t(2;11)(q37;q23) in AML

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Identity

$\text{t(2;11)(q37;q23)}$ by G-banding and FISH with dual-color, break-apart MLL probe; Cecilia, Manuel R Teixeira (left); partial GTG-banded karyotype of $\text{t(2;11)(q37;23)}$ and FISH analysis using probe LSI MLL DCBA demonstrating a $11\text{q23 MLL rearrangement with a fusion signal on the normal chromosome } 11$, a split 5’MLL signal on der(11) and a 3’MLL signal on der(2); courtesy Arjan Buijs and Ellen van Binsbergen (right).
Clinics and pathology

Disease
Rare type of acute non lymphocytic leukemia (ANLL) and therapy-related ANLL.

Phenotype / cell stem origin
No specific AML FAB sub-type (two cases M4, one M2, one M5a and one NOS).

Etiology
Either de novo or therapy-related (prior cancer is variable: breast cancer, non-Hodgkin lymphoma and LLA).

Epidemiology
Five cases known in the literature; four adults and one child, sex ratio 2M/3F; (age range 14.4-76).

Prognosis
Two cases showed poor survival, 9 and 17 months respectively, one case achieved remission after stem cell transplantation. The prognosis may be likely to be comparable with that of other entities with 11q23/MLL involvement, and worse in therapy related leukemias.

Genes involved and Proteins

SEPT2
Location: 2q37
DNA/RNA
The SEPT2 gene has 14 exons.
SEPT2 has four types of transcripts with 3.6 kb, 3.5 kb, 3.4 kb and 3.3 kb encoding the same protein, as a result of alternative splicing.

Protein
SEPT2 belongs to an evolutionarily conserved family of genes that encode a P loop-based GTP-binding domain flanked by a polybasic domain and (usually) a coiled-coil region, and assemble into homo- and hetero-oligomers and filaments with key roles in cell division cytoskeletal dynamics and secretion. The SEPT2 gene codes for a protein with 361 amino acids and a molecular weight of 41.5 kDa.

SEPT2 was identified as a gene expressed in early embryonic mouse brain and down-regulated during development. It is ubiquitously expressed in cell lines and tissues with the highest protein levels found in brain tissue.

The SEPT2 protein, like other septin family members, is thought to be cytoplasmic. SEPT2 co-localises with actin filaments in interphase cells, and in dividing cells concentrates at the cleavage furrow.

SEPT2 is a multifunctional protein that was shown to be required for cytokinesis and to bind actin and associate with focal adhesions. Recent data support the idea that SEPT2 can have a role in chromosome congression and segregation. Additional functions have also been suggested; for instance, in rat brain lysates SEPT2 is part of a multi-septin complex that interacts with the exocyst complex, which plays a role in secretion and neurite outgrowth. SEPT2 has also been localised to senile plaques of brains in patients with Alzheimer’s disease suggesting a role in neurodegeneration.

The SEPT2 protein belongs to an evolutionarily family of proteins with at least 14 members and shares a very high homology with septin 1, septin 4 and septin 5.

MLL
Location: 11q23
DNA/RNA
37 exons, spanning over 100 kb.
In a centromeric to telomeric direction; 13 and 15 kb; coding sequence: 11.9 kb.

Protein
3969 amino acids; 431 kDa; contains from N-term to C-term 3 AT hooks homologous to high mobility group proteins HMGAI and HMGAI2, binding to the minor groove of DNA; 2 speckled nuclear localisation signals; 2 repression domains RD1 and RD2: RD1 or CXXC: cystein methyl transferase, binds CpG rich DNA, has a...
transcriptional repression activity; RD2 recruits histone
desacylases HDAC1 and HDAC2; 3 plant
toothed domains (cystein rich zinc finger domains, with
homodimerization properties), 1 bromodomain (may
bind acetylated histones), and 1 plant homeodomain;
these domains may be involved in protein-protein
interaction; a FYRN and a FRYD domain; a
transactivation domain which binds CBP; may
acetylates H3 and H4 in the HOX area; a SET domain;
methyltransferase; methylates H3, including histones
in the HOX area for allowing chromatin to be open to
transcription. MLL is cleaved by taspase 1 into 2
proteins before entering the nucleus: a p300/320 N-
term protein called MLL-N, and a p180 C-term protein,
called MLL-C. The FYRN and a FRYD domains of
native MLL associate MLL-N and MLL-C in a stable
complex; they form a multiple complex with
transcription factor TFIIID.

**Results of the chromosomal anomaly**

**Hybrid gene**

**Description**

MLL-SEPT2. MLL exon 6 or 7 fused with SEPT2 exon 3.

<table>
<thead>
<tr>
<th>Anno</th>
<th>MLL</th>
<th>SEPT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5 6</td>
<td>3 4 5 6 7</td>
</tr>
<tr>
<td>B</td>
<td>5 6</td>
<td>7 3</td>
</tr>
</tbody>
</table>

**Fusion protein**

**Description**

AT hook, SNL-1, SNL-2 and DNA methyltransferase
domains from MLL fused to almost the entire open-
reading frame of SEPT2, except for the first three
aminoacids.

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