

## Leukaemia Section

### Short Communication

# t(3;5)(q26;q31) H2AFY/MECOM

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Published in Atlas Database: November 2018

Online updated version : [http://AtlasGeneticsOncology.org/Anomalies/t0305q26q31H2AFY\\_MECOMID1837.html](http://AtlasGeneticsOncology.org/Anomalies/t0305q26q31H2AFY_MECOMID1837.html)

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DOI: 10.4267/2042/70579

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## Abstract

Review on t(3;5)(q26;q31) H2AFY/MECOM, with data on clinics, and the genes involved.

### Keywords

Chromosome 3; chromosome 5; H2AFY; MECOM; Acute myelomonocytic leukaemia

## Clinics and pathology

### Disease

Acute myelomonocytic leukaemia (M4-AML)

### Epidemiology

Only one case to date, a 76-year-old male patient (Han et al., 2018).

### Evolution

He achieved complete remission (CR), but he relapsed and died 10 months after diagnosis.

## Genes involved and proteins

### MECOM (Ecotropic Viral Integration Site 1 (EVI1) and Myelodysplastic Syndrome 1 (MDS1-EVI1))

Location 3q26.2

### Note

MECOM is a nuclear transcription factor that plays an essential role in the proliferation and maintenance of hematopoietic stem cells and can inhibit myeloid differentiation. Two alternative forms exist, one generated from EVI1, the other MECOM (MDS1 and EVI1 complex locus) through intergenic splicing

with MDS1 (myelodysplasia syndrome 1), a gene located 140 kb upstream of EVI1.

### Protein

The protein encoded by this gene is a transcriptional regulator involved in cell differentiation and proliferation, and apoptosis. The encoded protein can interact with transcriptional coactivators (KAT2B (P/CAF), CREBBP (CBP)) and corepressors (CTBP1, HDAC) as well as other transcription factors (GATA1, SMAD3) (de Braekeleer et al., 2012)

### H2AFY (H2A histone family member Y)

Location 5q31.1

### Protein

**H2AFY codes for the proteins MACROH2A1.** The first exon is non-coding. Due to alternative exons 6 (coding exons 5), coding for amino acids (aa) 198-226 or 229, there are 2 isoforms. Isoform MacroH2A1.1: 369 aa; 39,1 kDa; Isoform MacroH2A1.2: 372 aa, 39,6 kDa; This protein comprises a histone H2A domain (aa: 2-117; length: 116 aa) with a HA2 signature: AGVIFPV (aa: 19-25), a Lys-rich region (aa: 118-162; length: 45 aa) with a SQ-motif (aa 139-140) which can be phosphorylated by PIKKs, and a macro domain (aa: 184-370; length: 187). Ubiquitination sites are at Lys115, Lys116 and Lys119 (Ogawa et al., 2005). Glycines (Gly224 and Gly314) are required for PAR (poly(ADP-ribose)) binding.

MacroH2A1.1 is mainly found in differentiated, non-proliferative tissues, MacroH2A1.1 is upregulated in senescent cells; MacroH2A1.2 is more generally expressed, including in tissues with ongoing cell proliferation (Sporn and Jung 2012).

MACROH2A1 regulates gene transcription, DNA damage response, mitochondrial respiration and senescence.

**Methylations/acetylations** MacroH2A1 is found on autosomes as part of facultative heterochromatin and is localized at two functionally distinct chromatin subtypes marked by trimethylation of histone H3 on lysine 27 (H3K27me3) or as part of transcriptionally active euchromatin marked by nine histone acetylations (H2B at K15 and K20; H3 at K4, K14 and K18; H4 at K91; and H2A at K5) where it can either positively or negatively regulate transcription (reviewed in Ruiz and Gamble 2018).

**MacroH2A1.1-PARP1 axis** Stressing signals generated during DNA damage repair, senescence, hormonal response, heat shock, or differentiation promote the binding of MacroH2A1.1 to activated PARP1 (poly(ADP-ribose) polymerase 1), creating the macroH2A1.1-PARP1 axis. MacroH2A1.1 recruit active PARP1 to chromatin and promotes the CREBBP -mediated acetylation of H2B K12 and K120, which either positively or negatively regulates the expression of MacroH2A1-target genes. On the other hand, when MacroH2A1.1 is highly expressed, MacroH2A1.1 can bind and inhibit PARP1 activity Chen et al., 2014; Hurtado-Bagès et al., 2018).

**MacroH2A1 regulates mitochondrial respiration** MacroH2A1.1 reduces nuclear NAD<sup>+</sup> consumption through PARP1 inhibition, allowing maintenance of mitochondrial NAD<sup>+</sup> pools that are critical for respiration (Posavec Marjanovic et al., 2014).

**Epithelial-mesenchymal transition** MacroH2A1.1 isoform, but not MacroH2A1.2, can suppress EMT induction.

**Cancer** Upregulation of mH2A1 induces SKP2 subsequent CDK8 downregulation contributes to growth defect, G2/M arrest, polyploidy and tumour suppression in breast cancer (Xu et al., 2015). MacroH2A1.2, one of the MacroH2A isoforms (see above), has an intrinsic ability to inhibit breast cancer-derived osteoclastogenesis and prostate cancer-induced osteoclastogenesis. Overexpression of mH2A1.2, but not mH2A1.1, in breast cancer cells significantly increased ERBB2 expression and tumorigenicity (Li et al., 2012). Re-expression of MacroH2A1.1 suppressed cancer cell proliferation, anchorage-independent growth and cell invasiveness in breast cancer, and suppressed metastasis of melanoma through regulation of CDK8. Loss of MacroH2A1.1 was associated with cell growth and metastasis and a worse outcome in colon cancer. Conversely, MacroH2A1.2 levels have been found to be similar in all tumors independently of proliferation (Sporn and Jung 2012). Patients with low MacroH2A1.1 levels in lung tumor samples recur more likely. MacroH2A1 downregulation enhances the stem-like properties of bladder cancer cells. In contrast, in the claudin-low subtype of triple

negative breast cancer (ESR1, PGR, normal ERBB2) presenting a high MacroH2A1.1 mRNA ratio exhibit a poor outcome, through epithelial-mesenchymal transition process towards metastatic development (Lavigne et al., 2014).

## Result of the chromosomal anomaly

### Hybrid gene

#### Description

5'H2AFY-3'MECOM. The breakpoint in 5q31.1 was located in intron 5 of H2AFY, and the breakpoint in 3q26 was located in intron 1 of MECOM. H2AFY exon 5 was fused to MECOM exon 2 (Han et al., 2018).

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*This article should be referenced as such:*

Huret JL. t(3;5)(q26;q31) H2AFY/MECOM. *Atlas Genet Cytogenet Oncol Haematol.* 2019; 23(10):310-311.