t(11;15)(q23;q14) KMT2A/ZFYVE19

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Diseases and pathology

Disease
Acute myeloid leukemia (AML).

Epidemiology
Only one case to date, a 11-year-old boy with de novo acute myeloblastic leukemia (AML-M2) (Chinwalla et al., 2003).

Genetics

Note
ZFYVE19 is located 170kb telomeric to CASC5 on chromosome 15. Two in-frame fusions were detected in this patient, in which 5’ MLL was fused both to ZFYVE19 and CASC5. Fusion junctions were: PPKTTTPSEPKKKQPPL from MLL (amino acid 1334), fused to PQNYKKRVAALEAKQK... from ZFYVE19 (amino acid 146), and APRPSIPVKQPKKEK from MLL, fused to IFDHHTEEDIDKSA... from CASC5.

Cytogenetics

Cytogenetics morphological
Complex karyotype.

Genes involved and proteins

KMT2A
Location 11q23.3
Note
KMT2A (HGNC official name!) is better known as MLL.

Protein
3969 amino acids; Transcriptional regulatory factor. MLL is known to be associated with more than 30 proteins, including the core components of the SWI/SNF chromatin remodeling complex and the transcription complex TFIID. MLL binds promoters of HOX genes through acetylation and methylation of histones. MLL is a major regulator of hematopoiesis and embryonic development, through regulation of HOX genes expression regulation (HOXA9 in particular).

ZFYVE19

Location 15q15.1
Note
ZFYVE19 is also known as ANCHR (for Abscission/NoCut Checkpoint Regulator), or MPFYVE (for MLL Partner Containing FYVE Domain).

Protein
471 amino acids. ZFYVE19 contains a Zinc finger FYVE-type (amino acids 74-133), MIM1 domains (type-I microtubule interacting and transport (MIT) domain-interacting motifs MIMs, to mediate interaction between ESCRT-III proteins and the VPS4 MIT domain): MIM1-A (aa 174-187) and MIM1-B (aa 326-339), and a B-box domain in C-term. Cytokinesis is the final stage of cell division. There is an abscession checkpoint (also termed "NoCut") which depends on AURKB (17p13.1).
The membrane abscission is mediated by the ESCRT machinery through the activity of the VPS4 proteins (VPS4A, 16q22.1 and VPS4B, 18q21.33). VPS4 localizes transiently to the midbody ring towards the end of cytokinesis. ZFYVE19 and CHMP4C bind VPS4 following checkpoint, and AURKB sustains this ternary complex. Termination of AURKB-mediated signalling results in dephosphorylation of CHMP4C, followed by dislocation of the ternary complex, and release of VPS4, which is then activated to complete abscission (Thoresen et al., 2014).

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**
Exon 7 of MLL was fused to exon 3 of ZFYVE19.

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**Fusion protein**

**Description**

The MLL/ZFYVE19 fusion protein is a 1435 amino acids protein with a molecular mass of 160 kDa. It contains the AT-hooks and the repression domain of MLL and the C-term of ZFYVE19, without the N-term Zinc finger FYVE-type domain of ZFYVE19.

**References**

Chinwalla V, Chien A, Odero M, Neilly MB, Zeleznik-Le NJ, Rowley JD. A t(11;15) fuses MLL to two different genes, AF15q14 and a novel gene MPFYVE on chromosome 15. Oncogene. 2003 Mar 6;22(9):1400-10


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