Leukaemia Section

Review

**dup(1q) in ALL**

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**Abstract**

Review on duplication of 1q in acute lymphoblastic leukemia, with data on clinics, and the genes involved.

**KEYWORDS**

Chromosome 1; Acute lymphoblastic leukemia; DAP3; B4GALT3; UCK2; RGS16; TMEM183A

**Identity**
dup(1q) in ALL

**Top:** G-banded hyperdiploid karyotype with duplication 1q from an ALL case. **Bottom:** G-banded hyperdiploid karyotype from ALL patient showing an unbalanced der(1;6)(q10;p10) resulting in gain/trisomy 1q.

dup(1q) in ALL. Fluorescence in situ hybridization with Vysis LSI 1p36/LSI 1q25 dual-color probe (Abbott molecular, US) showing 2 normal copies of 1q25 on normal (A) and 3 copies of green signal on metaphase with...
dup(1q) in ALL

1q duplication (B) and on metaphase with inverted 1q duplication (C). Partial karyotypes and metaphase with C-banding showing the inverted duplication of 1q (D) Courtesy Adriana Zamecnikova.

Clinics and pathology

Disease
Acute Lymphoblastic Leukemia (ALL)

Cytogenetic
Duplication or gain of 1q may result from a partial interstitial duplication of 1q or more often from an unbalanced translocation (Figure 1, 2). Although dup(1q) is rarely seen as a sole abnormality, it is mostly found in association with well-known primary cytogenetic abnormalities. In high hyperdiploid ALL, duplication of 1q is the most frequent structural aberration found in approximately 15% cases (Figure 1). Gain of 1q is also associated with t(1;19) translocation; 75% of those cases have an unbalanced translocation leading to gain/trisomy 1q. Additionally, partial trisomy of 1q is found in almost 25% of Burkitt lymphoma/leukemia (BL) cases in particular the endemic type. Therefore, duplication/gain of 1q in ALL is an apparently a secondary event.

The size of the duplicated region of 1q is variable but mostly reported form 1q21 -> qter. Using array CGH, Davidsson et al studied ten cases with duplicated 1q; six cases of B-cell precursor pediatric high hyperdiploid ALL and four cases of BL. The proximal breakpoints in all cases were near the centromere, mostly clustering within a 1.4 Mb segment at 1q12-21.1. There was no evidence hypomethylation of sat II DNA in ALLs with or without 1q gains indicating that aberrant methylation was not involved in the formation of dup(1q), as previously suggested for other neoplasms with 1q rearrangements. However, the 1q distal breakpoints were heterogeneous, being more distal in the ALLs than in the BLs. Thus, the minimally gained segment was larger in the ALLs (57.4 Mb) than in the BLs (35 Mb), corresponding to dup(1)(q22q32.3) and dup(1)(q12q25.2), respectively.

Prognosis
The presence of dup(1q) has no effect on the outcome of ALL patients with high hyperdiploidy (Paulsson et al, 2013). It is unclear yet whether the presence of balanced or unbalanced t(1;19)(q23;p13.3) in ALLs has an effect on the prognosis.

Genes involved and proteins

Note
The molecular characterization of dup(1q) in ALL is not well-defined and very limited data is available. However, the unbalanced nature of dup(1q) suggests that gene dosage effect is likely contribute to the neoplastic process. Nevertheless, gene expression profile revealed that five genes, DAP3, B4GALT3, UCK2, RGS16 and TMEM183A were significantly up-regulated in high hyperdiploid ALL carrying dup(1q) compared to those without dup(1q). DAP3 and UCK2 genes were among the highly expressed in BL with gain of 1q (Davidsson et al 2007).

DAP3 (death associated protein 3)

Location
1q22

Note
Alternative symbol MRPS29 (mitochondrial ribosomal protein S29).

Protein
DAP3 gene is transcribed into a 1.7-kb mRNA and translates into a 46 kDa protein located in the lower area of the small mitoribosomal subunit. This protein contains a P-loop motif that binds GTP and a highly conserved 17-residue targeting sequence responsible for its localization to the mitochondria. Many of the phosphorylation sites on this protein are highly conserved and clustered around GTP-binding motifs. DAP3 forms an important portion of the a 28S subunit protein of the mitochondrial ribosome and plays key roles in translation, cellular respiration, and apoptosis. The protein is normally reserved inactive as phosphoprotein. When activated, it co-localizes with FADD and participates in the formation of the death inducing signaling complex (DISC). Recent studies suggests that DAP3 is strongly associated with the Fas receptor related DISC. It is presumed that DAP3 may have tumor suppressant role predicated by its function as a pro-apoptotic molecule. Counterintuitively, DAP3 has a pro-survival role in mitochondrial function. The current literature places DAP3 at the link of several highly significant and occasionally antagonistic pathways (Kissil JL et al 1995, 1998).

There is limited literature with regards to DAP3 role in cancer. Studies have demonstrated low DAP3 expression in various tumors such as B-cell lymphoma, lung cancer, head and neck cancer, breast cancer, gastric cancer, and colorectal carcinoma, possibly due to hypermethylation of the gene's promoter (Wazir U et al, 2015). In breast cancer it has been demonstrated that this gene may have a tumor suppressor function through promoting apoptosis and could act as a useful prognostic indicator in breast cancer (Wazir U et al, 2012). Moreover, DAP3 expression has been positively correlated with improved cancer prognosis, indicating that the protein combats cancer progression through its proapoptotic function. As a result, DAP3 could serve as a potential biomarker to
monitor the effectiveness of therapeutic treatments (Wazir et al., 2015). However, Mariani et al. found an upregulated expression of DAP3 in glioblastoma multiforme and in glioma cell lines with induced migratory phenotype. These observations can be explained by the fact that P-loop mutant DAP3 is less effective in inducing apoptosis, and the COOH-terminal deleted protein (230 amino acids) acts in a dominant negative fashion, protecting cells from induced apoptosis (Mariani et al., 2001). Furthermore, such findings could reflect a different balance between the mitochondrial maintenance and the pro-apoptotic functions of the DAP3 levels in glioma.

**B4GALT3 (beta-1,4-galactosyltransferase 3)**

**Location** 1q23.3

**Protein** B4GALT3 gene encodes an enzyme belongs to the family of B4GALTs, which catalyzes the biosynthesis of poly-N-acetyllactosamines. B4GALTs transfer galactose from uridine diphosphate galactose to N-acetylglucosamine (GlcNAc)-terminated oligosaccharides to form N-acetyllactosamine. The B4GALT family consists of seven members with different tissue distributions, acceptor preferences and enzyme activities. Among its related pathways are transport to the Golgi and subsequent modification and metabolism. In colorectal carcinoma (CRC), the expression of B4GALT3 is negatively correlated with poorly differentiated histology, advanced stages and metastasis. It has shown that B4GALT3 may function as a metastasis suppressor in CRC through modulating β1 integrin glycosylation and activation (Chen et al., 2014).

**UCK2 (uridine-cytidine kinase 2)**

**Location** 1q24.1

**DNA/RNA** UCK2 gene contains 7 exons and spans over 19 kb

**Protein** It encodes a 261 amino-acid protein with a predicted molecular mass of 29 kDa. It is an enzyme, catalyzes the phosphorylation of uridine and cytidine to uridine monophosphate (UMP) and cytidine monophosphate (CMP), respectively. UCK2 has only been detected in human placental tissue and overexpressed in various tumor cells, including neuroblastoma. Recent studies suggest that UCK2 could be used as a selective target for chemotherapy delivery in neuroblastoma cells expressing this specific isoform of UCK while sparing normal tissues (van Kuilenburg and Meinsma, 2016).

**RGS16 (regulator of G protein signaling 16)**

**Location** 1q25.3

**Protein** This gene encodes protein belongs to the ‘regulator of G protein signaling’ family. It inhibits signal transduction by increasing the GTPase activity of G protein alpha subunits. Also it may play a role in regulating the kinetics of signaling in the phototransduction cascade. The RGS family, comprising 22 homologues of proteins, plays a role in cellular proliferation, differentiation, membrane trafficking, and embryonic development through the involvement of the mitogen-activated protein kinase signalling pathway. The activity and specificity of Rgs16 protein are regulated through phosphorylation, in which several oncogenes are involved, by modulating the phosphorylation on a tyrosine residue in the RGS box. Previous studies showed that RGS16 is overexpressed in high hyperdiploid ALL and several other cancers such as CRC. Patients with RGS16 high-expression had a poorer overall survival rate than patients with low-expression suggesting that RGS16 is useful as a predictive marker for patient prognosis of CRC (Miyoshi et al., 2009).

**TMEM183A (transmembrane protein 183A)**

**Location** 1q32.1

**Note** Also known C1orf37

**DNA/RNA** The TMEM183A is the parental gene of TMEM138B, which is a young gene derived through retroposition after the divergence of human and chimpanzee. There are only 6 nucleotide changes in the coding region between TMEM183A and TMEM183B genes (Yu et al., 2006).

**References**


van Kuilenburg AB, Meinsma R. The pivotal role of uridine-cytidine kinases in pyrimidine metabolism and activation of cytotoxic nucleoside analogues in neuroblastoma. Biochim Biophys Acta. 2016 Sep;1862(9):1504-12

This article should be referenced as such: