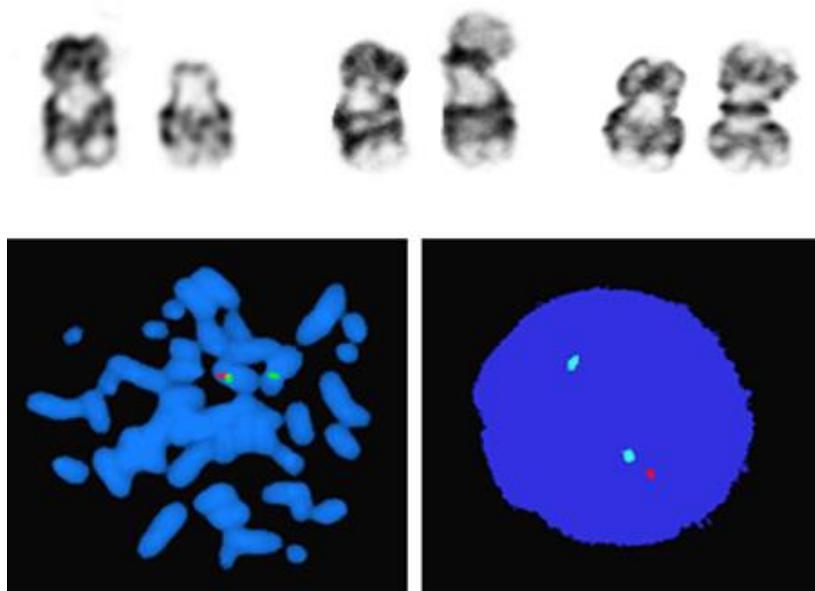


Figure 1; Top: Partial G-banded karyotype showing partial deletion 9p, der(9;16)(q10;p10), i(9)(q10) [left to right]. Bottom: FISH on metaphase cell (left) and interphase cell (right) showing one copy of CDKN2A (orange signal) and two copies of CEP 9 (green signal)

Yet, the recent study by Sulong et al concluded that CDKN2A deletion is a significant secondary genetic abnormality and variation in the incidence of CDKN2A deletion among the cytogenetic subgroups may explain its inconsistent association with outcome.

Conversely, the dicentric (9;12) has been associated with a favorable outcome in pediatric ALL.

In Adult B-ALL Patients with 9p deletions have significantly shorter overall survival when compared with patients with normal karyotypes. The overall survival is similar to that in the poor prognosis t(9;22)/BCR/ABL1-positive group (Nahi et al 2008).

In T-ALL The prognostic implications of loss of heterozygosity (LOH) of 9p were evaluated in pediatric T-ALL patients treated uniformly according to the Berlin-Frankfurt-Munster regimen. This study showed that LOH of 9p was associated with a favorable initial treatment response, and the event free survival was slightly favorable (Krieger et al 2010).

Cytogenetics

Cytogenetics morphological

The loss of material from 9p can result from a simple deletion in approximately 40% of cases or from various unbalanced translocations giving rise to a partial or complete loss of 9p such as isochromosome i(9)(q10), dicentric dic(9;12) and dic(9;20), whole arm der(V;9q10), and add(9p) [Figure 1].

The majority of 9p deletions are associated with a nonhyperdiploid karyotype (Heerema et al 1999). Although deletion of 9p occurs as a sole abnormality

in ~20% of cases, it is frequently accompanied by other primary genetic abnormalities such as t(1;19)(q23;p13.3), t(9;22)(q34;q11.2), t(12;21)(p13;q22), t(14q32) and inv(14)(q11.2q32) suggesting that 9p deletion is a secondary change.

Deletions of 9p often are not easily detected by G-banding.

Therefore, FISH testing targeting the CDKN2A gene provides an excellent method for detecting the majority of these deletions.

In large series studies, the frequency of CDKN2A/B deletions has been reported in 20%-34% of B-ALL but is significantly higher among T-ALL patients 50%-80%.

The distribution of 9p deletion among the cytogenetic subgroups varies. Patients with t(9;22) and t(1;19) have higher incidences of CDKN2A/B deletion (40%-60%) than patients with high hyperdiploidy, ETV6/RUNX1 fusion, or KMT2A (MLL)/11q23 rearrangements (11%-15%).

Both monoallelic and biallelic CDKN2A deletions are found in ALL with the latter being more prevalent in T-ALL (Sulong et al, 2009).

The deletions vary in size considerably from <1 Mb to 39 Mb, and the biallelic deletions consist of a large and small deletion. In contrast, inactivation of CDKN2A gene in ALL by mutation or hypermethylation appears to be low, ranging from 0-7%.

Genes involved and proteins

CDKN2A (cyclin dependent kinase 2a / p16)

Location

9p21.3

Note

CDKN2A (Cyclin Dependent Kinase Inhibitor 2A), alternative symbols included CDKN2, CDK4 inhibitor, multiple tumor suppressor 1(MTS1), TP16, p16(INK4), p16(INK4A)

DNA/RNA

CDKN2A consists of three coding exons spanning over 30kb.

Protein

CDKN2A gene encodes two major proteins p16(INK4) and p14(ARF) through the use of shared coding regions and alternative reading frames. Both act as tumor suppressors by regulating the cell cycle. The p16 prevents progression through the G1 cell cycle checkpoint by inhibiting cyclin-dependent kinases CDK4 and CDK6 to inactivate the retinoblastoma (RB1) family of tumor suppressor proteins.

The p14 protein acts primarily by deterring MDM2 and therefore, promotes p53 protein, consequently inducing cell cycle arrest in both G1 and G2/M phases as well as initiating apoptosis.

Somatic mutations

Somatic mutations of CDKN2A are common in human cancers, with estimates that CDKN2A is the second most commonly inactivated gene in cancer after TP53.

Germline mutations of CDKN2A are associated with familial melanoma, glioblastoma and pancreatic cancer.

CDKN2B (cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4))

Location

9p21.3

Note

CDKN2B (Cyclin-Dependent Kinase Inhibitor 2B), alternative symbols included; Multiple Tumor Suppressor 2 (MTS2), p15(INK4B), TP15, CDKN4B inhibitor.

Protein

CDKN2B encodes a cyclin-dependent kinase inhibitor "p15", which forms a complex with CDK4 or CDK6, and prevents the activation of the CDK kinases.

The p15 protein functions as a cell growth regulator that controls cell cycle G1 progression.

Somatic mutations

CDKN2B is tandemly linked to CDKN2A and frequently deleted in a significant proportion of ALL, but always in association with CDKN2A.

PAX5 (paired box gene 5)

Location

9p13.2

Note

PAX5 (Paired Box Gene 5), alternative symbols ALL3, BSAP

Protein

PAX5 gene encodes a B-cell-specific activator protein (BSAP), which is a member of a class of transcription factors that contains a DNA-binding domain. It is the only member of PAX family expressed in the hematopoietic system exclusively in B-cells. Expression of PAX5 is initiated in pre-pro-B cells and maintained throughout subsequent stages of B-cell development before it is down-regulated in plasma cell. It functions both as a transcriptional activator and as a repressor on different target genes, which are involved in B-lineage development.

Germinal mutations

Recently germline mutation of PAX5 gene was identified by exome sequencing in two unrelated families. The affected family members had B-cell precursor ALL and the diagnostic and relapse leukemic samples from both families demonstrated deletion of 9p through i(9)(q10) or dicentric (9q;v), both of which resulted in loss of the wild-type PAX5 allele and retention of mutated PAX5. The loss resulted in a marked reduction of normal PAX5 activity in the leukemia cells.

Somatic mutations

Somatic alterations of PAX5 gene due to deletions, point mutations, or translocations occur in approximately 30% of B-ALL and in up to 50% of the high-risk BCR-ABL1 positive and Ph-like ALL subtypes. Alterations of PAX5 are not associated with an adverse outcome in children or adult B-cell ALL (Mullighan et al 2012, Shahjehani et al 2015).

JAK2 (janus kinase 2)

Location

9p24.1

Note

JAK2 (Janus kinase 2 gene), alternative symbol JTK10.

Protein

JAK2 encodes a non-receptor tyrosine kinase that is involved in a specific subset of cytokine receptor signaling pathways. It has been found to be constitutively associated with the prolactin receptor (PRLR) and is required for responses to gamma interferon (IFNG). Upon receptor activation JAK2 phosphorylate the transcription factors "STATs" and initiate the JAK-STAT signaling pathway.

Somatic mutations

Mutations of JAK1/2 have been identified in 18%-35% Down syndrome - ALL and also occur in about

10% of high-risk pediatric B- ALL patients causing a constitutive activation of the JAK-STAT pathway. The most frequent site of mutation is at R683 in the pseudokinase domain of JAK2 which is distinct from the JAK2 V617F predominant mutation seen in polycythemia vera and other myeloproliferative neoplasms (Robert et al 2012, Hunger and Mullighan 2015). The presence of JAK mutations is significantly associated with alteration of IKZF1 and rearrangement of CRLF2 signifying a high risk disease and poor outcome. ALL cases harboring CRLF2 and JAK alterations may benefit from JAK inhibitors targeted therapy.

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