Leukaemia Section
Short Communication

TBL1XR1/MECOM fusion
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Published in Atlas Database: April 2018
Online updated version: http://AtlasGeneticsOncology.org/Anomalies/del3q26TBL1XR1-MECOMID1823.html
DOI: 10.4267/2042/70025
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Abstract
A novel TBL1XR1/MECOM fusion was identified in a patient with acute undifferentiated leukemia.

Keywords
chromosome 3 ; MECOM; TBL1XR1; acute undifferentiated leukemia; deletion 3q26.2q26.32 ; fusion gene

Identity
del(3)(q26.2q26.3) TBL1XR1/MECOM

Clinics and pathology

Disease
Acute undifferentiated leukaemia (classified in acute leukaemias of ambiguous lineage)

Phenotype/cell stem origin
This leukemia was CD34+high, CD38+ and CD117+-/ but negative for all lineage specific markers (cMPO-, CD13-, CD33-, CD7-, cCD3-, cCD79a-, CD19-, cCD22- cCD79a-).

Epidemiology
Only one case described, a 44-year-old-man (present report)

Cytology
Undifferentiated blasts, without criteria specific for either lineage (myeloid or lymphoid)

Treatment
The patient was treated according to the GRAALL-2014 protocol for adult acute lymphoblastic leukemia including induction, salvage course, then consolidation blocks and allo-HSCT transplantation.

Cytogenetics

Note
No abnormality detected on conventional karyotype: 46,XY[20]

Probes
XL MECOM D-5059-100-OG

Genes involved and proteins

MECOM (Ecotropic Viral Integration Site 1 (EV1) and Myelodysplastic Syndrome 1 (MDS1/EV1))

Location
3q26.2

Note
MECOM is also known as EV1 or PRDM3.
MECOM means MDS and EVI1 complex locus.

DNA/RNA
EV11 locus spans approximately 65 kb and contains 16 exons.
MDS1 locus spans approximately 500 kb and contains 4 exons.
The MDS1/EV1 transcript results from intergenic splicing of the second exon of MDS1 (telomere) to the second exon of EV1 (centromere)
FISH using a locus specific break-apart MECOM 3q26 probe (Metasystem XL D-5059-100-OG) confirmed the deletion at 3q26.2 locus telomeric to MECOM (loss of green signal).

**Protein**
MDS1/EVI1 protein contains a positive regulator domain (PR-domain) acting as a tumor-suppressor, a repression domain between two sets of several zinc finger motifs, and an acidic domain at its C-terminus. It is a nuclear transcriptional regulator involved in differentiation, proliferation and maintenance of hematopoietic stem cells. Deregulation of the proto-oncogene MECOM by the 3q rearrangements (inv3 or t(3;3)) reposition a distal GATA2 enhancer, inducing an aberrant expression of EVI1 and conferring GATA2 functional haploinsufficiency (Gröschel et al, 2014). This mechanism is implicated in leukemogenesis of MDS/AML with an extremely poor treatment outcome.

**TBL1XR1 (Transducin beta like 1 X-linked receptor 1)**

**Location**
3q26.32

**Note**
TBL1XR1 is also known as MRD41

**DNA/RNA**
TBL1XR1 locus contains 18 exons. It is a member of the WD40 repeat-containing gene family

**Protein**
The TBL1XR1 gene encodes a protein of 514 amino acids, which is a component of both N-CoR (nuclear receptor corepressor) and SMRT (silencing mediator of retinoid acid and thyroid hormone receptor) repressor complexes, which targeting nuclear receptor to repress transcription. TBL1XR1 is also required for transcriptional activation by many transcription factors (Li et al, 2015). The protein contains a LisH domain (Lis1 homology domain) and a F-box like domain in its N-terminal region, and 8 WD40 repeats at the carboxy-terminus. It seems to play a role in the maintenance of hematopoietic stem cells (Li et al, 2015). TBL1XR1 mutations and rearrangements have been described in several lymphoid malignancies including diffuse large B cell lymphoma, acute lymphoblastic leukemia and acute promyelocytic leukemia (Heinen et al, 2016).
Result of the chromosomal anomaly

Hybrid gene
Description
5’TBL1XR1-3’MECOM. TBL1XR1 exon 7 fused in-frame with MECOM exon 9 or 10.
Detection
RT-PCR using MECOM and TBL1XR1 primers.
Fusion protein

Schematic representations of TBL1XR1 and MECOM proteins and TBL1XR1/MECOM putative fusion proteins.

Description
The TBL1XR1/MECOM rearrangement may result in a putative hybrid protein containing the N-terminal portion (234 first aminoacids) of TBL1XR1 with its LisH, F-box and part of WD repeat domains and the C-terminal portion (381 last aminoacids) of MECOM retaining one set of zinc finger motif and the acidic domain.

References
Delwel R, Funabiki T, Kreider BL, Morishita K, Ihle JN. Four of the seven zinc fingers of the Evi-1 myeloid-transforming gene are required for sequence-specific binding to GA(C/T)AGA(T/C)AGATAA. Mol Cell Biol. 1993 Jul;13(7):4291-300

This article should be referenced as such: