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Leukaemia Section
Short Communication

TBL1XR1/MECOM fusion

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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

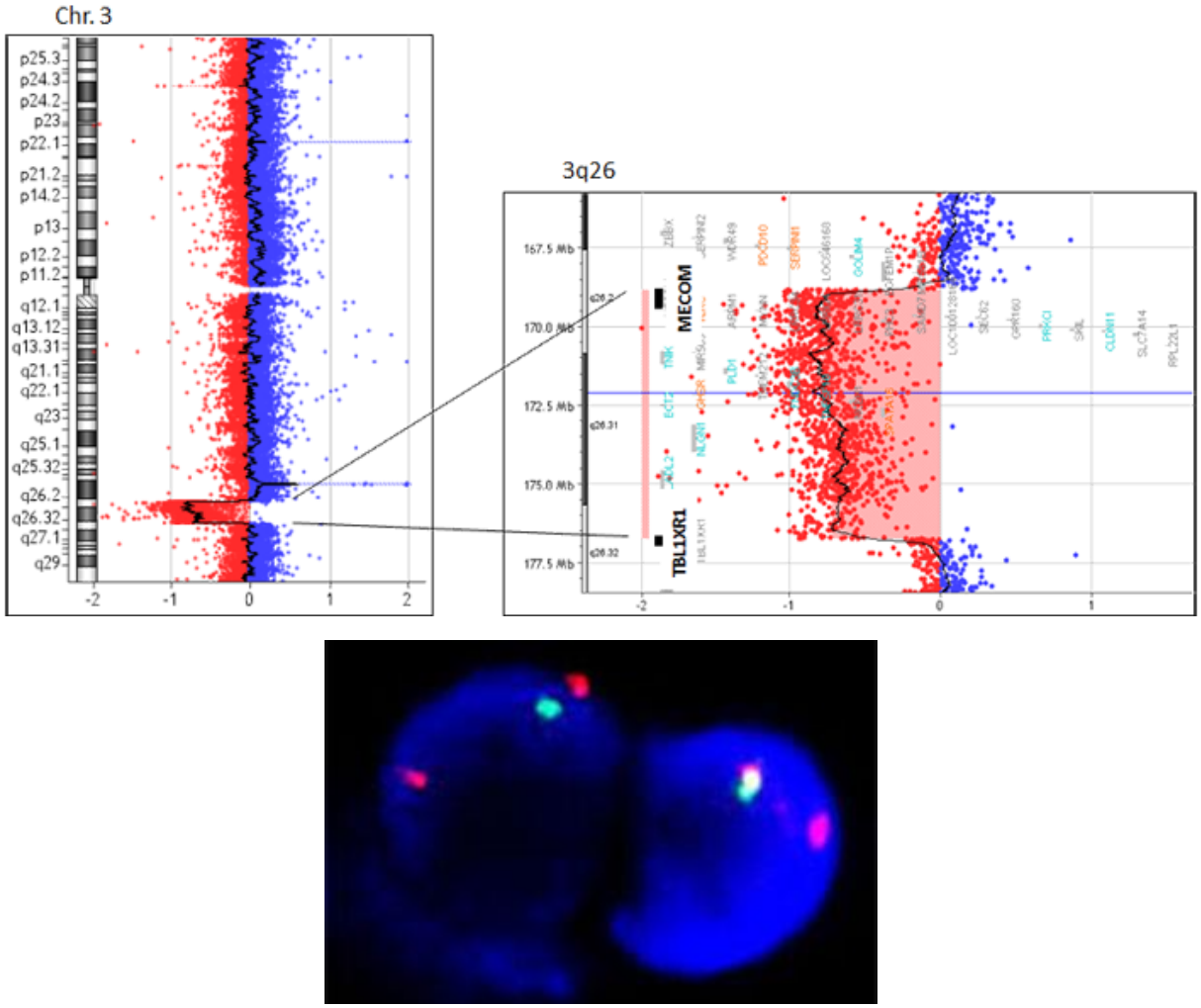
Genes involved and proteins

MECOM (Ecotropic Viral Integration Site 1 (EVI1) and Myelodysplasic Syndrome 1 (MDS1/EVI1))

Location
3q26.2

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

DNA/RNA
EVI1 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 EVI1 (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 fonctional 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

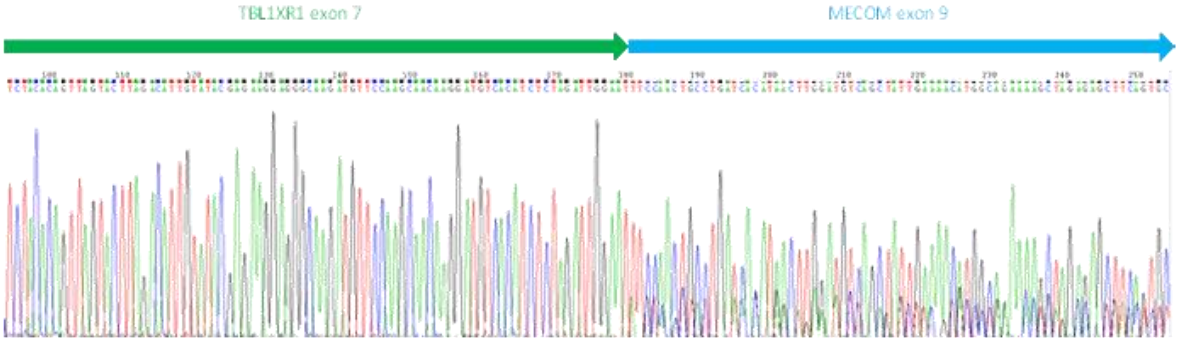
DNA/RNA

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

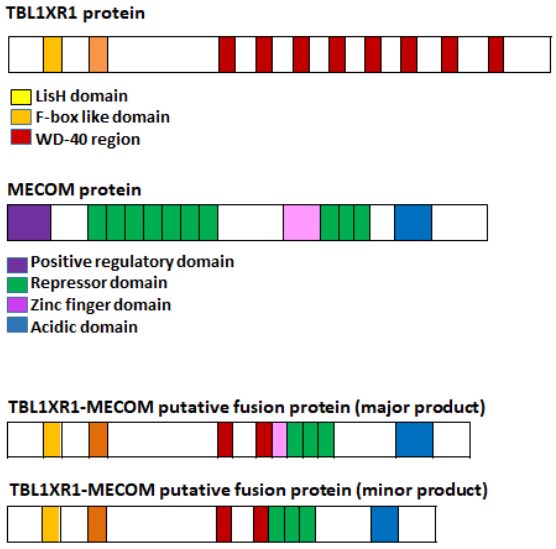
Description

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)AAGA(T/C)AAGATAA. Mol Cell Biol. 1993 Jul;13(7):4291-300

Goyama S, Yamamoto G, Shimabe M, Sato T, Ichikawa M, Ogawa S, Chiba S, Kurokawa M. Evi-1 is a critical regulator for hematopoietic stem cells and transformed leukemic cells. Cell Stem Cell. 2008 Aug 7;3(2):207-20

Gröschel S, Sanders MA, Hoogenboezem R, de Wit E, Bouwman BAM, Erpelinck C, van der Velden VHJ, Havermans M, Avellino R, van Lom K, Rombouts EJ, van Duin M, Döhner K, Beverloo HB, Bradner JE, Döhner H, Löwenberg B, Valk PJM, Bindels EMJ, de Laat W, Delwel R. A single oncogenic enhancer rearrangement causes concomitant EVI1 and GATA2 deregulation in leukemia. Cell. 2014 Apr 10;157(2):369-381

Heinen CA, Jongejan A, Watson PJ, Redeker B, Boelen A, Boudzovitch-Surovtseva O, Forzano F, Hordijk R, Kelley R, Olney AH, Pierpont ME, Schaefer GB, Stewart F, van Trotsenburg AS, Fliers E, Schwabe JW, Hennekam RC. A specific mutation in TBL1XR1 causes Pierpont syndrome. J Med Genet. 2016 May;53(5):330-7

Li JY, Daniels G, Wang J, Zhang X. TBL1XR1 in physiological and pathological states. Am J Clin Exp Urol. 2015;3(1):13-23

Maicas M, Vázquez I, Alis R, Marcotegui N, Urquiza L , Cortés-Lavaud X , Cristóbal I ,Garcèa-Sánchez MA, D. Odero MD. The MDS and EVI1 complex locus (MECOM) isoforms regulate their own transcription and have different roles in the transformation of hematopoietic stem and progenitor cells. Biochim Biophys Acta. 2017 Jun;1860(6):721-729

Wieser R.. The oncogene and developmental regulator EVI1: expression, biochemical properties, and biological functions. Gene 2007 Jul 15;396(2):346-57. Epub 2007 Apr 20.

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