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Short Communication

t(10;11)(p12;q23) KMT2A/NEBL

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Abstract

Review on t(10;11)(p12;q23) KMT2A/NEBL, with data on clinics, and the genes implicated.

Clinics and pathology

Disease

Infant acute myeloid leukemia (AML)

Phenotype/cell stem origin

AML-M5.

Epidemiology

Poorly defined, only one case described to date, a 11 month-old boy (Coser et al., 2010).

Prognosis

This infant was treated according to AML-BFM98 backbone adapted protocol and died 1 month later while in the aplastic phase of treatment (Coser et al., 2010).

Cytogenetics

Probes

MLL dual color break apart rearrangement probe.

Genes involved and proteins

MLL/KMT2A

Location
11q23

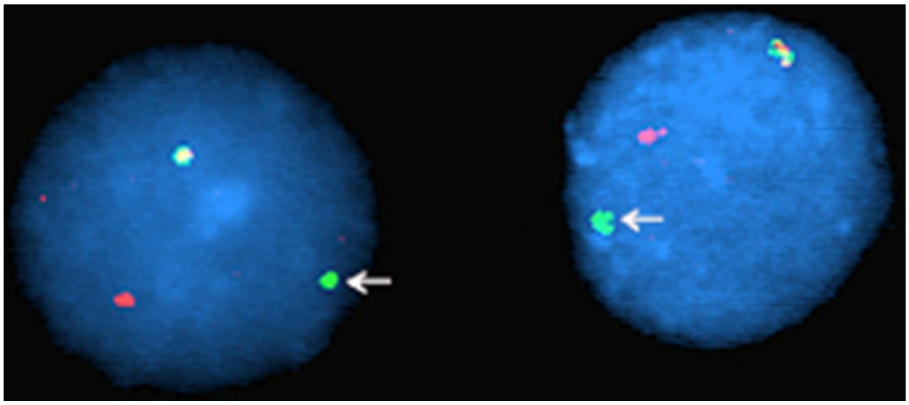
DNA/RNA
The Mixed-Lineage Leukemia gene consists of 37 exons, encoding a 3969 amino-acid nuclear protein with a molecular weight of nearly 431 kDa.

Protein
431 kDa; contains two DNA binding motifs (a AT hook and Zinc fingers), and a DNA methyl transferase motif; wide expression; nuclear localisation; transcriptional regulatory factor.

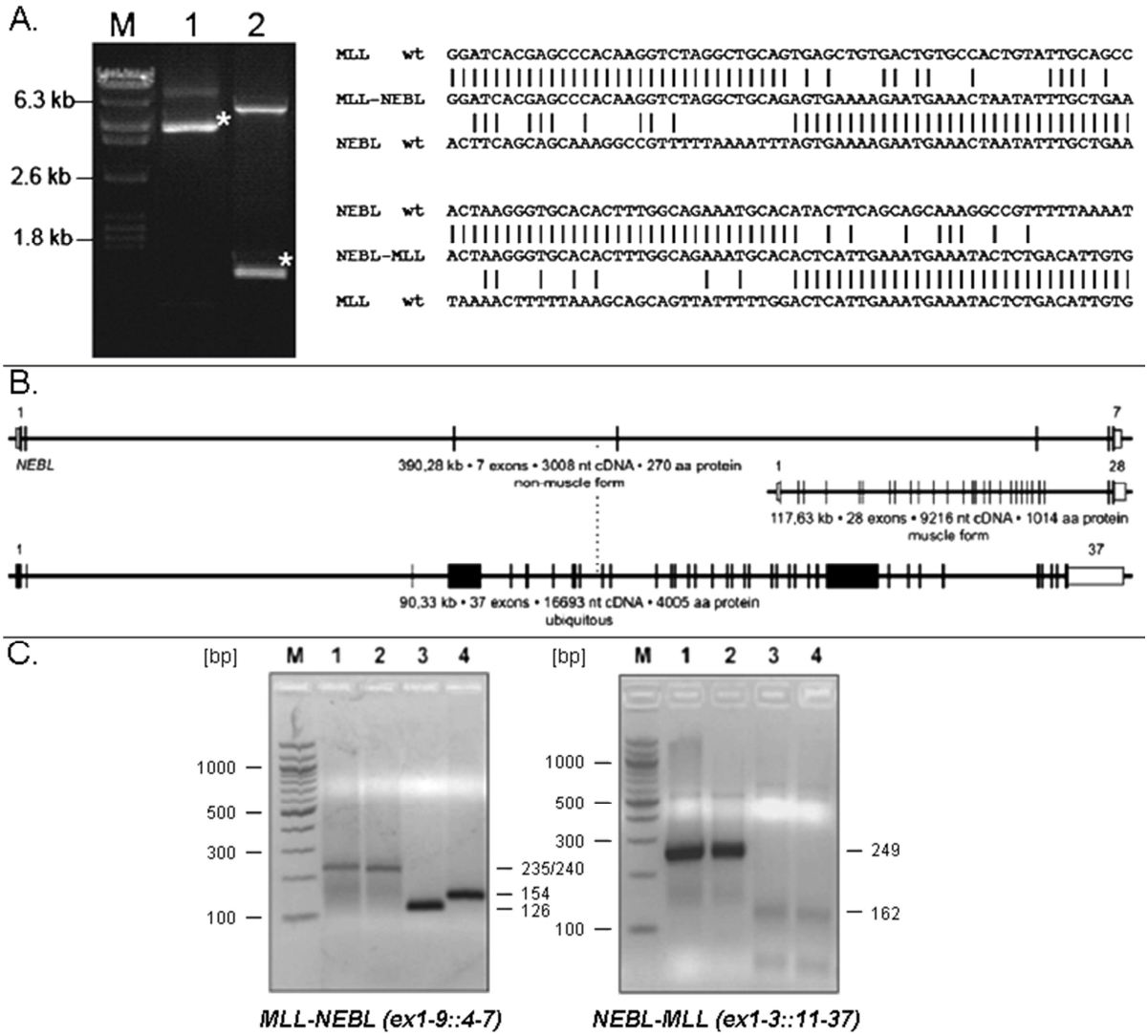
NEBL

Location
10p12

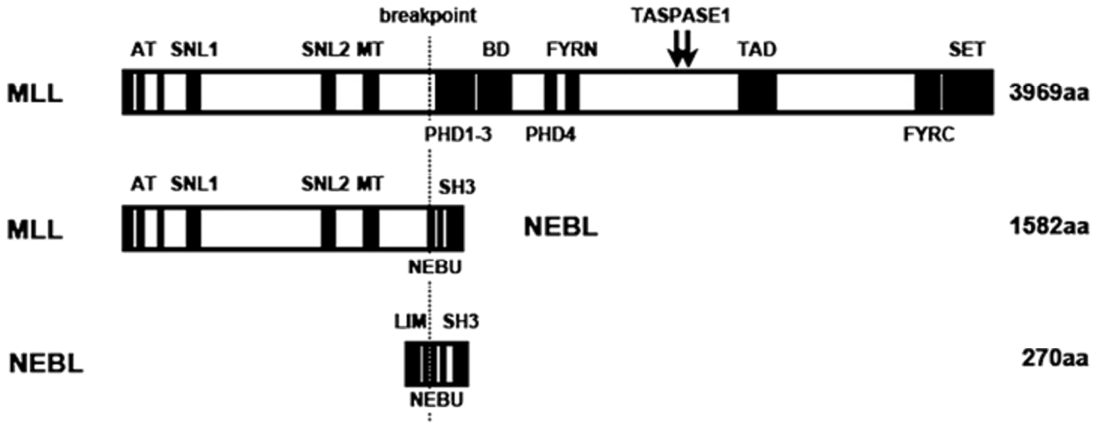
Note
Nebulette, non-muscle isoform.
There exists also a sacomeric isoform of the NEBL gene. Nebulette is the second member of the nebulin family fused to MLL.



The probe was hybridized to interphase nuclei and displayed one split hybridization (arrow) signal that indicates translocation with an unknown partner gene (Coser et al., 2010).



A. Left: Long-distance inverse polymerase chain reaction (LDI-PCR) analysis of both derivatives using genomic DNA. Lane M, size marker; lane 1, LDI-PCR analysis of der(11) showing the wild-type (wt) band and the der(11) band (asterisk); lane 2, LDI-PCR analysis of der(10) showing the wt band and the der(10) band (asterisk). **Right:** Genomic breakpoint sequence alignment of both derivatives (MLL/NEBL and NEBL/MLL) with respective wt sequences (Coser et al., 2010). **B.** The genetic fusion of MLL and NEBL in this AML patient occurred within the non-muscle form of the NEBL gene (intron 3) and within the known breakpoint cluster region of MLL (intron 9). The gene structures are indicated and the recombination site is indicated by a dashed line (Emerenciano et al., 2013). **C.** RT-PCR analyses of MLL-NEBL and NEBL-MLL fusion transcripts (Emerenciano et al., 2013).



Size and location of functional domains of the MLL wt, NEBL wt, and of the MLL-NEBL fusion protein. AT, AT hook, SNL, subnuclear localization; MT, methyltransferase; BD, binding domain; TAD, transcriptional activation domain; PHD, plant homeo domain; SET, Su(var)3e9; Enhancer-of-zeste, Trithorax; NEBU, nebulette units; SH3, SRC homology 3. (Coser et al., 2010).

DNA/RNA

The Nebulette non-muscle isoform consists of 7 exons, encoding a 270 amino-acid protein with a molecular weight of 31,2 kDa.

Protein

270 aa, 31,2 kDa.

Result of the chromosomal anomaly

Hybrid gene

Note

Fusion gene MLL-NEBL and NEBL-MLL was detected by LDI-PCR (Coser et al., 2010).

Description

In the described patient MLL exons 1-9 are fused to NEBL (non-muscle isoform) exons 4-6 due to translocation between MLL intron 9 and NEBL (non-muscle isoform) intron 3. NEBL (non-muscle isoform) exons 1-3 are fused to MLL exons 10-37 due to translocation between NEBL (non-muscle isoform) intron 3 and MLL intron 10.

Detection

Detection method RT-PCR.

Fusion protein

Description

The 1582 amino acid big fusion protein retains a major portion of MLL, including those domains known to be essential for leukemic transformation: the AT-hooks and the DNA methyltransferase domain (DNMT) which is fused two nebulin modules, the truncated serine-rich linker region and the SH3 domain of the NEBL protein.

To be noted

Note

Two other studies suggest that the reciprocal fusion gene NEBL-MLL might be of biological importance (Emerenciano et al., 2013; Wächter et al., 2014).

References

Cóser VM, Meyer C, Basegio R, Menezes J, Marschalek R, Pombo-de-Oliveira MS. Nebulette is the second member of the nebulin family fused to the MLL gene in infant leukemia. Cancer Genet Cytogenet. 2010 Apr 15;198(2):151-4

Emerenciano M, Kowarz E, Karl K, de Almeida Lopes B, Scholz B, Bracharz S, Meyer C, Pombo-de-Oliveira MS, Marschalek R. Functional analysis of the two reciprocal fusion genes MLL-NEBL and NEBL-MLL reveal their oncogenic potential. Cancer Lett. 2013 May 10;332(1):30-4

Wächter K, Kowarz E, Marschalek R. Functional characterisation of different MLL fusion proteins by using inducible Sleeping Beauty vectors. Cancer Lett. 2014 Oct 1;352(2):196-202

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