Uterus: Low-grade endometrial stromal sarcoma with t(X;17)(p11.2;q21.33) MBTD1/CXorf6

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Abstract

Short communication on t(X;17)(p11.2;q21.33) MBTD1-CXorf6 in low-grade endometrial stromal sarcoma.

Keywords
Low-grade endometrial stromal sarcoma, MBTD1, CXorf6, fusion

Classification

Note
Low-grade endometrial stromal sarcoma belongs to the uterine tumors of mesenchymal origin. According to the current World Health Organization classification (2013), uterine endometrial stromal and related tumors are categorized as benign endometrial stromal nodules (ESN), low-grade endometrial stromal sarcomas (LGESS), high-grade endometrial stromal sarcomas (HGESS), undifferentiated endometrial sarcomas (UES) and uterine tumors resembling ovarian sex cord tumor. Low- and high-grade endometrial stromal sarcomas are genetically heterogeneous group of tumours, frequently harbouring recurrent chromosomal translocations. The chimeric transcripts reported so far are JAZF1/SUZ12, YWHAE/FAM22, ZC7H/BCOR, and recombination of PFH1 with JAZF1, EPC1, or MEAF6 (Koontz et al., 2001; Micci et al., 2006; Lee et al., 2012; Panagopoulos et al. 2012; Panagopoulos et al., 2013; Oliva et al., 2013).

Clinics and pathology

Disease
Low-grade endometrial stromal sarcoma (LGESS) with t(X;17) translocation

Phenotype / cell stem origin
Unknown

Embryonic origin
The cellular origin of this low grade sarcoma is unknown, but the tumor cells presumably derive from the early mesenchymal endometrial progenitor cells.

Etiology
Unknown.

Epidemiology
The true incidence of t(X;17) LGESS is unknown. Two cases in females of respectively reproductive and postmenopausal age have been reported to date (Amant et al., 2003; Dewaele et al, 2014).

Clinics
The patients presented with abnormal uterine bleeding and abdominal pain.

Pathology
Classical cases of LGESS are composed of cells that morphologically resemble non-neoplastic proliferative-phase or hyperplastic endometrial stromal cells (Chiang and Oliva, 2013).
The tumors consist of cellular spindle cells aligned in short intersecting fascicles, without nuclear pleomorphism or atypia, and show rare mitotic figures (H&E; original magnification, x400).

On cut surfaces, the tumor lesions are solid and white-yellowish with a glassy appearance. Hematoxylin and eosin stained slides show myometrial permeation by wormlike masses and frequent lymphatic infiltration.

The tumor cells have bland nuclear features with monotonous oval to spindle cells concentrically proliferating around a rich vascular network of arterioles and capillaries.

Mitotic figures are rare. By immunohistochemistry, the tumour components are diffusely and strongly positive for CD10 antigen and for oestrogen and progesterone receptors (Oliva et al., 2013).

**Treatment**

Surgical resection of the tumor, followed by hormonal treatment

**Prognosis**

The two reported patients showed a relatively indolent clinical course in spite of their metastatic disease (Amant et al., 2003; Dewaele et al, 2014).
Cytogenetics

Cytogenetics Morphological

Reciprocal t(X;17)(p11.2;q21.33) translocation has been observed in all reported cases.

Cytogenetics Molecular

Metaphase FISH analysis of two LGESS cases using BAC RP11-379D19 DNA probe resulted in a split signal, which defined the 17q21.33 translocation breakpoint to the MBTD1 gene (data not shown). Using a panel of fosmid probes, a minimal shared breakpoint region in Xp11.22 could be mapped to position 51.136-51.321 Mb; this region contains three genes (NUDT10, CXorf67 and NUDT11). Whole transcriptome paired-end sequencing of two LGESS on Illumina HiSeq II platform identified CXorf67 as the partner gene on the X chromosome. One additional LGESS case with the MBTD1-CXorf67 fusion was identified using interphase FISH with probes that map to sequences covering the CXorf67 and MBTD1 genomic loci (Figure 3).

Genes involved and proteins

MBTD1

Location

17q21.33 (position 51,177,425-51,260,163 on the chromosome 17 genomic sequence according to the UCSC database; assembly of December 2013)

DNA / RNA

The gene consists of 17 exons that span 79.46 kb of genomic DNA in the telomere-to-centromere orientation. The translation initiation codon and the stop codon are predicted to exon 1 and exon 17, respectively. The corresponding wild-type mRNA transcript is 5.3 kb (NM_017643.2). MBTD1 shows high level expression in normal fallopian tube in comparison to medium level expression in normal endometrium.

Protein

The open reading frame is predicted to encode a 628 amino acid protein with an estimated molecular weight of 70 kDa.
**CXorf67**

**Location**
Xp11.22 (51,406,915-51,408,843 on the chromosome X genomic sequence according to the UCSC database; assembly of December 2013).

**DNA / RNA**
The gene consists of 1 exon that spans 1.92 kb of genomic DNA in the centromere-to-telomere orientation. It is entirely nested in another gene, namely in the intron 1-2 of the RP11-348F1.2 non-coding gene (Yu et al., 2005). The corresponding wild-type mRNA transcript is 1.929 kb (NM_203407). CXorf67 is highly overexpressed in normal oocytes in comparison to low-level expression in other tissues, including normal endometrium.

**Protein**
The CXorf67 open reading frame is predicted to encode a 503 amino acid protein (NP_981952.1).

**Result of the chromosomal anomaly**

**Hybrid Gene**

**Description**
The t(X;17)(p11.2;q21.33) results in a MBTD1-CXorf67 chimeric gene in which exon 16 of MBTD1 is fused to exon 1 of CXorf67.

**Transcript**
The MBTD1-CXorf67 fusion transcript is 3142 bp in length (2514 bp without UTR and without Stop codon).
The MBTD1-CXorf67 fusion formation is correlated with the CXorf67 3’ domains overexpression.

**Detection**
The hybrid gene can be visualized by FISH using gene specific probes or by RT-PCR.
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The sequence of the MBTD1-CXorf67 junction is shown, with the structure of the MBTD1-CXorf67 cDNA depicted below (the dashed arrow indicates the fusion point).

The predicted MBTD1-CXorf67 fusion protein is shown. Red boxes: the FCS and the four MBT domains of MBTD1; grey box: the Serine-rich domain of CXorf67.

**Fusion Protein**

**Description**

The MBTD1-CXorf67 fusion transcript is predicted to encode a chimeric protein of 839 amino acids that contains the FCS-type zinc finger domain and the four MBT domains of MBTD1 and the Serine-rich region of CXorf67.

**To be noted**

The aCGH data and gene expression data were submitted to the GEO database (Series GSE46285, SubSeries GSE46284: aCGH data; SubSeries GSE45783: gene expression profiling data).

**References**


This article should be referenced as such: