del(12)(q24q24) SETD1B/GTF2H3

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Abstract
We identified a novel SETD1B/GTF2H3 fusion gene in a polycythemia vera (PV) patient with complex karyotype, harboring a cryptic deletion involving chromosome band 12q24.31. This rearrangement led to the juxtaposition of the SETD1B (SET domain containing 1B) gene at intron 11 (chr12:122,257,801) with the GTF2H3 (general transcription factor IIH, polypeptide 3) gene at intron 5 (chr12:124,137,254). In silico translation showed a protein retaining SETD1B RNA binding domain (RRM_S) at its N-terminus and a portion of GTF2H3 DNA binding domain (Tfb4) at its C-terminus. We also provided evidences that SETD1B might be rearranged in an additional PV case, although in a small proportion of hematopoietic cells, indicating a possible role of SETD1B in disease pathogenesis.

Keywords
SETD1B, GTF2H3, polycythemia vera, deletion

Clinics and pathology

Disease
Polycythemia Vera

Note
Myeloproliferative neoplasm

Phenotype/cell stem origin
CD34+ cell

Etiology
SETD1B is a SET-domain containing protein with histone H3-Lys4 methyltransferase activity, which is associated with active gene expression (Lee et al. 2007).

SET-like enzyme genes include those implicated in various leukemias and cancers like MLL. SETD1B interacts with RBM15 through its LSD motif, creating a complex important for epigenetic regulation (Lee et al. 2002). RBM15 (RNA binding motif protein 15) utilizes the epigenetic mechanism to control alternative splicing of MPL (myeloproliferative leukemia virus oncogene), leading to the regulation of thrombopoietin response in hematopoietic stem cells (Xiao et al. 2014).

In the SETD1B/GTF2H3 chimeric protein, SETD1B loses the LSD domain, possibly leading to an altered epigenetic regulation. GTF2H3 has been related to the nucleotide excision repair pathway, and resulted upregulated in HL-60 cell line resistant to ATRA (Liu et al. 2014).

Epidemiology
The SETD1B/GTF2H3 rearrangement was found in only one out of 60 patients with myeloproliferative neoplasms evaluated. However, FISH analysis revealed a splitting signal in a very low percentage of nuclei (3/412, 0.7%) in one of 13 analyzed patients, suggesting a possible rearrangement of SETD1B with other partner genes (Storlazzi et al. 2014).
Partial karyotype of the patient with del(12) (lower panel), showing FISH analysis performed by using three BAC clones encompassing the SETD1B gene region (upper panel). The colored rectangles (blue, red, and green) correspond to the results obtained respectively for probes RP11-1066O14, RP11-7M8, and RP11-87C12. The deletion breakpoint in the patient was mapped within RP11-7M8, as its signal intensity on the deleted chromosome 12 [del(12)] was significantly fainter than the one on the normal homolog. RP11-1066D14 was retained on del(12), while RP11-87C12 was deleted on del(12).

**Clinics**
The SETD1B/GTF2H3 rearrangement has been found in a patient diagnosed with Polycythemia Vera that evolved in post-polycythemia vera myelofibrosis after two years.

**Cytology**
Blood smear showed no leukoerythroblastic picture but only few dacrocytes.

**Pathology**
The bone marrow biopsy showed the presence of hyperplasia of myeloid and erythroid lineages, increased scattered megakaryocytes without overt morphologic abnormalities and an increase in reticulin fibrosis compatible with grade 1 of 3 (European scale).

**Treatment**
The subject was treated with phlebotomies and hydroxyurea according to the European Leukemia Net (ELN) recommendations (Barbui et al. 2011), but considered as refractory/resistant to hydroxyurea (Barosi et al. 2010). The patient was then enrolled in a clinical trial with the histone deacetylase inhibitor givinostat, obtaining prompt relief from pruritus and rapid reduction up to stop of phlebotomies (Finazzi et al. 2013). However, the treatment was interrupted after six months because of progression of a pre-existing mild renal insufficiency, and the subject was shifted again to low-dose hydroxyurea plus phlebotomies.

**Evolution**
Two years after the detection of the SETD1B/GTF2H3 fusion gene, the patient was diagnosed with post polycythemia vera myelofibrosis according to the diagnostic criteria of the International Working Group for Myeloproliferative Disorders Research and Treatment (IWG-MRT) (Barosi et al., 2008). At that time, the gene fusion was still detectable in bone marrow sample.

**Cytogenetics**

**Note**
The rearrangement leading to the genesis of this fusion gene (a cryptic deletion on chromosome 12) was not evident at cytogenetic level.

**Cytogenetics morphological**
The only described PV patient harboring this novel fusion gene showed a complex karyotype.

**Cytogenetics molecular**
The SETD1B/GTF2H3 fusion gene was identified by genomic massive sequencing. FISH analysis with an appropriate probe set for SETD1B disclosed the occurrence of a 110Kb interstitial deletion, confirming the gene rearrangement.

**Additional anomalies**
A ins(6;15) insertion accompanied by chromosome losses at all the breakpoint regions [6p22.1p22.3

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Wild-type SETDB1 (grey), GTF2H3 (blue) and chimeric SETD1B/GTF2H3 predicted proteins, accordingly to ORF finder and BlastP analyses of the full-length transcripts. Red arrows indicate the breakpoints, respectively in SETD1B (Accession no. NP_055863, aminoacid no.1260), and in GTF2H3 (Accession no. NP_001507, aminoacid no.153). RRM_S: RNA recognition motif; N-SET, SET: catalytic domains for H3K4 trimethylation; P: cystein-rich motif; TBF4: transcription factor with DNA binding domain.

### Genes involved and proteins

**SETD1B**
- **Location**
  12q24.31 (chr12:122,242,638-122,270,562)
- **DNA/RNA**
  Homo sapiens SET domain containing 1B (SETD1B)
- **Protein**
  SET1B is a component of a histone methyltransferase complex that produces trimethylated histone H3 at Lys4.

**GTF2H3**
- **Location**
  12q24.31 (chr12:124,118,286-124,147,151)
- **DNA/RNA**
  Homo sapiens general transcription factor IIH, polypeptide 3. The gene encodes for four transcript variants.
- **Protein**
  GTF2H3 is a subunit of the core-TFIH basal transcription factor. It localizes to the nucleus and is involved in RNA transcription and nucleotide excision repair. Moreover, it associates with the Cdk-activating kinase complex.

### Result of the chromosomal anomaly

**Hybrid gene**
- **Description**
  5' SETD1B/3' GTF2H3. SETD1B (accession no. NM_015048) at exon 11 was fused in frame with GTF2H3 (accession no. NM_001516) at exon 7.

### Detection
- Genomic paired-end massive sequencing.
- The fusion transcript was validated by RT-PCR and Sanger sequencing.

### Fusion protein
- **Description**
  In silico translation of the fusion transcript, obtained by ORF finder, showed a putative protein maintaining the SETD1B RNA binding domain (RRM_S) at its N-terminus and a portion of GTF2H3 DNA binding domain (TBF4) at its C-terminus.

### References


Lee JH, Skalnik DG. Rbm15-Mkl1 interacts with the Setd1b histone H3-Lys4 methyltransferase via a SPOC domain that


This article should be referenced as such: