Leukaemia Section

Short Communication

t(4;11)(q21;q23) KMT2A/AFF1

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Published in Atlas Database: February 2017

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/t0411ID1051.html
Printable original version: http://documents.irevues.inist.fr/bitstream/handle/2042/68755/02-2017-t0411ID1051.pdf
DOI: 10.4267/2042/68755

This article is an update of:
Huret JL. t(4;11)(q21;q23). Atlas Genet Cytogenet Oncol Haematol 1997;1(2)

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Abstract

Review on t(4;11)(q21;q23) KMT2A/AFF1 with data on clinics and the genes involved.

KEYWORDS
Chromosome 4; Chromosome 11; KMT2A; MLL; AFF1; Acute myeloid leukemia; Therapy-related myeloid leukemia; Acute lymphoblastic leukemia

Identity

t(4;11)(q21;q23) KMT2A/AFF1  G-banding (left) Top two: - Courtesy Diane H. Norback, Eric B. Johnson, and Sara Morrison-Delap; bottom three: - Courtesy Adriana Zamecnikova; R- banding (right) - Jean Loup Huret (top), - Courtesy Christiane Charrin (middle), - Courtesy Hossein Mossafa (bottom and FISH above). FISH below: Hybridization with Vysis LSI MLL break apart rearrangement probe (Abbott Molecular, US) showing

Chromosome 4; Chromosome 11; KMT2A; MLL; AFF1; Acute myeloid leukemia; Therapy-related myeloid leukemia; Acute lymphoblastic leukemia
Disease
Translocation t(4;11)(q21;q23) leads to the production of the MLL/AF4 (now called KMT2A and AFF1 respectively) fusion gene. It accounts for approximately 5-10% of newly diagnosed cases of Acute Lymphoblastic Leukemia (ALL) mainly in children. Rarely this translocation has been reported in biphenotypic ALL, T-ALL, and in acute myeloid leukemia usually M4 or M5 subtypes.

Phenotype/cell stem origin
The mixed lineage leukemia (MLL) gene located at 11q23 is a frequently seen target of chromosomal translocations in acute leukemias. There are currently over 100 different KMT2A (MLL) rearrangements identified which can occur in both acute myeloid and acute lymphoblastic leukemias, with AFF1 (AF4) being the most frequently recognized fusion gene. Leukemias expressing KMT2A/AFF1, otherwise known as t(4;11)(q21;q23) are mainly diagnosed in patients with pro-B ALL (Marchesi et al, 2005). Cases of T-ALL, biphenotypic ALL and AML (M4 and M5 types) has also rarely been reported with one study showing that in 183 total cases with the t(4;11)(q21;q23) only six were AML, one was a T-ALL, and one was a biphenotypic ALL (Johansson et al, 1998 Leukemia). Treatment related ALL and AML has also been reported in the literature with this translocation.

Epidemiology
The majority of cases of t(4;11)(q21;q23) positive ALL occur in infants less than 6 months old, accounting for 50% of ALL in that each group. Translocation (4;11)(q21;q23) is detected in approximately 10% adults with newly diagnosed B-cell ALL, and 30-40% of pro-B ALL subtypes. (Moorman et al. Blood 2007). It can present in older ages with one study showing eleven percent occurring in patients 50 or older. Rarely this translocation can be seen in M4 or M5 AML, T-ALL or treatment related acute leukemia. In treatment related acute leukemia, ALL is more common than AML (Johansson et al, 1998, Leukemia). The disease seems to be more common in females than in males particularly in those who get the disease under six months of age and over 40 years of age.

Clinics
Patients typically present with features consistent with more aggressive leukemias, including hyperleukocytosis (median around 200 X 10^9/l), hepatosplenomegaly and CNS involvement. While DIC is uncommon in most forms of ALL, patients with this subtype of ALL have a higher incidence of DIC at the time of diagnosis. (Pui et al, 1991).

Pathology
Blast cells usually display features of early B cell leukemia including heavy chain immunoglobulin gene rearrangement, TDT, HLD-DR, CD34, Cd19, CD9 and CD 24 positivity. Expression of CD 10 and T cell antigens is rare. In cases of AML CD 15 and CD65 are positive and nonspecific esterase and myeloperoxidase staining (Carulli et al. 2012).

Treatment
Patients with this subtype of ALL have higher risk features at diagnosis and overall poor prognosis. Common treatment for ALL includes an induction, consolidation and maintenance treatment which typically lasts about two years. Drug combinations differ based on region and treating physician but typically including vincristine, a corticosteroid, anthracycline along with L-asparaginase. Cyclophosphamide and etoposide are also part of some treatment plans along with methotrexate or cytarabine. Intrathecal chemotherapy is given during inductoin to prevent CNS involvement. Allogenic bone marrow transplantation is indicated in certain cases as well. In patients with B-cell ALL rituximab is also used to target CD20. It is important to evaluate for minimal residual disease (MRD) by Polymerase chain reaction (PCR) as small studies have shown that MRD positivity after consolidation is associated with higher incidence of relapse and inferior overall survival. However, more data from larger studies is needed to establish evidence based guidelines for treatment of this subset of ALL. (Vey et al, 2012).

In rare cases of t(4;11) AML, induction chemotherapy with antracycline based treatment is indicated followed by consolidation and allogenic bone marrow transplantation.

Prognosis
Rearrangement of the MLL gene confers a poor prognosis in both children and adults. Patients with t(4;11)(q21;q23) are categorized as having high risk disease. Remission rates of 75 percent have been seen but median event free survival has been noted of seven months in adults. In children the complete remission rate is around 88% but a median survival of 10 months. (Meyer et al, 2006). In one study of infant ALL patients with t(4;11), the five year survival rate was only 29 percent (Hilden et al 2006).

Cytogenetics
**t(4;11)(q21;q23) KMT2A/AFF1**

![Image](90x644 to 262x771)

i(7q) R- banding - Jean-Loup Huret (left), - Courtesy Christiane Charrin (right).

**Additional anomalies**

Additional abnormalities are found in 1/4 of cases at diagnosis, clonal evolution to hyperploidy is frequent; additional anomalies by decreasing order: i(7q) in 10%, +X, + Mar, +6, +8, +19, +21, +13, +10, +14; no difference in outcome was found.

**Variants**

Three way complex t(4;11;Var) exist and showed that the crucial event lies on the der(11).

**Genes involved and proteins**

**Note**

The primary mode of action in which chromosomal aberrations can occur to the KMT2A (MLL) gene is the reciprocal translocation which results in in-frame fusion transcripts with various partner genes. There are more than 60 recognized translocation partner genes with the most common one being AFF1 (AF4). The translocation leads to the loss of the methyltransferase domain of KMT2A in the KMT2A fusion protein. While there are several hypothesis regarding the mechanism by which the translocation t(4;11)(q21;q23) leads to leukemogenesis, the exact mechanism is not known (Schnittger et al. 2000).

However, KMT2A/AFF1 binds to specific subsets of regulatory elements and direct part of the RUNX1 gene program, and many others; KMT2A/AFF1 binds to the BCL2 gene and directly activates it through DOT1L recruitment, KMT2A/AFF1 also controls the active transcription of MCL1 and represses BCL2L11 (BIM) (Konopleva et al. 2017; Stunnenberg and Martens, 2017).

**AFF1 (AF4/FMR2 family, member 1)**

**Location**

4q21.3

**Note**

AFF1 is the AF4/FMR2 family member 1, also known as AF4.

**DNA/RNA**

20 exons, transcript length: 9,390 bps

**Protein**

1,210 amino acids, 131 kDa; AFF1 is bound to CDK9 and CCNT1 and is present in all major positive transcription elongation factor b (P-TEFb) complexes, which stimulates RNA polymerase elongation (Lu et al., 2014).

**KMT2A (myeloid/lymphoid or mixed lineage leukemia)**

**Location**

11q23.3

**Note**

Better known as MLL

**DNA/RNA**

37 exons, spanning about 120 kb; 13-15 mRNA

**Protein**

3969 amino acids, 431 kDa; Transcriptional regulatory factor. KMT2A is known to be associated with more than 30 proteins, including the core components of the SWI/SNF chromatin remodeling complex and the transcription complex TFIID. KMT2A binds promoters of HOX genes through acetylation and methylation of histones. KMT2A is a major regulator of hematopoiesis and embryonic development, through regulation of HOX genes expression regulation (HOXA9 in particular).

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

5' KMT2A - 3' AFF1; breakpoints are variable.

**Fusion protein**

**Description**

e.g. 2319 amino acids; 240 kDa; N-term AT hook and DNA methyltransferase from KMT2A fused to AFF1 C-term; the reciprocal (AFF1/ KMT2A) may or may not be expressed; quite similar to the KMT2A/ MLLT1 fusion protein found with t(11;19)(q23;p13.3)

**Expression / Localisation**

Nuclear localization.

**References**


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