

Leukaemia Section

Review

del(6q)

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Abstract

Review on deletion of 6q in hematological malignancies, genes involved and clinical significances

Keywords

chromosome 6; acute lymphoblastic leukemia; chronic lymphocytic leukemia; Non-Hodgkin lymphoma; Hodgkin lymphoma; plasma cell myeloma; Waldenström macroglobulinemia; natural killer cell leukemia/lymphoma; myelodysplastic syndrome; acute myeloid leukemia.

Identity

Note

Deletions of 6q are characteristic of lymphoid malignancies, but rare in myeloid diseases. In solid tumor 6q deletions have been reported in melanoma, renal cell carcinoma, salivary gland adenocarcinoma, ovarian carcinoma and breast cancer highlighting the importance of this region in cancer development.

Clinics and pathology

Disease

Various hematological malignancies: B- and T-lineages acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), plasma cell myeloma (PCM), Waldenström macroglobulinemia (WM), natural killer cell

leukemia/lymphoma (NK), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML).

Epidemiology

Deletions affecting chromosome 6q are among the most commonly observed structural aberrations in lymphoid malignancies (Taborelli et al, 2006). Deletions can include the whole long arm or specific regions of 6q. The frequency of 6q deletions varies depending on disease histology and methodology used; the deletions have been identified by karyotype in 4% - 13% of ALL and in 13% - 33% of various subtypes of lymphoma. However, molecular studies of loss of heterozygosity (LOH) and fluorescence in situ hybridization (FISH) have detected a higher frequency of 6q deletions in up to 50% of lymphoma cases and in 30% of ALL cases.

Cytogenetics

In the majority of cases, loss of 6q results from an interstitial deletion. Other structural abnormalities leading to 6q deletions such as isochromosome 6p, add(6q) or der(6) are less frequent (Figure 1). The 6q deletion is usually associated with other karyotypic abnormalities; it is infrequently reported as the sole abnormality suggesting that 6q deletion is a secondary change play a relevant role in the progression of the disease.

The deletions of 6q are variable in size and have heterogeneous breakpoints. Based on chromosome analysis, Offit et al identified three regions of minimal cytogenetic deletions in a series of 94 NHL patients with deleted 6q; these regions were 6q21, 6q23, and 6q25-27 (Offit et al 1993).



Figure 1. Partial G-banded karyotypes showing various size of 6q deletions in lymphoid malignancies.

Further investigations, Zhang et al attempted to delineate deletions of 6q in a large series of B- and T-cell NHLs and acute leukemia using a panel of 36 YAC FISH probes distributed from 6q12 to 6q27 and a centromeric probe of chromosome 6 as internal control. They identified a commonly deleted region of 3 cM (4-5 Mb) in the 6q21 suggesting that this region harbors a putative tumor suppressor gene(s) involved in the pathogenesis of both low-grade and high-grade NHL as well as ALL (Zhang et al 2000).

Disease

Acute Lymphoblastic Leukemia (ALL)

Note

Based on banded chromosome, deletions of chromosome 6q occur in 4-13% of B-lineage ALL and in 20-30% of T-lineage ALL. Molecular studies of LOH in ALL have shown higher incidences of 6q deletions in 7-32% of cases with most of the deletions are being interstitial. In a large study conducted by Children Cytogenetic Group (CCG), Heerema et al reported deletions of 6q in 9% of a newly diagnosed pediatric ALL; 20% of those patients had 6q deletion as a sole abnormality and in other 13% the deletion was seen in a sideline as a secondary abnormality. Hayashi et al observed a common region of deletion at 6q21 in 45 children with ALL, and Takeuchi et al described two regions of deletion both involving 6q21 among 19 pediatric ALL cases with deleted 6q (Hayashi et al 1990; Takeuchi et al 1998). In contrast the deleted region appears to be more proximal in T-ALL at 6q16. Deletions of 6q occur most often with other recurring aberrations including 9p, 12p, 13q, 14q or 11q23 and/or trisomy of chromosome 16 or 21 but are less likely to be associated with a hyperdiploid karyotype (Heerema et al 2000). The use of FISH panel for clinical diagnosis reveals a strong association of 6q deletions with 12p ETV6/ RUNX1 positive ALL.

Clinics

ALL patients with deletions 6q are more likely to have high WBC counts at presentation, mediastinal mass, CNS involvement, T-lineage immunophenotype, and/or pseudodiploid karyotype.

Prognosis

The clinical data from large studies demonstrated that the outcome for patients with or without 6q deletion is similar regardless of NCI risk classification or immunophenotype. Thus, deletion of 6q is not associated with an adverse risk in ALL (Hayashi 1990, Heerema et al 2000).

Disease

Chronic Lymphocytic Leukemia (CLL)

Note

6q deletions are found in 3-6% of evaluable CLL cases by banded chromosomes. However, FISH on interphase cells has improved the sensitivity for detection of genetic abnormalities in B-CLL. In a large series of 285 CLL patients, two YAC FISH probes mapping to 6q21 and 6q27 regions were used. The deletions of 6q were identified in 7% of patients; the 6q21 region was deleted in all cases whereas the 6q27 region was deleted only in a third of those cases (Stilgenbauer S et al, 1999). Furthermore, this study found that patients with 6q deletions had higher white blood cell counts and more extensive lymphadenopathy but no inferior outcome. In another large study by Cuneo et al, chromosome and FISH analyses were performed on 217 CLL patients. The deletion of 6q21 was identified in 20 patients (7.2%) 13 of those (4.7%) had an isolated 6q21 deletion (Cuneo et al 2004). Recent study by Dalsass et al using a panel of four probes mapped to 6q16, 6q23, 6q25, 6q27 was performed on 107 CLL cases to evaluate the incidence and localization of the deleted region(s) at 6q.

They found 6q deletions in 11 cases (10.5%), a higher frequency than the previous reports; in five of

those cases (4.7%) 6q deletion was a sole abnormality. The additional abnormalities in the other six cases were trisomy 12, 13q-, 14q-, or complex karyotype. The most frequently deleted region in their study was in 6q16 (63.6%) followed by 6q25.2 (36.4%) region (Dalsass et al 2013).

Clinics

CLL patients with an isolated 6q21 deletion may represent a cytogenetic and clinicobiological entity characterized by relatively high WBC, high incidence of atypical morphology, classical immunophenotype with CD38 positivity, intermediate incidence of IGVH somatic hypermutation, and therapy demanding disease. These features with the clinical outcome place a 6q deletion CLL in an intermediate-risk group (Cuneo et al 2004). Lately, it was observed that deletion in 6q16 appears to be the most frequent region in CLL and could be associated with a more widespread disease when present as the sole abnormality (Dalsass et al 2013).

Prognosis

6q deletion in CLL is suggested to be an intermediate risk marker.

Disease

Lymphoma

Note

The frequency of 6q deletions in NHL ranges from 15-30% of cases by karyotype, mostly accompanied by other chromosomal abnormalities in particular t(14;18). In a large series of lymphoma cases, Offit et al found 6q deletions in 20% of cases. They identified three regions of minimal deletions that may be associated with specific subtypes of lymphomas and different clinical behavior; 6q24-q27 deletion in intermediate-grade NHL; and 6q23 deletion noted in low-grade lymphoma lacking t(14;18). Taborelli et al characterized 6q deletions in 35 malignant HL and NHL lymphomas, using conventional cytogenetics and FISH probes targeting 7 molecular regions along 6q. Conventional cytogenetics revealed a 6q deletion in 46% of lymphomas while interphase FISH demonstrated deletions in 94%; the deletions were discontinuous, involving nonadjacent molecular regions. They concluded although 6q deletion is a common lesion in all types of lymphomas, specific deletion patterns seem to characterize different histological types, suggesting that different tumor suppressor genes play different roles in different types of lymphomas. Two specific 6q regions deleted in diffuse large B cell lymphomas but not in follicular lymphomas that may be implicated in the disease transformation. On this basis of these observations, 6q deletion appears to be a dynamic mutation involving different molecular regions

during progression of the disease (Taborelli et al 2006).

In Hodgkin lymphoma, the incidence of 6q deletion is not well determined due to scarcity and low mitotic index of the Hodgkin and Reed Sternberg (H-RS) cells in culture. Using molecular approach, Re et al detected allelic losses and imbalances on chromosome 6q in most HL cases (78%). The detailed mapping using additional microsatellite markers on 6q led to delineation of a 3.3-Mb region on 6q25. They concluded that allelotyping of single H-RS cells revealed monoallelic chromosomal deletions and genomic imbalances on 6q that might affect genes critically involved in the pathogenesis of H-RS cells (Re et al 2003).

Clinics

Cytogenetic analyses indicate that different regions of loss define distinct clinical-pathological subsets of lymphoma.

Prognosis

Deletion of 6q21 is most frequently associated with a high-grade lymphoma and correlates with poor prognosis.

Disease

Waldenström Macroglobulinemia (WM)

Note

Lymphoplasmacytic lymphoma (LPL) is the pathological designation of WM as proposed by WHO Classification of Tumors. Cytogenetic studies on WM are limited due to rarity of the disease and low mitotic index of the tumor cells. Deletion of 6q is the most frequent recurrent aberration reported in 6-16% of WM cases by karyotype. However, FISH using probes targeting different chromosomal segments on 6q, Schop et al identified deletions of 6q in over 50% of WM cases. The minimal deletion region (MDR) was between 6q23 and 6q24.3 and the SHPRH gene locus at 6q24, was most frequently deleted (Schop et al 2006). High resolution array-CGH identified two non-overlapped regions in about 95% of WM cases covering 1.4 Mb and 3.4 Mb on 6q21-q22.1 (MDR1) and 6q23 (MDR2), respectively. Potential target genes localized inside those regions are PRDM1 (MDR1) and TNFAIP3 (MDR2), two tumor suppressor genes that have been associated with the pathogenesis of other B-cell neoplasia (Braggio et al, 2009).

Clinics

WM patients with deletion of 6q are more likely to display features of adverse prognosis, such as higher levels of beta2-microglobulin and monoclonal paraprotein and a greater tendency to display anemia and hypoalbuminemia. The incidence of 6q deletions is also higher among WM patients with advanced

disease but not in the premalignant phase of the disease (Ocio et al, 2006).

Prognosis

The cohort study from Spain (Ocio et al 2006) presented that WM patients with 6q deletions required earlier treatment, however, recent study (Chang et al 2009) found no significant difference in the requirement for treatment between 6q deleted and non-deleted groups, and the time to the treatment was also similar between these two groups. However, both studies demonstrated no significant difference in overall survival between WM patients with and without 6q deletions.

Disease

Natural Killer cell Lymphoma/Leukemia (NKLL)

Note

NK is a rare group of highly aggressive hematolymphoid malignancies characterized by neoplastic proliferation of NK-cells. Deletions of 6q have been identified in almost 50% of cases with a common region deletion at 6q21-q25. Molecular study on 25 NKLL cases identified LOH of 6q in 50% of NK leukemia and in 100% of NK lymphoma with 6q21 region being lost in most cases (Ohshima et al, 2002). PRDM1 and FOXO3 at 6q21 are considered to play an important role in the pathogenesis of NK-cell neoplasms.

Disease

Plasma Cell Myeloma (PCM)

Note

Deletions of 6q in PCM have been identified in approximately 1/3 of cases with abnormal karyotype; not seen as a sole abnormality. However; its clinical significance has been addressed yet (Mohamed et al 2007).

Disease

Myeloid Malignancies

Note

Deletion of 6q is an infrequent abnormality seen mostly in conjunction with a complex karyotype. However, as a sole abnormality it is very rare, described in isolated cases of MDS and AML (Hirata et al 1992; Gozzetti et al, 2009). The clinical significance of deletion 6q is not clear, due to small number of patients. The molecular mechanism by which this deletion causing MDS or AML is not addressed, but the most probable mechanism is loss of a tumor suppressor gene located on chromosome arm 6q.

Genes involved and proteins

Note

The variable size and the complexity the deleted segments of 6q suggest the presence of multiple and potentially cooperating tumor suppressor genes. Thelander et al outlined the deletion patterns of 6q using a chromosome 6 specific tile path array in four different types of hematological malignancies. The PRDM1, FOXO3A, and HACE1 genes at 6q21 and TNFAIP3 gene at 6q23.3 - 24.1 are considered candidate tumor suppressor genes that have been reported to be inactivated in B-cell malignancies (Thelander et al 2006). Other candidate genes proposed in T- cell neoplasms are EPHA7, CASP8AP2, and GRIK2 at 6q15-q16.

PRDM1 (PR domain containing 1, with ZNF domain)

Location

6q21

Note

PRDM1 (PR Domain-Containing Protein 1); alternative symbols; BLIMP1 (B Lymphocyte-Induced Maturation Protein 1); PRDIBF1 (Positive Regulatory Domain I-Binding Factor 1)

Protein

PRDM1 encodes BLIMP1 which is a zinc finger protein expressed upon plasmacytic differentiation but it is also expressed in T cells, granulocytes, macrophages, epithelial cells, and germ cells. BLIMP1 protein acts as a repressor of beta-interferon (IFNB1) gene expression. One major role for BLIMP1 inactivation is to block terminal differentiation of B cells by suppressing the expression of genes implicated in B cell receptor signals and cell cycle progression such as BCL6 and PAX5. This concept is supported by the observation that introduction of BLIMP1 into a diffuse large B cell lymphoma (DLBCL) cell line leads to G1 cell cycle arrest. Functional studies provided evidences that BLIMP1 is a tumor suppressor gene whose inactivation may contribute to lymphomagenesis by blocking post-GC differentiation of B cells toward plasma cells (Kwon et al, 2009; Mandelbaum et al, 2010).

Somatic mutations

Somatic mutations that induce inactivation of PRDM1 gene occur through a variety of genetic means including homozygous deletions, truncating or missense mutations, and transcriptional repression by constitutively active BCL6, in ~53% of ABC-DLBCL.

Most of these cases with inactive mutations are accompanied by heterogeneous 6q deletions or DNA methylation, indicating that biallelic inactivation occurs frequently.

FOXO3 (forkhead box O3A)

Location

6q21

Note

FOXO3A (Forkhead Box O3A); alternative symbol; FKHL1 (Forkhead in Rhabdomyosarcoma-Like 1); It has at least 3 exons and 2 introns, including an intron located within the coding sequence of the forkhead domain that spans at least 90 kb.

Protein

FOXO3A gene belongs to the forkhead family of transcription factors which are characterized by a distinct forkhead domain that is highly conserved among various biologic species. A variant of FOXO3A gene is associated with longevity in human. FOXO3A functions as a trigger for apoptosis through regulation of a large subset of genes involved in DNA repair, cell cycle regulation, and apoptosis. Translocation of this gene with the MLL (KMT2A) was found in a case of secondary AML with t(6;11)(q21;q23). FOXO3 expression was down-regulated in most NK-cell neoplasms and re-expression of FOXO3 suppressed proliferation of the NK cell line. It was shown that the inhibition of cell growth by FOXO3 is due to the induction of apoptosis and cell-cycle arrest. These findings indicate that FOXO3 plays a role as a tumor-suppressor gene in NK-cell neoplasms (Karube et al 2011).

Somatic mutations

Genomic sequences of protein-coding regions and splice junction were analyzed on 33 clinical samples of NK neoplasms (Karube et al, 2011). Somatic missense mutations were found in 3 clinical samples but, no mutations were detected in the splice junctions.

TNFAIP3 (tumor necrosis factor, alpha-induced protein 3)

Location

6q23.3

Note

TNFAIP3 (Tumor Necrosis Factor Alpha Induced Protein 3); alternative symbol; A20.

Protein

TNFAIP3 encoding A20 is a cytoplasmic zinc finger protein that acts as a negative regulator of the nuclear factor kappa-B (NFkB) activity and tumor necrosis factor (TNF)-mediated programmed cell death. TNFAIP3 polymorphisms have been associated with autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Schmitz et al demonstrated TNFAIP3 as a novel tumor suppressor gene by showing frequent somatic and clonal biallelic inactivation of this gene in HL and B-cell lymphoma. They presented evidence that loss of A20

function contributes to the constitutive activity of the transcription factor NFkB and the survival and/or proliferation of the cells (Schmitz et al 2009).

Somatic mutations

TNFAIP3 (A20) is inactivated by somatic mutations such as base pair deletions, duplication and a single base pair insertion all leading to truncated polypeptides lacking the functionally relevant domains. TNFAIP3 somatic mutations were reported in 44% of cHL, 36% of primary mediastinal B-cell lymphoma and 25% of marginal zone lymphoma (Honma et al, 2009). In most mutated cases, both TNFAIP3 alleles were inactivated, including frequent chromosomal deletions of TNFAIP3/6q23. Biallelic deletions of TNFAIP3 have also been identified in DLBCL and ocular adnexal marginal B-cell lymphomas. Recently, monoallelic deletions of TNFAIP3 were identified in 38% of WM patients and in those cases the TNFAIP3 transcript expression levels were significantly lower than in the group of patients with two copies of the gene. This suggests that haploinsufficiency of TNFAIP3 can predispose to the development of WM (Braggio et al, 2009).

HACE1 (HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1)

Location

6q16.3

Note

HECT1 (Domain and Ankyrin Repeat Containing E3 Ubiquitin Protein Ligase 1); alternative symbols; RPD3L1; KIAA1320

Protein

HACE1 gene encoding a protein belongs to the HECT family of ubiquitin ligases (HECT E3), which have intrinsic catalytic activity and specificity for substrates involved in the regulation of growth and apoptosis. HACE1 inhibits the tumor suppressor gene RARB, ubiquitylates RAC1, which is a rho-GTPase involved in cell proliferation and G2/M cycle progression and degrades cyclin D1 through the control of ROS1. HACE1 is down-regulated in Wilms tumors and gastrointestinal carcinomas, mediated through hypermethylation of the HACE1 promoter. In colorectal carcinomas hypermethylation of HACE1 is associated with the severity of clinicopathological findings, especially lymph node metastasis. The HACE1 was demonstrated to be a tumor suppressor gene in NK cell malignancies and to be down-regulated through a deletion and DNA hypermethylation, and its alteration may play a crucial role in NK cell lymphomagenesis (Karube et al blood 2011). Recently Bouzefen et al reported HACE1 as a candidate tumor suppressor gene in B-cells

lymphomas down-regulated by deletion and epigenetic mechanisms; deletions were observed in 40% of cases whereas hypermethylation of the HACE1 promoter CpG177 island was found in 60% of cases and in all tested B-cell lymphoma lines. They concluded that HACE1 can act as a haploinsufficient tumor suppressor gene in most B-cell lymphomas and can be downregulated by deacetylation of its promoter region chromatin, which makes HACE1 a potential target for HDAC inhibitors (Bouzelfen et al, 2016).

Somatic mutations

Mutations in HACE1 have not been found in the coding or promoter regions of any cancer studied to date.

EPHA7 (EPH receptor A7)

Location

6q16.1

Note

EPHA7 (Ephrin type-A receptor 7), alternative symbol; HEK11.

Protein

EPHA7 gene encoding 998 amino acids protein belongs to the ephrin receptor subfamily of the protein-tyrosine kinase family. EPH and EPH-related receptors have been implicated in mediating developmental events, particularly in the nervous system. Previous studies showed that the role of this gene in cancer development may be controversial. Although EPHA7 is upregulated in acute leukemia and in a variety of solid tumors, evidences of Epha7 downregulation have been reported in B-cell lymphoma, T-cell leukemia, and colon cancer. In lymphoma, Epha7 downregulation occur by promoter hypermethylation or loss of heterozygosity or a combination of both mechanisms. The pattern of DNA hypermethylation is similar in various lymphomas as well as in colorectal cancer, suggesting that a common methylation profile is shared by different type of tumors (Lopez-Nieva et al 2012). The study by Oricchio et al on follicular lymphoma demonstrated that the the expression of EPHA7 gene is completely lost in over 70% of cases. The loss of expression was affected by differential promoter methylation caused by extensive CpG island methylation or hemizygous 6q deletions. They concluded that EPHA7 acts as a tumor suppressor in follicular lymphoma and is a promising candidate for translational development. Specifically, they fused EPHA7 to the anti-CD20 antibody, to allow delivering EPHA7's tumor suppressive activity directly to the CD20 expressing lymphoma cells (Oricchio et al 2010 et al).

Somatic mutations

Oricchio et al study did not detect EPHA7 mutations in the 24 FL cases.

CASP8AP2 (caspase 8 associated protein 2)

Location

6q15

Note

CASP8AP2 (Caspase 8 Associated Protein 2); alternative symbols FLASH, RIP25.

Protein

CASP8AP2 gene encodes a protein highly similar to the mouse apoptotic protein FLASH. In human Casp8AP2 associates with CASP8 (caspase 8) to form the death-inducing signaling complex (DISC) which regulates the programmed cell death and cell cycle survival.

The clinical significance of CASP8AP2 expression was studied in pediatric ALL; patients with low CASP8AP2 expression at diagnosis displayed high minimum residual disease (MRD), high relapse rates, lower relapse-free survival and inferior overall survival, in comparison to the higher-expression group (Jiao et al 2012).

On the other hand high expression of this gene is associated with a greater tendency of leukemic cells to undergo apoptosis.

Flotho et al considered the CASP8AP2 expression is an independent prognostic marker for relapse in ALL (Flotho C et al., 2006).

Furthermore, Remke et al identified a deletion of 6q15-16.1 in 12% of T-ALL patients.

The deletion included the CASP8AP2 gene whose expression was the single most down-regulated among other genes in that region.

The down regulation of CASP8AP2 has been associated with poor early treatment response (Remke et al 2012).

The deletion of CASP8AP2 appears to interfere with the apoptotic pathways that are targeted by chemotherapy used in the induction phase of the ALL protocol.

Somatic mutations

While frame shift mutations of this gene have been describe in solid tumors, no mutations were found in DLBCL, pointing to a potential haploinsufficiency effect of this gene in lymphoma.

GRIK2 (glutamate ionotropic receptor kainate type subunit 2)

Location

6q16.3

Note

GRIK2 (Glutamate Ionotropic Receptor Kainate Type Subunit 2); alternative symbols GluK2, MRT6.

DNA/RNA

GRIK2 gene comprises 16 exons

Protein

GRIK2 gene encodes a subunit of a kainate glutamate receptor. Glutamate receptors mediate the majority of excitatory neurotransmission at many synapses in the central nervous system. Sinclair et al used FISH to identify a candidate tumor suppressor gene in ALL with 6q deletion. They identified a 4.8-Mb region of minimal deletion and singled out GRIK2 as the gene most frequently affected by deletions of 6q in ALL. This gene was additionally analyzed for inactivating mutations in cases of ALL carrying heterozygous chromosome 6q deletions and for levels of expression in a range of normal and malignant hematopoietic cells. Expression of GRIK2 was low in normal hematopoietic cells compared with levels in brain but was most prominent in those of T-lineage, and it was consistently detected among T-cell leukemias, except in the presence of 6q deletion.

These observations support the possibility that in at least T-ALL, haploinsufficiency might reduce GRIK2 expression below a critical tumor protective threshold level (Sinclair et al, 2004).

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