Leukaemia Section
Short Communication

ins(X;11)(q28;q23q23) KMT2A/FLNA
ins(11;X)(q23;q28q12) KMT2A/FLNA

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Abstract
Ins(11;X)(q23;q28q12) and ins(X;11)(q28;q23q23) are found so far in acute myelomonocytic leukaemia and carries a poor prognosis. The genes implicated in this disease are KMT2A and FLNA.

Keywords
Chromosome X; Chromosome 11; KMT2A (MLL); FLNA; Acute myelomonocytic leukaemia

Identity
The ins(X;11)(q28;q23q23) rearrangement is a form of ins(11;X)(q23;q28q12). The two chromosome anomalies are variants of each other, they lead to the formation of the same fusion gene KMT2A/FLNA.

Clinics and pathology

Disease
Acute myelomonocytic leukaemia (FAB-M4)

Phenotype/cell stem origin
Poorly defined, only three cases described to date, see Table 1 (De Braekeleer et al., 2009; Matveeva et al., 2015; Lentes et al., 2016).

Epidemiology
All 3 patients were boys, aged 5 to 13 months.

Cytology
Bone marrow aspirates demonstrated hypercellularity, blasts show typical AML-M4 features - high basophilic cytoplasm without Auer rods, moderate to high nucleocytoplasmic ratio.

Table 1. General characteristics and treatment course of patients with KMT2A/FLNA
CNS: CNS involvement; M4-AML: Acute myelomonocytic leukaemia; KMT2A/FLNA breakpoints
Reference: (1) De Braekeleer et al., 2009; (2) Matveeva et al., 2015; (3) Lentes et al., 2017.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Age/sex</th>
<th>WBC (x10^9/L)</th>
<th>CNS</th>
<th>Diagnosis</th>
<th>Survival</th>
<th>Karyotype</th>
<th>KMT2A/FLNA</th>
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<tr>
<td>1</td>
<td>5 mo/M</td>
<td>22</td>
<td>yes</td>
<td>M4-AML</td>
<td>2 mths</td>
<td>ins(11;X)(q23q28q12)</td>
<td>Intron 9 / exon 16</td>
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<tr>
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<td>81</td>
<td>no</td>
<td>M4-AML</td>
<td>3 mths</td>
<td>+6,ins(X;11)(q28q23q23)</td>
<td>Intron 10 / intron 19</td>
</tr>
<tr>
<td>3</td>
<td>13 mo/M</td>
<td>108</td>
<td>Unknown</td>
<td>M4-AML</td>
<td>1 mth</td>
<td>del(X)(q12),+del(X)(q12),+8,ins(11;X)(q23q28q12),+19</td>
<td>Exon 11 / exon 11</td>
</tr>
</tbody>
</table>
Cytogenetics

ins(11;X)(q23;q28q12) or ins(X;11)(q28;q23q23)

DNA/RNA
KMT2A gene consists of 37 exons encoding a 3969 amino-acid nuclear protein with a molecular weight of nearly 431 kDa.

Protein
431 kDa; contains two DNA binding motifs (a AT hook and Zinc fingers), and a DNA methyl transferase motif; wide expression; nuclear localization. KMT2A gene encodes a transcriptional coactivator that plays an crucial role in regulating gene expression during early development and hematopoiesis.

FLNA (filamin A)
Location Xq28
DNA/RNA
FLNA gene consists of 48 exons encoding a 2647 amino-acid protein with a molecular weight of 280739 Da.

Protein
280739 Da; belongs to the filamins family of high molecular mass structural proteins; contains N-terminal actin-binding domain; widely expressed; found in cytoplasm and cell cortex; involved into cell trafficking and actin cytoskeleton organization (Kim et al., 2011). Filamin A is an actin crosslinking phosphoprotein of the peripheral cytoplasm and interacts with Pho proteins. FLNA is crucial in many processes involving cytoskeletal reorganization (e.g. proliferation, differentiation, and apoptosis). It plays an important role in mitotic spindle function and is required for the G2/M cell cycle (Lentes et al., 2016).

Germinal mutations
Germline FLNA missense mutations are associated with otopalatodigital syndrome (OPD) spectrum of skeletal disorders. OPD is X-linked dominant and lethal in male patients. These mutations lead to a gain-of-function of filamin A (Clark et al., 2009).
On the other hand, loss-of-function FLNA mutations manifest as disorders of neuronal migration, also leading to early prenatal death in male patients (Kasper et al., 2013).

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

KMT2A/FLNA fusion gene contains 5’-portion of KMT2A and 3’-portion of FLNA. Breakpoints are various in both genes (Table 1). In the first case, the KMT2A/FLNA fusion showed a breakpoint in intron 10 of KMT2A and intron 19 of FLNA resulting in an in-frame fused mRNA (De Braekeleer et al., 2009). In the second one, an additional copy of 5’ KMT2A inserted into the long arm of the X chromosome resulting in an in-frame KMT2A/FLNA fusion gene with breakpoints in intron 9 of KMT2A and exon 16 of FLNA (Matveeva et al., 2015). And, in the third case, the breakpoint junction was localized in exon 11 of KMT2A and exon 11 of FLNA. However, a potentially functional transcript was generated by alternative splicing, where KMT2A exon 10 was spliced in-frame to the truncated FLNA exon 117 (Lentes et al., 2016).

**Transcript**

KMT2A/FLNA fusion transcripts were detected by RT-PCR in all cases (De Braekeleer et al., 2009; Matveeva et al., 2015; Lentes et al., 2016). It is notable that in two cases DNA junction was out-of-frame; nevertheless, functional transcripts were produced by alternative splicing (see above) either by intron retention (Matveeva et al., 2015) or by using a new splice acceptor site (Lentes et al., 2016).

**Detection**

KMT2A/FLNA fusion genes were detected by LDI-PCR (De Braekeleer et al., 2009; Matveeva et al., 2015; Lentes et al., 2016).

**Fusion protein**

**Oncogenesis**

Probably, the fusion KMT2A/FLNA has an oncogenic potential by functioning as gain-of-function mutants of KMT2A causing an upstream constitutive activation that promotes myeloid transformation and leads to AML. In all publications, due to lack of material, the existence of a functional protein has not been proven (Lentes, 2017).

**References**


This article should be referenced as such:

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